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Handbook of Medical Neuropsychology

Applications of Cognitive Neuroscience

Second Edition

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Foreword by Muriel D. Lezak

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Foreword to the First Edition

This handbook celebrates the abundantly productive interaction of neuropsychology and medicine. This interaction can be found in both clinical settings and research laboratories, often between research teams and clinical practitioners. It accounts for the rapidity with which awareness and understanding of the neuropsychological components of many common medical disorders have recently advanced. The introduction of neuropsychology into practice and research involving conditions without obvious neurological components follows older and eminently successful models of integrated care and treatment of the classical brain disorders.

In the last 50 years, with the growing understanding of neurological disorders, neuropsychologists and medical specialists in clinics, at bedside, and in laboratories together have contributed to important clinical and scientific advances in the understanding of the common pathological conditions of the brain: stroke, trauma, epilepsy, certain movement disorders, tumor, toxic conditions (mostly alcohol-related), and degenerative brain diseases. It is not surprising that these seven pathological conditions were the first to receive attention from neuropsychologists as their behavioral symptoms can be both prominent and debilitating, often with serious social and economic consequences.

However, many diseases affect behavior and cognition without directly involving brain substance. Yet only in the last two decades has a scientifically grounded understanding of the neuropsychological implications of such diseases become available as the neuropsychological enterprise broadened its purview from the common brain disorders to clinical care and research with patients whose medical conditions impaired their neuropsychological functioning. Thanks to the relatively recent emphasis on "holistic" medicine, physicians have increasingly become sensitive to the often subtle but functionally important psychological alterations of medical patients without diagnosable brain disease. This has led many to neuropsychology for reliable knowledge about the behavioral ramifications of these patients' disorders. This recent marriage of traditional medicine and neuropsychology has been

most fruitful, as attested to in the sections that deal with metabolic and endocrine disorders in particular, but also in chapters concerned with specific vascular and immune-mediated disorders occurring outside the brain.

By including sections on developmental disorders and rehabilitation this handbook effectively covers the full range of conditions with neurocognitive ramifications. It will become apparent to the reader that the interplay of medicine and neuropsychology has made possible the science and skills for today's best practices in the care of patients with these conditions.

Of the eight sections in this handbook, the first is devoted exclusively to central nervous system disorders: Four of the six diagnostic categories considered in *primary nervous system disease* concern brain conditions in which neuropsychologists have been involved for more than three decades: movement disorders, epilepsy, traumatic brain injury, and neurooncology (e.g., [1–6]). Although these disorders differ greatly in their etiologies, developmental histories, course, and susceptibility to amelioration, what they have in common is the significant role that their neuropsychological symptoms play in determining the conduct and quality of the patient's life. The large body of scientific literature for each of these categories testifies to the value of medical specialists and neuropsychologists working together on patient evaluation and treatment. Much of the research underlying improved care for these conditions comes from this cooperation and cross-fertilization.

A relative newcomer to the categories of neurological disorders with significant behavioral symptom is *autonomic nervous system disorders*. The recency of neuropsychologists' involvement may account for the paucity of neuropsychologically relevant research into this condition. This chapter and others, such as Hydrocephalus, make it evident that understanding subcerebral disorders. Whether psychological interventions may also ease the cognitive and emotional symptoms of these conditions remains to be seen.

The end product of all *cardiovascular diseases* is reduced availability of oxygen. Thus, by their very nature, these diseases breed neuropsychological disorders as a result of insufficient oxygenation of highly oxygen-dependent brain substance. Their neuropsychological symptoms vary, from the sudden, often dramatic, loss of significant abilities due to stroke or the progressive cognitive withering of vascular dementia to the subtle dampening of cognitive acuity that occurs with primary breathing disorders or the intermittent diminution of function accompanying many migraine headaches. The presentation of the broad range of cardiovascular disorders here should give the clinician an increased awareness of the neuropsychological manifestations of vascular disease, especially those all too common respiratory conditions in which subtle but important neuropsychological consequences have been unsuspected or overlooked, such as chronic obstructive pulmonary disease and sleep apnea.

Unlike some of the other conditions discussed in this handbook, neurobehavioral aspects of (the) most *developmental disorders* are too obvious to have been ignored. Thus, for all of these conditions, some references go

back 30 or more years; in this handbook one on dyslexia was published in 1891. Decades of study have given these disorders a substantial knowledge base which current studies refine but rarely revise. Treatment options are limited or even nonexistant for many of these lifelong conditions. Still, a full appreciation of their genetic, physiological, and cognitive features should enhance clinicians' abilities to work intelligently and sensitively with the patients and their often overly burdened families.

For example, the review of several well-studied developmental disorders —Down, fragile X, and Williams syndromes—relates specific genetic errors to discrete patterns of cognitive and behavioral dysfunction. Other developmental problems have their origins in a variety of structural anomalies, each impinging on different parts of the developing central nervous system with diverse etiologies and neuropsychological consequences. Like its childhood counterpart, adult-onset hydrocephalus bears many etiologic and structural similarities to the developmental condition but, if untreated, can evolve into a classical dementia. And then there are the etiologic puzzles presented by the autism—Aspergers range of neurobehavioral disorders which here are considered as neuropathologic phenomena with associated patterns of neurocognitive dysfunction.

The section on *aging* contains, as one might expect, a *Dementia* chapter which reviews not only the most prevalent of dementing diseases but also one of the rarest forms of dementia—the prion diseases. Although the most common prion diseases progress so rapidly as to be of little neuropsychological interest, neurobehavioral symptoms are prominent in a recently identified variant with a longer course.

Since aging and dementia are so often associated in reviews of neurobehavioral disorders, it is a pleasure to find a separate discussion of normal cognitive aging which not only documents the usual deficits that develop in the seventh and eighth decades, but also emphasizes the variability in cognitive functioning within the aging population. The good news is that high-functioning older people contribute to this variability as well as those whose faculties are exceptionally diminished.

The reviews here of multiple sclerosis and the HIV-AIDS complex are expected in a section on *immune-mediated disease*. An appreciation of the impact of multiple sclerosis on patients and families requires an understanding of how the complexity of the most typical symptoms—motor and cognitive deficits, emotional distress and fatigue—can interact to exacerbate the illness experience. Of especial value is a discussion of the importance of family understanding and support for patients' quality of life which, while focussed on the MS patient, speaks for all neuropsychologically impaired patients and their families.

Rheumatic conditions are widespread with prevalence increasing with age, although many young persons are also affected. The inclusion of chapters on rheumatic diseases may be unexpected but is appropriate and necessary, as cognitive symptoms develop along with the well-known

crippling effects of these diseases. Cognitive issues are complicated by pain and compromised mobility making these conditions almost ideal models for neuropsychological and medical cooperation in treatment as well as research. Included in the section on *rheumatologic conditions* are two disorders whose diagnostic validity has been subject to much debate: fibromyalgia and chronic fatigue syndrome. Whether or not these are distinctive diagnostic entities, persons diagnosed with these conditions do suffer cognitive dysfunction which can, in some cases, seriously compromise everyday life. The now documented neuropsychological repercussions of the Guillain–Barré syndrome have also been mostly ignored as it has been essentially considered to be a peripheral neuropathy.

The contributions of stress to neurobehavioral disorders become apparent in the review of *endocrine diseases*. The stress experiences—particularly repeated stress—with its responsive endocrine imbalances and the resulting behavioral and cognitive dysfunction are linked in a causal chain which should be of interest to society's leaders as well as neuropsychologists and endocrinologists. The direct cognitive consequences of medically well-studied endocrine disorders, such as diabetes, tend to be relatively subtle and thus less likely to be identified in these patients. That these cognitive disorders can compromise daily functioning and quality of life makes their recognition important for appropriate patient care.

Some *metabolic disorders* give rise to disease-characteristic behavioral anomalies that, as yet, have not been explained. One interesting example is visuoperceptual disturbances in hepatic disease which, on appropriate examination, show up as gross drawing distortions. On the other hand, some specific patterns of cognitive dysfunction associated with different toxic sources do have scientifically grounded explanations. Moreover, as in the case of the affinity of organic solvents for fatty tissue or the affinity of carbon monoxide for hemoglobin, these relationships have added to the understanding of brain physiology, tissue vulnerability, and neurobehavioral outcomes. The more or less specific and more or less severe motor abnormalities of mitochondrial disorders have tended to overshadow the associated cognitive disturbances which are—at last—considered here.

Among the latest advances in *rehabilitation* are technological marvels which may substitute for replace, augment, or retrain the impaired functional system. These nontraditional additions or alternatives to more orthodox rehabilitation procedures may open the way for radical rethinking of how to overcome the behavioral impairments due to brain damage.

The inclusion, in many chapters, of assessment recommendations by authors who have had intensive experience in their area of expertise will be appreciated by both newcomers to neuropsychology and older hands confronting patients with unfamiliar conditions. Knowledge of treatment possibilities and procedures—both medical and psychological—is important for neuropsychologists' understanding of and clinical response to these conditions; thus treatment is considered, often extensively, throughout this

handbook. Not least of the many values to be found between these covers are the very current reference lists, most containing over 100 references, several more than 200 making this handbook a treasure trove of knowledge for the active seeker.

Despite the rapidity with which new neuropsychological information becomes available, this handbook will remain relevant for some time as its contents are both current and comprehensive. It will serve clinicians and researchers alike as a ready resource for both the facts and the important references for just about all the brain and nonbrain disorders, conditions, and diseases that can affect cognition.

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References

1. Aminoff MJ, Marshall J, Smith EM, Wyke MA. Pattern of intellectual impairment in Huntington's chorea. Psychol Med. 1975;5:169–72.
2. Luria AR. Neuropsychological analysis of focal brain lesion. In: Wolman BB, editor. Handbook of clinical psychology. New York, NY: McGraw-Hill; 1965.
3. Lyle OE, Gottesman II. Premorbid psychometric indicators of the gene for Huntington's disease. J Consult Clin Psychol. 1977;45:1011–22.
4. Milner B. Intellectual function of the temporal lobes. Psychol Bull. 1954;51:42–62.
5. Smith A. Intellectual functions in patients with lateralized frontal tumors. J Neurol Neurosurg Psychiatry. 1966;29:52–9.
6. Teuber H-L. Some alterations in behavior after cerebral lesions in man. In: Bass AD editor. Evolution of nervous system control. Washington, DC: American Association for the Advancement of Science; 1959. pp. 267–96.

Preface to the Second Edition

Welcome to the second edition of the Handbook of Medical Neuropsychology: Applications of Cognitive Neuroscience. This second edition continues to take an in-depth approach to the medical conditions and methods of neurorehabilitation found in the first edition. The new chapters for the second edition reflect the changes in prominent problems found in the clinic and thus provide good insights for research investigation, and are described in this Preface to the 2nd Edition. This second edition includes one of the most prominent and difficult to treat conditions, **Substance Use Disorders**, and provides a great deal of guidance for both clinical and research purposes. A subject that has largely been missing from our literature yet affects the entire population is **Nutrition in Neurocognition and Mental Health**, and this rich and comprehensive chapter is critical for guiding work involving developmental and aging populations as well as the general population. Autoimmune diseases are increasing in frequency in the population, and we now include **Hypothyroidism and Hashimoto's Thyroiditis: Mechanisms, Diagnosis, Neuropsychological Phenotypes, and Treatments**, which addresses both endocrine and autoimmune features of these diseases. Few centers are as experienced in early childhood brain injury as the Murdoch Children' Research Institute, and this edition is grateful for their chapter on **Traumatic Brain Injury in Very Early Childhood**. Increasing rates of asthma led to the invitation for a chapter on this very common disorder that encompasses the problem across the lifespan and in the social context: **Cognitive Functioning in Asthma: Central Nervous System and Other Influences**. To learn about a critically important new approach to treatment in neurology, psychiatry, and psychology, meditation is discussed by an author with extensive experience and research, in **The Role of Mindfulness in Neurorehabilitation: From the Monastery to the Clinic**. These new chapters are discussed below, followed by the revisions and additions the reader will find in many of the chapters from the first edition.

Hypothyroidism and Hashimoto's Thyroiditis: Mechanisms, Diagnosis, Neuropsychological Phenotypes, and Treatments: This chapter provides the level of detail needed to understand the thyroid gland, and the role of thyroid hormones in our development and in relation to our anthropomorphic ecological practices and the health of our human communities.

The authors provide a careful analysis of the cognitive and mood findings in studies of individuals with different levels of abnormal thyroid levels. Consistent with other diseases, the authors found that cognitive screenings and brief assessments are less effective in measuring disease outcomes than disease-specific neurocognitive tests. As necessitated by their thorough review of the subject, results across the lifespan are presented. The background for complex interactions of genetics and environmental factors are considered in detail for various thyroid disorders. This chapter is an invaluable primer on the medical, immunological, genetic, and neuropsychological aspects of thyroid deficiencies as models of neurological immune diseases.

Traumatic Brain Injury in Very Early Childhood: The most current concepts in the consequences of childhood traumatic brain injury with an emphasis on preschool children are given in this new chapter. The young child's particular vulnerability to brain injury and the mechanisms that make them particularly vulnerable are well reviewed, including abusive head trauma. The neurocognitive conceptualization of the effects is reviewed in the context of the history and evolution of theory of how brain development of very young children is affected by traumatic injury. The nature of the cognitive systems that are most often damaged are explained as well as the impairments in social skills and attention-deficit/hyperactivity disorders that are so often observed as secondary consequences. The radiographic review demonstrates the cerebral substrate that is most vulnerable in young children. There is relatively sparse literature on treatment, and the authors are from a children's research and hospital who have a history of investigation in treatments, so that the chapter also provides very helpful and in-depth discussions on treatment models and methods, neuropsychological evaluations, and approaches in rehabilitation to the endemic behavioral problems, anxiety, and cognitive impairments, as well as parenting programs.

Substance Use Disorders: Cognitive Sequelae, Behavioral Manifestations, Neuroimaging Correlates, and Novel Interventions: Given that substance abuse is a national crisis, this new chapter is very welcome, and covers many different types of substance use: opioids, alcohol, stimulants, cannabis, benzodiazepines, synthetic substances, hallucinogens, prescription substances of abuse, and polysubstance use. The chapter emphasizes the patterns of neuropsychological deficits that characterize each disorder, the available neuroimaging studies, and the problems resulting from the course of use and abstinence. The authors report on intermediating factors in this field, including the variable response of use during adolescence versus adulthood. A critical issue in this field is that of neural and personality predisposition factors, and studies that have directly addressed predisposition are included.

Cognitive Functioning in Asthma: Central Nervous System and Other Influences: One of the most frequent medical disorders in the United States is asthma, found across the lifespan. This is an emerging field, and the author provides a comprehensive review of the evidence in the aspects of the scope of this public health problem, genetic candidates for the complex asthma phenotype, cognitive problems, the underlying cognitive neuroscience

theories for the associated deficits including the neural and neuroendocrine substrates, and the socioeconomic and ethnic interactions that influence this disease. An important discernment in this chapter is to provide the evidence for mechanisms and outcomes in children and adolescents versus adults and older adults. Finally, the critical clinical parameters and treatment issues are thoroughly reviewed to help clinicians and researches in knowing the state-of-the-art of healthcare for this population.

Nutrition in Neurocognition and Mental Health: Although studies abound of the possible benefits of nutritional status and supplements on brain development, degeneration, and psychiatric disorders, there is not yet much consensus, with some exceptions, and all are reviewed in this chapter. This chapter reviews the state of the science from prenatal to aging and disease considerations. It provides a valuable overview of micronutrients (folate and folic acid, vitamin B12, choline, vitamin D, iron, iodine, zinc, and multivitamins), fats (e.g., long-chain polyunsaturated fatty acids, docosahexaenoic acid (DHA), omega-3 and omega-6 fatty acids), dietary quality and specific diets, and being overweight or underweight on cognition and mood. The association of nutrition with depression, anxiety, attention-deficit disorders, autism, and dementia is reviewed. The authors examine the data on reversibility of the failure of intellectual or cognitive development with improvement in maternal status and temporal stage of development, and on dose effects. The section on polyunsaturated fatty acids is examined carefully and is particularly detailed in reference to neurodevelopment, cognition, mental decline, and psychiatric diagnoses. The authors provide critiques of current research and policy recommendations.

The Role of Mindfulness in Neurorehabilitation: From the Monastery to the Clinic: This field of science has developed a significant database of studies of a critical source of brain plasticity that this author has courageously taken on and analyzed carefully using a critical lens. The approach is very comprehensive, and neuroanatomical, behavioral, emotional, and clinical outcomes are reviewed. Based on the theory and empirical evidence, Dr. Smart has proposed a model of associations of meditation methods with neural plasticity and applications. There is no better source of information on the types and bases for meditation, its track record in a wide range of developmental (e.g., attention-deficit/hyperactivity disorder) and adult neurological diseases (traumatic brain injury, stroke, epilepsy, multiple sclerosis, Parkinson's disease, and late-life cognitive decline), and for applications to rehabilitation. The author handles clearly and with scientific caution the intricate interaction of factors in this emerging field, and the chapter is a pleasure to read. The author's recommendations for research are invaluable. Based on the available corpus of knowledge, this chapter will likely be the authoritative text on this subject. Finally, the chapter ends with case examples that combine meditative practice with cognitive behavioral therapy to demonstrate the potential effectiveness of this type of integrative therapy.

New Material in Chapters from the First Edition

Genetic Syndromes Associated with Intellectual Disabilities: Professor Abbeduto, Director of the MIND Institute at U. C. Davis, is a leading expert on the neurolinguistic features of genetically associated intellectual disabilities, and has focused this updated chapter on neurolinguistic features and prototypical neuropsychological profiles of Down syndrome, fragile X syndrome, and Williams syndrome. The chapter substantially expands on cognitive and linguistic patterns that were already addressed in detail in the first edition, but which provide more assistance to identify key features of the disabilities, and expands the patterns across the years of child development. For example, new studies examining the linguistic development and neuroimages of children with one of these disorders with a comorbid autism spectrum disorder are included in the second edition along with new studies of the social phenotypes. New studies are available that examine the influence of environmental interactions on language and communication. In general, this chapter examines new neurobehavioral and neuroimaging evidence that leads to better understanding of these disorders.

Neuropsychological Problems in Neuro-Oncology: This comprehensive survey of the neurological, neuroimaging, and neuropsychological problems in the assessment, treatment, and study of central nervous system cancers has been updated with a section on the emerging field of immunotherapy treatment in neuro-oncology, including the potential for neuropsychological complications of immunotherapy. New research results are added regarding developmental differences in memory decline following therapeutic irradiation, showing that while memory is vulnerable as early as four years after treatment, different memory systems are at risk for adults versus children, demonstrating the development problem in children, and the particular vulnerability of memory in adults.

Learning Disorders: This chapter by authors with decades of experience in the diagnosis and treatment of learning disorders has been updated in current understanding of diagnoses, and is integrated with the changes in definitions brought by the DSM-V. This is a very comprehensive and theory-based chapter that addresses all the major issues, discrepancies, and problems in identifying and treating individuals with LD. A very helpful level of detailed recommendations is given for a strong and clinically useful evaluation of learning disabilities. The use of performance validity tests for children is now covered in this chapter. Findings from molecular genetics and neuroimaging have been updated.

Chapter on Toxic Disorders and Encephalopathy: This chapter updates the multi-modal neurotoxic effects of organic solvents, lead, and carbon monoxide, and adds manganese toxicity in the new edition. The authors address the specific diagnostic symptom expressions and outcomes, and the nature of the associated cognitive dysfunction. Additional studies since the first edition lead the authors to be able to propose some principles for predicting the permanency and severity of encephalopathy as evidence converges. However, the authors also make clear the areas of research still

needed to understand the risks and protective/exacerbating factors that predict outcomes.

An Introduction to Congenital and Normal Pressure Hydrocephalus: This chapter uniquely contains explanations of ventricular functions, and the etiologies, mechanisms, and treatments of hydrocephalus as a balance of important buffering, signaling, and nutrient pathways "gone bad". This chapter is extensively revised, updated, and truly clarifies these disorders that are frequently encountered but poorly understood by neuropsychologists. A classification, if not taxonomy, of hydrocephalus related to genetic syndromes, and the search for cerebrospinal fluid biomarkers is now included, along with their role in diagnostic identification. Neuropsychological characteristics are described in detail and make this chapter an authoritative analysis of the literature. The diagnostic discrimination, e.g., normal pressure hydrocephalus versus depression or Alzheimer's disease, provided for each disorder is critical for neuropsychologists.

The Continuum of Traumatic Brain Injuries: Subconcussion to Chronic Traumatic Encephalopathy: This chapter provides a context to understand traumatic brain injury in the continuum concept that is based in the principal pathology of diffuse axonal injury, now better understood because of the wealth of studies using diffusion tensor imaging to understand the nature of injury and its evolution in trauma. The chapter includes new sections on blast-induced TBI injuries, chronic traumatic encephalopathy, and subconcussion. Although mood was previously addressed in relation to different trauma scenarios, there is now a new section in which mood disorders and behavioral change are addressed in-depth. Functional imaging has been updated. Expanded detailed emphases on mechanisms of injury, neuroimaging, frontal circuitry, and methods to diagnose damage to frontal systems also make this a very valuable chapter.

Cerebral Palsy: Effects of Early Brain Injury on Development: This chapter that emerges from a dedicated center for the treatment of cerebral palsy now includes new, heuristic methods of assessment that are more robust in measurement of cognition in children with CP-related spasticity that compromises the standardized measurement of verbal and nonverbal skills. The types of cerebral palsy are given in relation to their neural substrates. Neuropsychologists will be well prepared for best practices in clinical and research evaluations of this neurodevelopmental disorder. Updated methods are given for the use of event-related potentials for clinical purposes. The authors' serial studies related reaction time slowness and inaccuracy as some of the underlying causes of cognitive errors, and give new revelations about CP patients' motivation and internal error monitoring.

Current Approaches to Rehabilitation: Rehabilitation approaches have developed and matured greatly in the past 20 years, and fortunately Sarah Raskin is at the center of this development, and has given the reader both detailed methods and the broad picture of cognitive rehabilitation today. Also very helpful, the author has gone into depth into the problems of and approaches for impaired attention, which is central to perception, language, and reasoning, and is one of the most commonly impaired brain systems after brain injury. New to this edition is the review of several strategies that

comprise the corpus of metacognitive approaches to rehabilitation of executive functions and mood, including Von Cramon's training procedure, Marshall's effective problem-solving, Short-Term Executive Plus, Goal Management Training, BrightBrainer, and Advanced Cognitive Training for Independent and Vital Elderly. Very valuable is her review of neurofeedback, repetitive transcranial magnetic stimulation, Brain–Computer Interfaces, and the developing field of virtual reality rehabilitation techniques. The author's review also comes to the conclusion that emotional well-being and regulation need to be included in studies and in treatment programs that use cognitive rehabilitation techniques.

Executive Function Disorders in Pediatric Neuropsychology: Attention–Deficit/Hyperactivity Disorder and Tourette Disorder: This authoritative chapter updates the neuropathology of these disorders, including the most recent data on the implications of the default-mode circuitry and its inhibitory role and problematic reciprocity with other networks, the mechanism of the catecholaminergic neurotransmitter systems, and the abnormal brain volumes in ADHD. ADHD is problematic for the high rate of comorbidities in this disorder, and the chapter provides information on these problems due to the high frequency of ADHD as a secondary disorder to other neurological conditions such as carbon monoxide toxicity. Recommendations—medications and behavior management—and their limitations were impressive in the first edition chapter, and have been made stronger in this second edition. A new component that is especially important for new and experienced neuropsychologists is information on PANS—pediatric acute-onset neuropsychiatric syndrome—that was previously known as PANDAS, and its consideration as an etiology for Tourette Disorder (TD). Finally, the sections on neuropsychological components of TD and on treatments for TD have been greatly expanded.

Cerebrovascular Disease and Disorders: This chapter is unique because it informs and compares the predictable and rare neurocognitive disorders of stroke in both children and adults. In particular, Sabrina Smith is a rare cognitive neurology investigator and practitioner who focused on the cognitive neuroscience of stroke in children, and this chapter provides much needed information to guide assessment. New information is included on the effects of stroke on emotion and on behavior in children. The chapter's updates include unique information on the visuospatial deficits and long-term neurocognitive effects of stroke in the developing brain, areas for which there is little information to guide both assessment and recommendations for families.

Theoretical Perspectives on Cognitive Aging: The authors present much of the new science of aging including the role of life choices and environment on the process of aging. The authors of this chapter bring this critical perspective to this chapter, explaining it as a heterogeneous and dynamic process that is examined through the lens of traditional and new cognitive theoretical models. They propose how neuropsychologists can integrate life course into assessment of aging to inform long-term risks and protective factors. New neuroimaging studies reveal changes in neuronal receptors and volume changes. The authors present current research that examines how the

"relationship among lifestyle factors, environment influences, and cognitive aging … impact the understanding of neuropsychological assessment profiles from a single time point." Cognitive reserve, the scaffolding theory of aging and cognition, and other theories are critically reviewed. The authors pose that the increased variability among older adults is better understood by integrating life course factors.

Autism Spectrum Disorder: A Cognitive Neuroscience Perspective: This chapter has gone through major revisions with an addition of more than 125 references, primarily to add new information, address controversies that have arisen or been researched since the last edition of Handbook of Medical Neuropsychology, or integrate data for new perspectives and priorities for the diagnosis and care of this disorder. The authors' chapter will help to move the field in future directions by engaging with promising contributions from cellular and molecular differences in phenotypes, genetic patterns of transmission, epidemiological risks, neuroimaging, and possible new treatments. The chapter helps the reader to understand that there are networks of genes (and gene/environmental interactions) and variations of ASD phenotypes whose relationships are the subject of ongoing research. For example, ASD etiology may help to elucidate epigenetic mechanisms of neurodevelopmental injury prenatally. The conceptual model of Piven and colleagues is presented that connects the material brain changes in very early childhood with the emergence of autism behaviors. Finally, the neurocognitive features are comprehensively expanded in this edition, for example, the significance of abnormal orientation, reorientation, and attention disengagement, the controversies in findings on facial and affect perception, and the mediating effects of neural complexity.

Neuropsychology of Movement Disorders and Motor Neuron Disease: Parkinson's Disease, Progressive Supranuclear Palsy, Essential Tremor, Huntington's Disease, and Amyotrophic Lateral Sclerosis: This chapter updates five motor neuron diseases—Parkinson's disease, Progressive Supranuclear Palsy, Essential Tremor, Amyotrophic Lateral Sclerosis, and Huntington's disease—in their genetic associations and clinical criteria. Understanding of Parkinson's disease and of Amyotrophic Lateral Sclerosis have undergone significant revisions based on new scientific understandings, which are explained. This chapter also includes more information on the clinical tools and structures used to assess the functional status of individuals with these diseases, and to diagnose comorbid emotional and affective conditions, such as anxiety disorders and impulsivity. Advances in neuroimaging characteristics of the diseases are further elaborated.

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Preface to the First Edition

The burgeoning of molecular and genetic studies of neurological and developmental disorders has contributed to the continuing relevance of neuropsychological studies of medical disorders. Neuropsychologists who follow science have updated and expanded the tools of our field to increase understanding of the functional consequences of disease, disease progression, and treatments. Equally important are the theoretical models of neurocognition that have been developed and refined in conjunction with functional imaging and other tissue or neurotransmitter-specific neuroimaging techniques. Contributing to clinical neuroscience, neuropsychiatry, and developmental neuroscience requires a sophisticated understanding of the medical and biological elements and future directions in which progress is being made in order to remain relevant. The purpose of this book is to provide a current and cutting edge understanding of the various diseases and disorders covered within and their neuropsychological effects. The authors are academic clinicians and researchers who bring insight and carefully constructed explanations about their respective fields of research. The neuropsychological findings of the diseases and disorders that comprise this book are given in the context of the disease mechanisms. Rather than taking the route of quick summarization, the chapters are meant to be intently studied, as they are dense with information. These chapters should remain useful for a long time.

Handbook of Medical Neuropsychology: Applications of Cognitive Neuroscience aims to provide understanding of some topics that neuropsychologists confront frequently, such as cerebrovascular disease, dementia, learning disability, normal aging, and traumatic brain injury. These chapters provide incisive reviews of the state of the science, reveal the controversies in diagnosis, and give the current opinions about the most critical factors that characterize these diseases and variations of "normal" brain states (autism, cerebral palsy, and genetic disorders could also be characterized this way). All of the chapters will make the reader who immerses him/herself in the material ready to design a study or understand a clinical evaluation, by helping the reader to be oriented to the key issues, areas that lack clarity, and future directions.

Other diseases covered in this book are confronted less frequently, but are the focus of intense investigation, such as autism, cardiovascular disease, endocrine disease (diabetes), epilepsy, and HIV-AIDS. These chapters are particularly rewarding because of the wealth of information contained in them and the insights that the authors have given us. Those who wish to participate in the cognitive neuroscience of these fields through grant-funded research will find these chapters very valuable. Clinicians will be better able to understand the purposes of treatments and the neuropsychological behaviors of their patients.

Some diseases are included because they are actually relatively common, yet their neuropsychological symptoms and mechanisms are not often examined closely, such as various autoimmune diseases and endocrine disorders, hydrocephalus, migraine, neuro-oncologic disorders, stress disorders, stress/post-traumatic stress disorder, and toxic disorders/encephalopathy. These chapters are reviews that are broadly encompassing yet also focused on the inconsistencies and generalizations that are possible, based on the state of the science.

Today, neuropsychologists must integrate knowledge about neurodevelopmental disorders into their work, whether their focus is adults or children. We are fortunate to have such knowledgeable and elegant chapters about cerebral palsy, pediatric frontal lobe disorders, learning disability, and the language impairments of genetic disorders. These chapters are elucidating and will give the reader new insights.

There are also the chapters on classic, and in some cases not well-known, medical diseases that have direct effects on brain functions: autonomic nervous system disorders, hepatic encephalopathy, movement disorders, respiratory disorders, and rheumatologic conditions. Again, these chapters remain true to analyzing their fields through the mechanisms of the disease and how these mechanisms encompass cognitive dysfunction.

There is one other subject of great interest that is still emerging and that is neuropsychologically understudied: mitochondrial disorders. I am grateful to the author, Kevin Antshel, who has taken the proverbial bull by the horns and given us knowledge about the biomedical tools we need to approach the neuropsychological investigation of these diseases.

Last, but most certainly not least, is rehabilitation. This book views this field from two perspectives. One gives the conceptual underpinnings of cognitive rehabilitation as it is carried out in the best brain injury cognitive rehabilitation centers extant. The other approach is the integration of neural brain mechanisms with human perception, to alter the way humans control their movements and balance. The chapter entitled *Sensory Reweighting: A Rehabilitative Mechanism* is included to inspire our present and future generations of neuropsychologists to use neuroscience technologies that integrate sensory information to modify behavior.

Another intent for this book is to provide critiques of the neuropsychological tests that are useful in tracking these diseases. The authors have striven not only to indicate what the tests have shown but also to show that recent research demonstrates that the most informative measures are those with high specificity even in relatively diffuse diseases. The goal was to point

to the tests of cognition that are most informative regarding a disease process or disorder.

Finally, we will leave the reader with the insight of a scientist of the past, to remind us that we all can see most clearly if we stand on the shoulders of those who came before us. Neils Bohr, a physicist of the twentieth century whose work was critical for the development of quantum theory, said that the opposite of a truth is a falsity, but the opposite of a deep truth is often another deep truth.

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Part I
Primary Nervous System Disease

Chapter 1

Epilepsy and Cognitive Plasticity

Joseph I. Tracy, Cynthia Lippincott-Stamos, Karol Osipowicz, and Allison Berman

Introduction: Why Study Cognition in Epilepsy?

Epilepsy provided neuropsychology with the canonical cases of amnesia and episodic memory disorders. These cases strongly encouraged the development of modular conceptions of memory. As neuropsychology moves to develop non-modular, network approaches to cognition, it is ironic that epilepsy can be seen as providing clear, illustrative examples of a network disturbance in cognition. The key to understanding this shift in thinking is to grasp that the neural mechanism underlying network development (i.e., neuroplasticity) and the neuropathology of seizures are separated by little. Many of the neural mechanisms of learning are key factors in the regulation of seizures, and the highly plastic regions specialized for learning and memory are also prone to seizures. More than characterizing the effects of seizures, and determining the risks and outcomes of brain surgery, there are fundamental cognitive neuroscience reasons for the neuropsychologist to study epilepsy. Neuropsychology traditionally focuses on the clinical symptoms of cognitive disruption caused by epilepsy, but the neuroplastic mechanisms underlying the disorder are important in showing why the cognitive effects of epilepsy are so varied. This chapter will review the biological mechanisms for both epileptogenesis and neural plastic recovery from seizures. It will then review the range of neurocognitive impairments that are associated with epilepsy and associate these with the dynamic changes in neural networks. The epileptogenic factors that affect the development of cognitive impairment are examined because of their importance in understanding how difficult it is to predict cognitive function and dysfunction in epilepsy. The role of neuropsychologists in diagnosis and treatment of epilepsy is explained. An understanding of these new developments in the field of epilepsy will better prepare the neuropsychologist who intends to focus in this area for working with the team of specialists required to diagnose and treat these patients.

Mesial temporal lobe epilepsy (MTLE) is the prototypical epilepsy which has been written about extensively and is well characterized, particularly in terms of episodic memory dysfunction. In this chapter, I will cover some of the lesser known cognitive characteristics of this and other types of epilepsy. The process of developing epileptic foci in the brain (referred to as epileptogenesis), seizure spread, and the development of new epileptogenic foci bring issues of

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neuroplasticity to forefront for the neuropsychologist. Neuroplasticity and cognitive reorganization complicate neuropsychological assessment as they challenge our normative presumptions about brain/behavior relationships. However, these processes also inform us about the cognitive impact of neural network development and changes that can occur in standard brain/behavior relationships. The responsibilities of a neuropsychologist working in a surgical epilepsy center have evolved with the advent of new imaging technologies. I will discuss this changing role of the neuropsychologist, the new presurgical algorithm for epilepsy, and the benefits of combined use of the various imaging techniques.

Biological Bases for Epilepsy

Epileptogenesis is one model of neural network development. The International League Against Epilepsy (ILAE) defines an epileptic seizure as a "... transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [1]. Epileptogenesis, the process that generates the pathological state, can begin with a single neuron. A seizing neuron recruits adjacent neurons into a hyper-synchronous process, until a critical mass of tissue is acting as a single active unit whose components no longer respond to existing functional network connections. Aberrant though it may be, this process provides some important clues as to how complex brain networks are formed. The development of neural networks, through the classical Hebbian learning mechanisms of long-term potentiation (LTP) and long-term depression (LDP) involving the up- or downregulation, respectively, of communication between two neurons, bears a striking resemblance to the process of epileptogenesis. LTP and LDP are the main plastic processes of learning and remembering, and the temporal lobe contains the most plastic parts of the brain. This plasticity makes the temporal lobe extremely vulnerable to epileptogenesis, which is why pathology of medial temporal lobe (MTL) is so common. The anatomical features of some parts of the MTL also encourage aberrant connectivity; the laminar organization of the hippocampus provides a good architecture for memory but is also conducive to the spread of extracellular currents and hypersynchrony that characterize seizures.

Epilepsy is also connected to cell loss, neurogenesis, and gliosis. Mesial temporal sclerosis (MTS), for example, a common pathology for temporal lobe epilepsy, is characterized by atrophy and possible hardening of the cortex due to reactive gliosis. It also involves aberrant sprouting of glutamatergic axons in the dentate gyrus of the hippocampus and changes in the expression of glutamatergic neurons, the major excitatory neurotransmitter in the brain. Because of these anatomical changes MTLE is often refractory to the chemical alterations offered by medication.

Cellular attributes that promote plasticity, such as neutrophins (cellular growth factors) and factors that affect chemical transmission through the cell membrane, are the focus of intense investigation in epilepsy and the target of drug development. The main neurotransmitters involved in seizures such as GABA and NMDA are crucial to the capacity to learn. NMDA receptor density is high in regions prone to seizures such as the CA 1 and CA 3 regions of the hippocampus. To some degree, NMDA receptor density predicts both the probability of Hebbian learning and epileptogenicity [2]. Thus, the factors that upregulate plasticity also appear to set the stage for seizures.

In summary the process of epileptogenesis and seizure generalization lays down new neural communication networks. These consist of favored pathways that are distinct from developmentally formed neural networks. They can disrupt existing networks by coopting neurons from them and cutting off connections between distant networks and, in this way, affect the neural communication required for normal cognitive processes and responses. In this manner, the effects of epilepsy are not necessarily limited to the area in and around the seizure focus. These processes help explain the broad and complex scope of the epilepsy–cognition interaction.

General Cognitive Characteristics of Epilepsy

The cognitive profiles of various epilepsy syndromes are difficult to define. The impact of epilepsy changes over time due to the accumulative brain effects of recurrent seizure activity. The etiology, number and location of epileptogenic foci, and the spread pattern of seizures will vary across individuals and strongly influence the pattern of cognitive deficits observed in any given patient. Seizures are the final common pathway of a whole host of pathophysiologic processes: viral, fungal, parasitic, metabolic disturbance, ingestion or toxic agent, brain lesion, tumor, congenital defects, cerebral trauma, vascular, alcohol. Each will impose a unique pathophysiology. In addition, preexisting medical factors and individual differences in skill and intelligence, the amount of cognitive reserve available, all contribute to the diverse neurocognitive presentation of individuals with epilepsy. Nevertheless, the clinical characteristics of seizures do impart clues about the nature and extent of cognitive deficits. Also, common cognitive patterns emerge from the proclivity of seizures for regions such as the hippocampus and the likely reach of propagation patterns and secondary epileptogenesis.

The location of seizure activity and measurable cognitive deficits will not have a one-to-one correspondence. Often the brain areas recruited by the seizure show worse deficits than the area generating the seizure itself (referred to as the epileptogenic zone). Thus, neuropsychological deficits can greatly mislead about the location of the seizure focus. For instance, outside the epileptogenic zone, areas showing extensive spread with prolonged post-ictal slowing on EEG often display the most pronounced cognitive difficulties [3]. Yet, absence or brief partial onset seizures often show few long-term cognitive effects [4]. With so many regions of the brain connected to the thalamus, it is an ideal structure to generalize and spread a signaling pathology throughout the brain. Yet, standard neuropsychological tests cannot isolate and pinpoint the thalamus as a source of deficit. Generalized seizures tend to produce a wider set of deficits than partial, more focal seizures because of the wider seizure burden, with such individuals often expressing a very low IQ.

The structural lesion and the epileptogenic zone do not refer to the same region, as not all the diseased tissues will likely generate seizures. The symptomatic zone refers to the neurons responsible for clinically observable ictal behaviors and symptoms and comprises a region of gray matter that often extends well beyond the epileptogenic zone. Interestingly, the initial brain insult or pathology that might produce a seizure is often followed by a latency phase of epileptogenesis which can take many years before a threshold is passed and the seizures become observable. Even at that point there may not be demonstrable deficits on neuropsychological testing. This latency phase makes isolation of the cause of the seizures difficult. Once regular seizures begin, the disease can progress even during the subclinical, non-symptomatic interictal state (the period between the acute ictal events). Very little is known about the potentially unique cognitive impact of this interictal period. In animal models, chronic, uncontrolled seizures eventually do produce global deterioration. This is most likely related to excess glutamatergic excitation, a process known as excitotoxicity [5].

The classic cases of amnesia (e.g., HM) were epilepsy patients, helping to establish the hippocampus as a key structure in the consolidation of episodic/declarative memory. While declarative memory deficits in temporal lobe epilepsy are well known and characterized, the preservation of non-declarative memory in these patients has been important in showing that a variety of important memory systems are likely non-hippocampal in their underlying neuroanatomy. For instance, data from my laboratory [6] showed that patients without a hippocampus and surrounding structures (dominant anterior temporal lobectomy patients) produce a clear dissociation between impaired explicit, declarative memory and intact implicit memory. Thus, implicit memory must be reliant on structures outside the hippocampus. Squires and others have shown that these patients also maintain a variety of other non-declarative memory procedures such as procedural or skill-related learning, conditioning, and priming [7, 8].

Chronicity of Seizures

Still other factors that are important to understanding the neuropsychological status of epilepsy patients include the age at onset of the seizures and the duration of uncontrolled "active epilepsy." Early age seizures put individuals at risk for the effects of chronicity, yet also potentially permit cognitive reorganization, particularly if the seizures start before a critical period (around age 6). The young brain appears more prone to hyperexcitability [9], which is perhaps related to inadequate pruning of neurons. But the immature central nervous system also exhibits greater plasticity potential than the adult, and the best substantiated cases of cognitive reorganization involve individuals with early onset epilepsy [10].

In terms of the effects of chronicity, there is no exact number of seizures required before the cognitive effect of seizures becomes evident, as the impact of frequency and duration can vary widely across individuals. However, long duration events such as status epilepticus (SE) and more frequent seizures are clearly more likely to take a cognitive toll. Interestingly, animal models have shown that even brief, non-chronic seizures can reduce LTP [11] or cause impairment in spatial and emotional memory in animals [12]. Overall, the duration of active epilepsy is actually a better predictor of the severity of cognitive deficits than type or location of the seizures [13]. Since seizures represent disruption of normal brain activity, chronic seizures will cause more disruptions. Seizure-induced seizure chronicity has been suspected for a long time, but only in recent years have there been any clinical findings in humans to support this. Each seizure seems to increase the likelihood of more seizures [14], leading to a rapid increase in cognitive deficits once a critical threshold of seizure frequency is reached.

Seizures Initiate Neuroplasticity

The specific ramifications of epileptic activity in the brain include (1) cellular changes (i.e., expression of cellular proteins), (2) injury to cortical pyramidal neurons making membrane ion channels more amenable to excitatory input, (3) axonal sprouting within pyramidal cells that enhance excitatory connections, (4) hyperinnervation, (5) failure to prune immature connections, and (6) changes in glial cells [15] and in the organization of axons and dendrites [16]. All constitute mechanisms of neuroplasticity at different levels of organization. They can cause collateral and terminal axonal bud and dendritic spike sprouting and shifts in sensory receptive fields at the individual neuron level. This may enable unmasking of previously ineffective synapses due to retrieval of vacated synapses by healthy axons after release from inhibition or seizure cessation. These represent alterations in the structure of surviving synapses at the synaptic level and reorganization of surviving neural networks at the network level [17]. For example, Ben-Ari et al. found that newly formed synapses generated by an epileptic seizure had aberrant kainate sensitivity, leaving them more likely to be overstimulated in the future [14]. Both newly formed synapses and the timing of action potentials can disrupt cognition by interrupting normally induced synapse communication. Each level affects the one above it so that changes in individual neurons increase the probability of changes at a cognitive level.

We know neural firing alters the patterning of synaptic connections, but the long-term effects of seizures are not well understood. One means of verifying reorganization is to quantify mossy fiber sprouting within the hippocampus and the new synaptic connections that are formed as a result. Many studies evaluating patients with mesial temporal sclerosis and refractory temporal lobe epilepsy have reported evidence of mossy fiber sprouting in the dentate gyrus. Based on studies with rats, mossy fiber reorganization has been hypothesized to restore inhibition of neural activity after kainate-induced status epilepticus [18].

Kindling is known to arise from post-synaptic brain stimulation on the order of tenths of seconds to seconds in length. This makes it likely that even short duration seizure events cause alterations in synaptic networks of the dentate gyrus of the hippocampus for instance [19]. Synapses along the dendritic spines were once thought to be

relatively stable, but recent imaging experiments have shown that synapse turnover can actually occur on a timescale of minutes, particularly in response to deprivation or enrichment [20].

Other evidence of epilepsy-driven neural plasticity comes from Koh who showed that environmental enrichment over 7–10 days following induced seizures can improve cognitive activity such as exploratory behavior in rats [21]. Early life neural repair may deplete neural progenitor cells as these have a finite number of divisions in their lifetime. Kolb et al. found that when rats suffered early brain damage, hippocampal neurogenesis at adulthood was far below that of controls [22].

It must also be said that seizures can reduce neuroplasticity by several processes. For instance, seizures can diminish production of neuromodulatory agents that promote neural growth [23]. Anticonvulsant medication may also hinder development of healthy connectivity [24]. The forces increasing neuroplasticity seem to exceed those that work to reduce it. Factors such as age, cognitive reserve, and the duration and type of seizures (generalizing versus not) may affect the balance. To transition from the cellular explanation of increased sprouting and loss of inhibition to a cognitive level, we must first see that the end state of this epilepsy-induced neuroplasticity is to alter the established patterns of communication in the brain. This has a direct impact on the construction and deconstruction of cognitive networks.

Cognitive Deficits Outside the Epileptogenic Zone and the Development of Neural Networks

Declarative memory deficits associated with temporal lobe epilepsy are not the only deficits associated with the syndrome nor even the deficit most commonly reported by patients. Problems with naming and word retrieval are more commonly reported [25]. When localized epileptogenic tissue is malfunctioning it can adversely affect remote cerebral structures, resulting in additional cognitive deficits. There is a growing body of evidence that brain abnormalities in MTLE, even in well-defined cases of unilateral MTLE, are not limited to the epileptogenic region but extend into widespread areas of extrahippocampal and extratemporal regions [26]. Several studies have documented that cognitive dysfunction in MTLE can extend to other cognitive domains, including language and executive functions, that are not ordinarily considered to be affected by strictly mesial temporal lobe pathology [27–32].

There are several mechanisms that offer explanations for the extratemporal deficits, such as undiagnosed seizure activity elsewhere in the brain, or diffuse metabolic pathophysiology set off by seizures such as changes NAA/choline ratios [33]. These processes can potentially result in cognitive deficits in areas outside the known epileptogenic focus. However, several other processes are of particular interest because of their impact on remote neural activity and the cognitive skills they implement. These include diaschisis, seizure propagation, and secondary epileptogenesis.

Diaschisis and Inhibition

The concept of diaschisis, a disorder of connectivity first theorized in the early twentieth century, purports that damage to one part of the nervous system can have distant brain effects due to loss of input from the damaged area [34]. Diaschisis refers to transcallosal suppression and decreased oxygen metabolism between functionally connected sites where loss of input results in suppression of functional activity at the output site. Note, because the disconnection may result in the loss of inhibitory input to a region, diaschisis may actually result in disinhibition and an increase in the functional output of a given region. The effects of diaschisis were thought to occur following acute or sudden onset injury, but it is clear they can emerge from more chronic processes such as the development of seizure networks. For instance, temporal lobe hypometabolism is a common symptom of TLE. Hermann et al. suggested that executive impairment in TLE patients could result

from the "spread of temporal lobe hypometabolism to the thalamus secondarily affecting the frontal lobe," or possibly the "direct spread of temporal lobe hypometabolism to the frontal lobe" [35]. This observation suggests that reduction in frontal lobe function is caused by diaschisis and the loss of temporal lobe or thalamic inputs. This is supported by the fact that performance does not decline following resection of epileptogenic lesions, but rather often results in improvement ("normalization") of cognitive functions ipsilateral and contralateral to the damaged area. Frontal lobe function will be restored when surgery allows normal recovery mechanisms to act without interference from the epileptic network, and the disruptive effect of the lesioned tissue is removed. In our own work with the intracarotid amobarbital procedure (IAP) we have observed dysfunction in the unaffected hemisphere, and transient diaschisis from the amytal appears a tenable explanation. There is some evidence of this in studies using single photon emission computed tomography (SPECT) during the Wada exam [36, 37]. Such findings, however, do not fully address the issue of extratemporal deficits in TLE and their potential normalization post surgery.

Seizure Propagation

A simpler and more parsimonious explanation of extratemporal and other remote deficits outside the epileptogenic zone involves seizure propagation or generalization. The direction and extent of propagation can vary not just within individuals but each seizure can be different. In many respects, grasping the cognitive impact of seizure propagation is the Holy Grail of deficit localization in epilepsy. Propagation of ictal discharges to distal brain regions is accomplished through a number of neural pathways that connect one region of the brain to another. Propagation may take advantage of breakdowns in inhibition activity, allowing the seizure to spread. There is an abundance of association fibers within each hemisphere, as well as commissural fibers between hemispheres that are available as pathways for propagation [38]. Seizure spread is not random, but follows preferred propagation pathways which correspond to the neuroanatomical connections between both gray matter and white matter brain regions [39]. Invasive EEG procedures have demonstrated preferential spread of ictal activity from the mesial temporal lobe to the ipsilateral frontal region, and preferential propagation of interictal spikes from mesial temporal to contralateral mesial and orbitofrontal regions [30].

The mode of transhemispheric propagation is not entirely clear; it might be transcallosal after the ipsilateral frontal lobe is "ictally" activated [39] or after contralateral inhibition breaks down. The hippocampal commissure has also been implicated in interhemispheric propagation [40] and the thalamus seems a crucial structure governing propagation. Mesial structures tend to be propagated earlier than lateral structures [40]. Propagation impairs the functioning of both independent skills (those implemented without communicating with the original epileptogenic region) and dependent functions (cognitive skills that rely on the epileptogenic region for effectively carrying out an activity). In other words, seizure propagation and its enduring, residual effects can stop normal adaptive communication between regions in an otherwise functioning cognitive network.

The electrical burden of seizures is more than just propagation or the spread of excitation. The recruitment of inhibition may be just as important a factor in terms of understanding the cognitive effects of seizures. Non-epileptic brain areas surrounding the epileptic focus are often producing tonically high levels of inhibitory activity [41] in an effort to contain and control the seizure. The unique neural and cognitive burden imposed by this form of "natural" seizure control is quite unknown. Inhibition, because it can be a tonic neural activity as well as a phasic one (responding to individual acute seizures), may contribute significantly to neuronal dysfunction.

Secondary Epileptogenesis

The natural history of epilepsy is progressive, and repeated seizures may promote creation of

additional seizure foci, a process known as secondary epileptogenesis [42]. Secondary epileptogenesis occurs when a region, separated from the primary epileptogenic area by at least one synapse, shows signs of seizure creation [43]. Epileptogenesis evolves following plasticity responses in cortex remote from the primary seizure site. It most likely occurs due to kindling, a phenomenon characterized by repeated, brief low-frequency electrical stimulation of brain structures that produce spontaneous epileptiform activity after weeks to months [44]. Pathways in the limbic system and temporal lobes are particularly susceptible to kindling. The theory of kindling, originally described by Goddard, has been extensively studied for over 30 years in animals but has not been directly demonstrated in humans and therefore remains controversial [42, 44, 45]. Epileptogenesis potentiates remote cells for seizure activity, through initially these cells depend on the origin for their firing. These cells become more and more independent over time (e.g., referred to as a mirror focus when the cells are precisely contralateral). Thus, primary seizure activity in the brain initiates a whole host of neuroplastic responses, and through propagation or secondary epileptogenesis potentially forms new neural circuits.

Seizures as an Example of Maladaptive Plasticity

The adaptation responses that occur in a normal brain may be different than those that emerge from a pathologic brain. Neural plasticity as it emerges from either propagation or secondary epileptogenesis is not always adaptive nor constrained to make neuropsychological sense. For instance, when the cells of the primary focus fire, activation will be potentiated throughout the connected seizure network. The repetition of this epileptiform activity through processes similar to kindling builds up a set of biased, favored pathways in neural communication. Cells downstream will respond to the excitation of seizures as if learning occurred. In this sense, secondary epileptogenesis can be seen to involve processes very similar to LTP [46, 47]. It is possible that these pathologic connections are at work not just during clinically observable seizure activity but also during cognitive stimulation of the brain region that includes the primary epileptogenic site. Thus, plasticity responses in the epileptic brain serve as the substrate for cognitive activity. In this way, seizures produce a dysfunctional, maladaptive cognitive network by linking brain areas randomly through propagation and secondary epileptogenesis, rather through normal adaptive learning and experience-driven plasticity and connectivity.

Cognitive Reorganization from Epilepsy

The adult human brain is an adaptive structure and is not fixed in its representation or organization of functional skills. Predicting patterns of neuroplasticity in response to injury is difficult because the principles that govern cortical reorganization of function are unclear. For instance, we do not know the contextual characteristics of the brain that determine which regions might take up full implementation of a skill that is diminished by injury. Nor do we know if the loss of integrity in one region can compel reorganization of a skill whose primary network does not normally include the lost region.

Epilepsy has provided not just the canonical cases of anterograde amnesia and memory disorders but also some of the clearest cases of hemispheric reorganization. Epilepsy patients have much high rates of altered language lateralization (24% versus 6% for normals [10]), with much of the evidence emerging from studies using the intracarotid amobarbital procedure (IAP). Hemispheric dominance for language is thought to be established by age 6, and the onset of dominant temporal lobe seizures prior to that age leads to a more widespread or atypical distribution of language skills, particularly for naming and reading [8, 10, 48, 49]. Factors such as the temporal pattern of the brain insult (slow

versus rapid) change the likelihood of both reorganization and the restoration of function, with "slow growing" pathologies increasing the probability and efficiency of reorganization processes [50] particularly in regions more remote from the "at-risk" skill or function.

Language is not a monolithic function and it is not likely all language skills reorganize together. Most IAP-based research studies on language dominance have used a global index of language to determine laterality and have not provided detailed information on the integrity and lateralization of specific language skills such as reading, naming, speech, comprehension, and repetition. In the imaging and neuropsychology literature it is common to presume that language is represented in a monolithic fashion in the brain, with all skills bearing the same degree and pattern of laterality across the hemispheres. We tested this assumption during IAP utilizing five separate language skills: naming, comprehension, repetition, reading, and speech. The rates of atypical representation ranged from 25.8% for reading to 14.5% of the sample for speech [51]. A majority of patients (60%) showing atypical language representation did so on more than one skill. While multiple atypicalities were common, the proportion of patients showing atypical representation on all five skills was strikingly low (5.6% of the total sample). The data suggested that language systems are not independent and do not shift and reorganize in isolation, though no two language skills were coupled and more likely to reorganize than others. The data further suggest that the pressures compelling atypical representation do not affect all language skills equally. We are currently in the process of determining the lateralization patterns and concordance among three types of material-specific memory in order to gain a finer-grained knowledge of which skills are more likely to reorganize in response to intractable seizures.

There are many examples in the literature of cognitive reorganization compelled by epilepsy. Shimizu and colleagues studied hemispherectomized epilepsy patients using transcranial magnetic stimulation and demonstrated that motor cortical excitability of the unaffected hemisphere evoked motor responses not just in the contralateral but also in the ipsilateral muscles [52]. Bittar and colleagues studied hemispherectomized epilepsy patients and found that residual somatosensory function in the hand opposite the lesioned hemisphere was associated with FMRI activity in the secondary somatosensory area of the intact hemisphere [53]. Jokeit and colleagues used the intracarotid amobarbital procedure to show that the right hemisphere mediated memory in adults with left temporal lobe epilepsy in the setting of childhood seizure onset, however, this was not the case in those with adult onset seizures [54]. Thivard and colleagues conducted an FMRI study of left and right temporal lobectomy patients and found that right-sided patients showed responses to language tasks similar to normals but that the left temporal lobectomy patients had a different pattern implicating right hemisphere involvement, i.e., reorganization, of language skills [55].

The ability to predict which patients and what cognitive skills might reorganize following surgery would be a great asset in determining the neurocognitive risk of surgery. We have observed that the integrity of the dominant hippocampus plays a role in determining if language skills will reorganize to the contralateral hemisphere. Using FMRI to examine verbal fluency (verb generation) prior to and after dominant temporal lobectomy, regions in the contralateral, non-dominant hemisphere were recruited. These were standard "en bloc" temporal lobe resections. Results suggested that a reorganization of the cognitive network had occurred, potentially reflecting incorporation of contralateral processing regions into the network providing executive control functions or supplying cognitive reserve [56].

One intriguing possibility is that the hippocampus determines whether reorganization of language is intrahemispheric or interhemispheric. Dominant hippocampal resection necessitates interhemispheric reorganization as the original functional network connecting through the hippocampus is destroyed when the neurons are removed. The remaining hemisphere still has hippocampal neurons which can be reorganized. Along those lines, mesial temporal sclerosis, a common cause of early onset epilepsy, is

correlated with a higher incidence of interhemispheric reorganization for receptive language than are focal lesions in the primary language areas alone. In contrast, patients with lesions in language areas alone generally had an intrahemispheric shift, where the processing for those critical language skills was maintained in the same hemisphere in regions adjacent to the lesion [57]. It may be that individuals with a more damaged dominant hemisphere hippocampus are more prone to language reorganization and, if so, it may be more likely that these patients will evolve right hemisphere representation of language.

(1) Focal lesions are more constrained in effect than focal epilepsy and (2) ipsilateral regions are generally capable of taking on the function of the damaged region but we are illustrating why the mirror region is also likely to reorganize; the mirror region is more likely to be involved when a central processing area like the hippocampus is affected so that reorganization will occur on the side with the more intact central processing. The nature of this effect is unclear but it may reflect the dependence of language processors in the brain on the parsing, binding, and re-analyzing capabilities of medial temporal structures in order to understand or produce complex speech. The fact that reorganization is fairly common in temporal lobe epilepsy suggests there may be a dynamic force to reorganize. That is, an inherent drive is to seek out the input and computations typically provided by ipsilateral medial temporal structures in order to make sure such skills are available. More studies need to be undertaken to understand the role of medial structures in language processing networks so that care can be taken to spare these structures during temporal lobe resections whenever possible.

The Role of Neuropsychology in Epilepsy

Neuropsychology plays a limited role in epilepsy diagnosis. The clinical signs of seizures are typically strong, so early detection is common, and no neuropsychological markers of early seizure activity have been found. Neuropsychological deficits tend to come after a period of chronicity, although that period has not been specified. Neuropsychology does play a strong role in characterizing the chronic impact of seizures, determining the cognitive and behavioral effects from treatment (e.g., surgery, medication), and differentially diagnosing true versus psychogenic seizures.

Neuropsychology serves several purposes in the care of epilepsy patients. An important feature of neuropsychological data is that it brings corroborating information regarding the location of dysfunction (i.e., the possible seizure generators), particularly when a lesion is not observable on MRI. Thus, it can often lateralize and make broad neuroanatomical distinctions, but can rarely specifically localize dysfunction. For instance, certain patterns on memory testing can provide clues as to the likely location of the primary epileptogenic pathology. The medial temporal lobe system is preferentially involved in fast and time-limited consolidation processes of memory contents. A medial temporal pattern of dysfunction would show a rapid rate of forgetting. A more dorsolateral frontal–temporal pattern would involve data showing breakdown in the learning and acquisition phase of memory, also working memory. A more lateral neocortical temporal pattern would likely be associated with greater semantic knowledge deficits, and more anterior temporal and inferior frontal dysfunction would more likely relate to problems in word retrieval and verbal fluency. These distinctions are useful, but are also too simple. For instance, there is increasing evidence that medial temporal structures are involved in retrieval processes, not just the consolidation step in episodic memory [8].

Dichotomies of dysfunction are often present in epilepsy related to the geographical dynamics of neural recruitment into the pattern of hypersynchrony. One should always try to distinguish between anterior/posterior, dominant/nondominant, left/right, and in the case of temporal lobe epilepsies, between medial versus neocortical deficits. A pathology affecting the left temporal lobe will more likely create a predominantly left hemisphere picture of deficits, but not solely so.

Similarly, frontal lobe seizures will most likely disrupt frontal functions (e.g., motor skill) before affecting other functions. These distinctions will also affect understanding of the potential for reorganization and compensation of deficits. Some aspects of language functioning may have less redundancy and be less readily compensated for perhaps because they involve dedicated modules in the left hemisphere (e.g., inflectional morphology, parsing linguistic representations, syntactic comprehension such as odd word order), whereas other language functions (retrieval of whole words) may be more susceptible to reorganization because they invoke a broader network of cognitive components.

Early neuropsychological characterization of deficits can lead to early intervention (e.g., make clear the pressing need for surgery or lead to educational interventions and accommodations). Neuropsychological testing can help determine the risk for debilitating functional impairments postsurgery and identify "at-risk" skills. This supports a more accurate and specific informed consent process prior to surgery. For instance, neuropsychological assessment can gauge the level of memory, language, motor, or executive function skill and provide a rough estimate of the likelihood of lost function should surgery resect the eloquent tissue subserving these functions. Post-surgical neuropsychological assessments can be used to quantify and verify functional outcome both cognitive and emotional/psychiatric. Additional roles for neuropsychology reside in its ability to verify iatrogenic medication side effects. Lastly, neuropsychology is instrumental to setting expectations that guide vocational and life planning.

What are the predictors of a good cognitive outcome post-surgery? Shorter duration of seizures, focality/unilaterality of lesions, non-dominant hemisphere surgery, relatively preserved integrity of the contralateral brain tissue which provides cognitive reserve, earlier age of onset, strength of premorbid general neuropsychological skills, and integrity of specific "at-risk" cognitive functions housed near surgical target (high skill more to lose, less skill less to lose) are some of the factors associated with good outcome [36, 58]. A larger resection is also associated with greater impairment. Patients with bilateral temporal lobe damage are at greater risk than those with unilateral damage for postoperative memory impairment if memory skills are still present. Non-verbal memory measures (and other non-dominant cognitive skills) show less consistent change following non-dominant ATL, suggesting that these skills are less sensitive to non-dominant temporal lobe changes than verbal memory is to dominant temporal lobe changes. Neuropsychology with functional neuroimaging can help identify individuals who have undergone cerebral reorganization of cognitive skills as a result of early brain insult such as malformations, but ultimately the goal is to predict who will cognitively reorganize post-surgery.

The Changing Surgical Algorithm and Neuroimaging

At most centers the procedure followed for selecting patients for temporal lobe surgery involves an algorithm that includes scalp/sphenoidal ictal EEG (rhythmic 3–8 Hz over the temporal lobe within the first seconds of seizure onset), scalp interictal EEG (state-dependent localized spikes or focal slow wave activity), and MRI with evidence of spell out – MTS or gliosis (hippocampal atrophy and increased T2 signal). Additional criteria include FDG PET interictal hypometabolism in the temporal lobe, asymmetric language and memory findings from both the neuropsychological testing and the IAP implicating deficits on the surgery target side along with integrity in the contralateral side, semiology and EEG findings consistent with temporal lobe seizures, ictal SPECT hypoperfusion in the temporal lobe, and localized background EEG abnormalities in the temporal lobe. If the localization of seizures is equivocal, then cortical surface and possibly depth electrodes and electrocorticography procedures are used to better localize the epileptogenic zone. With implants in place, often as part of the same surgical procedure,

electrocortical stimulation (ECS) is undertaken to map out functions associated with the neural tissue adjacent to the implanted electrode.

FMRI and other functional imaging modalities are becoming part of the surgical algorithm. The most beneficial interaction of these different modalities is still unsettled and emerging. The choice of procedures undertaken emerges from a risk/benefit analysis, with the process halted once an adequate degree of confidence about seizure focus, surgical and neurocognitive risk, and projected outcome is reached. The major difference from the anatomical work-ups is that the future model will likely utilize diffusion tensor imaging (DTI) as part of the visual rendering of the anatomy.

In terms of functional assessments, FMRI and functional connectivity MRI (fcMRI) as brain mapping techniques may become as common an early step as neuropsychological testing, reducing the need for the IAP, which, because of its inherent risks, would be the last to use of the functional techniques. Also, repetitive transcranial magnetic stimulation (RTMS), or more recent versions involving direct brain stimulation (DBS), may be used as a tool to determine functional necessity and is less risky than the IAP. In terms of ictal source localization, magnetic source imaging (MSI) may be used more regularly as a means of gauging the levels of key neurotransmitter systems such as glutamate or GABA. Magnetic source imaging will be incorporated as MEG and MRI become seamlessly integrated.

Electrocortical stimulation will more systematically rely on neuropsychological testing and FMRI, in particular, as these techniques will generate hypotheses about cognitive functions potentially at risk from the surgery, and thereby guide both choice of the cognitive task and selection of the electrodes to be stimulated. For instance, if there is a right-sided lesion with expressive language deficits on NP testing and signs of right-sided dominance for speech and naming, then FMRI expressive language testing will be undertaken to verify the hypothesis of altered language representation and specify the exact regions involved. The IAP would also likely be undertaken to lateralize language. With all this information in mind, ECS in the right hemisphere would then be done to verify language skill knockout in specific regions. The hope is that techniques such as DTI and fcMRI will yield important information about the connectivity (network of white matter fibers linking gray matter regions from DTI, and resting state maps of communicating gray matter regions from fcMRI) that subserve the investigated cognitive functions and give anatomical grounding to the network of activation implied by FMRI. To the degree that MEG (or MSI) is utilized, the sequencing and timing of regional activations, along with their associated cognitive events, can be identified and depicted.

The added value of techniques such as FMRI depends on the validity of the tasks used and their reliability. It is important to develop a set of norms and expectations regarding the localization/activation properties of the tasks used, as well as their reliability (reproducibility). An important caveat is that the nature of the logical inference permitted by each brain mapping technique is different. For example, ECS and other functional knockout paradigms, such as RTMS, carry the causative power of lesion studies and indicate the necessity of a region. FMRI and other imaging modalities such as PET carry only the power of association (correlation) between the cognitive/behavioral function and the underlying structure. Given these differences, there is no reason to think that the techniques will yield completely overlapping and concordant results.

A goal in most centers conducting presurgical brain mapping is to render the numerous pieces of both structural (MRI, DTI, MRA) and functional (ECS, FMRI, fcMRI, PET, MEG) information in one accurately registered, high-resolution three-dimensional volume. However, as noted, the registration issues in doing so accurately are not minor because each technique is sensitive to different types of distortion (e.g., DTI, white matter around CSF; FMRI, near large arteries and veins) that produce inevitable co-registration errors. When post-surgical imaging studies are conducted, surgical centers are hoping to develop a database that will permit retrospective

identification of the presurgical structural and functional neuroimaging markers of positive outcome both in terms of neurocognitive status and seizure control.

FMRI and Other Neurocognitive Tools in Epilepsy

While FMRI is safer, cheaper, and able to provide a depiction of the full circuit of regions involved in a task, it has disadvantages. FMRI is a noninvasive technique that does not involve the use of contrast injection dye and is therefore the ideal modality to use in both children and for longitudinal studies requiring multiple scans of the same individual. FMRI activation maps are often rich with significant areas of activation even after thresholding. Determining the role of all these structures during a given task is quite difficult. It is not likely that all of the areas of activation represent areas necessary for carrying out the task. Many may involve basic brain responses to the particular conditions of your task presentation (e.g., pictures versus three-dimensional objects for a naming task, mode of input, nature of instructions given – was the subject told to guess if they did not know the answer).

Also, the MRI scanner is a difficult environment. There are emotional responses to this environment, and the level of effort and cooperation are large factors capable of influencing the activation pattern in significant ways. Processing parameters such as the statistical threshold can play a role. The lack of significance does not mean that a region is not involved, and among the regions of activation there is no way to rank their importance to the task. There is also the risk of subtracting out important task components with the control task. There is intra-subject variability in networks, particularly in abnormal, diseased brains. Depiction of the full extent of activity is likely to instill unnecessary caution in the neurosurgeon for fear of taking out areas presumed to be important because they are active in the FMRI map. Primarily, FMRI does not answer questions of necessity: can a task be performed without the affected brain area? FMRI does not test for necessity and may actually point to activation that is not completely necessary. If used with intraoperative cortical and subcortical stimulation to understand underlying anatomical–functional links, FMRI can play a major role in determining surgical options.

Intraoperative electrocortical stimulation (ICS) is the gold standard for localization in eloquent cortex. A craniotomy procedure is used and then in a stepwise fashion, voltage is applied to knockout function while the patient is awake. This shows necessary regions, not full circuits, but it too has problems. Time constraints and the limited spatial coverage of the craniotomy mean that the procedure maps only a limited area of brain (placement of the electrodes is often based on prior knowledge of the FMRI results). The depth of the electrical pulse is not known and the technique is also time consuming. The technique is stressful for the patient and requires their cooperation. ICS can also precipitate seizures which can then make identification of spontaneously generated epileptogenic region difficult. Using ICS as the gold standard, if the FMRI activation is off by more than 1 cm from the ICS mapping of the same skill, one should question the validity of the FMRI.

Brain stimulation techniques may usher in a new wave of cognitive rehabilitation therapies and may be of great help in sorting out the timing of different regions as they contribute to a task. In healthy adult volunteers, RTMS given in time with movement has been found to enhance the encoding of a motor memory in the primary motor cortex (M1) and to increase excitation in both local and remote brain regions. An even newer technique is transcranial direct current stimulation (TDCS), which modulates spontaneous firing rates of neurons, rather than excites neurons to fire directly, has the potential to produce longer effects, and appears to more clearly have the potential to improve behavior and functioning. For instance, TDCS applied to Wernicke's area in healthy adults has produced a transient improvement in a confrontation naming task administered immediately afterward [59].

Depth electrode placements in areas such as the hippocampus are done routinely to locate

seizure foci through passive EEG recordings. Depth electrodes are typically used when patients have a suspected focal seizure onset but surface EEG is equivocal. Presurgical mapping of cognitive function of eloquent neural regions near the sites of planned hippocampal surgery, however, is not routinely done. This may result in the assumption that surrounding subregions are not functionally important and, therefore, are potentially respectable. Electrical stimulation of such electrodes (i.e., DBS) provides the means to demonstrate the necessity of a particular pool of neurons for carrying a specific cognitive task. In contrast, FMRI has the ability to provide a complete map of the brain regions implementing a given task. In this sense, techniques such as DBS and FMRI are complementary. DBS can indicate the structures necessary for a task, while FMRI can depict the full neural circuit that is sufficient for its successful completion. To date, DBS concurrent with FMRI has yet to be undertaken during presurgical evaluation in epilepsy.

Future Directions

The impact of ictal focus activity on remote and downstream neural integrity is poorly quantified and unknown. A huge advance both clinically and scientifically would be to develop an early marker with prognostic value to detect patients at high risk for developing multiple foci or generalizing seizures, as these are generally poor prognostic markers in terms of seizure outcome. Similarly, as noted earlier, secondary epileptogenesis and seizure generalization are likely to negatively affect cognitive outcome. An early marker to detect patients at high risk for developing these problematic forms of epilepsy has not been identified. Functional connectivity magnetic resonance imaging (fcMRI) can be potentially used to detect existing or burgeoning seizure networks by detecting the development of biased, favored neural communication pathways as an early marker of dangerous seizure growth. In addition, fcMRI along with DTI and FMRI may, on the basis of changes in resting state connectivity, white matter density, or presurgical BOLD signal properties, provide a means to predict who may or may not cognitively reorganize following surgery.

Conclusion

Hopefully this chapter has broadened the reader's view of the interaction between seizures and cognition. It goes beyond a standard review of neuropsychological tests and their findings in epilepsy to characterize lesser known neurocognitive features of seizures and provides some understanding of the unusual patterns of deficits that can emerge outside the epileptogenic zone and pathologic seizure processes they reflect. The cognitive deficits of epilepsy can be understood only by identifying the crucial link between seizures and cognition, seeing the neuroplastic mechanisms initiated by epilepsy, and becoming aware of the cognitive impact of the neural networks that develop with seizures. Taking these issues into account and trying to measure their impact through new imaging technologies gives the neuropsychologist a more complex and sophisticated view of brain/behavior relations. It has also helped provide the impetus for changing the presurgical algorithm in epilepsy and provided the neuropsychologist with a valued role in epilepsy evaluation and treatment more generally.

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References

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46:470–2.
2. McClelland JL. Failures to learn and their remediation: a hebbian account. In: McClelland JL, Seigler RS, editors. Mechanisms of cognitive development: behavioral and neural perspectives. Mahwah, NJ: Lawrence Erlbaum Associates; 2001. p. 97–121.

3. Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. Epilepsy Behav. 2006;8:504–15.
4. Aldenkamp AP, Arends J, Overweg-Plandsoen TC, et al. Acute cognitive effects of nonconvulsive difficult-to-detect epileptic seizures and epileptiform electroencephalo-graphic discharges. J Child Neurol. 2001;16:119–23.
5. Thompson SM, Fortunato C, McKinney RA, Muller M, Gahwiler BH. Mechanisms underlying the neuropathological consequences of epileptic activity in the rat hippocampus in vitro. J Comp Neurol. 1996;372:515–28.
6. Del Vecchio N, Liporace J, Nei M, Sperling M, Tracy J. A dissociation between implicit and explicit verbal memory in left temporal lobe epilepsy. Epilepsia. 2004;45:1124–33.
7. Squires L, Knowlton B. The medial temporal lobe, the hippocampus, and the memory systems of the brain. In: Gazzaniga M, editor. The new cognitive neurosciences. 2nd ed. Cambridge, MA: MIT Press; 2000. pp. 765–79.
8. Helmstaedter C, Kurthen M, Linke DB, Elger CE. Patterns of language dominance in focal left and right hemisphere epilepsies: relation to MRI findings, EEG, sex, and age at onset of epilepsy. Brain Cogn. 1997;33:135–50.
9. Raol YS, Budreck EC, Brooks-Kayal AR. Epilepsy after early-life seizures can be independent of hippocampal injury. Ann Neurol. 2003;53:503–11.
10. Springer JA, Binder JR, Hammeke TA, et al. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain. 1999;122(Pt 11):2033–46.
11. Jiang M, Lee CL, Smith KL, Swann JW. Spine loss and other persistent alterations of hippocampal pyramidal cell dendrites in a model of early-onset epilepsy. J Neurosci. 1998;18:8356–68.
12. Majak K, Pitkanen A. Do seizures cause irreversible brain damage? Evidence from animal studies. Epilepsy Behav. 2004;5:S35–44.
13. Farwell JR, Dodrill CB, Batzel LW. Neuropsychological abilities of children with epilepsy. Epilepsia. 1985;26:395–400.
14. Ben-Ari Y, Crepel V, Represa A. Seizures beget seizures in temporal lobe epilepsies: the boomerang effects of newly formed aberrant kainatergic synapses. Epilepsy Curr. 2008;8:68–72.
15. Somera-Molina KC, Robin B, Somera CA, et al. Glial activation links early-life seizures and long-term neurologic dysfunction: evidence using a small molecule inhibitor of proinflammatory cytokine upregulation. Epilepsia. 2007;48:1785–800.
16. Jacobs KM, Graber KD, Kharazia VN, Parada I, Prince DA. Postlesional epilepsy: the ultimate brain plasticity. Epilepsia. 2000;41(Suppl 6):S153–61.
17. Sutula TP, Dudek FE. Unmasking recurrent excitation generated by mossy fiber sprouting in the epileptic dentate gyrus: an emergent property of a complex system. Prog Brain Res. 2007;163:541–63.
18. Hellier JL, Patrylo PR, Dou P, Nett M, Rose GM, Dudek FE. Assessment of inhibition and epileptiform activity in the septal dentate gyrus of freely behaving rats during the first week after kainate treatment. J Neurosci. 1999;19:10053–64.
19. Hannesson DK, Corcoran ME. The mnemonic effects of kindling. Neurosci Biobehav Rev. 2000;24:725–51.
20. Holtmaat A, De Paola V, Wilbrecht L, Knott GW. Imaging of experience-dependent structural plasticity in the mouse neocortex in vivo. Behav Brain Res. 2008;192:20–5.
21. Koh S, Chung H, Xia H, Mahadevia A, Song Y. Environmental enrichment reverses the impaired exploratory behavior and altered gene expression induced by early-life seizures. J Child Neurol. 2005;20:796–802.
22. Dallison A, Kolb B. Recovery from infant medial frontal cortical lesions in rats is reversed by cortical lesions in adulthood. Behav Brain Res. 2003;146:57–63.
23. Binder DK, Croll SD, Gall CM, Scharfman HE. BDNF and epilepsy: too much of a good thing? Trends Neurosci. 2001;24:47–53.
24. Aldenkamp AP, Bodde N. Behaviour, cognition and epilepsy. Acta Neurol Scand Suppl. 2005;182:19–25.
25. Schefft BK, Marc Testa S, Dulay MF, Privitera MD, Yeh HS. Preoperative assessment of confrontation naming ability and interictal paraphasia production in unilateral temporal lobe epilepsy. Epilepsy Behav. 2003;4:161–8.
26. Kim H, Yi S, Son EI, Kim J. Differential effects of left versus right mesial temporal lobe epilepsy on Wechsler intelligence factors. Neuropsychology. 2003;17:556–65.
27. Corcoran R, Thompson P. Epilepsy and poor memory: who complains and what do they mean? Br J Clin Psychol. 1993;32:199–208.
28. Hermann BP, Wyler AR, Richey ET. Wisconsin Card sorting test performance in patients with complex partial seizures of temporal-lobe origin. J Clin Exp Neuropsychol. 1988;10:467–76.
29. Martin R, Sawrie S, Edwards R, et al. Investigation of executive function change following anterior temporal lobectomy: selective normalization of verbal fluency. Neuropsychology. 2000;14:501–8.
30. Shulman MB. The frontal lobes, epilepsy, and behavior. Epilepsy Behav. 2000;1:384–95.
31. Strauss E, Hunter M, Wada J. Wisconsin card sorting performance: effects of age of onset of damage and laterality of dysfunction. J Clin Exp Neuropsychol. 1993;15:896–902.
32. Trenerry M, Jack C, Ivnik R. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology. 1993;43:1800–5.
33. Cendes F, Andermann F, Dubeau F, Matthews PM, Arnold DL. Normalization of neuronal metabolic

dysfunction after surgery for temporal lobe epilepsy. Evidence from proton MR spectroscopic imaging. Neurology. 1997;49:1525–33.
34. Finger S, Koehler PJ, Jagella C. The Monakow concept of diaschisis: origins and perspectives. Arch Neurol. 2004;61:283–8.
35. Hermann BP, Wyler AR, Steenman H, Richey ET. The interrelationship between language function and verbal learning/memory performance in patients with complex partial seizures. Cortex. 1988;24:245–53.
36. Tracy JI, Shah S. Presurgical functional brain mapping and neurocognitive testing in epilepsy. In: Morgan JE, Sweets S, editors. Textbook in clinical neuropsychology. New York, NY: Taylor & Francis; 2007.
37. Khan N, Hajek M, Antonini A, et al. Cerebral metabolic changes (18F-FDG PET) during selective anterior temporal lobe amobarbital test. Eur Neurol. 1997;38:268–75.
38. Emerson RG, Turner CA, Pedley TA, Walczak TS, Forgione M. Propagation patterns of temporal spikes. Electroencephalogr Clin Neurophysiol. 1995;94:338–48.
39. Wieser HG, Hane A. Antiepileptic drug treatment in seizure-free mesial temporal lobe epilepsy patients with hippocampal sclerosis following selective amygdalohippocampectomy. Seizure. 2004;13:534–6.
40. Adam C, Saint-Hilaire JM, Richer F. Temporal and spatial characteristics of intracerebral seizure propagation: predictive value in surgery for temporal lobe epilepsy. Epilepsia. 1994;35:1065–72.
41. Cope DW, Hughes SW, Crunelli V. GABAA receptor-mediated tonic inhibition in thalamic neurons. J Neurosci. 2005;25:11553–63.
42. Acharya JN. Recent advances in epileptogenesis. Curr Sci. 2002;82:679–88.
43. Eliashiv SD, Dewar S, Wainwright I, Engel J Jr., Fried I. Long-term follow-up after temporal lobe resection for lesions associated with chronic seizures. Neurology. 1997;48:1383–8.
44. Cibula JE, Gilmore RL. Secondary epileptogenesis in humans. J Clin Neurophysiol. 1997;14:111–27.
45. Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. Nature. 1967;214:1020–1.
46. Ben-Ari Y, Represa A. Brief seizure episodes induce long-term potentiation and mossy fibre sprouting in the hippocampus. Trends Neurosci. 1990;13:312–8.
47. Sutula TP. Secondary epileptogenesis, kindling, and intractable epilepsy: a reappraisal from the perspective of neural plasticity. Int Rev Neurobiol. 2001;45:355–86.
48. Devinsky O, Barr WB, Vickrey BG, et al. Changes in depression and anxiety after respective surgery for epilepsy. Neurology. 2005;65:1744–9.
49. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci. 1977;299:355–69.
50. Braun M, Finke C, Ostendorf F, Lehmann TN, Hoffmann KT, Ploner CJ. Reorganization of associative memory in humans with long-standing hippocampal damage. Brain. 2008;131:2742–50.
51. Tracy JI, Waldron B, Glosser D, et al. Hemispheric lateralization and language skill coherence in temporal lobe epilepsy. Cortex. 2009;45(10):1178–89.
52. Shimizu T, Nariai T, Maehara T, et al. Enhanced motor cortical excitability in the unaffected hemisphere after hemispherectomy. Neuroreport. 2000;11:3077–84.
53. Bittar RG, Ptito A, Reutens DC. Somatosensory representation in patients who have undergone hemispherectomy: a functional magnetic resonance imaging study. J Neurosurg. 2000;92:45–51.
54. Jokeit H, Ebner A, Holthausen H, Markowitsch HJ, Tuxhorn I. Reorganization of memory functions after human temporal lobe damage. Neuroreport. 1996;7:1627–30.
55. Thivard L, Hombrouck J, du Montcel ST, et al. Productive and perceptive language reorganization in temporal lobe epilepsy. Neuroimage. 2005;24:841–51.
56. Osipowicz K, Iloreta S, Sharan A, et al. An investigation of verbal fluency network changes following temporal lobectomy for epilepsy. In: Pietrini P, Bookheimer S, Clark V, editors. The 15th annual meeting of the organization for human brain mapping, 2009 June 20th. San Francisco, CA: Neuroimage; 2009. p. S97.
57. Pataraia E, Simos PG, Castillo EM, et al. Reorganization of language-specific cortex in patients with lesions or mesial temporal epilepsy. Neurology. 2004;63:1825–32.
58. Chelune GJ, Naugle RI, Hermann BP, et al. Does presurgical IQ predict seizure outcome after temporal lobectomy? Evidence from the Bozeman Epilepsy Consortium. Epilepsia. 1998;39:314–8.
59. Drager B, Breitenstein C, Helmke U, Kamping S, Knecht S. Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification. Eur J Neurosci. 2004;20:1681–7.

Chapter 2

The Continuum of Traumatic Brain Injuries: Subconcussion to Chronic Traumatic Encephalopathy

Terri Morris

Epidemiology

Traumatic brain injury (TBI) is a significant public health problem and a major cause of mortality in the United States [1]. It is a major cause of death and disability, accounting for about 30% of all injury deaths [1]. A TBI is caused by a bump, blow, or jolt to the head that disrupts the normal function of the brain [1]. More than 150 people in the U.S. die every day from injuries that include TBI and in 2013, approximately 2.8 million TBI-related emergency department hospitalizations and deaths (EDHDs) occurred in the United States [1]. The top three causes of injury were 1. falls, 2. being struck by or against an object, and 3. motor vehicle collisions, accounting for approximately 70% of all TBI-related EDHDs [1]. Males continued to have higher rates of emergency department visits compared with females [1]. Falls accounted for 47% of all TBI-related ED visits, hospitalizations, and deaths in the U.S. [1].

In the U.S. approximately half of all fall-related TBI-EDHDs occur in two age groups, those 4 years old or younger and those 75 years and older [1]. TBIs in these groups are notable for several reasons. In young children, neurologic development and the ability to meet developmental milestones can be impaired which leads to further problems with age such as declines in academic functioning and psychosocial problems to include emotional and behavioral disorders [1]. TBIs in older adults have a greater impact on daily living and are also more likely to lead to hospitalization, which may then be complicated by comorbidities to include interactions with medications such as anticoagulants, increasing the likelihood of intracranial hemorrhage or death [1].

Neurologic consequences of TBI are multiple. Any sensory, motor, or autonomic function may be compromised [2, 3]. Long-term sequelae such as movement disorders, seizures, headaches, visual defects, and sleep problems can result. Medical consequences can be pulmonary, metabolic, nutritional, or musculoskeletal [2]. Even injuries that are classified as mild can result in persistent neurobehavioral impairments. Impairments may be temporary or permanent causing partial or total functional disability [2, 3].

Heightened public awareness and concern about sports-related concussions and effects of TBI have been reported as factors leading people of all ages to more readily seek care, and increased awareness among healthcare providers and broader dissemination of validated assessment tools have likely resulted in more TBI diagnoses [2, 3].

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Etiology

Mechanisms of Injury

TBI can result from a direct blow to the head due to an external physical force such as a blunt object, bullet wound, or fall, or from a sudden change in movement of the brain within the skull without direct impact to the head [4]. Mechanisms of injury include coup contusions (bruises) occurring at the site of impact, and contrecoup contusions from the force of impact causing the brain to strike the opposite side of the skull [4]. The second type of injury is diffuse axonal injury (DAI) caused by sudden momentum or movement change, typically from a motor vehicle accident. DAI occurs from unrestricted movement of the head with the brain lagging behind the movement of the skull, resulting in shear, tensile, and compressive strains [5]. DAI is the principal pathology producing the continuum of brain injury from mild to severe and is thought to underlie all forms of TBI due to destruction of neurofilaments and microtubules running the length of the axon, leading to axonal swelling and disconnection [5, 6].

Primary and Secondary Injuries

Primary injury is the mechanical damage occurring at the moment of impact and secondary injuries are the nonmechanical aspects that result, including altered cerebral blood flow and metabolism, excitotoxicity, edema (swelling), and inflammatory processes [7]. The extensive tearing of nerve tissue throughout the brain causes these additional injuries since neurotransmitters are released, resulting in disruption of the brain's normal communication and chemical processes. Permanent brain damage, coma, or death is possible [7].

Types of Injury

Traumatic brain injuries have typically been classified as penetrating or closed. More recently, two new classifications, blast-related TBI (b-TBI) and chronic traumatic encephalopathy (CTE) have been added. Additionally, subconcussion has been increasingly recognized. The pathophysiological processes differ for each.

Penetrating Head Injury

Penetrating or open head injuries cause fracture or breach of the skull with laceration and/or destruction of brain tissue, and the mortality rate is much higher for this type of head injury [8]. Trauma to the skull results from low-velocity bullets, puncture, everyday objects that may become embedded, or from tangential injury whereby an object strikes the skull causing bone fragments to be driven into the brain [8]. In most cases, such focal lesions cause relatively circumscribed cognitive losses; however, penetrating objects may cause damage throughout the brain depending on shock wave or pressure effects from the speed and malleability of the penetrating object [8]. With penetrating injuries prevention of infection is key to avoid development of brain abscesses. Secondary injuries from metabolic and physiologic processes such as edema, ischemia, or post-traumatic epilepsy can be as or more damaging than the primary injury [7].

Closed Head Injury

In closed head injury (CHI), the most common type of TBI, the skull remains relatively intact. CHI primary effects include both coup and contrecoup contusions. DAI is common and considered to be responsible for persistent neurological effects [6]. CHI impacts the orbital and polar

aspects of the frontal lobes in particular [9–11]. Specificity for the frontal poles and the anterior temporal convexity is due to the proximity of these regions to the bony surfaces of the skull, such that movements of the brain cause compression against the falx and tentorium [12]. Although many lesions can be detected by modern visual imaging techniques, the extent of microscopic damage due to DAI cannot be fully documented; thus, it should be emphasized that damage after CHI is never circumscribed [10]. More importantly, frontal dysfunction includes not only damage to the frontal lobes per se but also disconnection to prefrontal regions from lesions elsewhere in the brain, for example, injury to dorsomedial thalamic nuclei or other anterior connections that can imitate effects of a frontal lesion.

Potential secondary effects of CHI include development of subdural hematoma, intracerebral bleeding, increased intracranial pressure, hypoxia, obstructive hydrocephalus, and post-traumatic epilepsy [12]. Cognitive and behavioral changes are often the most salient features after closed head injury of any severity, and the extent of impairment reflects the severity of the DAI, length of post-traumatic amnesia (PTA), extent of generalized atrophy, and the location, depth, and volume of focal cerebral lesions [13]. The nature and frequency of the cognitive and/or behavioral difficulties are due to concentration of damage in the anterior brain regions [13].

After a CHI, a person may experience any of the following symptoms: loss of consciousness, dilated/unequal pupils, vision changes, dizziness, balance problems, respiratory failure, coma, paralysis, slow pulse, slow breathing rate, vomiting, lethargy, headache, confusion, tinnitus (ringing in ears), cognitive changes, inappropriate emotional responses, loss of bowel/bladder control, speech changes, or body numbness or tingling [3].

Blast-Induced Traumatic Brain Injury (B-TBI)

TBI in the combat environment is not uncommon and is often associated with severe multi-trauma or PTSD. Blast explosions, largely attributed to improvised explosive devices (IEDs) caused a higher percentage of TBIs in the Iraq and Afghanistan wars than in any other large-scale conflict [14]. Blast-related traumatic brain injury (b-TBI) was among the most frequent injuries sustained by soldiers and other personnel who served in Operation Iraqi Freedom and Operation Enduring Freedom [14, 15]. Estimates of the prevalence of b-TBI in military personnel have been as high as 19 to 23% and TBIs accounted for approximately 2/3 of all combat injuries in OIF and OEF [15]. Mild TBI was the most common single injury. The majority of the explosion episodes resulted in more than one injury, and the variety of injuries across nearly every body region suggests a complex nature of explosion injuries [15].

Four types of blast injury have been defined:

1. *Primary blast injury:* Rapid shifts in air pressure with the direct effect of blast overpressure on organs.
2. *Secondary blast injury:* Flying debris or impacts with munitions fragments, shrapnel, objects, or materials hurled at victims.
3. *Tertiary blast injury:* Caused by victims being propelled or thrown by a blast wind and flung through the air and/or striking other objects.
4. *Quaternary blast injury:* Burns produced by thermal effects from detonation [16].

Blasts inflict damage to the brain directly, resulting in chronic cognitive impairment especially in set-shifting, a relevant aspect of executive function [17]. These findings are consistent

with past meta-analyses on multiple mild TBIs and correspond with past neuroimaging research on the cognitive correlates of white matter damage common in mTBI [17]. Indirect brain damage results from injuries to other organs from air emboli, hypoxia, and shock. The brain is vulnerable to both secondary and tertiary blast injuries from penetrating and blunt trauma that is not unlike head injuries from causes other than explosions [15].

Blast injuries range from mild to fatal. Edema, contusion, diffuse axonal injury (DAI), hematomas, and hemorrhage have all been observed following a b-TBI [18]. Blast exposure at the milder end of the spectrum has been reported to produce neurological complications loosely described as "shell shock" or "blast concussion." The symptoms present after b-TBI are varied but like other types of TBI include physical, behavioral, cognitive, and psychological symptoms, i.e., depression, anxiety and/or post-traumatic stress disorder (PTSD). Symptoms are often referred to as post-concussive syndrome (PCS) and include anterograde and retrograde amnesia, compromised executive function, headache, confusion, difficulty concentrating, mood disturbance, alteration in sleep patterns, and anxiety [17–19].

Chronic Traumatic Encephalopathy

Traumatic brain injury (TBI) can lead to delayed-onset degenerative diseases including Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) [20]. CTE was first recognized in the early 1900s as "punch drunk" syndrome and "dementia pugilistica" in association with boxing [7]. CTE is a neurodegenerative disease found in individuals with a history of repetitive head impacts sustained through high impact contact sports such as American as football, soccer, professional wrestling, and hockey [20]. Brain damage is a frequent result of a career in professional boxing and neuropsychological investigations have documented impairments in memory, speed of information processing, complex attention, and executive functioning. In one study, neuropsychological impairments were found in 87% of 18 former boxers and all subjects had abnormal results on at least one neuropsychological test [20].

CTE has also been found in domestic abuse victims, those who have engaged in military combat, and individuals with self-inflicted head banging behavior [20]. CTE has gained attention owing to increasing media coverage of neuropsychiatric dysfunction in players of high impact sports such as boxing and American football [20]. While CTE is thought to be a manifestation of repetitive trauma, whether it can be caused by a single TBI has not been determined.

Stages of progression of CTE have been identified [21]. Initial symptoms are insidious, manifested by deterioration in attention, concentration, and memory, as well as disorientation and confusion, and are accompanied by dizziness and headaches [21]. This progresses to include lack of insight, poor judgment, and overt dementia. Some cases are accompanied by progressive slowing of muscular movements, a staggered propulsive gait, masked facies, impeded speech, tremors, vertigo, and deafness [21]. Social instability, erratic behavior, memory loss, and symptoms of Parkinson's disease appear in the second stage. The third stage consists of full blown Parkinsonism as well as speech and gait abnormalities [21]. The severity of the disorder appears to correlate with the length of time engaged in the sport and/or number of traumatic injuries. Of 51% of neuropathologically confirmed cases of CTE, 90% have occurred in athletes [22, 23].

The number of years of exposure, not the number of concussions, has been significantly associated with worse tau pathology in CTE, suggesting that the chronic and repetitive nature of head trauma, irrespective of concussive symptoms, is the most important driver of disease [24]. In a heterogeneous cohort of 114 deceased athletes and military veterans (mean age of 60) with neuropathologically confirmed CTE, AB deposition was present in 52% of subjects [25]. AB deposition occurred at an accelerated rate and with altered dynamics in the

athletes compared to CTE in a normal aging population. AB is associated with both pathological and clinical progression of CTE independent of age [25].

The neuropathology of CTE includes decreased brain mass, septal fenestrations, enlarged lateral ventricles, enlarged third ventricle, generalized atrophy particularly in the frontal and temporal lobes, atrophy in the medial temporal lobe, mammillary bodies and thalamus, and pallor in the locus coeruleus and substantia nigra [25]. The clinical presentation of CTE is distinct from the long-term sequelae of post-concussion syndrome and is not the accumulation of symptoms from the earlier injuries [25]. Rather, the symptoms of CTE, like other neurodegenerative diseases, result from the progressive decline in functioning of neurons and progressive neuronal death. When there is sufficient disruption of neuronal functioning, symptoms specific to the area(s) of that disruption will begin to show [25].

The symptoms of CTE begin insidiously and are apparently unrelated to earlier impairment. In other cases PCS symptoms may completely abate months or years before the onset of CTE symptoms. In still other cases there may be overlap; that is, the PCS symptoms may begin to abate but CTE symptoms gradually worsen at the same time [25]. Typically, CTE symptoms present in midlife, usually years or decades after the end of exposure to repetitive brain trauma. When symptoms begin the onset is generally earlier than that of sporadic Alzheimer's disease, frontotemporal lobar degeneration, or frontotemporal dementia (FTD). Progression is slow and gradual, often over several decades [25].

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CTE is the only known neurodegenerative dementia with a specific identifiable cause, i.e., head trauma. [22]. All confirmed cases of CTE to date have had a history of multiple head injuries. Microscopically, CTE is characterized by neurofibrillary tangles (NFTs), neuropil threads (NTs), and glial tangles (GTs) [25]. The main protein composing NFTs is tau and CTE shares many microscopic similarities with Alzheimer's disease and other tauopathies; however, it has several distinguishing features [25]. First, the distribution of tau pathology is found in the more superficial cortical laminae layers II and III, whereas tau NFTs in AD are preferentially distributed in large projection neurons in layers III and V. Second, regional tau pathology is irregular, largely confined to uneven foci in the frontal, temporal, and insular cortices, unlike NFT distribution seen in AD, which is more uniform [25]. Beta-amyloid deposits are found in 40 to 45% of individuals with CTE, in contrast to extensive deposits in nearly all cases of AD.

American football players may be at increased risk of long-term neurological conditions, particularly CTE [26]. In one study of 202 deceased former football players, with median age of death at 66 years, CTE neuropathology was diagnosed in 177. The neuropathological severity of CTE was distributed across all players, with all three former high school players having mild pathology and the majority of former college 55%, semiprofessional 56%, and professional 86% players having severe pathology [26]. Among 27 participants with mild CTE pathology, 96% had behavioral or mood symptoms or both, 85% had cognitive symptoms, and 33% had signs of dementia. Among 84 participants with severe CTE pathology, 89% had behavioral or mood symptoms or both, 95% had cognitive symptoms, and 85% had signs of dementia [26].

Subconcussion

A subconcussive blow is a head injury that does not meet criteria for diagnosis of mild TBI yet has adverse effects on some individuals, particularly those with repeated injuries [27, 28]. Human studies of the neurological and neuropsychological impact of immediate and long-term effects of subconcussive blows in athletes participating in full contact sports [29].

Clinical studies have identified athletes with no readily observable symptoms who have exhibited functional impairment as measured by neuropsychological testing and functional MRI and these findings have been corroborated by diffusion tensor imaging studies (DTI) demonstrating axonal injury in asymptomatic athletes at the end of a season [28]. Autopsy data have shown subsets of athletes in contact sports who do not have a history of known or identified concussions but nonetheless have neurodegenerative pathology consistent with chronic traumatic encephalopathy (CTE). Emerging laboratory data have demonstrated significant axonal injury, blood–brain barrier permeability, and evidence of neuroinflammation, all in the absence of behavioral changes [28]. The data suggest that subconcussive level impacts can lead to significant neurological alterations, especially if the blows are repetitive, such that subconcussion has been proposed as a new category requiring thorough consideration of the potential role it plays in causing sufficient anatomical and/or physiological damage in athletes and military personnel [28].

Neurological performance in the presence of head collision events in high school football players using longitudinal measures of collision events, neurocognitive testing, and functional magnetic resonance imaging (fMRI) have been examined [29]. Subjects were in three groups:

1. No clinically diagnosed concussion and no changes in neurological behavior.
2. Clinically diagnosed concussion with changes in neurological behavior.
3. No clinically observed symptoms associated with concussion but measurable neurocognitive impairment (primarily visual working memory) and neurophysiological change (altered activation in the dorsolateral prefrontal cortex) [29].

The third category was also associated with significantly higher numbers of head collision events to the top-front of the head, directly above the dorsolateral prefrontal cortex (DLPFC), suggesting that more players are suffering neurological injury than are currently being detected using traditional concussion assessment tools [29]. These individuals are unlikely to undergo clinical evaluation and thus may continue to participate in football-related activities even when changes in brain physiology (and potential brain damage) are present which will increase the risk of future neurological injury [29, 30].

Rating Severity of TBI

TBI severity is based on rating the presence or extent of loss of consciousness (LOC) and post-traumatic amnesia (PTA) and both are used in the classification of TBI as mild, moderate, or severe.

Loss of Consciousness

The most commonly used instrument for grading LOC is the Glasgow Coma Scale [31], which rates verbal responses, eye opening behavior, and best motor responses on a 0–15 point scale with 15 indicating best performance. GCS ratings for severity level are as follows:

Mild = 13–15 points,
Moderate = 9–12 points, and
Severe = 8 or fewer points.

The GCS appears most sensitive to moderate and severe injuries and less sensitive to mild TBI [31]. More current classification systems have acknowledged that loss of consciousness is not necessary for a diagnosis of TBI [3].

Post-traumatic Amnesia

The second measure of TBI severity is post-traumatic amnesia (PTA), defined as anterograde memory loss for events occurring immediately following the injury and retrograde loss for events immediately prior to the injury [32]. During this acute phase learning and

memory are significantly disrupted and deficits are on a temporal gradient with older memories being more resistant to disruption [32]. There are different systems for grading PTA [33]. A commonly used system classifies PTA as follows:

Mild—PTA of less than 1 hour,
Moderate—PTA of 1–24 hours, and
Severe—PTA of greater than 24 hours.

Other systems have distinguished the following six categories:

Very Mild—PTA of less than 5 min,
Mild—PTA of 5–60 min,
Moderate—PTA of 1–24 h,
Severe—PTA of 1–7 days,
Very Severe—PTA of 1–4 weeks, and
Extremely Severe—PTA of greater than 4 weeks.

PTA length is generally more accurate than duration of LOC in predicting recovery of function. Longer periods of PTA are associated with more severe brain injury and poorer recovery. Because it is a prognostic indicator, acute care facilities place emphasis on measuring PTA [3]. One of the most widely used brief instruments that can be administered bedside is the Galveston Orientation and Amnesia Test (GOAT) [34] and it is most appropriate for use in a hospital setting since PTA is often acute and time-limited.

Due to the nature of PTA, relying on brief screening measures alone is problematic and can result in misclassification since recovery is gradual and may include periods of intact orientation or memory in a patient who is still in the midst of general confusion and disorientation [35]. Attention in particular is noted to be a key component in early recovery after TBI, and postconfusional state (PCS) is preferred by some investigators to more fully describe the syndrome that includes impaired cognition, attention, and consciousness. PTA may also be accompanied by significant behavior problems such as agitation, restlessness, confabulation, or lethargy. PTA does not end when the patient begins to register experience again but only when registration is continuous [35]. Another concern is the reliability of the patient's report of the PTA period itself since it can be difficult for the examiner or the patient to distinguish what the patient actually recalls about the time period versus what the patient has been told by others. For these reasons, in the acute care setting, even though the TBI patient may seem to be improved based on normal screening scores or brief interviews, the examiner should remain cognizant that fluctuations in mental status are likely, and some patients may still be in PTA at the time of discharge from the hospital [35].

Severity Classifications

Traumatic brain injuries are generally classified as mild, moderate, and severe, and some systems have added very mild and very severe categories [3].

Mild TBI

Several systems have been used for categorizing mild TBI, with differences generally centering around loss of consciousness. More contemporary systems such as the definition proposed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (MTBIC-ACRM) [36] or other systems acknowledge that TBI can and does occur without loss of consciousness. The MTBIC-ACRM definition identifies the mild TBI symptom constellation as including previous labels such as minor head injury, post-concussive syndrome, traumatic head syndrome, traumatic cephalgia, post-brain injury syndrome, and post-traumatic syndrome [36]. The definition further states that only one of the following manifestations is needed to indicate the presence of mild TBI:

A. Any period of loss of consciousness.
B. Any loss of memory for events immediately before or after the accident.
C. Any alteration in mental state at the time of the accident such as feeling dazed, confused, or disoriented.
D. Focal neurological deficit which may or may not be transient.

Furthermore, the severity of the injury cannot exceed loss of consciousness of 30 min, initial GCS score of 13–15, or PTA greater than 24 hours. The symptoms may not be documented in the acute stage and some patients may not become aware of or admit to symptoms until they try to resume their normal daily routines. In such cases, symptomatology which can be linked to a head injury can suggest the existence of a mild TBI [36].

Mild TBI has greater consequences than formerly assumed [37]. Of all hospital emergency department visits for TBI, more than half involve mild closed head injuries that do not require hospital admission yet a significant percentage of the patients return to the hospital clinic weeks or months afterward complaining of symptoms from the original head injury [38]. Standard neuroimaging, including CT, MRI, and EEG are often normal yet mental status changes can still occur, indicating that functioning has been altered [37, 38] and that DAI is present which can result in temporary or permanent damage. Symptoms may also continue for varying periods of time and some patients will exhibit persistent emotional, cognitive, behavioral, and physical symptoms, alone or in combination, producing a functional disability [39].

Moderate TBI

Moderate TBI is defined as loss of consciousness lasting from a few minutes to no more than 6 hour, a GCS score of 9–12, and PTA from 1 to 24 hours [40]. Confusion may last from days to weeks, and physical, cognitive, and emotional impairments can persist for months or be permanent [40]. Patients with moderate injury may display the full spectrum of cognitive and behavioral impairments. Evidence of contusions, edema, bleeding, etc., on standard CT/ MRI will be more likely at this stage.

Severe TBI

Severe injury involves loss of consciousness with a GCS score of 8 or less. Loss of consciousness can last days, weeks, or months. Recent investigations have noted different subgroups within the severe TBI category [3] as follows:

I. *Coma*: Unarousable unconsciousness with no eye opening, no command following, no intelligible speech, no purposeful movement, no defensive movements, and no ability to localize noxious stimuli.
2. *Vegetative State*: Like coma with no signs of conscious behavior but differing in that there is spontaneous eye opening, evidence of sleep–wake cycles on EEG, and mechanical respiration or other life support measures are not required. Persistent vegetative state is vegetative state with duration longer than 1 month.
3. *Minimally Conscious State*: Severely altered consciousness in which minimal but definite evidence of self- or environmental awareness is demonstrated with ability to follow simple commands and have intelligible verbalization though these behaviors may occur inconsistently.
4. *Akinetic Mutism*: Resulting from damage to the dopaminergic pathways causing minimal body movement, little to no spontaneous speech, infrequent or incomplete ability to follow commands, but with preserved eye opening and visual tracking. Akinetic mutism differs from the minimally conscious state in that the lack of movement/speech is not due to neuromuscular disturbance.
5. *Locked-in Syndrome*: A rare condition in which the person cannot physically move any part of the body except the eyes, and vertical eye movements and eye blinks are used to communicate.
6. *Brain Death*: Resulting from severe injury, and in this condition the brain shows no sign of functioning [3].

Patterns of recovery vary after severe brain injury. Some individuals rapidly emerge from coma and briefly remain in the minimally conscious state before recovering a higher level of consciousness with mild impairments. Others may have a longer period in the minimally conscious state after emerging from the vegetative state and then have a greater degree of long-term

impairment. Occasionally persons remain in the vegetative or minimally conscious state for an extended period of time and in rare cases these conditions may be permanent [3].

Mood Disorders and Behavioral Change Post TBI

Mood disorders occur in the context of cognitive and emotional processing changes and are highly prevalent in TBI with anxiety, depression, and somatic preoccupation being most common [41]. In one study of a health maintenance organization patient population, psychiatric illness after TBI occurred in 49% in the first year following moderate to severe TBI [41].

Many of the population-based estimates of post-traumatic stress disorder (PTSD) in the general community are at 7 to 8% but are much higher in risk groups such as those serving in the military [42, 43]. The prevalence of PTSD and mild TBI in American service members returning from Operation Enduring Freedom and Operation Iraqi Freedom were reported to be as high as 13.8 and 19.9%, respectively [43]. A study of 2,525 U.S. Army infantry soldiers also showed high rates of PTSD-MTBI comorbidity. Of that group, 124 (4.9%) reported injuries with loss of consciousness, 260 (10.3%) reported injuries with altered mental status, and 435 (17.2%) reported other injuries during deployment [43]. Of those reporting loss of consciousness, 43.9% met criteria for post-traumatic stress disorder (PTSD), as compared with 27.3% of those reporting altered mental status, 16.2% of those with other injuries, and 9.1% with no injury. Soldiers with mild traumatic brain injury, primarily those who had loss of consciousness, were significantly more likely to report poor general health, missed workdays, medical visits, and a high number of somatic and post-concussive symptoms than were soldiers with other injuries [43].

Personality change due to TBI may include mood instability, disinhibited behavior, and hypersexuality [44]. Post-traumatic stress disorder is more likely to be associated with mild TBI than moderate or severe TBI [44]. The detrimental effect of prefrontal injury has been shown to disrupt social cognition which negatively impacts interpersonal relationships [45]. Treatment approaches that have been effective with traumatic stress and depression have been adapted for use with individuals who have symptoms or problems that are partially or largely related to mild TBI [45].

Neuroimaging and TBI

Structural Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) detect structural changes within the brain including tissue or fluid volume and have been the most available and commonly used procedures for detection of damage from TBI; however, they are less sensitive to the diffuse axonal injuries in mild TBI since clinically significant injuries from TBI are at the micron level, whereas detection of abnormality via CT or MRI is based on larger resolution capability which is measured in millimeters [46]. Therefore a "normal" scan means the pathology has not reached the threshold of 1 mm or more, so standard MRI or CT cannot image brain lesions that are microscopic and below their level of detection [46].

With these stipulations, CT is still the preferred method of imaging for head trauma in the acute phase since it can be done quickly and is most appropriate for detection of treatable lesions such as subdural hematoma, cortical contusions, skull fractures, intraparenchymal hemorrhage, or edema [46]. Magnetic resonance imaging is superior to CT in resolution, but is generally not used during the acute phase due to increased chance of motion artifact, length of scan time, and decreased sensitivity in detection of skull fractures. CT has not been useful in predicting outcome of TBI since it takes days or weeks for brain lesions to evolve and months before stable degenerative patterns are established [46]. MRI

imaging studies have been more effective in documenting such chronic effects occurring over an extended period in mild and moderate TBI. Parenchymal and whole brain atrophy after mild and moderate brain injury have been detected on MRI an average 11 months post injury [46], presumably as a result of cellular loss.

Diffusion Tensor Imaging

Newer tools that use MRI technology such as diffusion tensor imaging (DTI) allow for specific examination of integrity of the white matter tracts which are especially vulnerable to mechanical trauma. DTI is more sensitive in identifying impairment in mild TBI than standard MRI [47]. DTI has detected abnormalities in white matter representing axonal swelling, which is an early step in the process of axonal injury in mild TBI, and such white matter changes have correlated with poor clinical outcomes. In some mild TBI patient samples with no macroscopically detectable or obvious lesions, disruptions of the corpus callosum and fornix have been demonstrated [47]. When performed more than 45 days post injury, DT imaging has detected chronic or long-term lesions associated with TBI such as shear injury, white matter abnormalities, and frontal atrophy, and these abnormalities have correlated with neurobehavioral deficits [47]. Data indicate that white matter changes exist on a continuum, and TBI patients have reduced white matter integrity relative to controls. An index of global white matter neuropathology has been found to be related to cognitive functioning, such that greater white matter pathology predicts greater cognitive deficits [47].

Magnetic Resonance Spectroscopy

The prognostic role of magnetic resonance spectroscopy (MRS) in detection of underlying pathophysiology and severity of injury in TBI has also been active area of investigation [48]. MRS is a noninvasive and quantitative way to evaluate brain changes at the atomic level, including metabolite changes such as N-acetylaspartate (NAA) concentrations which are decreased in areas of contusion as well as normal appearing frontal white matter, occipital gray matter, and parietal-occipital white matter [49]. MRS is appropriate for evaluating diffuse injury associated with mild TBI and has been found to be more sensitive for detecting metabolic changes that are associated with poor clinical outcomes yet are not observable on CT or MR imaging [50]. MRS has detected widespread metabolic changes following mild TBI in regions that appeared structurally normal on standard MRI at 1 month post injury [50]. Differences in N-acetylaspartate (NAA), total creatine (Cr), and total choline (Cho) were found in mild TBI as compared to controls, which was consistent with diffuse cellular injury seen in postmortem examinations [50]. Gray matter and white matter atrophy have been documented in mild TBI patients with whole brain NAA concentrations showing a 12% deficit compared with controls, and these findings were apparent in patients with and without visible MRI imaging pathology. In summary, MRS has documented neuronal injury beyond the minimal focal visible lesions in mild TBI.

Functional Neuroimaging

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) involve the use of isotope tracers to measure functional activity in the brain and have been used to evaluate cerebral metabolism in TBI [51]. Magnetoencephalography (MEG) records the brain's magnetic fields produced by electrical activity. Comparison studies of SPECT, MEG, and MRI imaging have found evidence of abnormal cerebral metabolism in mild TBI patients with persistent post-concussive somatic and cognitive symptoms [51]. MEG has been informative in preliminary studies, with significant correlations found between regional abnormalities and specific cognitive problems [51]. SPECT and MEG have demonstrated more sensitivity than routine MRI

in detecting abnormalities in mild head trauma patients. In one moderate TBI patient sample PET imaging demonstrated abnormal focal uptake extending beyond the abnormal regions documented on CT and MRI [52]. Significant correlation between neuropsychological findings and PET in mild TBI patients have been demonstrated [53] with PET documenting metabolic abnormalities that were pronounced in frontal and anterior temporal regions. No differences were noted in those patients with or without loss of consciousness [53].

Functional MRI (fMRI), which measures regional changes in blood perfusion and blood oxygenation, has also demonstrated the ability to detect brain abnormalities in mild TBI that are not detectable on standard imaging [54]. Using fMRI, investigators have shown smaller increases in brain activity in mild TBI patients relative to healthy controls on working memory tasks [55, 56] and have demonstrated significant reductions in activation of right prefrontal and medial temporal regions in mild TBI patients relative to healthy controls. Self- reported TBI symptoms have been shown to predict changes on fMRI as well, with decreased activity in prefrontal regions corresponding to the extent of complaints, i.e., a high number of complaints was predictive of significantly reduced activity while a mild number of complaints indicated less but still significantly reduced activity [57, 58].

Frontal Systems, Cognition, and Behavior

Both frontal and temporal lobe regions are affected by traumatic brain injury, with the frontal lobes being the most significantly impacted [59]. Effects of TBI on temporal lobe functioning are well known and extensively described in the extant literature; however, adequate characterization of frontal systems and measurement of executive functions are often inadequate. Distinct behavioral and cognitive syndromes correspond to three frontal lobe systems: the dorsolateral prefrontal, orbitofrontal, and anterior cingulate circuits, with the orbitofrontal system being substantially impacted in TBI of all severities [59, 60]. Each system is considered separately, with particular focus on the orbitofrontal circuit.

Dorsolateral Prefrontal Circuit

The dorsolateral prefrontal circuit consists of the dorsolateral prefrontal cortex which projects to the lateral region of the caudate nucleus. This circuit is the neuroanatomical basis for organizing behavioral responses to solve complex problems, such as learning new information, systematically searching memory, or activating remote memories. Patients with damage to this circuit exhibit poor organization strategies, poor word list generation, reduced design fluency, poor sorting behavior, stimulus-bound behavior, environmental dependency, concrete proverb interpretations, imitation behavior, utilization behavior, and impaired cognitive set-shifting and maintenance [61]. Not all skills are affected by any one lesion or process and patients with dorsolateral prefrontal dysfunction have varied clinical presentations.

Orbitofrontal Circuit

The orbitofrontal circuit includes the lateral orbitofrontal cortex which sends projections to the ventromedial caudate and the medial orbitofrontal cortex which projects to the ventral striatum. The two systems overlap in anatomy and behavioral functions. The orbitofrontal circuit mediates empathic, civil, and appropriate social behavior, and damage to this region results in impaired emotional reactivity and processing, personality change, tactlessness, undue familiarity, irritability, poor impulse control, increased aggression, and mood instability [62].

Socially inappropriate behavior is evident in TBI patients and has been well documented in studies of patients with damage to the orbitofrontal regions or [62]. One of the more famous patients was Phineas Gage, a supervisor of a railroad construction work crew who in the 1800 s sustained severe injury to the

orbitomedial frontal regions after an explosion. A tamping iron was propelled into his left maxilla, exiting through the mid-frontal regions [63]. After this injury, a significant alteration in personality and judgment was reported by friends and coworkers. Gage apparently changed from a responsible well-functioning individual into one who was no longer employable and was given to "fits" of anger and profanity [63].

Changes in emotional reactivity and behavior have been demonstrated in more recent studies of orbitomedial damage as well. In some investigations, patients with damage to this region exhibited both antisocial behavior and abnormal autonomic responses to socially meaningful stimuli, i.e., "acquired sociopathy" [64]. Damasio et al. [65] found defective emotional responses to socially significant stimuli as measured by skin conductance in subjects with bilateral ventromedial frontal lesions who also had severe deficits in social conduct/social judgment compared with subjects who had brain injury without ventromedial involvement and no acquired deficits in social conduct. Rolls et al. [66] found orbitomedial pathology to be significantly associated with disinhibited and socially inappropriate behavior and with difficulty in modifying responses when followed by negative consequences.

Orbitomedial frontal dysfunction increases the probability of aggression and several investigators have demonstrated the role of medial and orbital-frontal regions in aggressive and violent behavior. In a study of 279 Vietnam veterans, head-injured veterans who had focal ventromedial frontal lobe injuries had a significantly higher frequency of aggressive and violent behavior when compared to controls or subjects who had brain lesions elsewhere [67] Functional neuroimaging has also correlated injury to this region with highly abnormal behavior including reductions in prefrontal lobe glucose metabolism on positron emission tomography (PET) imaging in lateral and medial prefrontal cortex in murderers [68].

The orbitomedial prefrontal circuit has also been shown to mediate social cognition in general [67–69]. One aspect of social cognition, theory of mind (ToM), defined as the ability to recognize and make inferences about other peoples' intentions and beliefs, is considered necessary for effective social communication [70]. ToM includes the ability of an individual to understand that another may hold a false belief, to recognize faux pas in one's own behavior, i.e., that he or she said something they should not have said and realizing they should not have said it, and the ability to detect sarcasm or irony [70, 71]. Theory of mind is frequently disturbed after TBI as indicated by family reports of TBI patients' changes in behavior including lack of empathy, unconcern, and inability to appreciate humor [71]. Patients with ventromedial, but not dorsolateral, prefrontal lesions were significantly impaired on tests of irony and faux pas compared with patients with posterior lesions or normal controls, and lesions in the right ventromedial area were associated with the most severe ToM deficit [71].

Anterior Cingulate

The anterior cingulate, termed the "motivation circuit" [72], includes the forebrain, composed of the anterior cingulum, nucleus accumbens, ventral palladium, and ventral tegmental area. It is the neuroanatomical basis of motivated behavior and apathy is the most distinguishing characteristic of damage. The most severe damage to this circuit, akinetic mutism, caused by bilateral lesions of the anterior cingulate, results in profound apathy, lack of movement or rare movement, incontinence, eating/drinking only when fed, speech limited to monosyllable responses, and no display of emotions. Unilateral lesions display less dramatic apathetic syndromes, though with impaired motivation, apathy, poverty of spontaneous speech, and poor response inhibition [72, 73]. A method for evaluating and quantifying apathy or loss of motivation is the Apathy Evaluation Scale (AES) [73] which has strong construct validity and can be administered as a self-rated scale, a caregiver paper-and-pencil test, or a clinician rated inventory. The AES has been found to be sensitive in a severe TBI population [73].

Neuropsychological Assessment of TBI

Attention, memory, and executive functions are primarily affected in TBI and are discussed separately with particular attention to executive functions since these functions are critical in TBI yet comprehensive assessment has often been incomplete and/or problematic.

Attention

Impaired attention is prevalent if not universal after TBI at all levels of injury, whether diffuse or focal [74]. Attention underpins all aspects of cognition and even mild impairments can restrict other processes such as learning or problem-solving. Common complaints from patients that reflect attention problems include mental slowing, trouble following conversation, losing train of thought, or difficulty attending to several things simultaneously [74].

Attention is not a unitary phenomenon, but includes at the most basic level arousal and alertness. Useful tools for evaluation of attention in acute phase TBI patients include tests of delirium such as the Cognitive Test for Delirium and the Moss Attention Rating Scale (MARS) [75–77]. The MARS has differentiated various aspects of disordered attention in acute TBI, such as restlessness/distractibility, initiation, and sustained/consistent attention, and can be used to monitor changes over time as well as treatment response [75, 76].

Post-acute assessment of attention includes measures of auditory and visual attention and several tests are well standardized and widely used. Tests generally range from simple to more complex tasks that require speed of information processing and working memory. For general span or amount of information that can be held in mind at one time, span for digits [78] or for visual targets from the Wechsler scales is appropriate [79]. Attentional vigilance or being able to select target information and inhibit irrelevant stimuli can be measured by tasks such as the Continuous Performance Test of Attention [80] and the Stroop test [81]. Shifting or dividing attention between two or more sources of information is generally assessed by tasks such as the Trailmaking Test Part B [82] or the Paced Auditory Serial Addition Test (PASAT) [83]. Working memory can also be evaluated by Wechsler subtests of mental arithmetic and auditory sequencing.

Memory

Impairment of memory is also a cardinal feature after TBI and may be temporary or permanent. In penetrating head injuries (PHI), memory deficits may be material specific depending on the site of the injury. Memory for personal information or facts is most impacted after TBI in contrast to procedural memory which is outside conscious awareness and is relatively spared. On neuropsychological evaluation, both immediate and delayed memory are evaluated. In mild TBI, problems are generally more with acquisition and/or with the strategic aspects of registering material into memory, i.e., immediate recall, than with consolidation or retention of material that is registered. In moderate to severe injuries, acquisition and consolidation generally are both affected, reflected by deficits in immediate recall as well as delayed recall/retention.

The neuropsychological evaluation typically involves assessment of acquisition and recall aspects of verbal and visual memory. For auditory memory, verbal learning tasks such as the California Verbal Learning Test-II [84] are appropriate due to serial position learning, semantic organization, interference effects, cued recall, recognition, and monitoring aspects. Similar verbal learning/recall tasks include the Hopkins Verbal Learning Test [85] and the Rey Auditory Verbal Learning Test [86]. Additional measures of immediate and delayed auditory verbal memory include paragraph or story recall from the Wechsler Memory scale [87]. Nonverbal memory is generally assessed by visual recall and reproduction of simple designs, recognition memory for faces, or recall of scenes and recall

of complex figures [88]. Complex figural memory is evaluated by reproducing complex figures after copying and tactile and spatial memory can be evaluated by the use of tasks that allow tactile but no visual access [89].

Executive Functions

There is substantial agreement among investigators that executive functions are significantly impacted by TBI due to the preponderance of frontal system injuries. The definition of executive functions has varied among investigators but it is generally acknowledged as involving self-regulatory functions that organize, direct, and manage other cognitive activities, emotional responses, and behavior [90]. This regulatory function includes the ability to initiate behaviors, inhibit competing actions or stimuli, select relevant task goals, plan, organize, solve complex problems, shift strategies appropriately when necessary, regulate emotions, monitor and evaluate behavior, and hold information in mind in order to guide cognition and behavior. Though executive functions are a critical determinant of functional outcome after TBI and are among the most disabling aspects of cognitive impairment following TBI, they continue to be inadequately assessed. Comprehensive evaluation of these functions has been problematic for several reasons including lack of tests that are sensitive or specific to the differing frontal circuits, lack of recognition of the importance of the orbitofrontal circuit which leads to underdetection of deficits associated with this region, and the nature of the standardized testing environment, which is artificial, highly structured and does not elicit the types of errors commonly reported by TBI patients that occur during everyday activities. Each of these is considered separately.

1. *Test Sensitivity and Specificity*. While many examiners prefer the use of general-purpose or "fixed" batteries with the advantage that such batteries provide standardized procedures and allow for comparisons, the disadvantage is that fixed batteries are not fully complete for any one patient and this results in overtesting and/or undertesting of specific functions. Evaluation of frontal systems functioning has been particularly problematic as many tests comprising fixed neuropsychological batteries lack specificity or sensitivity to the differing frontal circuits and/or unique deficits exhibited by the TBI patient yet are widely used as tests of executive functions. Examples include the Stroop Color–Word Test [81] and the Trailmaking Test B [82] which are sensitive to general cerebral pathology, but are not specific to frontal system functioning in TBI. Such widely used tests have demonstrated sensitivity to diffuse cerebral dysfunction in addition to dorsolateral prefrontal functioning.
2. *Underdetection of Orbitofrontal Functioning*. Though traditionally used tests of general or dorsolateral prefrontal brain function have been valuable in detecting cognitive deficits in patients who might not appear to be cognitively impaired to the typical observer, they fail to capture the real-life social functioning and behavior linked to the orbitofrontal regions which bear the brunt of TBI. Ways to correct this situation have been recommended including the use of adjunctive structured interviews, self-report, and informant-report instruments or by use of questionnaires regarding behavioral disorders. Examples include instruments such as the Behavioral Rating Inventory of Executive Function (BRIEF-A) [91] and Frontal Systems Behavior Scale (FrSBe) [91], which assess degree of apathy, disinhibition, or other behavioral/ emotional dysregulation occurring in everyday life and also have the advantage of allowing for comparisons between patient and caregiver ratings.

Another issue is that the most widely used tests of executive functioning are "veridical" in nature rather than "actor centered." Tests of frontal systems functioning commonly used in neuropsychological batteries, i.e., the Wisconsin Card Sort [92], Stroop Color–Word Test [93], and Category Test [94], are veridical in that patient responses on these tests are either correct or incorrect.

Individual preferences or biases have no bearing on patient responses; their answers are simply "right" or "wrong." In contrast, actor-centered tests are guided by patient priorities, and the responses made depend on the patient needs and/or perception of those needs. An actor-centered test is the Iowa Gambling Task (IGT) [95].

The IGT has been standardized and validated and has demonstrated sensitivity to ventromedial prefrontal lesions [96]. The IGT requires decision-making by the use of advantageous and disadvantageous strategies, and failure to choose advantageously results from insensitivity to future consequences, with immediate prospects overriding any future prospects. The test simulates a gambling situation with differing cost and payout ratios, i.e., preferences for strategies that result in high immediate reward but lower overall payout vs. strategies that are low in immediate reward but result in higher overall payout in the long run. This test has demonstrated predictive ability in substance abuse, relapse, and ability to hold gainful employment due to decision-making deficits linked to ventromedial prefrontal cortical dysfunction [5]. Performance on the IGT has also correlated significantly with emotional intelligence, as patients with bilateral ventromedial frontal injury and/or right unilateral lesions in the amygdala have demonstrated significantly lowered judgment and decision-making as well as lower emotional/social intelligence despite average levels of cognitive intelligence when compared to patients with lesions outside these regions [97]. In everyday life, such actor-centered decision-making is predominant, yet neuropsychological and/or executive function batteries in common usage do not reflect this but rather are comprised of tests that are veridical [97].

Experimental measures have also been employed to evaluate orbitofrontal functioning. Investigators have differentiated aspects of social cognition in frontal lesion patients using ToM tasks that involve detecting deception, faux pas, irony, or understanding mental states of others. The right hemisphere in particular has been implicated in ToM. Investigators have evaluated subjects with focal frontal and non-frontal lesions on visual perspective taking (ability to infer the visual experience of another) and detecting deception (ability of the patient to infer that someone was trying to deceive them [98]. Lesions throughout the frontal lobes, with most robust findings in the right frontal lobe, were predictive of deficits in visual perspective taking. Medial frontal lesions, particularly right ventromedial, were implicated in detection of deception. Bilateral, particularly right orbitomedial lesions impaired patients' capacity to incorporate the experience of another's deceptions into their own plans, consistent with existing knowledge about damage to this region [98]. ToM tasks are not yet in common clinical usage, as validity and reliability studies are still in progress.

3. *The Laboratory Testing Environment.* The third problem in assessment of executive functions is the failure of laboratory testing to reflect problems in cognition or behavior as they are manifested in everyday life. Executive functions are dynamic, and unlike evaluation of more specific functions such as motor skills, problem-solving behavior includes planning or decision-making is more difficult to fully capture in a controlled environment [99]. In particular, patient errors when performing everyday activities are less likely to be manifested in the laboratory than they are in the natural setting [100]. TBI patients, when compared to normal controls, have been shown to have a high error rate, for both detecting and correcting errors made in performance of everyday actions [100].

The Naturalistic Action Test (NAT) [101] was developed to assess everyday actions and has shown promise in evaluating functioning in a way that simulates the natural environment. The NAT is sensitive to errors of action in performing basic everyday activities such as making coffee, toast, packing a lunch, etc. The necessary items for a particular task are placed on a table in a standardized fashion in front of the patient who is then instructed to complete it, and performance is observed and errors are recorded. The complexity of tasks can be manipulated to place increasing demands on attentional resources, for

example, in the simple condition, items are placed in front of the subject along with distractor items whereas in the complex condition some target items are hidden in a box placed in a particular spot on the table. Competing stimuli can also be introduced to increase complexity. Errors are recorded and coded as to type, such as omitting steps, performing actions at the wrong time, perseveration, using the wrong object in place of the target object, misjudging the relationship between two objects, or omitting the use of or misusing tools. Error rates increase with level or severity of the patient and/or task complexity. Reliability and validity of the NAT have been demonstrated in various populations, including stroke and TBI [101], and adaptations of the NAT have been useful in differentiating patients with Alzheimer's dementia from normal controls [102, 103]. Unfortunately, tests of naturalistic action are not part of standard neuropsychological batteries outside of rehabilitation settings, though they clearly capture significant problems experienced and commonly reported by TBI patients and patient caregivers, suggesting possibly greater ecological validity than many tests in common usage.

Executive Functions: The Need for Subcategories

Executive functioning is a multifactorial rather than unitary construct. Given the diversity of the frontal systems underpinning the executive functions, no one test can be sensitive to all aspects of dysfunction.

Subdividing the executive functions to correspond to distinct frontal systems has been recommended. Different systems for this subdivision have been offered, including executive cognitive functions, behavioral self-regulatory functions, activation–regulation functions, and metacognitive processes. In general, subdivisions that capture both the cognitive and the behavioral/emotional aspects of executive functions are emphasized because they provide the necessary framework for a systematic evaluation strategy. Assessment of executive functioning must therefore include measures of:

1. Cognitive aspects, generally mediated by the dorsolateral prefrontal circuit, such as planning, organizing, monitoring, working memory, set-shifting, and set maintenance.
2. Behavioral self-regulatory/social-emotional aspects regulated by the orbitofrontal circuit and limbic nuclei, i.e., emotional reactivity, preferences and biases in judgment in problem-solving, ability to take another's perspective, personality changes, empathy, and mood changes.
3. Activation and motivation processes, served by the anterior cingulate.

Accurate assessment of executive functioning that encompasses all frontal systems will best be accomplished by expanding the traditional neuropsychological battery to include standardized procedures in current usage which have demonstrated utility in evaluating general cognitive as well as dorsolateral prefrontal functioning, incorporating newer measures such as self-report inventories, informant-report inventories, and actor-centered tests that are sensitive to the orbitofrontal circuit, using apathy evaluation scales for assessment of anterior cingulate functions (motivation), and using tasks that assess errors of action in a more natural environment. Supplementation with more experimental procedures such as ToM tasks may also be indicated.

Neuropsychological Assessment as a Dynamic Process

Effects of, and recovery from, TBI are ongoing, changing processes. Consequently, the neuropsychological evaluation should be flexible and accommodating to the emergent cognitive and behavioral changes marking the phases of recovery. In the hospital setting where neuropsychological evaluations are generally used to assist with discharge and treatment planning, strengths and limitations of certain assessment instruments (PTA, delirium questionnaires, etc.)

should be discussed on an ongoing basis with treating professionals and patient caregivers in order to avoid overemphasis on a single score. This will help with adjusting expectations about the patient's capabilities and insure proper treatment planning. The neuropsychologist must emphasize to those concerned with patient treatment that recovery can be a slow, nonlinear process. Discussion of results with the patient's family, treatment team members, nursing staff, and physicians is necessary and helpful to guide rehabilitation efforts.

In the acute recovery phase, the patient is likely to be confused, fatigued, and have reduced tolerance, sensory/perceptual limitations, and/or post-traumatic amnesia. Testing should be brief and repeatable with focus on level of consciousness, attention, information processing, and memory. This can be accomplished by the use of short tests, repeated interviews, behavioral observations, and attention to mental status observations from treating health professionals and caregivers over the course of days or weeks. For those patients who have difficulty rating their own mood states, whether from lack of awareness or confusion, direct observation of their interactions with family members and therapy providers, particularly occupational, speech, and physical therapists will be the most helpful as these providers generally spend more time with patients.

In the post-acute phase of TBI, after the patient has regained sufficient alertness, attention, and/or motivation, a more thorough evaluation of neuropsychological functioning should be undertaken. Within the context of a complete evaluation, there should be detailed and thorough assessment of functions known to be particularly vulnerable to TBI, i.e., attention, processing speed, short-term memory, executive functions, and mood/behavior change. When evaluating the executive functions multiple procedures will be required, including patient self-reports, tests sensitive to dorsolateral and orbitofrontal functioning, observation, and/or tasks measuring everyday action errors. Use of multiple measures that reflect the different frontal circuits is recommended. Results should be correlated with neuroimaging studies if possible, and should also be discussed with the patient and/or family and significant others if possible, and any recommendations for brain injury rehabilitation should be explored.

Summary

Traumatic brain injuries are prevalent in the U.S. and the world, resulting in neurological, cognitive, emotional, and behavioral sequelae and causing long-term disability in a significant number of patients. Mild traumatic brain injury (mTBI) is the most common form and has greater consequences than previously assumed. Causes of TBI have expanded to include those resulting from explosive blasts (b-TBI) which have become common in recent wars, chronic traumatic encephalopathy (CTE) resulting from repeated injuries which postmortem studies have shown to have characteristic pathological changes, and subconcussion, which does not meet criteria for mild TBI yet has resulted in adverse effects in particular for those with repeated injuries from contact sports and is a growing concern.

Neuroimaging, particularly newer functional imaging methods such as diffusion tensor imaging (DTI), positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) are more sensitive in detection of the microscopic abnormalities in mild TBI that are often minimized by computed tomography (CT). Diffusion tensor imaging (DTI) in particular is important for delineating and correlating separate cognitive functions to distinct neuroanatomical regions, thus furthering understanding of frontal systems and injuries in TBI.

TBI is not an "event" but rather an ongoing process in any patient. Neuropsychological evaluations of TBI patients should reflect this and the assessment battery must be tailored to the stage of recovery of the patient. Assessment should be dynamic in nature to accommodate the evolving nature of TBI, so serial evaluations will

be necessary to adjust patient and caregiver expectations and help guide treatment. The evaluation must be comprehensive with particular focus on attention, memory, executive functions, and mood change as these are particularly impacted by TBI. Evaluation traditionally has employed standardized tests associated with general cerebral and/or dorsolateral prefrontal functioning, with the result that orbitofrontal functions have been underevaluated despite the vulnerability of this region in TBI. Effective assessment will best be accomplished by understanding executive functioning as multifactorial, consisting of subdivisions and employing tests and procedures that measure functions associated with each subdivision. A combination of assessment procedures including standardized tests, informant-report and self-report inventories, naturalistic observations of the patient, and thorough interview of patients and caregivers is essential to evaluate all aspects of cognitive, behavioral, emotional, and social consequences of TBI.

References

1. Taylor CA, Bell, JM, Breiding, MJ, et al. Traumatic brain injury emergency department visits, hospitalizations and deaths in the United States, 2007–2013. Morbidity and Mortality Weekly Report, 2017; 66 (No SS-9): 1–16. http://dx.doi.org/10.15585/mmwr.ss6609a1.
2. National Institutes of Health Consensus Conference on Rehabilitation of Persons with Traumatic Brain Injury. 1998; http://consensus.nih.gov/1998.
3. Brain Injury Association of America. Types of Brain Injury. www.biausa.org/abouttbi.
4. Varney NR, Varney RN. Brain injury without head injury: some physics of automobile collisions with particular reference to brain injuries occurring without physical head trauma. App Neuropsychol. 1995;2:47–62.
5. Gennarelli TA, Graham DI. Neuropathology. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Publishing, Inc.; 2005. p. 27–50.
6. Bazarian JJ, Zhong J, Blyth B, et al. Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. J Neurotrauma. 2007;24:1447–59.
7. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99:4–9.
8. Peek-Asa C, McArthur D, Hovda D, et al. Early predictors of mortality in penetrating compared with closed brain injury. Brain Inj. 2001;15:80.
9. Hannay HJ, Howieson DB, Loring DW, et al. Neuropathology for neuropsychologists. In: Lezak MD, Howieson DB, Loring DW, editors. Neuropsychological assessment. 4th ed. New York, NY: Oxford University Press; 2004. p. 157–85
10. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, editors. The human frontal lobes: functions and disorders. New York, NY: Guilford Press; 1999. p. 3–26.
11. Schnider A, Gutbrod K. Traumatic brain injury. In: Miller BL, Cummings JL, editors. The human frontal lobes: functions and disorders. New York, NY: Guilford Press; 1999. p. 487–506.
12. Adams JH. The neuropathology of head injury. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology: head injury. Amsterdam: Elsevier Science; 1975. p. 35–65.
13. McCullagh S, Feinstein A. Cognitive changes. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury-1st Edition. Washington, DC: American Psychiatric Publishing, Inc.; 2005. p. 321–35.
14. Eskridge SL, Macera CA, Galameau MR, et.al. Injuries from combat explosions in Iraq: injury type, location, and severity. 2012, Injury, October; 43 (10): 1678–1682.
15. Kocsis J, Tessler A. Pathology of blast-related brain injury. J Rehabil Res Dev. 2009;46(6):667–72.
16. Hicks RR, Fertig SJ, Desrocher RE, et.al. Neurological effects of blast injury. 2010 J. of Trauma, May 68(5) 1257–1263.
17. Karr, JE, Areshenkoff, CN, Duggan, EC, et al. Blast-related mild traumatic brain injury: A bayesian random-effects meta-analysis on the cognitive outcomes of concussion among military personnel. Neuropsychol Rev. 2014;24.
18. Schwartz I, Tuchner M, Tsenter Z, et al. Cognitive and functional outcomes of terror victims who suffered from traumatic brain injury. Brain Inj. 2008;22:255–63.
19. Ling G, Bandak F, Armonda R. Explosive Blast Neurotrauma. J Neurotrauma. 2009;26:1–11.
20. DeKosky ST, Blennow K, Ikonomovic MD, et al. Acute and chronic traumatic encephalopathies: pathogens and biomarkers. Nat Rev Neurol. 2013;9:192–200.
21. Saulle M, Greenwald BD. Review Article: Chronic Traumatic encephalopathy. Rehabilitation Research and Practice, Vol 2012; Article ID 816069.
22. Stein TD, Alvarez VE, McKee, AC. Concussion in chronic traumatic encephalopathy. Curr Pain Headache Report. 2015, October 19 (10): 47.
23. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport

related concussive and subconcussive head trauma. Clin Sports Med. 2011;30:179–88.
24. Iverson GL, Gardner AJ, McCrory P et.al. A critical review of chronic traumatic encephalopathy. Neurosci Biobehav Rev. 2015; 56: 276–293.
25. Stein TD, Montenigro PH, Alvarez VE, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. Acta Neuropath. 2015;130 (1) 21–24.
26. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA. 2017;318(4):360–370.
27. Stein TD, Alvarez VE, McKee AC. Concussion in chronic traumatic encephalopathy. Curr Pain Headache Rep. 2015;19(10):47.
28. Bales JE, Petraglia AL, Omalu BI, et al. Role of subconcussion in repetitive mild traumatic brain injury. J Neurosurg. 2013;119(5):1235–45.
29. Talavage TM, Nauman EA, Breedlove EL, et al. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. J Neurotrauma. 2014;(31):327–38.
30. Graham R, Rivara FP, Ford MA, et al. Sports related concussions in youth. 2014: The National Academies Press, Washington, D.C.
31. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet. 1974;13:81–4.
32. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet. 1974;13:81–4.
33. Fortuny LA, Briggs M, Newcombe F, et al. Measuring the duration of posttraumatic amnesia. J Neurol Neurosurg Psychiatry. 1980;43:377–9.
34. King NS, Crawford S, Wenden FJ, et al. Measurement of posttraumatic amnesia: how reliable is it? J Neurol Neurosurg Psychiatry. 1997;62:38–42.
35. Levin HS. O'Donnell, VM, Grossman, RG. The Galveston Orientation and Amnesia Test: a practical scale to assess cognition after head injury. J Nerv Ment Disease. 1979: 167: 675–84.
36. Stuss DT, Binns MA, Carruth FG, et al. The acute period of recovery from traumatic brain injury: post traumatic amnesia or posttraumatic confusional state? J Neurosurg. 1999;90:635–43.
37. American Congress of Rehabilition Medicine (ACRM). Definition of Mild Traumatic Brain Injury. J Head Trauma Rehabilitation 1993; 8(3): 86–87.
38. MacKenzie JD, Siddiqi F, Babb JS, et al. Brain atrophy in mild or moderate traumatic brain injury: a longitudinal quantitative analysis. Am J Neurorad. 2002;23:1509–15.
39. Lewine JD, Davis JT, Bigler ED, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. J Head Trauma Rehabil. 2007;22:141–55.
40. Kay T, Harrington DE, Adams R. Definition of mild traumatic brain injury J Head Trauma Rehab. 1993;8:86–7.
41. Hannay HJ, Howieson DB, Loring DW, et al. Neuropathology for Neuropsychologists. In: Lezak MD, Howieson DB, Loring DW, editors. Neuropsychological Assessment. 4th ed. New York, NY: Oxford University Press; 2004. p. 157–85.
42. Fann JR, Burlington B, Leonetti A, et al. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry. 2004;61:53–61.
43. Vasterling JJ, Bryant RA, Keane TM. PTSD and mild traumatic brain Injury; 2012, Guilford Press.
44. Hogue CS, McGurk D, Thomas JL, et.al. Mild traumatic brain Injury in U.S. soldiers returning from Iraq. New Eng J of Med; 2008, 358: 453–463.
45. Jorge RE, Robinson RG. Mood Disorders. In Textbook of Traumatic Brain Injury, Second edition. Silver JM, McAllister TW, Yudofsky SC, eds. 2011, American Psychiatric Publishing.
46. Bibby H, McDonald S. Theory of mind after traumatic brain injury. Neuropsychologia. 2005;43:99–114.
47. Bigler ED. Structural imaging. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. 1st ed. Washington, DC: American Psychiatric Publishing, Inc.; 2005. p. 79–105.
48. Kraus MF, Susmaras T, Caughlin BP, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain. 2007;130:2508–19.
49. Shutter L, Tong KA, Lee A, et al. Prognostic role of proton magnetic resonance spectroscopy in acute traumatic brain injury. J Head Trauma Rehab. 2006;21:334–49.
50. Govindaraju V, Gauger GE, Manley GT, et al. Volumetric proton spectroscopic imaging of mild traumatic brain injury. Am J Neurorad. 2004;25:730–7.
51. Cohen BA, Inglese M, Rusinek H, et al. Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. Am J Neurorad. 2007;28:907–13.
52. Lewine JD, Davis JT, Bigler ED, et al. Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. J Head Trauma Rehabil. 2007;22:141–55.
53. Jansen HM, van der Naalt J, van Zomeren AH, et al. Cobalt-55 positron emission tomography in traumatic brain injury: a pilot study. J Neurol Neurosurgery Psychiatry. 1996;60:221–4.
54. Ruff RM, Crouch JA, Troster AI, et al. Selected cases of poor outcome following a minor brain trauma: comparing neuropsychological and positron emission tomography assessment. Brain Inj. 1994;8:297–308.
55. Ptito A, Chen JK, Johnston KM. Contributions of functional magnetic resonance imaging (fMRI) to

sport concussion evaluation. NeuroRehabilitation. 2007;22:217–27.
56. McAllister TW, Saykin AJ, Flashman LA, et al. Brain activation during working memory one month after mild traumatic brain injury: an fMRI study. Neurology. 1999;53:1300–8.
57. McAllister TW, Sparling MB, Flashman LA, et al. Differential working memory load effects after mild traumatic brain injury. NeuroImage. 2001;14: 1004–12.
58. Chen JK, Johnston KM, Frey S, et al. Functional abnormalities in symptomatic concussed athletes: an fMRI study. NeuroImage. 2004;22:68–82.
59. Chen JK, Johnston KM, Collie A, et al. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. J Neurol Neurosurg Psychiatry. 2007;78:1231–8.
60. Chow TW, Cummings JL. Frontal-subcortical circuits. In: Miller BL, Cummings JL, editors. The human frontal lobes: functions and disorders. New York, NY: Guilford Press; 1999. p. 3–26.
61. Goldberg E. The executive brain. New York, NY: Oxford University Press; 2001. 61. Luria AR. Higher cortical functions in man. New York, NY: Basic Books, Inc.; 1980.
62. McDonald S, Flanagan S. Social perception deficits after traumatic brain injury: interaction between emotion regulation, mentalizing ability, and social communication. Neuropsychology. 2004;18:572–9.
63. Stuss DT, Gow CA, Hetherington CR. No longer gage: frontal lobe dysfunction and emotional changes. J Consult Clin Psychol. 1992;60:349–59.
64. Blair RJR, Cipolotti L. Impaired social response reversal: a case of 'acquired sociopathy'. Brain. 2000;123:1122–41.
65. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res. 1990;41:81–94.
66. Rolls ET, Hornak J, Wade D, et al. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry. 1994;57:1518–24.
67. Grafman J, Schwab K, Warden D, et al. Frontal lobe injuries, violence, and aggression: a report of the Vietnam head injury study. Neurology. 1996;46:1231–8.
68. Raine A, Buchsbaum MS, Stanley J, et al. Selective reductions in prefrontal glucose metabolism in murderers. Biol Psychiat. 1994;36:365–73.
69. Wood JN. Social cognition and the prefrontal cortex. Behav Cog Neurosci Rev. 2003;2:97–114.
70. Shamay-Tsoory SG, Tomer R, Berger BD, et al. Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. Cogn Behav Neurol. 2005;18:55–7.
71. Milders M, Letswaart M, Crawford JR, et al. Impairments in theory of mind shortly after traumatic brain injury and at one-year follow-up. Neuropsychology. 2006;20:400–8.
72. Marin RS, Chakravorty S. Disorders of diminished motivation. In: Silver JM, McAllister TW, Yudofsky SC, editors. Textbook of traumatic brain injury. Washington, DC: American Psychiatric Press; 2005. p. 337–52.
73. Andersson S, Bergedalen AM. Cognitive correlates of apathy. Neuropsychiat Neuropsychol Behav Neurol. 2002;15:184–91.
74. Gronwall D. Minor head injury. Neuropsychology. 1991;5:254–65.
75. Hart T, Whyte J, Millis S, et al. Dimensions of disordered attention in traumatic brain injury: further validation of the moss attention rating scale. Arch Phys Med Rehabil. 2006;5:647–55.
76. Whyte J, Hart T, Bode RK, et al. The moss attention rating scale for traumatic brain injury: initial psychometric assessment. Arch Phys Med Rehabil. 2003;84:268–76.
77. Kennedy RE, Nakase-Thompson R, Nick TG, et al. Use of the cognitive test for delirium in patients with traumatic brain injury. Psychosomatics. 2003;44:283–9.
78. Wechsler D. Digit span subtest; from the Wechsler Adult Intelligence Scale Fourth Edition. San Antonio, TX: The Psychological Corporation; 19.
79. Wechsler D. Symbol search subtest. From the Wechsler Adult Intelligence Scale, 4th edition. San Antonio, TX: The Psychological Corporation; 1999.
80. Cicerone K. Clinical sensitivity of four measures of attention to mild traumatic brain injury. Clin. Neuropsy. 1997;11:266–72.
81. Golden CJ. Stroop color and word test. Chicago, IL: Stoelting Co.; 1978.
82. Reitan RM, Wolfson D, editors. The Halstead-Reitan neuropsychological test battery: Trailmaking Test-B. Tucson, AZ: Neuropsychology Press; 1993.
83. Gronwall D. Paced auditory serial addition task: a measure of recovery from concussion. Percept Mot Skills. 1977;44:367–73.
84. Delis DC, Kaplan E, Kramer JH, et al. California verbal learning test. 2nd ed. San Antonio, TX: The Psychological Corporation; 2001.
85. Brandt J. Hopkins verbal learning test: development of a new memory test with six equivalent forms. Clin Neuropsychol. 1991;5:125–42.
86. Schmidt M. Rey auditory and verbal learning test: a handbook. Los Angeles, CA: Western Psychological Services Inc; 1996.
87. Wechsler D. Wechsler memory scale. 4th ed. San Antonio, TX: The Psychological Corporation; 1999.
88. Meyers, JE, Meyers, KR. Rey Osterrieth Complex Figure Test and Recognition Trial: Professional Manual. PAR, Inc.
89. Reitan, RM, Wolfson, D. eds. Tactual Performance Test. From the Halstead-Reitan neuropsychological test battery: theory and clinical interpretation. Tucson, AZ: Neuropsychology Press; 1993.

90. Roth RM, Isquith PK, Gioia, GA. Behavioral Rating Inventory of Executive Function-Adult Version (BRIEF-A). Psychological Assessment Resources Inc.; 2005.
91. Grace J, Malloy PF. Frontal Systems Behavior Scale (FrSBe). Lutz, FL: Psychological Assessment Resources; 2002.
92. Heaton RK. Wisconsin Card Sorting Test. Odessa, FL: Psychological Assessment Resources; 1981.
93. Golden, CJ. Stroop Color-Word Test; Chicago, Il.; Stoelting Co.; 1978.
94. Reitan, RM, Wolfson, D. Category Test. From the Halstead-Reitan neuropsychological test battery: theory and interpretation. Tucson, AZ: 1993.
95. Bechara A. Iowa gambling task. Lutz, FL: Psychological Assessment Resources, Inc.; 2007.
96. Bar-On R, Tranel D, Denburg NL, et al. Exploring the neurological substrate of emotional and social intelligence. Brain. 2003;126:1790–800.
97. Goldberg E, Bougakov D. Neuropsychologic assessment of frontal lobe dysfunction. Psychiatr Clin North Am. 2005;28:567–80.
98. Stuss DT, Gallup GG, Alexander MP. The frontal lobes are necessary for 'theory of mind". Brain. 2001;124:279–86.
99. Tranel D, Anderson SW, Benton AL. Development of the concept of 'executive function' and its relationship to the frontal lobes. In: Boller F,.
100. Hart T, Giovannetti T, Montgomery MW, et al. Awareness of errors in naturalistic action after traumatic brain injury. J Head Trauma Rehabil. 1998;13:16–28.
101. Schwartz MF, Segal M, Veramonti T, et al. The naturalistic action test: a standardized assessment for everyday action impairment. Neuropsychol Rehabil. 2002;12:311–39.
102. Chaytor N, Schmitter-Edgecombe M. Fractionation of the dysexecutive syndrome in a heterogeneous neurological sample.
103. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promises and challenges for clinical research. J Neuropsychiatry Clin Neurosci. 2002;14:377–405.

Chapter 3

Traumatic Brain Injury in Very Early Childhood

Louise M. Crowe, Clara Chavez Arana, and Cathy Catroppa

Much research has been published on the cognitive and behavioural outcomes of traumatic brain injury (TBI) sustained by school age children [1–3]. In comparison, limited research has focused on the recovery of children injured at preschool age and younger. This chapter focuses on (TBI) in infants and young children. In this chapter we focus on TBI occurring from infancy up to five years of age, referring to this age group as 'young children'. The chapter highlights the differences in epidemiology and physiology in this age group from older children and goes on to discuss the associated cognitive and behavioural outcomes within this age group.

Epidemiology of TBI in Young Children

TBI occurs at high rates in young children and is a major cause of death and disability [4]. For example, work by Bayreuther et al. [5] found that infants had almost double the incidence of injuries to the head than older children. Although there is a focus on abusive head trauma (AHT) in the younger age group, the majority of TBI are the result of accidents [6]. Major causes of TBI in children under 3 years of age are falls of short distances, often from furniture such as beds, couches, and change tables [7, 8]. In children aged 3–6 years, TBIs also occur from falls from playground equipment, bicycles and scooters [9, 10]. Motor vehicle accidents and AHT are the main cause of severe TBIs in young children [6]. However, riding a bicycle without a helmet is associated with significant TBI [9].

The Influence of Head and Neck Physiology of Young Children's Vulnerability to TBI

The physiology of the young child's skull and neck makes them particularly vulnerable to increased damage to the brain from a TBI. In infants, the skull is thin and pliable allowing the head to move through the birth canal. Whilst a

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necessary feature for a natural birth in the event of a TBI, the softness of the skull offers the brain little defence from external trauma [11]. From birth to two years of age, the skull becomes thicker and the sutures fuse. Prior to closing, the sutures are described as 'fibrous connections' offering minimal protection of the brain [11, 12]. In younger children the head, relative to body size, is disproportionately larger, and weighs between 10 and 15% of the total body weight compared to adults whose head contributes only 2–3% of total body weight [11]. The muscles of the neck are weak and therefore the head is not well supported [11, 12]. The combination of a large head and weak neck muscles makes the young child more susceptible to rotational and shearing forces [13]. The limited ability of the young child's skull to absorb biomechanical force means the brain is susceptible to significant injury [14] with an increase in diffuse as opposed to focal injury [12–15]. Significant brain damage including large lesions, subdural haematomas, and lesions in the subcortical white matter and frontal lobes are all found more frequently in young children compared to older children after a TBI [13]. TBI in a young child is more likely to produce shearing injury to the brain over contusions [16]. These differences are due to the young child's brain being a softer consistency, with myelination and development of glial cells ongoing combined with higher water content and smaller axons [11]. The subarachnoid space of the child up to 2 years of age is also thinner, providing less of a buffer if the head is subjected to trauma [11].

Neurological Outcomes of Accidental TBI in Young Children

As we have mentioned, the majority of TBI in young children are from accidental causes. The immaturity of the young brain results in intracranial trauma that differs to older children and adolescents. For example, coup and contrecoup contusions are commonly associated with falls in children and adolescents, however, these injuries occur rarely for younger children under 4 years of age [11]. Coup and contrecoup contusions result from acceleration–deceleration forces, however, young children are typically close to the ground and the acceleration produced is not sufficient to cause the contusions [11]. Falls from a low height, such as falling off a bed or couch, are generally not sufficient to cause a significant head trauma, unless the head strikes a hard surface (e.g. solid stone, concrete) at a particular angle [17]. Falls over 1 m are likely to result in TBI and falls greater than 1.5 m are associated with both skull fractures and intracranial trauma [17]. Skull fractures are commonly seen in young children with TBI [17] and are often associated with epidural haemorrhage.

Neurological Outcomes of Abusive Head Trauma in Young Children

TBI in children from AHT are generally only seen up to 3 years of age and most occur within the first year of life [18]. Autopsy studies report that subdural haemorrhage is commonly seen with AHT as opposed to epidural hematoma [18]. Skull fracture is also common [19]. Gedde's landmark papers in the area refuted earlier assertions that AHT was commonly associated with traumatic diffuse axonal injury [20]. Early research suggested that shaking a baby caused rotational forces on the brain and resulted in traumatic insult, however, there is debate about whether the shaking is the main cause of significant intracranial trauma, with the damage generally prescribed to occur when the infant strikes a solid surface with force or speed (i.e. thrown against wall, etc.). Duhaime et al. [21] concluded from dummy model studies that shaking alone did not reach the thresholds for concussion, subdural haemorrhage or diffuse axonal injury [21]. Difficulties with understanding the differences in AHT to accidental TBI are further hampered by the reluctance of caregivers responsible for the injury to give accurate details on mechanism as well as timing.

History of Traumatic Brain Injury Research and Evolution of Theory in Very Young Children

The recovery of young children from TBI has been an area of intense debate. Margaret Kennard, a neurologist, principally studied the effects of neurological damage on primates. Her work led to the creation of the Kennard Principle, which posited a negative linear relationship between age of the organism at the time of a brain lesion, and the outcome expectancy. She concluded that the earlier in life a brain lesion occurs, the more likely it is for a compensation mechanism minimise the consequences [22]. In line with the Kennard Principle, authors have argued in prior research that young children recover better from TBI than adults, citing protective physiological factors including the relative flexibility of the child's skull, the lower frequency of intracranial haematomas, and the plasticity of the developing brain [22].

The opposing position is that the immaturity of the central nervous system young children present with poorer cognitive outcomes. Between one and two years of age, the neuronal proliferation and synaptogenesis in the frontal cortex reaches a peak. However, white matter development continues to age three or four years, and the frontal lobes and their functions as well as myelination continue developing until early adulthood [23]. As a consequence, early TBI may cause deficits in already acquired skills and hamper those functions yet to emerge [24], which leads to a reduced predictability of outcomes [25]. A critical review of the literature by Spencer-Smith and Anderson [26] concluded that neither early plasticity nor early vulnerability theories adequately and reliably explain the range of outcomes following injury to the brain at a young age and that such theories are likely an oversimplification.

In line with this, critical periods theories have been proposed and are the focus of more modern research. Critical periods in brain development consist of peaks and plateaus, characterized by the refinement and consolidation of neural networks [24, 27]. Recent theory postulates that a TBI during very early childhood disrupts the development of skills that are emerging and impede the acquisition of new skills, where skills that were acquired before the injury onset, are temporarily diminished and may return to pre-injury level [28–31]. As a consequence, younger age at injury onset has been associated with more severe damage of neural networks and skill development [29, 31]. However, the relationship between age and outcome depends on the neurological and cognitive maturational stage at the time of injury onset, which is not linear and varies among cognitive skills [26, 28, 31, 32].

Cognitive skills with a short window of development are less vulnerable to injury compared to those with an extended developmental trajectory [29]. High order cognitive skills require more time to develop therefore there is an increased vulnerability and reduced capacity for recovery [29]. For instance, focal and selective attention are relatively better preserved, and if affected commonly recover after TBI, but complex types of attention, such as shifting or encoding, are particularly vulnerable to early brain insult [28, 29, 33]. The extended developmental trajectory of the prefrontal cortex is the reason why executive function impairments are commonly seen after early TBI [26, 31]. During the first years of life brain networks are not yet refined and more brain regions necessarily participate in specific functions [26, 31]. As a consequence, early TBI often leads to generalized impairment [26, 31].

Neurocognitive Systems That Are Affected by Early TBI

A TBI sustained during early childhood has been associated with social skills, executive function, and memory deficits combined with compromised behavioural and emotional difficulties [34–36]. The prefrontal cortex plays a major role in the development of these functions, which are commonly affected by early TBI [36, 37]. A TBI during early childhood can alter the development

between the prefrontal cortex regions and the thalamus, basal ganglia, limbic system and posterior cortical systems [37]. Eslinger et al. [37] consider that an early brain lesion within the frontal lobe has a localized effect, also resulting in a reverberating effect that causes a disruption in the interaction among brain regions which are undergoing maturation. Brain lesion volume seems to be a predictor of cognitive impairment [34, 38]. Overall, recent studies support that early brain injury leads to a disruption of child development which is unlikely to recover to normal levels without the implementation of an intervention program [34, 36–38]. In particular, attention, working memory and social skills are vulnerable to early TBI [29].

Attention problems commonly hinder high order thinking functions, the child´s ability to acquire new knowledge, and later academic performance [29]. The attention models proposed by Posner and Rothbart [39] and by Mirsky et al. [40] had been well accepted in the field of neuropsychology. Posner and Rothbart [39] identified three networks: (1) alerting network, maintains and achieves sensitivity to incoming stimuli; (2) orienting network, selects relevant information from the incoming stimuli; (3) executive attention network, monitors and solve conflicts between thoughts, emotions and responses. The networks proposed in Posner´s model are drawn from neuroimaging studies that associated each network with different brain structures and chemical modulators [39]. Similarly, Mirsky et al. [40] consider attention a complex set of processes that can be subdivided into four distinct components: (1) focus attention, refers to the capacity to select specific information; (2) sustained attention, refers to the ability to maintain the focus and alertness during a period of time; (3) shift attention, refers to the capacity to change the focus of attention in a flexible and adaptive way; (4) encode attention, refers to the ability to register, recall and manipulate information. These components are underpinned by specialized brain regions that form part of an organized system [40] and can be impaired after the onset of TBI. For example, lesions in the orbitofrontal cortex had been associated with attention deficit/hyperactivity disorder (ADHD) after TBI onset [39].

Substantial studies described that children with early TBI are at risk of presenting new onset of ADHD [41–43]. ADHD is three times more common in children with a TBI [41]. However, these ADHD symptoms are less likely to be reported in young children with TBI, and become noticeable between middle to late childhood [43]. Pre-injury family psychosocial adversity and pre-injury child adaptive functions have been identified as predictors of ADHD secondary to TBI [41, 42]. Nonetheless, it is important to consider that children with ADHD have a higher tendency to experience a TBI [44], which may explain why pre-injury child adaptive function seems to be a predictor of secondary ADHD.

Working memory is a multicomponent system with limited capacity to store information temporarily during the performance of cognitively complex [45]. The components in this hierarchical model are: central executive, phonological loop, visuospatial sketchpad and episodic buffer [45]. The central executive controls attention, verbal and acoustic information is held by the phonological loop, visual information is held by the visuospatial sketchpad and the buffer episodic holds episodes through which information across space and time is integrated [45]. More severe injuries, earlier age at insult and attention span are predictors of impairments in working memory [46]. In addition, more time since injury is associated with a decline of verbal and visual-spatial working memory [47, 48]. The vulnerability towards impairments in working memory in younger children with TBI could be explained by the prolonged maturation process of the frontal cortex [47].

Impairments in social skills have a negative impact on children's quality of life [49]. The Social-Cognitive Integration of Abilities Model (SOCIAL) is a seminal model that defines essential aspects of social competency [49]. The first component of SOCIAL involves internal factors (temperament, personality, physical attributes) external factors (family environment, socio-economic status, culture) and brain development (neural base of social skills) as

mediators. The second component refers to emotional and cognitive elements (attention, socio-emotional and communication skills) required for the integrity of social skills [49]. These components interact at neural and behavioural levels resulting in social competence [49]. Theory of mind (ToM: ability to ascribe psychological states to others) and pragmatic language (ability to infer social meaning from complex language) are essential social skills that emerge during early childhood and are commonly impaired after TBI [50–53] Younger age at insult is a predictor of impairments in pragmatic communication [54]. However, these deficits may not be evident until later stages of life when social skills are expected to reach maturity [55]. Contrary to what is seen in young children, older children and adolescents are more likely to recover pragmatic communication and reach an adaptive level [54].

Radiological Predictors of Neuropsychological Outcomes—CT, PET, MRI

There is substantial research describing correlations between CT and MRI results with school problems, difficulties seen on a neuropsychological assessment, and overall recovery [56–58]. Beauchamp et al. [59] compared CT scans with susceptibility-weighted imaging MRI sequence (SWI/MRI) in children with TBI [59]. Their findings show that SWI/MRI technique can identify subtle neuroanatomic changes that CT scans overlook [59]. CT scans are effective in identifying injuries that require neurosurgical treatment [59]. However, SWI/MRI techniques can identify fine parenchymal lesions associated with cognitive and behavioural symptoms without exposing children to radiation, as opposed to CT scans [59]. Due to the diffuse nature of most TBI, cutting edge neuroimaging can link structural and microstructural findings with cognitive and behavioural outcomes [59]. There is an association between the number of lesions identified through SWI/MRI and intellectual functioning at 6-months post-injury [60]. Greater number of lesions have been found to lead to disruption of multiple neural networks and cognitive functions [60]. However, these studies were conducted in older children (5–16 years of age) and neuroimaging studies of social skills in early childhood are scarce.

More recently, using structural MRI, Ryan et al. [61] studied the association between ToM and neuroanatomical abnormalities in grey matter macrostructure at 24-months post-injury. They found that poor ToM was associated with neuroanatomical abnormalities in neural networks involved in social-affective processes.

To obtain more evidence of the neural regions implicated in the social brain network, Ryan et al. [62] investigated the neuroanatomic differences that children (aged 8–15 years) with TBI present in white matter microstructure with DTI. They found that at six months post-injury, poor ToM and pragmatic language was associated with abnormal diffusivity of the splenium of the corpus callosum, uncinate fasciculus, sagittal stratum, middle and superior cerebellar peduncles [62]. These are all structures that are comprised of white matter bundles with critical cortico-subcortical functional connectivity. While at 2 years post-injury, the same cognitive deficits were associated with abnormalities in the dorsal cingulum and middle cerebellar peduncle [62]. Their findings highlight the importance of studying changes in brain connectivity through the lifespan and indicate that using high-resolution imaging can allow early identification of children who are at risk of presenting with social cognitive dysfunction after TBI [61, 62].

Genc et al. [63] studied white matter microstructure with DTI during the subacute phase and its relation with injury severity and cognitive outcomes in children and adolescents (5–15 years) with TBI. Their results indicate that more severe injuries are associated with greater damage on white matter microstructure in the corpus callosum [63]. These microstructural disturbances were also associated with diminished information processing speed at 2 years

post-injury [63]. Injury severity and processing speed were key determinants of abnormalities in white matter development after paediatric TBI [63].

Using structural MRI, Yu et al. [64] investigated the long-term impact of childhood TBI on white matter, inhibition and cognitive flexibility at 16 years post-injury. They found that in healthy adults, inhibition and cognitive flexibility improved with increased cortical white matter [64]. In contrast, in survivors of childhood TBI, increase in white matter was associated with poorer inhibition and cognitive flexibility [64]. This study provides further evidence that TBI during childhood has a long-term impact on brain-behaviour connections that require further study [64].

High-resolution MRI techniques are specialized for intracranial arterial pathology and can provide more detail on the integrity of the developing brain after child TBI [65]. While the implementation of these techniques is limited due to clinical setting considerations, rapid advancements in the neuroimaging field may increase its accessibility [65].

Post-injury Management of Paediatric TBI

Phases of Post-injury Management

The recovery process can be divided into three phases [66]. However, these phases vary depending on the injury severity and case. The severity of the TBI is determined based on several parameters including level of consciousness, duration of altered consciousness and posttraumatic amnesia, evidence of skull fracture or cerebral pathology, and mental and neurologic condition. In a serious injury, the first phase in the recovery process is when the child is still in coma. During this phase the main goal is to maintain basic functions (feeding and physical strength) and monitored progress or deterioration [66].

The second phase starts when the child is medically stable and is able to receive an intensive rehabilitation. The goal of this second phase is to facilitate the child´s recovery and move towards discharge [66]. The nurse coordinates communication between medical, nursing and an allied health team. The allied health team may involve a Speech Therapist, to assess speech and language, an Occupational Therapist, to assess motor skills, a Neuropsychologist, to assess cognitive outcomes, a Social worker, to discuss family issues, a Clinical Psychologist, to assess adaptive behaviour issues, and Educational consultants, to communicate with the school staff [66]. The allied health team discusses rehabilitation priorities and works with the family to help them understand and enhance the recovery process. The time of discharged is decided based on the child's function, family's adjustment and the capacity of local services to provide ongoing therapy [66].

The final phase of recovery process follows hospital discharge; in this phase children are treated as outpatients and school teleconferences with teachers and school visits may be required. The main intention is to encourage independence in day-to-day life and ease the child´s return to school and reintegration into the community [66]. During this phase physical (adaptive equipment, such as wheelchairs), environmental (extra time for tasks, well-structured classroom environment) and instructional (educational programs, individual tuition, retraining of social skills) adaptations need to be considered [67]. In periods of transition, children with serious injuries tend to require more medical input and rehabilitation [68]. The allied health team share responsibility and work together with the child and family participate in the identification of goals and decision-making process. This collaborative approach seems to improve family´s feeling of competency, engagement with goals and outcomes [69, 70].

Neuropsychological Assessment in Paediatric TBI

Obtaining extensive information of pre- and post-injury function from the family provides qualitative data unlikely to be obtained elsewhere. This history informs selection of assessment measures, and can highlight areas that might be challenging for the family and child. Routinely, following childhood TBI, assessment does not occur in the acute stages post-injury. Rather, comprehensive assessment is conducted prior to school reintegration, in order to best inform educational management. Even at that point, hallmark impairments in attention, speed of processing and fatigue need to be considered when testing and interpreting findings. Standardized assessment methods are not always helpful for children with severe injuries. Severe cases required the use of other techniques, including contextual observation (at clinic, home or school), and parent and teacher's ratings. Parents and teachers may complete questionnaires to provide information about the child's functioning. In addition, follow-up assessments one year after injury onset and reviews during transitional stages should be implemented.

Neuropsychological assessments in children with TBI aim to (1) provide information about the integrity of brain functions; (2) detect and diagnose symptoms or disorders; (3) identify child´s strengths and weaknesses; (4) guide rehabilitation; and (5) monitor cognitive and behavioural changes over time, including those caused by treatments or interventions [65]. The location of the injury may guide hypothesis testing, but due to the diffuse nature of most lesions is important to assess all cognitive domains [65]. Once the pre- and post-injury history was obtained, the neuropsychological assessment begins by assessing intellectual function using standardized test batteries. Bayley Scales of Infant and Toddler Development is used to assess global functioning in children from 1 to 42 months of age [71]. Intellectual functioning is usually assessed with the Wechsler Preschool and Primary Scale of Intelligence in children from 2.6 to 7.7 years of age [72]. However, it is important to consider that global intellectual functioning can be insensitive to the cognitive consequences of TBI [73, 74]. A neuropsychological battery typically involves assessment of motor skills, sensory skills, attention, working memory, problem solving, social perception, long-term learning and memory, language, visuospatial perceptual skills, and behavioural and adaptive function [65]. NEPSY-II can be used in children from 3 to 16 years of age for most of those cognitive domains, including social perception [75]. The Behavior Rating Inventory of Executive Function (EF)—Preschool Version is a questionnaire regarding behaviours thought to be associated with EFs in daily activities, based on the family's and teachers' reports, for children between 2 and 5.11 years of age [76]. Other EFs can be evaluated with tests for school age children: the Test of Everyday Attention for Children assesses attention through tasks designed for children between 6 and 15 years of age [77], and the Delis–Kaplan Executive Function System involves verbal and spatial tasks for individuals of 8–89 years of age [78].

Behaviour and adaptive function are usually measured using parents' and teachers' questionnaires. The most common are the Child Behavior Checklist [79], Behavior Assessment System for Children [80], Eyberg Child Behaviour Checklist [81], and the Strengths and Difficulties Questionnaire which is available online in various languages [82]. Some of these questionnaires provide a score of social function, which does not reflect the child´s social cognition [83]. Therefore, to date, social cognition is assessed with experimental and a few clinically standardized tasks. For example, The Jack and Jill task is used to measure false belief understanding, Theory of Mind (NEPSY-II) tests understanding of the thought process of others, Affect Recognition (NEPSY-II) and Emotional and Emotive Faces Task assess a child's ability to discriminate among affective expression and emotive communication, and The Ironic Criticism and Empathic Praise task to measure understanding of how indirect speech acts are

used to impact the mental or emotional state of the listener [84].

Additionally, the clinician may decide to measure proximal environmental factors (parenting practices, parental stress, family functioning and parent mental health) that influence children´s development after TBI [65, 85, 86]. These factors can be assessed with the parent stress index [87], parenting scale [88], family burden injury interview [89] and depression and anxiety stress scale [90].

Approaches in Rehabilitation of Behaviour, Anxiety and Cognition

There is poor evidence from research focused on the rehabilitation of children after very early TBI. For this reason, in this section the rehabilitation approach implemented in the general paediatric population is discussed. An essential step in child rehabilitation is to provide caregivers and teachers information about the possible behavioural, emotional, social and cognitive short-term and long-term consequences of TBI [91, 92].

Woods et al. [93] developed the booklet 'Dealing with a Head Injury in the Family' (ABI booklet) and its accompanied facilitator manual [94], to provide parents of children with TBI information about the consequences of TBI and how these may limit child´s ability to cope with daily activities. One of the most challenging behavioural consequences of early TBI is difficult behaviour [95] and parents do not always understand that this is associated with the TBI or know how to respond to help the child redevelop adaptive capacity. The methods evaluated by a number of studies reduced behaviour problems in children with TBI by including parents in the intervention. Woods et al. [94] studied the efficacy of 'Signposts for Building Better Behavior' (Signposts) combined with the ABI booklet [93] in reducing challenging behaviour in children with acquired brain injury (ABI) and improve family-parental well-being and functioning. Signposts teach parents strategies to help them manage their child behaviour, parents set their own goals and put into practice strategies according to their child needs [96]. Signposts in combination with the ABI booklet demonstrated efficacy in preventing and reducing challenging behaviour in children with TBI and improving parental well-being within an Australian and Mexican population, and it is currently being studied in preschool children [97–99].

Similarly, Brown and colleagues [100] found that a parenting program in combination with Acceptance Commitment Therapy (ACT) were effective in decreasing a child´s behaviour and emotional symptoms, and reducing dysfunctional parenting practices. The ACT is part of a larger family of behavioural and cognitive therapies [101] that emphasizes acceptance rather than behaviour change only [102]. Take a Breath (TAB: 103) is an intervention programme that adapted ACT and problem-solving skills strategies for parents of children with life-threatening illness, including TBI [104]. TAB showed promising results in reducing parental stress and posttraumatic stress symptoms while improving parental psychological flexibility and mindfulness in parents [104]. This novel intervention is delivered via video conference to facilitate parent participation [105].

Children with TBI are at risk of presenting anxiety symptoms [106]. Some methods treat dysregulation symptoms, including depressive and anxiety symptoms [106]. Interventions aiming to improve dysregulation symptoms in children commonly use a cognitive behaviour therapy (CBT) approach [106]. A CBT program for managing anxiety [106] is being studied in children with TBI. The adapted program and the corresponding facilitator manual is now complete [107].

Attention and memory deficits are a common consequence of early TBI onset [108]. The Amsterdam Memory Attention training (AMAT-C) aims to improve children´s attention and memory after TBI [109–112]. This program was developed based on a model described by

Sohlberg and Mateer [113] in which cognitive domains are targeted based on its difficulty, from basic to complex. In AMAT-C daily tasks are done by the child under supervision of a coach (parent or teacher), in combination with weekly face-to-face sessions with the therapist [109–112]. Currently, our laboratory is studying whether replacing the face-to-face sessions with weekly online sessions increases participation [114].

There is substantial evidence describing social skills impairments in children with TBI [71, 115]. Social skills deficits negatively impact child psychological well-being, by diminishing the child´s ability to participate within their environment and develop meaningful relationships [51, 52]. However, there are no ecologically sensitive measures to identify impairments in this domain [116]. Our laboratory developed the Paediatric Evaluation of Emotions, Relationships, and Socialisation (PEERS) that will be the first ecologically sensitive, well-validated measure to detect social skills impairment in children [117]. PEERS aims to identify social skills strengths and challenges in children with TBI and other clinical groups [117].

Environmental Factors

A child´s development depends on an intact central nervous system and is shaped by proximal (within the family) and distal (outside the family) environmental factors [15, 53]. In comparison to older children, young children have few acquired skills. Young children develop cognitive precursors that will lead to high order thinking skills [53]. For example, joint attention and imitation are precursors of social skills, young children also develop inhibition which is required to regulate behaviour [118–120]. TBI in early childhood can interfere with the refinement and consolidation of neural networks and skills, alter proximal environmental factors (parenting practices, family functioning, parent mental health), and therefore disrupt a child´s cognitive, behavioural, social and functional development [85, 121].

Proximal (family functioning, parenting practices, parent mental health) and distal (social risk) environmental factors have been associated with a child´s risk of sustaining a TBI and the child´s functioning post-injury. Family factors associated with higher risk of TBI include low income, reliance on welfare benefits, minority status, frequent moves and high levels of parental stress [122–125].

Several studies found an association between family burden with child´s post-injury outcomes [126–129]. Proximal factors play an important role in young children's recovery [129]. High level of cohesiveness, supportive family relationships and low level of control had been associated with better outcomes post-injury and children from dysfunctional families present a higher risk of developing psychopathology post-injury [129]. Studies suggest that family environment pre- and post-injury influence behavioural and cognitive recovery [129–131].

Another environmental factor is parenting practices, commonly classified as authoritarian, authoritative and permissive styles [132]. The authoritative parenting style has been associated with positive outcomes post-injury [86, 133]. It consists of providing children clear expectations and reasonable limits, and encouraging them to formulate their own perspective and goals [133, 134]. The authoritarian style is characterized by the use of power and punishment to restrict the child [132]. Parents with permissive style allow children to regulate their activities and avoid setting limits [132]. Authoritarian and permissive parenting practices exacerbate internalizing and externalizing behaviours after TBI [86]. In contrast, the authoritative style benefits the child´s behavioural recovery [86]. Parenting practices are influenced by parents' mental health. In particular, high levels of parental stress hinder parents' ability to engage in warmth interactions with the child, and lead to dysfunctional parenting practices that may intensify as they face challenges associated with the brain injury, such as the need for rehabilitation, advocacy and additional support [134–136].

Social risk has been associated with outcomes after TBI [83, 137]. Social risk factors associated

with the parents include a low level of education of the primary caregiver, an unskilled occupation of the primary income earner, maternal age younger than 21 years of age during the child´s birth, single parents and English as a second language [137, 138]. Socio-economic status, family function and access to resources and support influence children´s recovery after TBI [83, 137].

Summary

Due to the flexibility of the skull, weak muscles of the neck and elasticity of the blood vessels, young children are more vulnerable to increase brain damage after TBI than adults. Primary and secondary mechanisms of TBI cause damage to the brain and may predict cognitive, behavioural social and functional outcomes. TBI at a young age disrupts the refinement and consolidation of neural networks and skills, and alter environmental factors. Due to the nonlinear maturational process of the neural networks, outcomes of TBI are not linear and vary among cognitive skills. However, cognitive skills with an extended developmental trajectory are more vulnerable to TBI. To study cognitive, behavioural, and social brain functions, cognitive models have been developed (e.g. attention, working memory and social competency). These cognitive models serve as a basis for assessment and management of early TBI. Post-injury management requires the participation of an allied health team to monitor progress, facilitate child´s recovery and encourage child´s independence. Neuropsychological assessments are part of the post-injury management. There are several assessment tools. PEERS is a novel assessment tool recently developed at the Murdoch Children's Research Institute that elucidates social cognition. Current studies are investigating intervention programs to treat behaviour problems, dysregulation symptoms, working memory, parenting practices, and parent mental health. Finally, environmental factors have a strong influence of early TBI outcomes that are considered during the post-injury management.

References

1. Catroppa C, Anderson V. Children's attentional skills 2 years post-traumatic brain injury. Dev Neuropsych. 2003;23(3):359–73.
2. Catroppa C, Anderson V, Beauchamp MH, Yeates KO. New frontiers in pediatric traumatic brain injury. An evidence base for clinical practice. New York: Routledge; 2016.
3. Ryan N, Catroppa C, Godfrey C, Noble-Haeusslein LJ, Shultz SR, O'Brien TJ, et al. Social dysfunction after pediatric traumatic brain injury: a translational perspective. Neurosci Biobehav Rev. 2016;64:196–214.
4. Kraus J, Rock A, Hemyari P. Brain injuries among infants, children, adolescents and young adults. Am J Dis Child. 1990;144:684–91.
5. Bayreuther J, Wagener S, Woodford M, Edwards A, Lecky F, Bouamra O, et al. Paediatric trauma: injury pattern and mortality in the UK. Arch Dis Child. 2009;94(2):37–41.
6. Crowe L, Babl F, Anderson V, Catroppa C. The epidemiology of paediatric head injuries: Data from a referral centre in Victoria. Australia J Paediatr Child Health. 2009;45:346–50.
7. Crowe L, Catroppa C, Anderson V, Babl F. Head injuries in children under 3 years. Injury. 2012;43:2141–5.
8. Durkin M, Olsen S, Barlow B, Virella A, Connolly E. The epidemiology of urban pediatric neurological trauma: evaluation of, and implications for, injury prevention programs. Neurosurg. 1998;42:300–10.
9. Kaushik R, Krisch I, Schroeder DR, Flick R, Nemergut ME. Pediatric bicycle-related head injuries: a population-based study in a county without a helmet law. Inj Epidemiol. 2015;2(1):16.
10. Loder RT. The demographics of playground equipment injuries in children. J Pediatr Surg. 2008;43(4):691–9.
11. Case ME. Forensic pathology of brain trauma in children. Brain Pathol. 2008;18:562–4.
12. Margulies S, Thibault K. Infant skull and suture properties: Measurements and implications for mechanisms of pediatric brain injury. J Biomech Eng. 2000;122:364–71.
13. Hahn YS, Chyung C, Barthel MJ, Bailes J, Flannery AM, McLone DG. Head injuries in children under 36 months of age: Demography and outcome. Child's Nerv Syst. 1988;4:34–40.
14. Lallier M, Bouchard S, St-Vil D, Dupont J, Tucci M. Falls from heights among children: A retrospective study. J Pediatr Surg. 1999;34:1060–3.

15. Ommaya A, Goldsmith W, Thibault K. Biomechanics and neuropathology of adult and paediatric head injury. J Neurosurg. 2002;16:220–42.
16. Keenan H, Runyan D, Marshall S, Nocera M, Merten D, Sinal S. A population-based study of inflicted traumatic brain injury in young children. JAMA. 2003;290:621–6.
17. Johnson K, Fischer T, Chapman S, Wilson B. Accidental head injuries in children under 5 years of age. Clin Radiol. 2005;60:464–8.
18. Case ME. Abusive head injuries in infants and young children. Legal Med;9:83–7.
19. Duhaime AC, Christian CW, Rorke LB, Zimmerman R. Nonaccidental head injury in infants – the "shaken-baby syndrome". N Engl J Med. 1998;338:1822–9.
20. Geddes JF, Hackshaw AK, Vowles GH, et al. Neuropathology of inflicted head injury in children. I. Patterns of brain damage. Brain. 2001;124:1290–8.
21. Duhaime AC, Gennarelli TA, Thibault LE, Bruce DA, Margulies SS. Wiser R The shaken baby syndrome: a clinical, pathological, and biomechanical study. J Neurosurg. 1987;66:409–15.
22. Dennis M. Margaret Kennard (1899-1975): Not a 'principle' of brain plasticity but founding mother of developmental neuropsychology. Cortex. 2010;46(8):1043–59.
23. Lewis JD, Evans AC, Tohka J. T1 white/gray contrast as a predictor of chronological age, and an index of cognitive performance. NeuroImage. 2018;173:341–50.
24. Thatcher R. Maturation of the human frontal lobes: Physiological evidence for staging. Dev Neuropsych. 1991;7:387–419.
25. Anderson V, Catroppa C, Haritou F, Morse S, Rosenfeld J. Identifying factors contributing to child and family outcome 30 months after traumatic brain injury in children. J Neurol Neurosurg Psychiatry. 2005;76(3):401–8.
26. Spencer-Smith M, Anderson V. Healthy and abnormal development of the prefrontal cortex. Dev Neurorehabil. 2009;12(5):279–97.
27. Hudspeth WJ, Pribram KH. Stages of brain and cognitive maturation. J Educ Psych. 1990;82 (4):881–4.
28. Crowe L, Catroppa C, Babl F, Rosenfeld J, Anderson V. Timing of traumatic brain injury in childhood and intellectual outcomes. J Pediatr Psychol. 2012;37(7):745–54.
29. Spencer-Smith M, Anderson P, Jacobs R, Coleman L, Long B, Anderson V. Does timing of brain lesion have an impact on children's attention? Dev Neuropsychol. 2011;36(3):353–66.
30. Kolb B, Gibb R. Searching for the principles of brain plasticity and behavior. Cortex. 2014;58:251–60.
31. Jacobs R, Harvey AS, Anderson V. Are executive skills primarily mediated by the prefrontal cortex in childhood? Examination of focal brain lesions in childhood. Cortex. 2011;47(7):808–24.
32. Anderson V, Ylvisaker M. Executive function and the frontal lobes- Themes for child development, brain insult and rehabilitation. Dev Neurorehabil. 2009;12(5):253–4.
33. Crowe L, Catroppa C, Babl F, Anderson V. Executive function outcomes of children with traumatic brain injury sustained in infancy. Child Neuropsychol. 2013;19(2):113–26.
34. Di Stefano G, Bachevalier J, Levin HS, Song J, Scheibel RS, Fletcher B. Volume of focal brain lesions and hippocampal formation in relation to memory function after closed head injury in children. J Neurol Neurosurg Psychiatry. 2000;69(2):210–6.
35. Garth J, Anderson V, Wrennall J. Executive functions following moderate to severe frontal lobe injury: impact of injury and age at injury. Pediatr Rehabil. 2009;1(2):99–108.
36. Williams D, Mateer CA. Developmental impact of frontal lobe injury in middle childhood. Brain Cogn. 1992;20:196–204.
37. Eslinger PJ, Flaherty-Craig CV, Benton AL. Developmental outcomes after early prefrontal cortex damage. Brain Cogn. 2004;55(1):84–103.
38. Slomine BS, Gerring JP, Grados MA. Vasa R, Brady KD, Christensen JR, et al. Performance on measures of 'executive function' following pediatric traumatic brain injury. Brain Inj. 2009;16(9):759–772.
39. Posner MI, Rothbart MK. Research on attention networks as a model for the integration of psychological science. Annu Rev Psychol. 2007;58:1–23.
40. Mirsky AF, Anthony BJ, Duncan CC, Ahear MB, Kellam SG. Analysis of the elements of attention: a neuropsychological approach. Neuropsychol Rev. 1991;2(2):109–145.
41. Li L, Liu J. The effect of pediatric traumatic brain injury on behavioral outcomes: a systematic review. Dev Med Child Neurol. 2013;55(1):37–45.
42. Max JE, Schachar RJ, Levin HS, Ewing-Cobbs L, Chapman SB, Dennis M, et al. Predictors of secondary attention-deficit/hyperactivity disorder in children and adolescents 6 to 24 months after traumatic brain injury. J Am Acad Child Adolesc Psychiatry. 2005;44(10):1041–9.
43. Narad ME, Kennelly M, Zhang N, Wade SL, Yeates KO, Taylor HG, et al. Secondary Attention-Deficit/Hyperactivity Disorder in children and adolescents 5 to 10 years after traumatic brain injury. JAMA Pediatr. 2018;172(5):437–43.
44. Liou YJ, Wei HT, Chen MH, Hsu JW, Huang KL, Bai YM, et al. (2018). Risk of traumatic brain injury among children, adolescents, and young adults with Attention-Deficit Hyperactivity Disorder in Taiwan. J Adolesc Health. 2018;63(2):233–238.
45. Baddeley A. The episodic buffer the new element or working memory. Trends Cogn Sci. 2000;4 (11):417–22.

46. Conklin HM, Salorio CF, Slomine BS. Working memory performance following paediatric traumatic brain injury. Brain Inj. 2008;22(11):847–57.
47. Levin HS, Hanten G, Zhang L, Swank PR, Ewing-Cobbs, L, Dennis M, et al. (2004). Changes in working memory after traumatic brain injury in children. Neuropsychology, 2004;18(2):240–247.
48. Gorman S, Barnes MA, Swank PR, Prasad M, Ewing-Cobbs L. The effects of pediatric traumatic brain injury on verbal and visual-spatial working memory. J Int Neuropsychol Soc. 2012;18(1):29–38.
49. Beauchamp M, Anderson V. SOCIAL: An integrative framework for the development of social skills. Psychol Bull. 2010;136:39–64.
50. Didus E, Anderson V, Catroppa C. The development of pragmatic communication skills in head injured children. Pediatr Rehabil. 1999;3(4):177–86.
51. Rosema S, Crowe L, Anderson V. Social functioning in children and adolescents after brain injury: a systematic review since 1989. J Neurotrauma. 2011;29(7):1277–91.
52. Ryan NP, Catroppa C, Godfrey C, Noble-Haeusslein LJ, Shultz SR, O'Brien TJ, et al. Social dysfunction after pediatric traumatic brain injury: A translational perspective. Neurosci Biobehav Rev. 2016;64:196–214.
53. Siegler R, Saffran JR, Eisenberg N, DeLoache J, Gershoff E, Leaper C. How Children Develop. 5th ed. New York: Worth Publishers Macmillan Learning; 2017.
54. Ryan NP, Catroppa C, Beare R, Coleman L, Ditchfield M, Crossley L, et al. Predictors of longitudinal outcome and recovery of pragmatic language and its relation to externalizing behaviour after pediatric traumatic brain injury. Brain Lang. 2015;142:86–95.
55. Ryan NP, Catroppa C, Cooper JM, Beare R, Ditchfield M, Coleman L, et al. The emergence of age-dependent social cognitive deficits after generalized insult to the developing brain: A longitudinal prospective analysis using susceptibility-weighted imaging. Hum Brain Mapp. 2015;36(5):1677–91.
56. Moura LM, Crossley NA, Zugman A, et al. Coordinated brain development: exploring the synchrony between changes in grey and white matter during childhood maturation. Brain Imaging Behav. 2017;11(3):808–17.
57. Dennis EL, Faskowitz J, Rashid F, et al. Diverging volumetric trajectories following pediatric traumatic brain injury. Neuroimage Clin. 2017;15:125–35.
58. Klarborg B, Skak Madsen K, Vestergaard M, Skimminge A, Jernigan TL, Baare WF. Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. Hum Brain Mapp. 2013;34(12):3216–32.
59. Beauchamp MH, Ditchfield M, Babl FE, Kean M, Catroppa C, Yeates KO, et al. Detecting traumatic brain lesions in children: CT versus MRI versus susceptibility weighted imaging. J Neurotrauma. 2011;28(6):915–27.
60. Beauchamp MH, Beare R, Ditchfield M, Coleman L, Babl FE, Kean M, et al. Susceptibility weighted imaging and its relationship to outcome after pediatric traumatic brain injury. Cortex. 2013;49 (2):591–8.
61. Ryan NP, Catroppa C, Beare R, Silk TJ, Hearps SJ, Beauchamp MH, et al. Uncovering the neuroanatomical correlates of cognitive, affective and conative theory of mind in paediatric traumatic brain injury: a neural systems perspective. Soc Cogn Affect Neurosci. 2017;12(9):1414–27.
62. Ryan NP, Genc S, Beauchamp MH, Yeates KO, Hearps S, Catroppa C, et al. White matter microstructure predicts longitudinal social cognitive outcomes after paediatric traumatic brain injury: a diffusion tensor imaging study. Psychol Med. 2018;48(4):679–91.
63. Genc S, Anderson V, Ryan NP, Malpas CB, Catroppa C, Beauchamp MH, et al. Recovery of white matter following pediatric traumatic brain injury depends on injury severity. J Neurotrauma, 2017;34(4):798–806.
64. Yu K, Seal ML, Reyes J, Godfrey C, Anderson V, Adamson C, et al. Brain volumetric correlates of inhibition and cognitive flexibility 16 years following childhood traumatic brain injury. J Neurosci Res. 2018;96(4):642–51.
65. Catroppa C, Anderson V, Beauchamp MH, Yeates, KO New frontiers in pediatric traumatic brain injury: an evidence base for clinical practice; 2016: New York: Routledge.
66. Anderson V, Northam E, Hendy J, Wrennall J. Developmental neuropsychology: clinical approach. London: Psychology Press; 2002.
67. Case RJL, Starkey NJ, Jones K, Barker-Collo S, Feigin V. New Zealand teachers' understanding of childhood mild traumatic brain injury: investigating and enhancing teacher knowledge and practice. New Zealand J Educat Stud. 2017;52(1):159–76.
68. Catroppa C, Anderson V. Children's attentional skills 2 years post-traumatic brain injury. Dev Neuropsychol. 2003;23(3):359–73.
69. Cusick A, McIntyre S, Novack I, Lannin N, Lowe K. A comparison of goal attainment scaling and the Canadian occupational performance measure for paediatric rehabilitation research. Pediatr Rehabil. 2006;9(2):149–57.
70. Brewer K, Pollock N, Wright V. Addressing the challenges of collaborative goal setting with children and their families. Phys Occup Ther Pediatr. 2014;34(2):138–52.
71. Elliott CD. Differential Ability Scales-Second Edition: Introductory and technical handbook San Antonio. TX: Psychological Corporation; 2007.

72. Wechsler D. The Wechsler preschool and primary scale of intelligence—fourth edition (WPSSI-IV). London: The Psychological Corporation; 2012.
73. Dennis M, Francis DJ, Cirino PT, Schachar R, Barnes MA, Fletcher JM. Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. J Int Neuropsychol Soc. 2009;15(3):331–43.
74. Crowe L, Catroppa C, Babl F, Anderson V. Intellectual, behavioral and social outcomes of accidental traumatic brain injury in early childhood. Pediatrics. 2012;129:262–8.
75. Korkman M, Kirk U, Kemp S. NEPSY—Second Edition (NEPSY-II). San Antonio, TX: Harcourt Assessment; 2007.
76. Gioia GA, Andrews Espy K, Isquith PK. Behavior rating inventory of executive function—preschool version: PARiConnect; 2002.
77. Manly T, Anderson V, Crawford J, George M, Underbjerg M, Robertson IH. Test of everyday attention for children. 2nd ed. UK: Pearson UK; 2016.
78. Delis DC, Kaplan E, Kramer JH. Delis-kaplan executive function system (D-KEFS). San Antonio, TX: The Psychological Corporation; 2001.
79. Achenbach T, Resco L. Manual for the ASEBA school-age forms & profiles. United States of America: ASEBA; 2001.
80. Reynolds CR, Kamphaus RW. Behavior assessment system for children: Circle Pines, MN: American Guidance Service; 1992.
81. Eyberg S, Pincus D. Eyberg child behavior inventory and sutter-Eyberg student behavior inventory-revised. USA: PAR; 1999.
82. Goodman R. The strengths and difficulties questionnaire. J Child Psychol Psychiat. 1997;38 (5):581–6.
83. Catroppa C, Hearps S, Crossley L, Yeates KO, Beauchamp MH, Anderson V. Social and behavioral outcomes following traumatic brain injury. J Neurotrauma. 2016;34(7):1439–47.
84. Dennis M, Agostino A, Taylor HG, Bigler ED, Rubin K, Vannatta K, et al. Emotional expression and socially modulated emotive communication in children with traumatic brain injury. J Int Neuropsychol Soc. 2013;19:34–43.
85. Rashid M, Goez HR, Mabood N, Damanhoury S, Yager JY, Joyce AS, et al. The impact of pediatric traumatic brain injury (TBI) on family functioning: a systematic review. J Pediatr Rehabil Med. 2014;7 (3):241–54.
86. Woods D, Catroppa C, Barnett P, Anderson V. Parental disciplinary practices following acquired brain injury in children. Dev Neurorehabil. 2011;14 (5):274–82.
87. Abidin R. Parent stress index (Fourth Edition ed.): PAR; 2012
88. Arnold D, O´Leary S, Wolff L, Acker M. The parenting scale: a measure of dysfunctional parenting in discipline situations. Psychol Assess. 1993;5 (2):137–4.
89. Wade S, Stancin T, Taylor HG, Drotar D, Yeates KO, Minich NM. Interpersonal stressors and resources as predictors of parental adaptation following pediatric traumatic injury. J Consult Clin Psychol. 2004;72(5):776–84.
90. Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales. Sydney, Australia: Psychology Foundation of Australia; 1995.
91. Bauml J, Frobose T, Kraemer S, Rentrop M, Pitschel-Walz G. Psychoeducation: a basic psychotherapeutic intervention for patients with schizophrenia and their families. Schizophr Bull. 2006;32(Suppl 1):S1–9.
92. Dise-Lewis JE, Lewis HC, Reichardt CS. Brain-STARS- pilot data on a team-based intervention program for students who have acquired brain injury. J Head Trauma Rehabil. 2009;24(3):166–77.
93. Woods D, Woods, Catroppa C, Anderson V. Dealing with a head injury in the family: ABI Booklet. Collingwood.: Gill Miller Press; 2008a.
94. Woods, Catroppa C, Anderson V. Dealing with a head injury in the family: facilitator manual. Collingwood: Gill Miller Press; 2008b.
95. Feeney T, Achilich J. Structured flexibility and context-sensitive behavioral support for the chronically cranky. NeuroRehabilitation. 2014;34 (4):709–723.
96. Hudson A, Cameron C, Matthews J. The wide-scale implementation of a support program for parents of children with an intellectual disability and difficult behaviour. J Intellect Dev Disabil. 2008;33(2):117–26.
97. Chavez-Arana C, Catroppa C, Yáñez Téllez G, et al. Feasibility and effectiveness of a parenting program for Mexican parents of children with acquired brain injury-case report. Brain Injury; 2017.
98. Taylor K, Catroppa C, Godfrey C, McKinlay A, Ponsford J, Matthews J, et al. Managing challenging behaviour in preschool children post-traumatic brain injury with online clinician support: protocol for a pilot study. Pilot Feasibility Stud. 2017;3:30.
99. Woods D, Catroppa C, Godfrey C, Giallo R, Matthews J, Anderson V. Challenging behaviours following paediatric acquired brain injury (ABI): the clinical utility for a manualised behavioural intervention programme. Social Care Neurodisab. 2014;5(3):145–59.
100. Brown FL, Whittingham K, Boyd RN, McKinlay L, Sofronoff K. Improving child and parenting outcomes following paediatric acquired brain injury: a randomised controlled trial of Stepping Stones Triple P plus Acceptance and Commitment Therapy. J Child Psychol Psychiatry. 2014;55(10):1172–83.
101. Hayes SC, Levin ME, Plumb-Vilardaga J, Villatte JL, Pistorello J. Acceptance and commitment

therapy and contextual behavioral science: examining the progress of a distinctive model of behavioral and cognitive therapy. Behav Ther. 2013;44 (2):180–98.
102. Morris E, Johns LC, Oliver JE. Acceptance and commitment therapy and mindfulness for psychosis; 2013. https://ebookcentral.proquest.com/.
103. Heaton RK, Temkin N, Dikmen S, Avitable N, Taylor MJ, Marcotte TD, et al. Detecting change: a comparison of three neuropsychological methods, using normal and clinical samples. Arch Clin Neuropsychol. 2001;16:75–91.
104. Burke K, Muscara F, McCarthy MC, Dimovski A, Hearps S, Anderson V. Adapting acceptance and commitment therapy for parents of children with life-threatening illness- Pilot study. Fam Syst Health. 2014;32(1):122.127.
105. Rayner M, Dimovski A, Muscara F, Yamada J, Burke K, McCarthy M, et al. Participating from the comfort of your living room: feasibility of a group videoconferencing intervention to reduce distress in parents of children with a serious illness or injury. Child Fam Behav Ther. 2016;38(3):209–24.
106. Rapee R, Lyneham H, Schniering C, Wuthrish V, Abbott M, Hudson J, Wignall A. Cool Kids (School version). Centre for Emotional Health; 2006.
107. Soo C, Catroppa C, Anderson V. Cool Kids program for adolescents with anxiety following traumatic brain injury. In preparation.
108. Catroppa C, Stone K, Rosema S, Soo C, Anderson V. Preliminary efficacy of an attention and memory intervention post-childhood brain injury. Brain Inj. 2014;28(2):252–60.
109. Catroppa C, Anderson V, Muscara F. Rehabilitation of executive skills post-childhood traumatic brain injury (TBI): a pilot intervention study. Dev Neurorehabil. 2009;12(5):361–9.
110. Catroppa C, Anderson V. Recovery and predictors of language skills two years following pediatric traumatic brain injury. Brain Langu. 2004;88(1):68–78.
111. Van't Hooft I, Andersson K, Bergman B, Sejersen T, von Wendt L, Bartfai A. Beneficial effect from a cognitive training programme on children with acquired brain injuries demonstrated in a controlled study. Brain Inj. 2005;19(7):511–8.
112. Van´t Hooft I, Andersson K, Sejersen T, Bartfai A, von Wendt L. Attention and memory training in children with acquired brain injuries. Acta Paediatr 2003;92(8):935–40.
113. Sohlberg MM, Mateer CA. Effectiveness of an attention-training program. J Clin Exp Neuropsychol. 1987;9(2):117–30.
114. Catroppa C, Stone S, Hearps SJC, Rosema S, Soo C, Anderson V. Evaluation of an attention and memory intervention post childhood acquired brain injury: Preliminary efficacy immediate and 6 months post-intervention. Brain Inj. 2005;29 (11):1317–24.
115. Anderson V, Beauchamp MH. Developmental social neuroscience and childhood brain insult: theory and practice: New York: Guilford Press; c2012.
116. Crowe L, Beauchamp M, Catroppa C, Anderson V. Social function assessment tools for children and adolescents: A systematic review from 1988 to 2010. Clin Psychol Rev. 2011;31(5):767–85.
117. Thompson EJ, Beauchamp M, Darling SJ, Hearps SJ, Brown A, Charalambous G, et al. Protocol for a prospective, school-based standardisation study of a digital social skills assessment tool for children: the Paediatric Evaluation of Emotions, Relationships, and Socialisation (PEERS) study. BMJ Open. 2018;8(2):e016633.
118. Barkley RA. The executive functions and self-regulation- an evolutionary neuropsychological perspective. Neuropsychol Rev. 2001;11(1):1–27.
119. Charman T, Baron-Cohen S, Swettengam J, Baird G, Cox A, Drew A. Testing joint attention, imitation, and play as infancy precursors to language and theory of mind. Cogn Develop. 2000;15:481–98.
120. Cirino PT. The interrelationships of mathematical precursors in kindergarten. J Exp Child Psychol. 2011;108(4):713–33.
121. Catroppa C, Godfrey C, Clasby B, Anderson V. Children with Traumatic Brain Injury. In B. A. Wilson, J. Winegardber, C. M. Van Heugten, & T. Ownsworth (Eds.), Neuropsychological rehabilitation. The International Handbook. London and New York: Routledge; 2017.
122. Goldstrohm S, Arffa S. Preschool children with mild to moderate traumatic brain injury: An exploration of immediate and post-acute morbidity. Arch Clin Neuropsychol. 2005;20:675–95.
123. Lalloo R, Sheiham A. Risk factors for childhood major and minor head and other injuries in a nationally representative sample. Injury. 2003;34:261–6.
124. Petridou E. Incidence and risk factors of fall injuries among infants. Arch Pediatr Adolesc Med. 2004;158:1002–6.
125. Spady D, Saunders D, Schopflocher D, Svenson L. Patterns of injury in children: a population-based approach. Pediatrics. 2004;113(3):522–9.
126. McKinlay A, Grace R, Horwood L, Fergusson D, Ridder E, MacFarlane M. Prevalence of traumatic brain injury among children, adolescents and young adults: Prospective evidence from a birth cohort. Brain Inj. 2008;22(2):175–81.
127. Kinsella G, Prior M, Sawyer M, Ong B, Murtagh D, Eisenmajer R, et al. Predictors and indicators of academic outcome in children 2 years following. J Int Neuropsychol Soc. 1997;3:608–16.
128. Max J, Koele SL, Smith WL, Sato Y, Lindgren SD, Robin DA, et al. Psychiatric disorders in children and adolescents after severe traumatic brain injury-

a controlled study. J Am Acad Child Adolesc Psychiatry. 1998;37(8):832–40.
129. Rivara JB, Jaffe KM, Fay GC, Polissar NL, Martin KM, Shurtleff HA, et al. Family functioning and injury severity as predictors of child functioning one year following traumatic brain injury. Arch Phys Med Rehabil. 1993;74:1047–55.
130. Taylor HG, Yeates K, Wade S, Drotar D, Klein S, Stancin T. Influences on first-year recovery from traumatic brain injury in children. Neuropsychology. 1999;13(1):76–89.
131. Yeates KO, Taylor HG, Drotar D, Wade SL, Klein S, Stancin T, et al. Preinjury family environment as a determinant of recovery from traumatic brain injuries in school-age children. J Int Neuropsychol Soc. 1997;3(6):617–30.
132. Braumind D. Current Patterns of Parental Authority. Developmental Psychology Monographs of the Society for Research in Child Development. 1971;4(1):1–103.
133. Bernier A, Carlson SM, Whipple N. From external regulation to self-regulation: early parenting precursors of young children's executive functioning. Child Dev. 2010;81(1):326–39.
134. Prinzie P, Stams GJ, Dekovic M, Reijntjes AH, Belsky J. The relations between parents' Big Five personality factors and parenting: a meta-analytic review. J Pers Soc Psychol. 2009;97(2):351–62.
135. Jordan J, Linden MA. 'It's like a problem that doesn't exist': the emotional well-being of mothers caring for a child with brain injury. Brain Inj. 2013;27(9):1063–72.
136. Prigatano GP, Gray JA. Parental concerns and distress after paediatric traumatic brain injury: a qualitative study. Brain Inj. 2007;21(7):721–9. https://doi.org/10.1080/02699050701481605.
137. Anderson V, Godfrey C, Rosenfeld JV, Catroppa C. Predictors of cognitive function and recovery 10 years after traumatic brain injury in young children. Pediatrics. 2012;129(2):e254–61.
138. Murray AL, Scratch SE, Thompson DK, Inder TE, Doyle LW, Anderson JF, et al. Neonatal brain pathology predicts adverse attention and processing speed outcomes in very preterm and/or very low birth weight children. Neuropsychology. 2014;28(4):552–62.

Chapter 4

Neuropsychological Problems in Neuro-Oncology

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Introduction and History

Neuropsychological studies in the field of Oncology are related to neuro-oncology: (1) brain tumors – which arise from neurons and other brain tissues, cranial nerves, leptomeninges, neuroendocrine glands, skull, and blood vessels, and (2) treatment effects. The neurocognitive effects of brain tumors themselves are variable, and require close examination of the cognitive underpinnings of composite test scores. Other cases present fascinating classical syndromes when tumors occur in eloquent brain loci. After providing basic biomedical background on tumors in children and adults, the questions of tumor site and metastatic spread as well as treatment effects on brain and cognitive and emotional function will be examined in this chapter. Information will also be presented on the techniques for diagnosing and treating tumors, and on issues to be considered in doing research in neuro-oncology. Finally, this chapter will discuss how disorders and syndromes that result from brain tumors and their treatments differ from more classical or traditionally understood forms of the disorders.

References to the behavioral effects of brain masses are found in the early common era (e.g., references in the Talmud), with descriptions of severe pain. Documented descriptions of the behavioral effects of masses in the brain are traced to the 16th and 17th centuries, when complaints of pain, drowsiness, and general distress were associated with masses [1]. More direct associations of psychiatric behaviors with brain masses had to wait until the 1800s, when late in that century a movement emerged that integrated neurology and psychiatry. "Psychical" disturbances were thought to be a result of a cerebral tumor if the primary and secondary effects of the tumors were global (such as affecting multiple areas of the meninges or bihemispheric disease [1]). This awareness of neurobehavioral abnormalities associated with brain regions coincides with the localizationist movement of the late 1800s represented by pioneers such as Paul Broca and Hughlings Jackson. Finally, surgical resection of tumors begins in this era, with beneficial effects on behavior, though the problems of postsurgical infection were yet to be worked out. The observations of behavioral disturbance seem to have needed a great deterioration to be noticed, as patients were described as developing "imbecility" and "dementia" [1]. Thus, the problem

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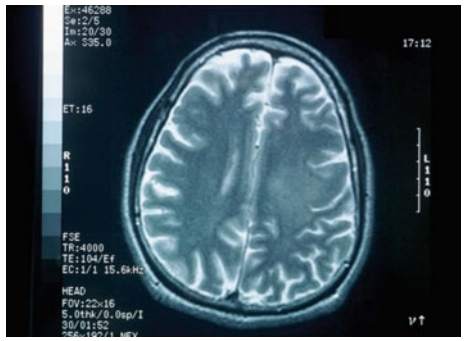

Fig. 4.1 Large, white, cloudy area of left frontoparietal region is a presumed low-grade glioma, which cannot be biopsied or resected; before radiation therapy

of identifying the behavioral effects earlier in the course of the tumor development, allowed by modern diagnostic and treatment techniques, is a contemporary issue.

Brain tumors and cancers that metastasize to the brain allow cancerous cells to pervade normal tissue, and to exist in areas where healthy neural tissue can still function. Furthermore, brain tumors are not fully visualized on brain scans (see Fig. 4.1 for example of the diffusiveness of some tumors), and both the actual extent of the neoplasm and the dissemination of the tumor cells through cerebrospinal fluid may not be fully known. These characteristics raise questions about the mechanisms by which brain tumors cause neurocognitive damage. The evidence for the mechanisms for damaging treatment effects on cognition continues to grow. The problem of iatrogenic treatment effects broadens the questions for neuropsychology to include how surgery, chemotherapy, and radiotherapy affect the brain. A model is emerging that is constructed by injury to epithelial, glial, and neuronal cells, their effects on brain tissue, and resulting inflammatory processes in the brain.

Frequency of CNS Tumors

Overall rates of brain and other CNS tumors in the United States, based on the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) 2002–2006 data (www.seer.cancer.gov/statfacts/html/brain.html), are 7.6 per 100,000 in men, and 5.4 per 100,000 in women. In most ethnic groups, the ratio of males to females is about 1.4, according to the SEER data. Although only about 20% of all brain and nervous system tumors are diagnosed under the age of 20 years, brain tumors are the second most common malignancy of childhood and account for 20% of all childhood cancers [2].

Race is a significant factor in the incidence of brain and CNS cancers, in that a greater risk is incurred by European-Americans (E-A, "White" excluding Latino). In fact, SEER data show that rates of these types of cancer have increased in E-A males and females between 1975 and 2006, while rates have stayed the same or declined in African-Americans (Af-A, "Black"); rates for the Latino ("Hispanic") grouping generally fall between that of E-A and Af-A. Race does not seem to influence survival rates in patients with malignant gliomas, in part because of the limited benefit of therapy for this disease [3]. SEER data from 1999 to 2005 show that the survival rates for 5-years (the conventional metric for "cure" in the field of oncology) were 32.4% for E-A men, 36.1% for E-A women, 33.9% for Af-A men, and 43.7% for Af-A women. The five-year survival rate for children is considerably higher – nearly 60% [2]. Children and adults have different distributions of tumor subtypes and different 5-year mortality rates for a given type.

Biological Processes of Brain Neoplasms

The Genesis of Brain Tumors

Brain tumors are solid neoplastic masses of genetically disregulated cells that divide at elevated rates, have lost their differentiated cellular functions, and rapidly transform surrounding cells and tissues. The tumorigenic process involves multiple steps during which the normal controls of cell proliferation and cell-to-cell interactions are inactivated or lost, and the normal cell is transformed into a tumor cell [4]. Normally, tumor-suppressor

genes (e.g., chromosome 22, TP53, Rb) act to inhibit cell proliferation and growth, so that cells have a normal lifespan. However, oncogenes are abnormally activated versions of normal cellular genes that promote cellular proliferation and growth, so that a cell has a pathologically exaggerated tendency to grow and divide. Tumor suppressors and oncogenes are not just pathological; they also act as fundamental regulators of cell growth and differentiation during normal development [5]. There are regulators that cause programmed cell death or apoptosis that may also be altered in malignancy. There are also DNA repair genes that may be altered by disease (e.g., NF1) or age, that may lead to tumor formation. Additionally, on a genetic level there are probable interactions of growth regulators, which also affect development, progression, and/or resistance of tumors. These areas of molecular biologic studies of tumors are rapidly developing.

Other cancerous and noncancerous diseases associated with brain tumors

(a) *Gliomatosis cerebri*. Gliomatosis cerebri is a rare neoplasm characterized by individual neoplastic cells that diffusely permeate the brain, rather than form a primary solid tumor mass. Although in theory not malignant, it behaves malignantly and presently remains a fatal disease. As with many glial tumors, which originate in the white matter, there is little involvement of the cerebral cortex and subcortical gray matter. Cognitive findings are those associated with extensive white matter involvement [6]. Impairments can present as higher cognitive dysfunction, such as executive dysfunction and memory impairment, as psychiatric features, and as sensorimotor impairments, depending on the location of the burden of lesion, but it can also progress to a frank dementia. Most patients over time experience severe progressive neurocognitive loss both by site of disease but also due to progressive seizures.

(b) *Metastases from other cancers*. The most common sites for metastatic disease are brain, lungs, bone, and liver. The cancers that most often disseminate to the brain via blood or CSF are, in order of decreasing frequency, aggressive cancers of the lung, especially small-cell lung cancer, breast cancer, melanoma, renal cancer, and colon cancer. Certain subtypes of lymphomas and leukemias receive prophylactic therapy because of their risk to disseminate to the brain. There are also less common primary meningeal leukemias and primary CNS lymphomas. In childhood, cancers that may metastasize to the brain include soft tissue (rhabdomyosarcoma, Ewing's sarcoma) and bone sarcomas (osteogenic sarcoma). The improved prognosis for cancer and longer life span of cancer patients is leading to a higher incidence of brain metastases, which are the most common brain tumor in adults, but not in pediatrics [7, 8].

(c) *Neurofibromatosis*. Neurofibromatosis occurs both as an autosomal dominant trait disorder and as a spontaneous mutation. NF1 has a higher incidence in children than in adults, and about half are from spontaneous mutations (Friedman 1999). The higher incident neurofibromatosis 1 (NF1: 1 in every 3,000 to 4,000 births) (Friedman, J. M., Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999, 89(1), 1–6), also called von Recklinghausen disease, and much less common neurofibromatosis 2 (NF2: 1 in every 50,000 births), are both associated with heightened risk of brain tumors [9, 10]. NF1 is commonly associated with optic gliomas and gliomas in other brain sites, spongiform dysplasia in typical cortical, subcortical, and cerebellar sites, as well as peripheral nerve sheath tumors (neurofibromas). NF1 is associated with chromosome 17, and thought to involve 17q11.2. NF2, on the other hand, is associated with meningiomas and schwannomas of the cranial nerves and spinal cord, and acoustic neuromas in particular, often bilateral. Furthermore, NF2 has been linked to chromosome 22. NF2 is a progressive, ultimately fatal disease.

There are few studies of the neuropsychological impairments in adults with NF1 except

that neurocognitive deficits vary widely [11], and affect reasoning, visuoconstructive skill, visual and tactual memory, logical abstraction, coordination, and mental flexibility. Rates of learning disability in NF1 have been estimated between 30 and 65% [12, 13], while estimates of an attention-deficit disorder have been 39–49% of the children with NF1 [14, 15]. However, children with NF1 without apparent learning disabilities have higher rates of neuropsychological impairments [16]. A longitudinal study of 32 children with NF1 and 11 of their unaffected siblings was conducted, with the second neuropsychological evaluation and MRIs occurring after an eight year interval [17]. No improvement in cognition was observed as children matured into adults, even though the number, size, and intensity of T2-hyperintensities on MRI decreased over the interval. T2 hyperintensities in childhood were a better predictor of the cognitive dysfunction in adulthood, than were current adult hyperintensities. In a larger group of 81 children with NF1 and 42 unaffected siblings, the cognitive functions most sensitive to NF1 were in sustaining and switching attention (but not in selective or divided attention), in spatial relations, and in planning and reasoning [18]. There is great debate about the extent and nature of memory impairment in this disease. Individual patterns can be expected to be related to the location of tumors and spongiform dysplasia within the brain. The extent of impairment related to tumor versus spongiform dysplasia is not known.

(d) *Paraneoplastic syndromes*. Paraneoplastic processes involve antineuronal antibody immune responses [19]. The pathogenic role of the antineuronal antibodies is not clear, but the antibodies are studied as markers of paraneoplastic syndromes and tumors. As such, paraneoplastic processes can occur as immunological responses to neurons in the presence of oncogenes that are rapidly dividing, and cause neurological syndromes in patients with tumors of the brain and other cancers. Some paraneoplastic syndromes result from tumor secretion of antibodies, hormones, and cytokines, or neurologic dysfunction may result from tumor competition with the nervous system for essential substrates; other paraneoplastic syndromes may result from T-cell mediated mechanisms [19]. Neuronal antibody markers have been associated with limbic encephalitis, brainstem encephalitis, cerebellar ataxia, chorea, and peripheral neuropathy, among other disorders [20].

(e) *Tuberous sclerosis*. Tuberous sclerosis is a rare genetic disease that causes benign brain tumors to grow on the cerebral cortical surface and on the walls of the ventricles. However, the genetic disorder also results in other major disorders such as seizures, skin growths, autism, behavioral problems, and mental retardation. Standard treatment is limited to symptom management, including antiepileptic medications. Some patients have mild symptoms and can lead a full life. There is also an increased incidence of malignant tumors, especially sarcoma and brain tumors, and of the rare tumor, chordoma. There have been recent reports of effective treatment of the astrocytomas of tuberous sclerosis with Rapamycin [21]. A possible action of the hamartin-tuberin complex of tuberous sclerosis is to inhibit cellular signaling through the mammalian target of Rapamycin (mTOR) [22].

(f) *Radiotherapy-induced brain tumors*. Radiotherapy itself, used to control brain tumors, has a risk of causing brain tumors decades after treatment, depending mainly on dose and age at exposure; risk for other cancers are even higher [23]. Some studies have examined the effects of ionizing radiation treatments encompassing the brain for nonneoplastic disease, such as treatment for tinea capitis, a skin disorder, and for interventional radiotherapy. A review of 52 studies of radiotherapy for primary brain tumors reported that radiation-induced malignant gliomas (glioblastoma and anaplastic astrocytoma) occurred within 10 years after radiotherapy in 81% of patients who were treated prophylactically for acute lymphoblastic

leukemia/lymphoma, and in 59% of patients who were originally treated for primary brain tumors [24]. A study of lifetime risk of brain tumors in 49 pediatric patients undergoing intracranial embolization found that the lifetime risk of a brain tumor was increased over baseline population rates by 3–40% depending on dose, age at exposure, and gender [25]. Studies report greater risk with younger age (e.g., [26]).

Radiation-induced tumors are not uniquely or specifically identifiable, and their study has focused on similar pathways and malignant conversion that characterize tumor development [27]. Complex forms of DNA double-strand breaks are the most significant type of lesion caused by ionizing radiation. DNA repair kinetics, which is stimulated by radiation, is error prone and thought to lead to mutations and chromosome damage. The most common mutations are deletions, rather than base-pair changes in genes. Tumor-suppressor gene inactivation is expected to occur through such deletions. Oncogene activation is thought to occur through forms of induced chromosome translocation, another potential mechanism. Inherited genetic susceptibility (e.g., NF1) is another factor thought to be related to radiation-induced cancers. The "young age" effect of cancer development after irradiation (i.e., greater risk) is thought to be more consistent with tumorigenesis – i.e., tumor initiation – rather than with acceleration of preexisting neoplasms [27].

Diagnosis of Brain Neoplasms

Risks for Developing a Brain Tumor

In many cases, a brain tumor is found incidentally after an individual falls or has an accident, though the role of the quiescent tumor in the individual's behavior before diagnosis cannot be fully understood because the onset of the tumor cannot be estimated for most tumor types. Risk factors for developing a tumor are not fully known, but risks include serious head injury decades before the tumor is diagnosed (meningioma), prior radiation exposure decades before (including radiotherapy for a brain tumor or skin disease, occupational hazards, and diagnostic X-rays), immune suppression leading to lymphomas, and genetic disorders [28, 29]. Also suspected are environmental carcinogens and viruses.

Brain Tumor Classification and Histologic Groupings

Tumors are defined by the cells from which they were generated in their uncontrolled genetic forms. Diffuse, fibrillary astrocytomas are the most common type of primary brain tumor in adults [4]. Low-grade astrocytomas are the most common benign tumor in children, and medulloblastoma is the most common malignant tumor in children [2]. The World Health Organization (WHO) classifies tumors of the CNS; the most recent classification of 2007 [30] shows the following tumor groups with their potential malignancy classification[1] given for histologic examples:

- *Astrocytic tumors*: ranging from 1:pilocytic astrocytoma, to 3: fibrillary astrocytoma, glioblastoma, and gliomatosis cerebri
- *Oligodendrogliomas*: 3
- *Oligoastrocytic tumors*: 3
- *Ependymal tumors*: ranging from 1: subependymoma, to 3: anaplastic ependymoma
- *Choroid plexus tumors*: ranging from 0: choroid plexus papilloma to 3: choroid plexus carcinoma
- *Other neuroepithelial tumors*: ranging from 1: chordoid glioma of the third ventricle, to 3: astroblastoma
- *Perineurioma*: 0: perineurioma, NOS, and 3: malignant perineurioma.

[1]The grading system used in the 2007 classification uses the numbers following the tumor group to indicate whether they are malignant (3), borderline or uncertain (1), or benign (0).

- *Malignant peripheral nerve sheath tumor*: 3
- *Tumors of meningothelial cells*: ranging from 0: fibrous meningioma, to 1: atypical meningioma, to 3: rhabdoid meningioma
- *Mesenchymal tumors*: ranging from 0: hemangiomas, to 3: rhabdomyosarcoma, and other sarcomas
- *Neuronal and mixed neuronal-glial tumors*: ranging from 0: dysembryoplastic neuroepithelial tumor, to 1: ganglioglioma, and 3: anaplastic ganglioglioma
- *Tumors of the pineal region*: ranging from 1: pineocytoma, to 3: pineoblastoma
- *Embryonal tumors* (found mainly but not exclusively in children): 3, including medulloblastoma, CNS primitive neuroectodermal tumors (PNET), atypical teratoid/rhabdoid tumors
- *Tumors of cranial and paraspinal nerves*: ranging from 0: schwannomas and plexiform neurofibromas, 1: hemangiopericytoma, and 3: Kaposi and Ewing sarcomas
- *Primary melanocytic lesions*: ranging from 0: diffuse melanocytosis, to 1: melanocytoma, and 3: malignant melanoma
- *Other neoplasms related to the meninges*: 1: hemangioblastoma
- *Lymphomas and hematopoietic neoplasms*: 3, including plasmacytoma and malignant lymphomas
- *Germ cell tumors* (found mainly in children): ranging from 0: mature teratoma, to 1: teratoma, to 3: germinoma and mixed germ cell tumor
- *Tumors of the sellar region*: ranging from 0: granular cell tumor, to 1: craniopharyngioma
- *Metastatic tumors*: hematogenously seeded tumors that occur at the gray-white junction.

Tumor Grading

The current method for tumor grading is a four-level system derived by the American Joint Commission on Cancer, and previously was based on a three-level system by the WHO. The system of grading generally determines the degree of malignancy of a tumor, and classifies cells in terms of abnormal characteristics, which informs the prognosis and treatment options. The specific characteristics differ in reference to different tumor types. In general, brain tumor types are graded by how abnormal the cancer cells and milieu appears, and by direct observation of mitoses or genetic markers of such, which indicate how likely the tumor will grow or disseminate.

The tumor grading shown below is used for the most common tumors – gliomas – and comes from the American Joint Commission on Cancer. A general classification of brain tumors is (1) well differentiated and low grade; (2) moderately differentiated and intermediate; (3) poorly differentiated and high grade; (4) undifferentiated and high grade. Some of the histologic abnormalities that are considered in tumor grading include the degree of pleomorphism (change in the structure of a neural cell), nuclear atypia (abnormalities within the nuclei of brain cells), endothelial proliferation (blood vessels with multiple endothelial layers and disorganized vessel walls), mitotic rates, and focal or superpalisading necrosis (a palisading pattern of necrosis in the tissue around the abnormal cancer cells). There are a variety of molecular staining techniques that are used that also indicate the rate of proliferation and potential for malignancy, such as the Ki-67 protein antigen. The tumor grading criteria are specific for different tumor types. For example, gliomas are classified as [31]:

(1) low grade/I: tumor cells remain well differentiated and without other signs of abnormality in cell nuclei or tissue structure. The tumor cells grow slowly, rarely grow into surrounding tissue, and may be gross totally resected.
(2) low grade/II: considered moderately differentiated but still benign. Grade II tumors have a greater chance of de-differentiation and transformation into a more malignant tumor, and may have spread into surrounding tissue.

(3) anaplastic/III: the tumor cells are poorly differentiated, the tumor has likely spread into surrounding tissue, and the tumor is malignant.
(4) high grade, undifferentiated, and highly malignant and aggressive/IV (for example, glioblastoma is grade IV).

Neuropsychological Mechanisms

The cognitive effects of brain tumors of similar histology and location are known to be highly variable. There is evidence that functional brain tissue remains intermingled with tumor tissue, and this conveys with it unpredictability in knowing the nature of neurocognitive impairment caused by a tumor in a specific location in any one individual. Although tumor histology itself does not appear to influence the severity or type of cognitive impairment [32] (aside from the location of the tumor), one can state in a qualified way that tumor grade is associated with the severity of neuropsychological deficit. High-grade tumors can cause more impairment to the extent that they grow more aggressively and quickly, are larger, may invade the contralateral hemisphere, and thus are more disruptive of neural connections. Even smaller, less invasive low-grade tumors disrupt neural connectivity [33]. The cognitive dysfunction associated with brain tumors, while most often observed as problems of working memory, memory encoding and retrieval, attentional dysregulation, and slowed information processing, can also cause syndromes including aphasia, dyspraxia, amnesia, and executive dysfunction when individuals are examined.

Effects of Tumors on Cognitive Function

The theory of how brain tumors cause functional damage has traditionally been based on the observation that brain tumors are associated with less functional damage than other more rapidly acquired brain injuries such as head injuries and stroke. The actual effects of a tumor and its related necrotic tissue on an individual are not revealed by group studies of effects of neoplastic lesions on cognitive function because the pre-tumor scores are rarely known, but case studies show that the change in function can be major [34]. Tumors can masquerade as dementia [35], and as psychiatric syndromes. Brain tumors damage normal tissue by compression and infiltration; related biomechanical causes are herniation, edema, obstruction of interventricular CSF with resulting hydrocephalus, and seizure genesis. Surgical techniques attempt to limit the resection within the confines of the tumor lesion, sparing normal-appearing cortex and subcortical white matter. Preoperative PET scans, and intraoperative CT and mapping are also used to discriminate functional from necrotic tissue. A neurosurgery study analyzed the intraoperative functional maps of language, movement, or sensation (frontal, frontotemporal, temporal, frontoparietal, and insular tumor sites) for 28 patients with gliomas, and found more than one type of functional tissue within the tumor center in 25% of the patients, and some functional tissue in all the 28 patients [36]. Whether the relatively slow growth of brain tumors permits a neuroplasticity response in the brain, or whether the tumor mass effect and vasogenic edema results in less injury than in acutely acquired tumors, tumors seem to result in less injury than expected based solely on their dramatic presentation on brain scan images. A rapidly acquired brain injury also involves secondary mechanisms of neural injury and death, such as flooding of glutamate, causing neural toxicity, that have not yet been associated with brain tumors.

The relative cognitive damage caused by brain tumors and strokes was investigated by Anderson et al. [37] in a systematic comparison of partially demographically matched adult patients with single, unilateral brain tumors (glioma or meningioma) or strokes. Lesions were anatomically matched between the two groups on multiple slices using CT or MRI, and cognitive outcomes that were nearly concurrent with scans were examined. Tumor patients had received no

interventions, and stroke patients were studied at least four weeks after the event. Case by case matching was done to equate location and size of the lesion, and a tumor lesion was required to be as large as, or larger than, a stroke lesion, as seen on scans. The outcomes of this study emphasize the unpredictable nature of tumor effects on cognition as well as sensorimotor function. For example, lesions involving Wernicke's area reliably caused some language impairment in all of the stroke patients, but none of the tumor patients had paraphasic speech or made repetition errors. The tumor patients had more difficulty in linguistic comprehension using a Token Test procedure, but less so than did the stroke patients. The effects of right hemisphere lesions on visuospatial functions also were more difficult to detect in tumor patients but were quite obvious in stroke patients.

Tumors can infiltrate but not destroy tissue (until tumors become massive or bilateral), allowing some neural function, and standard MRI scans do not reveal the degree of necrosis and hypoxia within the tumor that marks the more malignant and treatment-resistant lesion. Injury is manifestly from tumor mass effects and vasogenic edema, or the related problems of hydrocephalus, ischemia, encephalomalacia, and seizures. PET and perfusion scanning techniques are measure tumor hypoxia, and diffusion tensor imaging and tractography can reveal loss or displacement of white matter fiber tracts caused by tumors (Fig. 4.2).

Do Tumors Cause Regional Cognitive Effects?

Studies [37, 38] have been consistent only in broad generalizations about structure-function; verbal functions are associated with left hemisphere tumor lesions, and visuospatial functions with right hemisphere lesions. Individual patients may not conform if the tested function, such as facial recognition, requires a dedicated brain region that was not involved in the tumor or surgical lesion. This pattern of hemispheric specialization holds not only for cortical tumors, but to a degree for cerebellar tumors as well [39]; that is, right cerebellar tumors result in greater linguistic and sequential processing dysfunction, and left hemisphere tumors effect greater visuospatial impairment.

Assumptions about left/right hemisphere dissociations in neuropsychological test outcomes have been challenged in studies using functional imaging, or in more controlled lesion studies. The presumed construct involved in a neuropsychological test may be too narrowly defined, and greater complexity of cognitive process leading to a complex behavior often reveals the association of multiple brain regions to accomplish the task. Our neuropsychology laboratory at the Children's Hospital of Philadelphia conducted a series of studies to investigate the regional associations of well-known neuropsychological tests and constructs in brain tumor patients, prior to

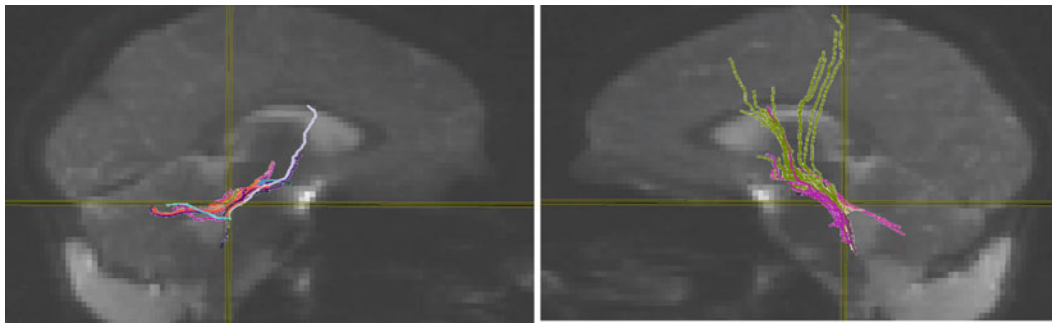

Fig. 4.2 Fiber tracking in a child with a resected cerebellar tumor and history of radiotherapy. Fiber tracks on the left are ipsilateral to tumor, and contralateral to tumor on the right (from Timothy Roberts, Ph.D., Children's Hospital of Philadelphia)

chemotherapy and radiotherapy. One study examined the assumption that verbal fluency impairments would be associated with brain tumors of the left hemisphere more than the right, and specifically of the left anterior brain region [40]. Both phonemic ("FAS") and semantic fluency (animal naming) tests were given to 51 young and middle age adults with single, well-circumscribed, low-grade brain tumors, and to 57 age and education matched normal control subjects, comparing anterior to posterior regions, and left to right hemisphere locus of injury in the patients. No significant effect of anterior lesion locus was found for either fluency task, although patients' scores were lower than the controls, and were lowest in the anterior regions. Both left and right hemisphere patients produced fewer phonemic fluency responses than the control group, but there was no significant difference between left and right frontal groups. Semantic fluency was significantly inferior in the left hemisphere group. These findings are consistent with functional imaging and lesion studies that show that multiple brain regions are involved in verbal fluency [41, 42].

The lack of inferior scores in a bilateral anterior brain tumor group challenged the regional specificity assumption in the Wisconsin Card Sorting Test (categories achieved and perseverative errors) as well, especially as patients performed just as well as the normal control group [43]. However, a left frontal effect was found due to fewer categories and more perseverative errors; the right frontal and nonfrontal groups performed as well or better than the controls.

Memory and attention tests also reveal partially atypical findings. Hemispheric effects were not found in word versus picture recognition [44]; patients with tumors in the left hemisphere were just as accurate as right hemisphere patients in recognizing words they had just seen, although there was a trend towards slower reaction time to recognize words in the left hemisphere tumor group. Accuracy was similar between the groups in picture recognition (familiar objects from the Snodgrass and Vanderwart picture set [45]), and again the left hemisphere group was slower in recognition time. Although it was possible that the higher proportion of temporal lobe involved tumor sites in the left hemisphere group (50% vs. 25% in the right hemisphere group) could have caused the slower reaction time, there was no effect on accuracy, which is not expected because reaction time and accuracy are positively correlated in recognition memory. It is possible that the low-grade tumor patients were able to compensate for their struggle to recall the seen items by taking longer to retrieve. If so, this provides a good example of the subtle effects of brain tumors on brain functions.

Hypothesizing that the frontal lobes are more critical to all types of attentional processing, and that the parietal lobes are intricately involved in spatial attention, Goldstein and colleagues examined regional effects in tests of attention in 58 adult patients with cortical (gliomas and cortical surface meningiomas) versus deep (pineal, pituitary, and meningiomas in the falx and cavernous sinus) low-grade brain tumors [46]. Principal components factor analysis found three partially independent factors comprising the attention tests, consistent with Parasuraman's domains of attention – Selection, Vigilance, and Control – based on a combination of visual and auditory, selective, sustained, switching of orientation, and divided attention tests: the Auditory Selective Attention Test, Bells Test (visual selective attention), Symbol Digit Modality Test-oral, Visual Pursuits, Wisconsin Card Sorting Test, Digit Span Test, Visual Memory Span Test, and the Paced Auditory Serial Addition Test. The authors considered that the lack of association with brain regions was due to the distributed nature of attention, which tends to lack modularity. However, the deep tumor patients tended to have the lowest scores among the left and right hemisphere and normal control groups. Although left hemisphere patients scored lower on speeded tests and digit span, and right hemisphere patients scored lower on visual memory span, few significant group differences were found.

Conclusions: Our studies all focused on patients without the confounding effects of radiation therapy and chemotherapy, to which

cognitive impairments from brain tumors have often been attributed. The series helps to identify the cognitive effects of invasive tumors that do not respect vascular distribution, sulcal boundaries, or even cortical and subcortical divisions. Measures of reaction time in neurocognitive tests are often more sensitive to the effects of brain tumors, than accuracy rates. Tests of resource-limited cognitive functions are more sensitive to tumor disruptions of neural networks. Statistically significant effects are not always found in brain tumor studies, and regional patterns tend to be more qualitative, reflecting variability among the subjects presumably because tumor effects on cognition are less severe.

Regional Effects in Individuals

The slow growth of many tumors, which moderates the interference with cognitive dysfunction, may also be followed by reduced cognitive recovery. Longitudinal clinical evaluations reveal stability at best, or a slow decline in specific cognitive functions over time. In patients with nonprogressive tumors, generalized decline in cognition is rare under current treatment regimens, and when a general decline occurs in an individual, it is cause for concern. In contrast, the relative stability of cognitive function in the presence of a stable tumor can be dramatically disturbed following resection. Patients often report significant change in cognitive function and behavior after resection; longitudinal studies show significant improvement for 1–2 years after resection, that putatively involves morphologic adjustment and neural plasticity. In some cases, surgical resection can result in subjective improvement in function. For example, a teenage boy was quiet, withdrawn, and sullen until his left frontal tumor was resected, after which he became communicative and subjectively felt much happier.

Individualized Approach to Neuropsychological Evaluation, and Case Examples

The diffuse nature of even solid mass tumors requires a more individualized approach to interpretation of neurocognitive evaluation, as typical syndromes and agnosias may not be seen. However, consistent neuropsychological batteries should be used with greater emphasis on component neuropsychological functions, rather than composite measures, such as for IQ or general memory indices. Disconnection syndromes can be quite evident when multiple lesions exist in critical locations. Extensive tumors can, in some individuals, have remarkably little manifest damage, in part due to the sparing of critical regions or lack of disconnection of strategic white matter tracts. However, a relatively small tumor in an eloquent brain region can cause a striking and unique impairment, even in the context of otherwise unimpaired cognition, and can be quite instructive in understanding brain organization. Diagnosis of neurocognitive impairment in patients with brain tumors focuses on the consistencies and inconsistencies with the examiner's expectation of the function associated with the tumor region, and is a useful teaching technique in understanding systems of brain associated with cognition.

Case 1: A seven-year-old, right-hand dominant boy presented with an anaplastic astrocytoma in the right medial inferior occipital lobe and the posterior aspect of the right medial temporal lobe, which fully integrated the right fusiform gyrus that is associated with facial processing. In this case, the child was consistently and almost exclusively impaired in all tasks involving facial processing, including attention (impaired in detecting faces in a cancelation task, but not other objects), in memory only for faces, and in facial perception and discrimination (Benton's Facial Recognition Test).

Case 2: A left posterior temporal lobe tumor in a 12-year-old, right-hand dominant boy was in a region of the middle temporal gyrus associated with semantic fluency and syntactic processing. Characteristics of a transcortical sensory aphasia were observed, including symptoms of impaired comprehension (especially for syntactic complexity), intact repetition, and difficulties in naming. Also present were impairments in encoding of grammatical phrases, sequencing letters and linking word forms, speeded naming of grammatical forms, and spelling. He was observed to stutter only at the beginning of words and stuttering was suppressed by repetition, which was a symptom of semantic dysfluency rather than stuttering per se.

Case 3: A 12-year-old, right-hand dominant individual with a left lateral temporal lobe tumor, gross total resection, and associated seizures, showed impairments only in tasks that involved rapid sequential processing of information: auditory selective attention, following grammatical/syntactic sentence strings (Token Test), speeded naming of visual objects, and visual tracking/matching tasks (Trail Making Test and Symbol Digit Modalities Test-oral).

Case 4: Patients with thalamic tumors have selective difficulty with multi-tasking and other aspects of attention. For example, a 57-year-old patient with a biopsied low-grade, right thalamic tumor was impaired only in tests requiring auditory attention, finger motor speed, and in visuospatial perceptual organization (complex figure). One year later, this patient was stable with no tumor recurrence, and neuropsychological impairments were unchanged except for a decline in visual attention. Cerebellar tumor patients can also present attention as their most severe impairment, possibly due to injury to the ascending cerebellar-thalamo-cortical tracts.

Cases 5 and 6: One six-year-old, partially left-hand dominant patient had a low-grade, medial left temporal tumor and minimal distortion of the hippocampus. This tumor caused less memory impairment than might be expected, yet also demonstrated that memory association, encoding, and retrieval is not solely dependent on the hippocampal memory system. Memory processes of encoding and retrieval have multiple neural substrates (prefrontal and ventromedial frontal), which helped to compensate for the injury to hippocampus. Other temporal lobe tumors can cause severe memory deficits, but rarely cause amnesia. One 50-year-old, right-hand dominant man with a left anterior temporal lobe tumor extending into the insula was impaired in memory before surgery, and became amnestic after surgical resection of his tumor.

Case 7: Frontal lobe tumors will almost invariably cause memory impairment in the encoding and/or retrieval and recognition of material requiring association, as predicted by Tulving's Hemispheric Encoding/Retrieval Asymmetry theory [47]. For example, a 28-year-old, right-hand dominant patient with a right frontal low-grade glioma with gross total resection but no other treatment, manifested verbal and visual associative memory impairment (but not simple working memory impairment), discriminative recognition memory impairment, impaired phonological and semantic verbal fluency, decline in reversal operations, and relative left-hand motor slowing though still mid average; no frank attentional impairments emerged.

The cases of low-grade tumors also raise the issue of whether tumors of different histologic types can cause cognition dysfunction differently if the subsumed neural tracts and interneuron populations are differently affected by the biomarkers of low-grade versus high-grade tumor proliferation. Scheibel and colleagues examined the traditional view that tumors of greater malignancy, or higher grade, caused greater cognitive impairment. They found that after the tumor was resected, there was no basis for a malignancy effect in a large group of screened adults with unilateral intracerebral gliomas who were given a broad neuropsychological battery. Glioblastomas comprised one group (grade IV), and all other tumors, that would have included malignant grade III tumors, were in the other group that was therefore comprised of a mixed low-grade and high-grade (anaplastic) group. The lack of greater

impairment in the glioblastomas was thought to have been reduced or eliminated when the mass volume was reduced through neurosurgery.

Sensitivity of Neuropsychological Evaluation

The more individualized approach can be quite sensitive, as demonstrated by studies that compared the sensitivity of neuropsychological tests versus MRI to detect tumor recurrence. Studies by Christina Meyers and colleagues demonstrated which tests from a broad cognitive battery were most sensitive to tumor recurrence in 80 malignant glioma patients. Testing patients monthly, they reported that the most predictive measures of tumor recurrence were two indices of verbal memory (recall and recognition of a word list), which positively correlated with longer survival [48]. The glioblastoma patients, who had the largest and most aggressive tumors, had a statistical tendency to achieve poor maintenance of cognitive set, exhibited by their performance on the Trail Making Test. Formal measures of daily performance and quality of life were unrelated to survival. This group also reported that neuropsychological scores declined as much as six weeks before MRI demonstrated tumor growth.

This method, a sensitive brief battery, was compared with a patient-specific method to predict the growth or recurrence of low-grade brain tumors in a study to identify a method for earlier tumor detection and control [49]. Results showed that a patient-specific model was superior to a brief but generally sensitive model in predicting tumor growth prior to clinically scheduled MRI scans. To test the feasibility of these prediction models, 34 patients with supratentorial, low-grade brain tumors were prospectively administered a series of comprehensive neuropsychological exams. Eleven patients had recurring tumors during the series. The general model based on tests that Meyers identified as sensitive to malignancy and white matter disease was compared with a tumor-specific model based on indices related to each patient's tumor locus. A proportional hazards model identified that only the tumor-specific predictor variables significantly changed immediately prior to recurrence ($p < 0.02$). The tumor-specific index decline of one standard deviation was a fivefold increase in the probability of tumor recurrence over the brief sensitive battery. Although this method needs to be tested with more frequent and regular observations and with a larger sample, the results suggest that a subject-specific model can predict recurrence, and may be more sensitive than general testing batteries. This technique is suitable to a disorder that is associated with highly variable cognitive impairments because it increases the specificity to the disease mechanisms.

Effects of Neurosurgery on Cognitive Function

Tumor effects on sensation (e.g., visual fields), motor function, and cognition can be exacerbated following surgical resection, and new impairments can emerge. Patients with surgical resection of tumors often have sudden onset disruptions in speech, motor function, cognition, and affect immediately after resection, even without surgical complications. Sometimes resection causes an improvement in cognition, personality, or mood, depending on tumor location, putatively related to alleviation of mass effects. In a systematic study of functional change after brain tumor resection, 73% of the patients had an immediate decline in neurological functioning, which remitted to 23% after three months of recovery [36]. Our longitudinal research at the University of Pennsylvania Department of Neurology and Children's Hospital of Philadelphia has shown that cognitive function takes at least two years for recovery, based on a continuous slope of improvement over that time period [50]. This was seen both in improvement in sensitive tests, and in the mean intrasubject variation of test scores, which was highest after surgery and plateaued at a lower level a few years later (unrelated to radiotherapy).

Syndromal Neuropsychiatric Disturbances and Treatments Associated with Brain Tumors

Neurobehavioral abnormalities caused by brain tumors are not limited to depression, which is the most studied disorder, but also include anxiety, and a number of psychiatric syndromes. Many pose problems for treatment.

Depression and fatigue: Depression is at least twice as prevalent in cancer patients than in all other medical inpatients combined [51]. However, adult and pediatric patients who have newly diagnosed brain tumors report relatively low levels of depression that are not consistent with these estimates in general oncology populations [52–54]. Aside from the role of premorbid risk for baseline depression, this finding has been attributed to psychological defenses such as repression and denial. However, brain tumors may produce less stress than other cancers because the treatment period for brain tumors is shorter than for other common cancers such as leukemia and lymphoma. Three studies reported a longitudinal view, and their converging results suggest that depression levels are lowest at the time of the emergence of tumor symptoms and diagnosis in samples of brain tumor patients, but may intensify at later time points [55–57] due to fears of relapse, prolonged side effects of medical treatments, and loss of vocational standing and social supports.

A study of the clinical predictors of poor quality of life for adult patients with brain tumors pointed to being female, being divorced, having bilateral tumor involvement, having received chemotherapy, and having a poor performance status [58]. Financial risks, marital stresses, loss of work status, and inactivity are other factors contributing to late developing clinical depression in patients with brain tumors [57, 59]. Our lab found that depression levels became clinically elevated four to six years after diagnosis, and were unrelated to stable fatigue levels [57]. A study of the association of brain tumor locus with depression found an association between deteriorated mood state and location of the tumors in heteromodal frontal, parietal, and paralimbic regions of either hemisphere [60]. Brain tumors in the frontal lobes have the highest regional association with depression in this population [61], and can be mistaken for a neuropsychiatric syndrome such as depression [62], which is a significant risk because depression has a much higher base incidence than brain tumors and the behaviors can be misattributed.

Serotonin reuptake inhibitors (SSRIs) are the medication of choice to treat adults and children with tumor and treatment-related depression and anxiety. Methylphenidate is also used, intended to have beneficial effects on depressed mood, fatigue, and cognition, but very few studies have been done, and no clear benefit is observed. In a double-blind, randomized, placebo-controlled study of benefits of methylphenidate to improve mood and fatigue before, during, and after radiation treatments, no difference between groups was found [63]. Methylphenidate improved attention to targets in a mixed group of pediatric patients (acute lymphoblastic leukemia and brain tumors) while taking the drug, but no benefit to memory or learning was observed [64]. Parent and teacher reports improved, however, in a randomized, double-blind, placebo-controlled study of a large group of mixed acute lymphoblastic leukemia and brain tumor pediatric patients [65]. Methylphenidate is frequently used in the clinical management of adults with depression and cognitive impairment, and in children with learning impairments, even though the most supportive evidence appears based on adult subjective observations.

Modafinil (Provigil) is being evaluated for its effectiveness in treating fatigue and cognitive impairment in patients with cancer. An open label study in adults with brain tumors revealed consistently better scores after use of modafinil in neuropsychological tests measured by speed of processing (Trail Making Test (A&B), Symbol Digit Modality Test (oral and written), verbal fluency), as well as lower scores on tests of depression and fatigue [66]. A recent randomized clinical trial of modafinil in adults with breast cancer showed improvements in memory in patient groups prior to randomization, and then

improvements in memory and attention in the group that continued on modafinil versus placebo [67]. Studies have shown adverse side effects that are fairly well tolerated. However, Stevens–Johnson Syndrome, which can be life-threatening, can occur with modafinil (and other medications), and patients require medical monitoring while taking modafinil.

Anxiety: Anxiety is also a frequent psychiatric disorder associated with cancer [68]. Although 40% of CNS tumor patients exhibit behavioral and/or emotional problems [69], very little attention has been paid to characterizing these problems. The majority of anxiety-related research in pediatric cancer has focused on posttraumatic stress symptoms (PTSS) in children with leukemia [70, 71], but PTSS has been shown to be more likely in parents of survivors rather than in the children with disease [72]. Our study at the Children's Hospital of Philadelphia examined anxiety symptoms (Screen For Child Anxiety Related Emotional Disorders – Child and Parent versions [73]) in 25 pediatric patients with quiescent brain tumors. Significant levels of anxiety were reported by 32% of the patients [74], which exceeds levels reported in the general population; in contrast, depression was reported by 12% of the sample. MRI studies showed that all the anxious patients had tumors either in the right cortex, often temporal lobe, or left cerebellar hemisphere. In fact, 80% of the patients with tumors in the right cortex or left cerebellum reported elevated anxiety symptoms. The association of anxiety and tumor loci was not confounded by demographic, disease, or treatment variables. Results evidenced the risk that neuro-oncology patients face for developing significant anxiety symptoms that may not rise to the awareness of parents or the treatment team.

Asperger's Syndrome/mild autism: The rate of autism spectrum disorder (ASD) diagnosis in the population of individuals with brain tumors is not known. However, children with brain tumors sometimes present with a preexisting diagnosis of ASD, typically Asperger's syndrome. In our experience at the Children's Hospital of Philadelphia and the University of Pennsylvania, few of these children met the full criteria for Asperger's or mild autism, yet some have autistic-like characteristics. Making a correspondence between the autistic-like behaviors and the brain tumor is not trivial. Clinical observations suggest that children with those behaviors, that is, with (1) abnormalities in social cognition or social behaviors, (2) distress when environmental structure or schedule is altered, (3) hyperfocus on limited personal interests, and (4) stereotypical body or speech expressions, often have lesions in the cerebellar hemispheres and/or the temporal lobes. Both locations are also very common sites for spongiform dysplasia in children with NF1, with or without additional brain tumors being present, and one study reported an elevated rate of autism in patients with NF1 [75], and elevated rates of neurofibromatosis are found in autism (e.g., [76],). The cerebellum and temporal lobes have been the regions most closely associated with autism (see chapter on Autism by Dr. Jeanne Townsend in this volume). Diagnosis of ASD in these cases requires the application of formal diagnostic criteria using autism measurement instruments, clarification of whether the child meets criteria, and characterization of the autistic-like behaviors secondary to brain tumor or spongiform dysplasia. For individuals with brain tumors, secondary neurobehavioral diagnoses should make clear that the terms are used descriptively, and that the full syndrome may not be present. The potential benefits of treatments for ASD should be considered.

Cognitive Affective Syndrome: The cognitive affective syndrome, defined by significant deficits in executive function (planning and set shifting), spatial cognition, language (nonmotor expressive), abstract reasoning, attentional regulation, memory, and personality (hyperactivity, impulsivity, disinhibition, and emotional lability), is associated with bilateral or large unilateral lesions in the posterior cerebellar lobes, vermis, and in pan cerebellar disorders [77]. It was first described

by Schmahmann and Sherman in 1997 [78], and is often associated with cerebellar mutism.[2] The cognitive affective syndrome has been a very useful diagnosis to describe the complex and uncontrolled behaviors of adults and children with tumors in this location. While other neurological disorders and even congenital cerebellar disorders can also cause this disorder [84], such behavioral abnormalities can be difficult to understand in someone who has a tumor in the cerebellum. The co-occurrence of the cognitive and affective symptoms is thought to arise from the disruption of the cerebello-thalamo-cortical and cortical-pontine-cerebellar tracts connecting the cerebellum with frontal, parietal, temporal, and limbic cortices. There are no known medications that address the symptoms of the cognitive affective syndrome. However, behavioral techniques applied from the field of autism can be helpful, along with careful construction of daily routines and sleep hygiene habits.

Obsessive-Compulsive Disorder: Obsessive-compulsive disorders (OCD) can also be a consequence of brain tumors. OCD in patients with brain tumors has been mainly dependent on individual case reports, but a systematic study examined the obsessionality scores with tumor locations, and found higher ratings of obsessionality three months after surgery in frontal locations and women [85]. While psychiatry has had a worthy degree of success in the cognitive behavioral treatments for OCD, the presence of OCD resulting from a brain tumor, resection, and/or resulting encephalomalacia affecting the frontal lobes, may have atypical characteristics that can make it difficult to treat. Psychiatric treatment of OCD symptoms is dependent, in part, on identifying the sources of anxiety that lead to the obsessive behaviors, and then using various behavioral and psychopharmacologic treatments to decrease sensitivity to the anxiety-causing thoughts. However, anxiety may not be the primary mediating factor in OCD resulting from brain tumors. Of course, the etiology is neurological, and thus less amenable to change. Therefore, more comprehensive methods may be needed, including holistic learning environments and therapeutic milieu residential programs if the OCD behaviors are very disruptive and maladaptive.

Hypothalamic syndromes: Tumors originating in the hypothalamus are, first, associated with disorders of eating behavior, often causing hyperphagia, and with symptoms similar to anorexia [86] that are actually loss of appetite, or even cachexia. However, they produce other symptoms that lead to changes in growth rate, and to hyperactivity, irritability, attacks of anxiety, euphoria, aggressiveness, disruptions of vision, sleep disturbance, and headaches. Seizures disorders, sometimes refractory, are also associated with these tumors. Gelastic seizures (inappropriate episodes of smiling, giggling, or laughter that are accompanied by electroencephalographic changes) are a rare hypothalamic phenomenon. A study of a small group of children (n = 12) with histories of hypothalamic hamartomas and gelastic seizures, given structured interviews along with an unaffected sibling, had an elevated rate of psychiatric conditions [87]. Most common, in decreasing order, were aggression, oppositional defiant disorder, attention-deficit/hyperactivity disorder, learning impairment, and anxiety and mood disorders. However, in its more subtle and perhaps more frequent form, the patient is troubled by constant irritability and mild hyperactivity, which has effects on the development of satisfying social relationships. There are no known treatments for the more severe forms of behavioral disturbance caused by hypothalamic tumors or hamartomas.

[2]Cerebellar mutism is an acquired complete loss of speech, transient in nature, most often following surgical resection of cerebellar or intrinsic posterior fossa tumors, or following stroke or trauma. It is an element of the posterior fossa syndrome, but can occur alone. Resolution of the mutism typically occurs within days, but has been reported to take up to four months, and is followed by dysarthria that improves over time, and more subtle present linguistic disorders [79–83].

Effects of Adjuvant Treatments on Cognition

Radiation Therapy (Radiotherapy)

Types of radiotherapy: (1) Stereotactic radiotherapy is multiple small fractions of ionizing radiation given over time to a highly focal area. Either high energy photons (linac) or cobalt 60 (gamma knife) are used. (2) Stereotactic radiosurgery is a single (or two) high dose fraction to destroy tumor tissue. Both stereotactic techniques are used to treat small targets. (3) Conformal radiotherapy uses small fractions of high energy photon radiation directed to three spatial dimensions (3-D) calculated with computer technology to more precisely target a tumor. Typically 30 treatments (one in each 24 h period, which permits maximum DNA repair) are given. (4) Intensity-modulated radiotherapy is a kind of 3-D conformal treatment that is becoming the standard of care for nondisseminated brain tumors. It targets high energy particles of varying intensities to small areas of tissue, with the purpose of maximizing dose to tumor and minimizing dose to surrounding normal-appearing tissue. A collimator is rotated around the patient's head so that radiation is delivered from different angles. (5) Proton beam therapy, first proposed by Robert Wilson in 1946, now increasing in availability, uses subatomic particles instead of photons, and allows a highly localized deposition of the energy in the Bragg Peak. In practice, protons differ from photons by having the property of increasing the dose very gradually with increasing depth, and then rising to a peak at the end of its range (the Bragg Peak); thus, it delivers less radiation in front of the tumor and no radiation behind the tumor target. Evidence is emerging that the differences in dose distribution for proton therapy will result in lowering of mean dose [88], and thus better long-term advantages. The improvements for survival and quality of life by proton therapy are, of course, not yet proven. (6) There are also internal types of radiation, called brachytherapy, that implant radiation doses at the site of the tumor in the form of wires, catheters, ribbons, capsules, or seeds.

Cognitive effects of radiotherapy: The cognitive functions most often cited that are specific to radiation effects are multimodal (verbal, visual, spatial) memory functions, novel problem solving, and attentional control [89–92]. Study designs that control for the effect of the disease versus radiotherapy reveal that most impairment can be traced to the tumor. Cognitive impairment from radiation is related to radiation dose [89], and is first seen in the early-delayed phase in memory [89, 91, 93, 94, 95]. The onset of a late-delayed irreversible memory impairment first appears several years after treatment [50], and may be progressive (manuscript in preparation). Although prior studies of children focused on IQ, more recent studies have also shown effects in neuropsychological functions of attention and memory [96–99]. Donepezil, an anticholinesterase medication, is another promising candidate to treat cognitive impairment, though only one open label study has been conducted in patients with brain tumors [100].

The concerns about the iatrogenic side effects of radiotherapy for patients who survive their period of treatment and years beyond, have changed since the early outcome studies of treatments used in the '70s and '80s that reported cases of dementia and mental retardation. Converging results of multidisciplinary studies of the risks of radiotherapy have led to several observations about the key variables: brain volume burden, dose effects, multiple phases of delayed radiotherapy, age effects, and combinations with other treatments.

Brain volume and dose: Whole brain radiotherapy is used mainly to destroy tumor cells that have seeded through blood or cerebrospinal tissue to the brain. It is also used prophylactically to prevent the development of metastatic disease from tumors that often seed distantly to the brain, such as small-cell lung cancer or from some cancers of lymphatic or blood-producing tissues such as leukemia. Increasingly in childhood

leukemia, nervous system prophylaxis is accomplished with chemotherapy both intrathecal, intra-Ommaya, and/or systemic rather than with radiation. Although whole brain irradiation carries significant neurological and neurocognitive risk, the predominant risk variable is the dose. Lower whole brain doses appear to be less damaging than high doses focused on the involved field [101]. This observation is based on the more robust functional impairment from high doses, even to focal brain regions. It is consistent with the results from stereotactic techniques, which deliver the highest and most focused doses to dense tumor targets, and have demonstrated no general cognitive decline posttreatment, but are associated with focal and severe neurological impairment in some cases depending on which structures were within the field. Studies are underway to evaluate the treatment benefit and risks to cognition from the lowest dose currently in use (1800 cGy) of whole brain radiation in children with brain tumors that often disseminate.

Multiple phases of radiotherapy effects: There are presently known three temporal phases of the side effects of radiotherapy on neuropsychological function.

(1) The acute phase occurs during radiation, marked by somnolence, depression, and nausea. Radiotherapy is tolerated differently by individuals, whether adults or children, and not everyone experiences debilitation during the acute phase [102]. Memory and attention impairments have also been identified during this phase [103]. However, the acute phase is not prognostic of later complications from radiotherapy [104].

(2) The early-delayed phase of radiotherapy, also referred to as the subacute phase, occurs during approximately a few weeks to six months after completing the full dose of radiotherapy, and is marked by a temporary decline in memory. Our lab has isolated this effect to verbal semantic memory by identifying a double dissociation from visual, configural memory. The verbal semantic effect was independently replicated in another lab [94], and confirmed by a group controlled study [105]. The effects on memory reverse by one year after treatment, as long as there is no disease progression. The early-delayed impairment may not be prognostic of the late developing cognitive impairment [50].

(3) The late-delayed phase of radiotherapy effects has the least temporal precision, but longitudinal studies suggest that the harbinger of this irreversible decline in cognition is, again, associative memory. The time course appears to begin about five years posttreatment [50, 106]. Our laboratory's studies to eight years posttreatment show that the associative memory impairment is more general than in the early-delayed phase, and continues to decline from five to eight years, without declines in working memory, other memory functions, divided attention, processing speed, visuospatial functions, verbal fluency, language, or reasoning [107].

Biological mechanisms for neurocognitive damage: Therapeutic dose irradiation causing damage to glial stem cells has been documented in rats in the subependymal zone of the cerebral ventricles [108]. Effects on myelination and on blood vessel-dependent endothelial cells are also suspected, and neuroimaging studies most often report white matter hyperintensities with onset within the 3.5 years of treatment [50, 105]. Animal studies have shown changes in neural stem cells in the dentate gyrus of the hippocampus that may account in part for the changes in memory [109, 110]. Previous models of the biological mechanisms that underlay cognitive impairments are that the radiation causes acute cellular death of the *endothelial* cells needed for blood vessels, of the *glial* cells needed for myelination and regulation of neurons, oligodendrocytes, and the vasculature, and of the *neuronal progenitor stem cells* of the hippocampus. An updated model presents burgeoning evidence that radiotherapy-induced injury also induces a recovery/repair response in the form of immune-mediated processes involving specific cytokines, persistent oxidative stress,

and chronic inflammation [111]. Data from the hippocampal studies showed that radiotherapy administered to rats to mimic the clinical temporal phase effects in humans, resulted in marked activation of microglia in the neurogenic zone, thus inhibiting hippocampal neurogenesis [109, 110]. Furthermore, inhibition of microglial activation with indomethacin restored the rates of neuronal progenitor cells [112]. Oxidative stress has also been associated with disruption of mitochondrial function that compromised the growth rate of the hippocampal neural precursor cells, and also increased their radiosensitivity [111].

Neuroimaging and mechanisms for cognitive impairment: White matter abnormalities seen on neuroimaging also are dose dependent, but the time to onset of white matter abnormalities is not consistent across patients beyond one year posttreatment. The timing of white matter abnormalities due to radiation effects can be partially discriminated from chemotherapy effects. Leukoencephalopathy secondary to chemotherapy alone typically appears on neuroimages within one year of treatment while radiation-related damage to the white matter is more often reported after one year posttreatment [113]. However, white matter abnormalities are robust in adults and children [98]. In addition to the new evidence showing damage to the hippocampal milieu from loss of neural progenitors and inflammation, structural loss of hippocampal white matter volume and integrity has been measured using neuroimaging techniques [114, 115]. White matter abnormalities have been associated with increased permeability of the blood–brain barrier during radiotherapy, and increases in vascular volumes with the early-delayed memory changes from radiotherapy [116]. Dose-dependent responses of the tumor and of surrounding brain tissue are seen with positron emission tomography of blood flow and both glucose and amino acid metabolism (e.g., [117, 118]).

Developmental and Aging effects: Prospective studies show that younger age poses significantly greater neurological risk for children. Older age also puts individuals at greater risk because of the underlying dynamic of normal effects on the brain's white matter caused by normal aging. Despite the limitations of IQ as a measurement of RT effects, it does appear to decline over time in children who have received therapeutic irradiation. The mechanism of the change in IQ is problematic. Learning difficulty may be caused by the tumor itself, surgical intervention, chemotherapy, stress, and radiotherapy; in addition, a child losing significant time in school and even two years of minimal academic exposure is not uncommon. The decline in IQ post radiotherapy may represent a decline in school performance for multiple causes that include the tumorigenic and iatrogenic treatment injury to neurodevelopment.

Children are predisposed to deficits in fine motor coordination/dexterity and novel problem-solving deficits due to the high rate of the location of tumors in the posterior fossa, in addition to the attention and memory impairments that are ubiquitously reported among all age groups. There is one study to date [119] that indicates progressive decline, although the outcomes reported in children extend to only five or six years. Another study found an initial decline at two years in pediatric patients with mixed tumor types, but no evidence of further IQ decline when their patients were subsequently tested at the 5-year follow-up [120]. Palmer and colleagues [97] followed IQ scores for six years in a mixed-age group of 50 children with medulloblastoma with craniospinal radiotherapy at a moderate dose of 35–40 Gy (posterior fossa boost of 50.8–59.4 Gy), surgical treatment, and mixed chemotherapy treatments. They reported that cognitive decline emerged immediately in the younger children (2.26–8 years of age) beginning at two years posttreatment, with a plateau by six years posttreatment. Decline in IQ appeared later in the older (8–15.76 years of age) children. The plateaus in cognitive function after an initial decline, though limited to IQ in these latter two longitudinal studies, raises the question of whether other biological processes are being measured. Encephalomalacia often develops in brain tumor patients, particularly in the cerebellum, over the period of the cognitive decline

measured in the studies, and patients are also prone to postoperative strokes. Also, data following subtle recurrence or growth of unresected tumors are not always censored in the analyses of brain tumor outcomes.

In adults, patterns of abnormality on neuroimaging (e.g., abnormalities in the periventricular and deep white matter) are supportive of the idea that vascular tissue is particularly vulnerable to radiation effects. The vulnerability of vascular tissue appears to account for the greater decline reported in patient groups that are comprised of elderly adults. The evidence of cognitive decline limited to memory impairment, and the relatively slow rates of decline, as late as eight years after treatment, suggest that patients do not decline in their cognitive function at similar rates, that host factors lead some patients to be more radiosensitive, and that the time course is longer than previously thought using current treatment techniques.

Both the hippocampus and the neocortical semantic memory systems have been implicated in radiation injury as shown by our programmatic research. We used age-corrected cognitive scores to compare children and adults in the changes in cognition over time that occurred four years after pre-RT baseline. Adults and children demonstrated vulnerability of different memory systems (recent unpublished study). Adults demonstrated significant decline in delayed visual (Complex Figure) recall, showing that hippocampus-dependent consolidation memory for visual material appeared susceptible to late radiation effects even four years after treatment. Children demonstrated a different pattern: they declined significantly in delayed recall (consolidation) of meaningful words (Rey Auditory Verbal Learning uses unrelated supraspan word lists), which suggests that their neocortical semantic memory system might be particularly vulnerable to therapeutic irradiation injury. No statistically significant difference was found between adults and children in the speed of recognizing meaningful pictures (Picture Recognition Test). One intermediating factor is that adults have a stronger verbal semantic foundation than children and thus a more elaborated semantic network that is activated during retrieval. Not only do children with brain tumors who require irradiation have the disadvantage of a weaker semantic memory foundation, but their scores demonstrate that their rate of learning does not keep up with that of the age-corrected healthy and typically developing children. However, because the declines four years after treatment were found only in the delayed recall scores, the hippocampal memory system of children is also implicated.

The questions about the late effects of radiotherapy on neurocognitive function, if considered in detail, emphasize the number of relevant clinical variables that need to be controlled or addressed in analyses when doing research in this area. The predictability of iatrogenic treatment problems occurring in one individual is reduced by confounding factors of age-related clinical effects, predisposition to morbidity conferred by the nature of the cancer or tumor diagnosis, concurrent treatments, differential time-related effects, and the lack of a long enough period of known natural history to determine the true temporal development of what we know could become a devastating injury to the brain.

Effects of multiple treatments: Chemotherapy alone – particularly intrathecal/intravenous – is known to be neurotoxic with negative neurobehavioral sequelae found in the majority of the studies (see next section). Treatment interaction effects are known to exist and to significantly increase the risk for neurocognitive impairment, but are beyond the scope of this chapter, and the reader is referred to a review [101].

Chemotherapy: Chemotherapy is a classification of drugs that interfere with a cells ability to grow and reproduce. Since rapidly dividing cells are most sensitive to the effects of chemotherapy, healthy cells may also be affected in addition to the tumor cells. These other cells include the bone marrow, lining of the gastrointestinal tract, hair, and skin. Some chemotherapy has already been shown to have significant neurotoxic and neurocognitive effects [101]. To fully understand the impact of chemotherapy, it is vital to have a simple, yet clear understanding of the types of chemotherapy used, mechanism of action, and

overall toxicity, both in neurocognition and to the entire body.

Types of Chemotherapy: Tumor cancer cells reproduce abnormally and divide and grow in dysregulated ways. There exist several different types of chemotherapy used to attack the abnormal cell at varying stages of the cell's cycle of growth. The growth and division of a cell occur in a cascade of events called the cell cycle and this cycle is further divided into phases. The classic antitumor drugs called chemotherapy are classified based on their activity during phases of the cell cycle. Some drugs are cell cycle specific and others are cell cycle nonspecific. The most common types of chemotherapy used in treating CNS tumors are listed below with a brief explanation of their mechanism of action.

Alkylating agents. All cells use DNA and RNA to make exact copies of themselves, and it is the alkylating agents that block this interaction and prevent cell reproduction. Common alkylating agents are Cyclophosphamide (Cytoxan) and Temozolomide (Temodar).

Nitrosureas are group of drugs that are similar to the alkylating agents in their disruption of RNA and DNA replication, but have lipid solubility, and thus, theoretically, can gain better access to the central nervous system and have a key role in treatment of CNS tumors. They include the common drugs in brain tumor protocols lomustine (CCNU) and carmustine (BCNU)

Platinating agents work by inhibiting DNA replication, RNA transcription, and protein synthesis. Common platinum agents are Carboplatin and Cisplatin.

Antimetabolites are drugs that actually starve cells by replacing essential nutrients needed for cell synthesis with the chemotherapy drug. These drugs attack the cell as it prepares to divide and are most effective against rapidly growing tumors. The antimetabolites can be further divided into the pyrimidine analogues which include Cytarabine (ARA-C), the purine analogues which include 6MP(Mercaptapurine) and 6TG (Thioguanine), and the folic acid antagonists which includes Methotrexate, which may be used systematically with CNS penetration or intrathecally/intraventricularly.

Alkaloids are a category of chemotherapy drugs derived from plants that interrupt cell division by interfering with cell synthesis, enzyme activity, cell division, and membrane disruption. These mitotic inhibitors are vital to cell death on many varying levels and a key component to chemotherapy protocols used in neuro-oncology. The most common plant alkaloid is derived from the periwinkle plant (Vinca rosea) and is called Vincristine. Vincristine has activity on micro-tubulin. This drug has been a component of many neuro-oncology treatment protocols for CNS tumors, and is also used as a radiation sensitizer in many treatment protocols. Epipodophyllotoxin (Etoposide (VP-16)) is also commonly used in neuro-oncology treatment protocol and is cell cycle specific, while a category referred to as antibiotics (amino glycosides) weaken the outer cell membrane and interfere with the enzymes needed in cell reproduction. Vinblastine is another mitotic inhibitor with similar mechanism of action as vincristine and both are cell cycle specific. There is also laboratory evidence (Kieran) that weekly Vinblastine (Velban) has anti-angiogenesis activity.

Anti-angiogenesis agents disrupt the blood supply to a tumor, thus depriving the tumor of nutrients it needs to grow and reproduce. Their role in future neuro-oncology treatment protocols should prove vital as many malignant tumors are complicated by an often complex abnormal network of blood vessels. Bevacizumab now being used in some studies has offered the challenge of managing hypertension, thromboembolic events, bleeding, and wound healing problems [121]. Bevacizumab and Irinotecan in recent trials have shown the longest disease-free survival in adult glioblastoma coupled with radiation.

As molecular biology is uncovering subunits of growth regulators, many of the newer chemotherapy drugs are targeting these abnormal or dysregulated subunits. Abnormalities in sonic hedgehog signaling (e.g., medulloblastoma), VEGF, tyrosine kinase, RAS protein, MGMT expression (e.g., high-grade glioma), etc., are a

few of such abnormalities that the targets of translational neuron-oncologic therapeutic studies. Drugs that may have activity in brain tumors in these categories are too new to know long-term effects on neurocognition.

Administration of Chemotherapy: The most common method for delivery of chemotherapy drugs during treatment for CNS tumors are intravenously in which medication is delivered directly into the bloodstream. Drugs can also be administered by mouth where they are directly absorbed into the lining of the stomach and intestines. Oral chemotherapy may be more limited by inter- and intra-patient bioavailability. The intrathecal route of administration of chemotherapy is achieved by performing a spinal tap and injecting the drug directly into the cerebrospinal fluid, thus avoiding the blood–brain barrier completely. Medication given into the ventricles can be accomplished by use of an Ommaya catheter.

Dosages: Although the dosages of chemotherapy agents vary from one treatment protocol to another, most are based on a person's body surface area. Using current weight and height the body surface area is calculated in Meters squared (m^2) and is a standard and effective way to balance safe dosing with a child's risk of overall toxicity.

General toxicity of chemotherapy: Chemotherapy drugs can destroy healthy, normally developing cells in addition to the destruction of cancer cells. Because hair follicles grow quickly, they are a common target and chemotherapy can cause all or some hair to fall out. When combined with radiation therapy, the extent and permanence of the hair loss can be variable for most patients. When chemotherapy is used in combination with cranial radiation for treatment of CNS tumors, hair loss can be permanent.

Chemotherapy can also kill the rapidly dividing cells inside the bone marrow and lower the number of circulating blood cells in one's body. Therefore, many patients receiving chemotherapy for CNS tumors need transfusions with red blood cells and possibly platelets to replenish the supply until one's body is generating its own new circulating blood cells. These transfusions help to treat anemia and prevent bleeding. It is also important to remember that when a patient's white blood cells are low, the patient is at higher risk of a life-threatening infection.

Other overall side effects of chemotherapy include those associated with the effect of these drugs on the lining of the gastrointestinal tract. They can include nausea, vomiting, diarrhea, and constipation. Fatigue is a common side effect to treatment for most chemotherapy patients and can range from being a minor problem to complete debilitation. Cranial radiation combined with chemotherapy can add to the overall feeling of general weakness. Nutritional side effects of chemotherapy can include changes in taste and smell that often lead to an aversion to some foods. Because of the lowering of a patient's white cell count during chemotherapy, the patient is at risk for skin and nail changes as well as mouth and throat sores [122].

Many patients require the concomitant use of steroids such as prednisone, dexamethasone, and hydrocortisone during cancer treatment with chemotherapy and/or radiation. Corticosteroids are used to treat tumor-associated and radiation-induced cerebral edema, with the hope of managing malignant tumors and reducing clinical symptoms. Drugs in this category can cause many unpleasant side effects such as high blood pressure, weight gain, elevated blood sugar, sleep disturbances, muscle weakness, and bone weakening. The use of steroids during chemotherapy and treatment for CNS tumors can be challenging as some patients can develop untoward behavior changes and mood swings making it difficult to establish a baseline neurological examination and assessment. Steroids can cause convulsions, headache, vertigo, and more concerning-psychiatric disturbances [123].

Cognitive Effects of specific drugs used in neuro-oncology: Many of the antitumor drugs and the immunosuppressive treatment needed to treat CNS tumors involve multiple organ damage, and, more specifically, damage to normal, developing brain tissue. While considering treatment side effects, other causes that must be excluded include tumor progression, paraneoplastic disease, diabetes, hypertension, organ failure, and infection [124]. Many studies have

shown that chemotherapy alone can be neurotoxic and include behavioral challenges as well [101]. When Methotrexate and ARA-C are given intrathecally (directly into the spinal fluid), those effects may be magnified. Armstrong's review [101] also reports that when chemotherapy is used in conjunction with radiation, it may affect tolerance to the radiation and affect injury thresholds. In fact, there is much data from studies of the effects of Methotrexate in treatment of leukemia that shows that radiation injury appears to be enhanced when given prior to radiotherapy. Some chemotherapy may add to a patient's risk of developing white matter changes. In addition, chemotherapy, especially when used together with radiation, may predispose a patient to an earlier onset of these white matter changes than in radiation used alone [101]. Although the literature hints that some patients are at a greater risk of neurotoxicity from treatment, their predisposing factors are unclear and hard to predict [125]. With children, the known risk factors for a child's developing nervous system include their specific treatment regimen, dosages, combination of radiation with chemotherapy, genetic background, and age [125].

The addition of newer therapies such as anti-angiogenesis agents, radiosensitizers, blood–brain barrier inhibitors, and other immune therapies will offer additional challenges to clinicians trying to determine if one's neurological complications are a result of treatment, effects, metastasis, necrosis, or new hemorrhages.

Many patients will report a syndrome they casually refer to as "chemo brain" during the acute phase of treatment. It describes their subjective impression that short-term memory and learning feel "sluggish" and not as sharp. Meyers [126] reported that many preclinical studies have focused on the acute effects of chemotherapy on these aspects of neurocognition, yet many patients report issues with memory retrieval and executive function as well.

Methotrexate remains the most singly neurotoxic drug when given either intrathecally or intravenously. Its most toxic effects include white matter or focal necrosis, and younger children are at greater risk for iatrogenic injury to neurodevelopment when Methotrexate is used with radiation. Erbetta [124] reported an acute neurological syndrome in three patients after its concomitant use with other agents. An MRI revealed posterior reversible encephalopathy in two of the cases [124]. Methotrexate has been reported to cause headaches, paraplegia, and brain atrophy [123]. Mental impairment has been noted after intrathecal methotrexate and in brain radiation followed by intravenous methotrexate.

Cytarabine is the antimetabolte that has been associated with a few cases of paraparesis after intrathecal use. Clinicians need to pay close attention to the patient during administration for signs of cerebellar toxicity and peripheral neuropathy in high dose therapies. Dizziness and somnolence have also been seen in cytarabine use. Cisplatin has been associated with peripheral neuropathy as its most significant neurological toxicity. However, patients also report seizures, change in taste, cortical blindness, and L'Hermitte's sign (a sensation of electric shock or tingling in arms and legs or both on neck flexion). Ifosphamide can cause instances of lethargy and confusion making the clinician's frequent neurological assessment critical during administration.

Vincristine is the plant alkaloid that can cause toxicity to peripheral nerve fibers with complaints of parasthesias in hands and feet, loss of deep tendon reflexes, foot drop, and ptosis (droopy eyelids). Patients need to be carefully evaluated for these peripheral neurotoxicities, and older patients tend to be more sensitive to the neurotoxicity associated with vincristine. Reversal of these symptoms does occur over the course of many months after therapy has stopped.

Other preclinical studies have reported that drugs like 13-cis-retinoic acid, often used in CNS tumor treatment protocols, can impair spatial learning and memory in young adult mice because of the effect on neurogenesis in the hippocampus and subventricular zone [126]. In addition, three of the widely used drugs mentioned earlier, cisplatin, carmustine, and cytosine arabinoside were found also to be more toxic to

CNS progenitor cells, thus causing increased cell death in the same areas in mice [126].

Intrathecal chemotherapy and intrathecal chemotherapy when combined with intravenous chemotherapy appear to demonstrate an earlier development of white matter changes [101]. There is also a concern that drugs presumed to cross the blood–brain barrier carry a greater risk of neurocognitive effects and neuropsychological impairment. These drugs include cisplatin, nitrosureas, and methotrexate. The combination of these agents with radiation therapy further increases the risk of serious sequelae such as leukoencephalopathy, stroke, myelopathy, and various neuropathies [101]. In conclusion, chemotherapy used alone may offer the least damaging effects on the central nervous system, yet when combined with radiation or used with other high dose multiple drug regimens, the risk of white matter changes increases [101].

Immunotherapy

A recent promising treatment under development is immunotherapy, and the field of immune-oncology may result in less toxic and more effective outcomes. Immunotherapy stimulates the patient's tumor-specific immune response to overcome self-protective immunosuppressive strategies that have made cancers so successful, and work with other treatments to kill tumor cells. Patients with refractory leukemia (B lineage) have received major benefit from chimeric antigen receptor (CAR) T-cell therapy. Immunotherapy utilizes vaccines, adoptive T cells, and immune checkpoint inhibitors several types of cancers. Limiting factors include for insufficient immunogenicity, and inadequacy to prevent or reduce immunosuppressive factors that tumors exploit [127]. However, outcomes from use of single-agent immunotherapeutics may be short lived or beneficial outcomes may be limited to a relatively small percentage of treated patients. As clinical trials in this field are new, little is known about the potential of immunotherapy in brain cancer, e.g., why some cancers are more responsive than others, and an open question is whether central nervous system tumors may be different from other cancers in their interactions with immunotherapy targets.

Glioblastoma multiforme and brain metastases are targets of intensive research for identifying immunotherapeutic solutions. Although there are limited preclinical investigations of combined therapeutics, future benefit will rely on multiple therapies and radiation techniques, which include cytotoxic agents, for the potential of creating a systemic immune response. There is evidence that antiangiogenic therapies, such as vascular endothelial growth factors (VEGF) shift the tumor microenvironment by diminishing immunosuppressive features and enhancing an immunosupportive phenotype.

Immunotherapy responses have presented different physiological and temporal outcomes, and a working group has been formed to create immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria for patients with neuro-oncological malignancies [128]. Long-term survival and tumor regression may occur in the presence of delayed responses or therapy-induced inflammation or may be confused with pseudoprogression [129]. For example, progressive imaging findings after immunotherapy do not preclude later therapeutic benefit, because immune responses might take time to evolve while early imaging demonstrates true disease progression, and the mode of action of immunotherapy might include an inflammatory responses that mimic radiological features of tumor progression with increased enhancement and edema [129]. Pseudoprogression in these new temporal dynamics lead to questions to prevent premature declaration of tumor progression, about the time posttreatment for radiographic tumor imaging, how long progressive imaging should continue after starting immunotherapy, and percent decrease or increase in enhancing disease on scans [128]. Another treatment change is that patients being administered immunotherapy should have as little dexamethasone as possible before starting treatment, though higher doses may later become necessary

to control symptoms. Increased corticosteroid use within two weeks of MRI assessment makes the patient's disease non-evaluable [130].

The neuroinflammatory responses are linked with fatigue, major depression, memory complaints, Alzheimer's disease, and cerebral ischemia, among other neurological diseases, and are investigated in the pathogenesis of cancer and cancer treatment-related cognitive difficulties. Little research is available to examine the association of fatigue, anorexia, and pain in patients with cancer who receive immunotherapy, in particular the checkpoint inhibitor immunotherapies (Ipilimumab, Pembrolizumab, Nivolumab) [131]. The potential with checkpoint inhibitors to produce cognitive difficulty is that they induce a proinflammatory environment. Future studies will be important for these patients who have the potential to achieve durable cancer remission requiring chronic treatment.

Conclusions

Neuro-oncology presents many challenges to treating physicians, patients, and families, and to the neuropsychologist who tries to contribute to understanding the functional effects of tumors and their treatments. It is critical to take an individual approach when evaluating patients clinically by close examination of both subtle individual effects and disconnection syndromes. Cerebellar tumors can be expected to have profound effects on cognition and emotion. The more invasive the tumor, the greater neurocognitive impairment can be expected. It is also important to screen for mood disorders and other emotional abnormalities, such as behavioral disinhibitions, which can belie tumor effects. Neuropsychological tests that decompose cognition into specific functions, rather than composite scores, are unarguably more useful and sensitive in understanding how a tumor and treatments have affected functioning. Individual responses can be widely varying in the individual's susceptibility and resistance to treatment benefits and side effects, and genetic profiling information continues to emerge that is informing which tumors are more malignant and likely to recur, and which individuals are more responsive to treatments.

Future directions for research include understanding the effects of tumors, surgical resection, and other treatments on cortical and subcortical connectivity, using both tractography and voxel-based lesion symptom mapping. In pediatric neuro-oncology, the cerebellum is so often the locus of lesion, that future studies, including those in our laboratory, will be examining with greater specificity how cerebellar injury affects the development of cognitive function.

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References

1. Jarquin-Valdivia AA. Psychiatric symptoms and brain tumors: a brief historical overview. Arch Neurol. 2004;61:1800–4.
2. Fisher M, Phillips P. PET imaging of brain tumors. In: Charron M, editor. Practical Pediatric PET Imaging. New York: Springer Science + Business Media Inc; 2006. p. 175–219.
3. Simpson JR, Scott CB, Rotman M, et al. Race and prognosis of brain tumor patients entering multicenter clinical trials. Am J Clin Oncol (CCT). 1996;19:114–20.
4. Louis DN, Cavenee WK. Molecular biology of central nervous system tumors. Boston: Massachusetts General Hospital, MGH Neurosurgical Service, Brain Tumor Center, 2005; http://brain.mgh.harvard.edu/MolecularGenetics.htm.
5. Wechsler-Reya R, Scott MP. The developmental biology of brain tumors. Ann Rev Neurosci 2001;24.
6. Filley CM, Kleinschmidt-DeMasters BK, Lillehei KO, et al. Gliomatosis cerebri: neurobehavioral and neuropathological observations. Cogn Behav Neurol. 2003;16:149–59.
7. Wen PY, Loeffler JS. Management of brain metastases. Oncology. 1999;13(941–954):957–61.
8. Posner J. Management of brain metastases. Revue Neurologique. 1992;148:477–87.
9. Armstrong CL. Neurofibromatosis Type 1. In: Kreutzer J, DeLuca J, Caplan B, eds. Encyclopedia of clinical neuropsychology. NY: Springer; 2010.

10. Armstrong CL. Neurofibromatosis Type 2. In: Kreutzer J, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. NY: Springer; 2010.
11. Zoller ME, Rembeck B, Backman L. Neuropsychological deficits in adults with neurofibromatosis type 1. Acta Neurol Scand. 1997;95:225–32.
12. Moore BD, Denckla MB. Neurofibromatosis. In: Yeates KO, Ris MD, Taylor HG, editors. Pediatric neuropsychology: research, theory and practice. New York: The Guilford Press; 2000.
13. Rosser TL, Packer RJ. Neurocognitive dysfunction in children with neurofibromatosis type 1. Curr Neurol Neurosci Rep. 2003;3:129–36.
14. Barton B, North K. Social skills of children with neurofibromatosis type 1. Development Med Child Neurol. 2004;46.
15. Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Dev Med Child Neurol. 2002;44:164–70.
16. Krab LC, Aarsen FK, de Goede-Bolder A, et al. Impact of neurofibromatosis type 1 on school performance. J Child Neurol. 2008;23:1002–20.
17. Hyman SL, Gill DS, Shores EA, et al. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. Neurology. 2003;60:1139–45.
18. Hyman SL, Shores EA, North KN. Learning disabilities in children with neurofibromatosis type 1: Subtypes, cognitive profile, and attention-deficit-hyperactivity disorder. Dev Med Child Neurol. 2006;48:973–7.
19. Dalmau J, Gultekin HD, Posner J. Paraneoplastic neurologic syndromes: pathogenesis and physiopathology. Brain Pathol. 1999;9:275–84.
20. Honnorat J, Cartalat-Carel S, Ricard D, et al. Onco-neural antibodies and tumour type determine survival and neurological syndromes in paraneoplastic neurological syndromes with Hu or CV2/CRMP5 antibodies. J Neurol Neurosurg Psychiatr. 2009;80:412–6.
21. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol. 2006;59:490–8.
22. Tee AR, Fingar DC, Manning BD, et al. Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc Nat Acad Sci USA. 2002;99:13571–6.
23. Inskip PD, Heineman EL. New malignancies following cancer of the brain and central nervous system. In: (SEER) SEaER, ed. Brain and Other CNS, 2008:363–373.
24. Paulino AC, Mai WY, Chintagumpala M, et al. Radiation-induced malignant gliomas: is there a role for reirradiation? Int J Rad Onc Bio Phys. 2008;71:1381–7.
25. Thierry-Chef I, Simon SL, Land CE, Miller DL. Radiation dose to the brain and subsequent risk of developing brain tumors in pediatric patients undergoing interventional neuroradiology procedures. Radiat Res. 2008;170:553–65.
26. Zacharatou JC, Paganetti H. Risk of developing second cancer from neurtron dose in proton therapy as function of field characteristics, organ, and patient age. Int J Rad Onc Bio Phys. 2008;72:228–35.
27. NRC NRCUS. Radiation-induced cancer: Mechanisms, quantitative experimental studies, and the role of genetic factors. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2: National Academies Press; 2006.
28. Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. Can Res. 1989;49:6137–43.
29. Wrensch M, Minn Y, Chew T, et al. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-Oncology. 2002;4:278–99.
30. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114:97–109.
31. American Joint Commission on Cancer. AJCC cancer staging manual. 6th ed. New York: Springer; 2002.
32. Kayl AE, Meyers CA. Does brain tumor histology influence cognitive function? Neuro-Oncology. 2003;5:255–60.
33. Bosma I, Douw L, Bartolomei F, et al. Synchronized brain activity and neurocognitive function in patients with low-grade glioma: a magnetoencephalography study. Neuro-Oncology. 2008;10:734–44.
34. Sands S, Van Gorp W, Finlay J. A dramatic loss of non-verbal intelligence following a right parietal ependymoma: a brief case report. Psycho-Oncology. 2000;9:259–66.
35. Sahadevan S, Pang WS, Tan NJL, et al. Neuroimaging guidelines in cognitive impairment: lessons from 3 cases of meningiomas presented as isolated dementia. Singapore Med J. 1997;38:339–43.
36. Skirboll SS, Ojemann GA, Berger MS, et al. Functional cortex and subcortical white matter located within gliomas. Neurosurgery. 1996;38:678–85.
37. Anderson S, Damasio H, Tranel D. Neuropsychological impairments associated with lesions caused by tumor or stroke. Arch Neurol. 1990;47:397–405.
38. Scheibel R, Meyers C, Levin V. Cognitive dysfunction following surgery for intracerebral glioma: influence of hisopathology, lesion location and treatment. J Neurooncol. 1996;30:61–9.
39. Riva D, Giorgi D. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. Brain. 2000;123:1051–61.

40. Goldstein B, Obrzut, J.E., John, C., Hunter, J.V., Armstrong, C.L. The impact of low-grade brain tumors on verbal fluency performance. J Clin Experiment Neuropsychol. 2004;26.
41. Gourovitch ML, Kirkby BS, Goldberg TE, et al. A comparison of rCBF patterns during letter and semantic fluency. J Int Neuropsychol Soc. 2000;14:353–60.
42. Stuss DT, Alexander MP, Hamer L et al. The effects of focal anterior and posterior brain lesions on verbal fluency. J Int Neuropsychol Soc. 1998;4.
43. Goldstein B, Obrzut JE, John D, Ledakis G, Armstrong CL. The impact of frontal and non-frontal brain tumor lesions on Wisconsin card sorting test performance. Brain Cogn. 2004;54:110–6.
44. Goldstein B, Armstrong CL, Modestino E, et al. Picture and word recognition memory in adult intracranial tumor patients. Brain Cogn. 2004;54:1–6.
45. Snodgrass JG, Vanderwart M. A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. J Experiment Psychol Human Learn Memory. 1980;6:174–215.
46. Goldstein B, Armstrong CL, John C. Neuropsychological effects of intracranial tumors on attention. J Clin Exp Neuropsychol. 2003;25:66–78.
47. Tulving E, Kapur S, Craik F, et al. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Nat Acad Sci. 1994;91:2016–20.
48. Meyers C, Hess K, Yung W, Levin V. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol. 2000;18:646–50.
49. Armstrong CL, Goldstein B, Shera D, et al. The predictive value of longitudinal neuropsychological assessment in the early detection of brain tumor recurrence. Cancer. 2003;97:649–56.
50. Armstrong CL, Hunter JV, Ledakis GE, et al. Late cognitive and radiographic changes related to radiotherapy: initial prospective findings. Neurology. 2002;59:40–8.
51. Newport DJ, Nemeroff CB. Assessment and treatment of depression in the cancer patient. J Psychosom Res. 1998;45:215–37.
52. Pringle AM, Taylor R, Whittle IR. Anxiety and depression in patients with an intracranial neoplasm before and after tumour surgery. Br J Neurosurg. 1999;13:46–51.
53. Giovagnoli AR. Quality of life in patients with stable disease after surgery, radiotherapy, and chemotherapy for malignant brain tumour. J Neurol Neurosurg Psychiatr. 1999;67:358–63.
54. Radcliffe J, Bennett D, Kazak AE, et al. Adjustment in childhood brain tumor survival: Child, mother, and teacher report. J Pediatr Psychol. 1996;21: 529–39.
55. Suzuki R, Hirao M, Miyo T, et al. Changes in QOL in patients with brain tumors measured by mood changes during and after treatment. No Shinkei Geka. 1998;26:795–801.
56. Osteraker A-L, Kihlgren M, Melin L. Long-term psychosocial consequences for families with children treated for brain-tumor and other malignancies. J Int Neuropsychol Soc. 1999;5:108.
57. Armstrong C, Goldstein B, Cohen B, et al. Clinical predictors of depression in patients with low-grade brain tumors: consideration of a neurologic versus a psychogenic model. J Clin Psychol Med Settings. 2002;9:97–107.
58. Weitzner M, Meyers C, Byrne K. Psychosocial functioning and quality of life in patients with primary brain tumors. J Neurosurg. 1996;84:29–34.
59. Kaplan CP, Miner ME. Relationships: importance for patients with cerebral tumours. Brain Inj. 2000;14:251–9.
60. Irle E, Peper M, Wowra B, Kunze S. Mood changes after surgery for tumors of the cerebral cortex. Arch Neurol. 1994;51:164–74.
61. Wellisch DK, Kaleita TA, Freeman D, et al. Predicting major depression in brain tumor patients. Psycho-Oncology. 2002;11:230–8.
62. Habermeyer B, Weiland M, Mager R, et al. A clinical lesson: glioblastoma multiforme masquerading as depression in a chronic alcoholic. Alcohol Alcoholism. 2008;43:31–3.
63. Butler JM Jr, Case LD, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation. Int J Radiat Oncol Biol Phys. 2007;69:1496–501.
64. Thompson SJ, Leigh L, Christensen R, et al. Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. J Clin Oncol. 2001;19:1802–8.
65. Mulhern RK, Khan RB, Kaplan S, et al. Short-term efficacy of methylphenidate: A randomized, double-blind, placebo-controlled trial among survivors of childhood cancer. J Clin Oncol. 2005;22:4795–803.
66. Kaleita TA, Wellisch DK, Graham CA, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. J Clin Oncol. 2006;24:1503.
67. Kohli S, Fisher SG, Tra Y, et al. The effect of modafinil on cognitive function in breast cancer survivors. Cancer. 2009;115:2605–16.
68. Redd WH, Silberfarb PM, Andersen BL, et al. Physiologic and psychobehavioral research in oncology. Cancer. 1991;67:813–22.
69. Mulhern R, Crisco J, Kun L. Neuropsychological sequelae of childhood brain tumors: a review. J Clin Child Psychol. 1983;12:66–73.
70. Kazak AE, Barakat LP, Meeske K, et al. Posttraumatic stress, family functioning, and social support

in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol. 1997;65:120–9.
71. Pelcovitz D, Libov BG, Mandel F et al. Posttraumatic stress disorder and family functioning in adolescent cancer. J Traumatic Stress. 1998;11.
72. Libov BG, Nevid JS, Pelcovitz D, Carmony TM. Posttraumatic stress symptomatology in mothers of pediatric cancer survivors. Psychol Health. 2002;17.
73. Birmaher B, Brent D, Chiappetta L, et al. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatr. 1999;38:545–53.
74. Moitra E, Armstrong CL. Tumor locus moderates anxiety symptoms in a pediatric neuro-oncologic sample. Child Neuropsychol; 2009.
75. Williams PG, Hersh JH. Brief report: the association of neurofibromatosis type 1 and autism. J Autism Dev Disord. 1998;28:567–71.
76. Mouridsen SE, Andersen LB, Sorensen SA, et al. Neurofibromatosis in infantile autism and other types of childhood psychoses. Acta Paedopsychiatr. 1992;55:15–8.
77. Schmahmann JD. Disorders of the cerebellum: Ataxia, dysmetria of thought, and the c erebellar cognitive affective syndrome. J Neuropsychiatr Clin Neurosci. 2004;16:367–78.
78. Schmahmann JD. Therapeutic and research implications. Int Rev Neurobiol. 1997;41:637–47.
79. VanDeinse D, Hornyak J. Linguistic and cognitive deficits associated with cerebellar mutism. Pediatr Rehabil. 1997;1:41–4.
80. Pollack IF, Polinko P, Albright AL, et al. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery. 1995;37:885–93.
81. Ferrante L, Mastronardi L, Acqui M, Fortuna A. Mutism after posterior fossa surgery in children. J Neurosurg. 1990;72:959–63.
82. Ersahin Y, Mutluer S, Caglil S, Duman Y. Cerebellar mutism: report of seven cases and review of the literature. Neurosurgery. 1996;38:60–6.
83. Miyakita Y, Taguchi Y, Sakakibara Y, et al. Transient mutism resolving into cerebellar speech after brain stem infarction following a traumatic injury of the vertebral artery in a child. Acta Neurochir. 1999;141:209–13.
84. Tavano A, Grasso R, Gagliardi C, et al. Disorders of cognitive and affective development in cerebellar malformations. Brain. 2007;130:2646–60.
85. Mainio A, Hakko H, Niemelä A, et al. Level of obsessionality among neurosurgical patients with a primary brain tumor. J Neuropsychiatr Clin Neurosci. 2005;17:399–404.
86. Price TRP, Goetz KL, Lovell MR. Neuropsychiatric aspects of brain tumors. In: Yudofsky SC, Hales RE, editors. Essentials of neuropsychiatry and clinical neurosciences. Arlington, VA: American Psychiatric Publishing Inc; 2004. p. 373–98.
87. Weissenberger AA, Dell ML, Liow K, et al. Aggression and psychiatric comorbidity in children with hypothalamic hamartomas and their unaffected siblings. J Am Acad Child Adolesc Psychiatr. 2001;40:696–703.
88. Merchant TE, Hua CH, Shukla H, et al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive dysfunction. Pediatr Blood Cancer. 2008;51:110–7.
89. Klein M, Heimans J, Aaronson N, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. Lancet. 2002;360:1361–8.
90. Armstrong C, Corn B, Ruffer J, et al. Radiotherapeutic effects on brain function: Double dissociation of memory systems. Neuropsychiatr Neuropsychol Behav Neurol. 2000;13:101–11.
91. Armstrong C, Ruffer J, Corn B, et al. Biphasic patterns of memory deficits following moderate dose/partial brain irradiation: Neuropsychologic outcome and proposed mechanisms. J Clin Oncol. 1995;13:2263–71.
92. Lee P, Hung B, Woo E, et al. Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. J Neurol Neurosurg Psychiat. 1989;52:488–92.
93. Reimers TS, Mortensen EL, Schmiegelow K. Memory deficits in long-term survivors of childhood brain tumors may primarily reflect general cognitive dysfunctions. Pediatr Blood Cancer. 2007;48:205–12.
94. Llanes S, Torres IJ, Roeske A, et al. Temporal lobe radiation and memory in adult brain tumor patients. J Int Neuropsychol Soc. 2004;10(S1):185.
95. Armstrong C, Stern C, Ruffer J, Corn B. Memory performance used to detect radiation effects on cognitive functioning. Appl Neuropsychol. 2001;8:129–39.
96. Mulhern R, Palmer S, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol. 2005;23:5511–9.
97. Palmer S, Gajjar A, Reddick W, et al. Predicting intellectual outcome among children treated with 35–40 Gy craniospinal irradiation for medulloblastoma. Neuropsychology. 2003;17:548–55.
98. Palmer S, Reddick W, Glass J, et al. Decline in corpus callosum volume among pediatric patients with medulloblastoma: Longitudinal MR imaging study. Am J Neuroradiol. 2002;23:1088–94.
99. Mulhern R, Palmer S, Reddick W, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol. 2001;19:472–9.

100. Shaw EG, Rosdhal R, D'Agostino RBJ, et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. J Clin Oncol. 2006;24:1415–20.
101. Armstrong C, Gyato K, Awadalla A, et al. A critical review of the clinical effects of therapeutic irradiation damage to the brain: the roots of controversy. Neuropsychol Rev. 2004;14:65–86.
102. Welzel G, Fleckenstein K, Mai SK, et al. Acute neurocognitive impairment during cranial radiation therapy in patients with intracranial tumors. Strahlenther Onkol. 2008;184:647–54.
103. Merchant TE, Kiehna EN, Miles MA, et al. Acute effects of irradiation on cognition: changes in attention on a computerized continuous performance test during radiotherapy in pediatric patients with localized primary brain tumors. Int. J Rad Onc Biol Phys. 2002;53:1271–8.
104. Berg R, Ch'ien L, Lancaster W, et al. Neuropsychological sequelae of postradiation somnolence syndrome. Development Behavior Pediatr. 1983;4:103–7.
105. Armstrong CL, Guglielmi L, Seiler CB. Early delayed radiotherapy damage affects widespread semantic memory networks. J Int Neuropsychol Soc (abstr.). 2004;10(S1):97–8.
106. Mettler F, Upton A. Medical effects of ionizing radiation. 2nd ed. Philadelphia: W.B. Saunders; 1995.
107. Viner K. Cognitive changes in response to treatment of brain tumors: the late-delayed effects of radiation therapy. Psy.D. Dissertation. Chester, PA: Widener University; 2008.
108. Bleyer A, Geyer J, Taylor E, Hubbard B. The susceptibility of the cerebral subependymal zone (SEZ) to chemotherapy (CT) and radiotherapy (RT): mechanism of clinical neurotoxicity caused by CT and RT (Abstr.). Proc Am Soc Clin Oncol. 1989;8:84.
109. Monje ML, Mizumatsu S, Fike S, Palmer TD. Irradiation induces neural precursor-cell dysfunction. Nat Med. 2002;8:955–62.
110. Monje ML, Palmer T. Radiation injury and neurogenesis. Current Opinions Neurol. 2003;16:129–34.
111. Shaw EG, Robbins ME. Biological bases of radiation injury to the brain. In: Meyers CA, Perry JR, editors. Cognition and Cancer. Cambridge, England: Cambridge University Press; 2008. p. 83–96.
112. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science. 2003;302:1760–5.
113. Armstrong CL, Hunter JV, Hackney D, et al. MRI changes during the early-delayed phase of radiotherapy effects. Int J Radiat Oncol Biol Phys. 2005;63:56–63.
114. Nagel BJ, Palmer SL, Reddick WE, et al. Abnormal hippocampal development in children with medulloblastoma treated with risk-adapted irradiation. Am J Neuroradiol. 2004;25:1575–82.
115. Armstrong CL, Hampstead B, Guglielmi L. Hippocampal response to neuro-oncological stressors [abstract]. J Int Neuropsychol Soc. 2004;10(S1):65.
116. Cao Y, Tsien CI, Sundgren PC, et al. Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for prediction of radiation-induced neurocognitive dysfunction. Clin Cancer Res. 2009;15:1747–54.
117. Hahn CA, Zhou SM, Raynor R, et al. Dose-dependent effects of radiation therapy on cerebral blood flow, metabolism, and neurocognitive dysfunction. Int J Radiat Oncol Biol Phys. 2009;73:1082–7.
118. Sato K, Kameyama M, Kayama T, et al. Serial positron emission tomography imaging of changes in amino acid metabolism in low grade astrocytoma after radio- and chemotherapy. Neurol Med Chir (Tokyo). 1995;35:808–12.
119. Walter A, Mulhern R, Grajjar A et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at St. Jude Children's Research Hospital. J Clin Oncol. 1999;17:3720–3728.
120. Radcliffe J, Bunin G, Sutton L, et al. Cognitive deficits in long-term survivors of childhood medulloblastoma and other noncortical tumors: Age-dependent effects of whole brain radiation. Int J Develop Neurosci. 1994;12:327–34.
121. Blowers E, Hall K. Adverse events in bevacizumab and chemotherapy: patient management. British Journal of Nursing. 2009;18:424–8.
122. Shiminski-Maher T, Cullen P, Sansalone M. Childhood brain and spinal cord tumors: a guide for families, friends, and caregivers. Sebastopol, CA: O'Reilly and Associates; 2002.
123. Fischer D, Knobf MT. The cancer chemotherapy handbook. St. Louis, MO: Mosby Year Book; 1989.
124. Erbetta A, Salmaggi A, Sghirlanzoni A, et al. Clinical and radiological features of brain neurotoxicity caused by antitumor and immunosuppressant treatments. Neurol Sci. 2008;29:131–7.
125. Perry A, Schmidt RE. Cancer therapy-associated CNS neuropathology: an update and review of the literature. Acta Neuropathol. 2006;111:197–212.
126. Meyers CA. How chemotherapy damages the nervous system. J Biol. 2008;7:II.
127. Reardon DA, Gilbert MR, Wick W, and Liau L. Immunotherapy for neuro-oncology: the critical rationale for combinatorial therapy. Neuro Oncol. 2015;17(7):vii32–vii40.

128. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015;16(15):e534–3542.
129. van West SE, de Bruin HG, van de Langerijt B, Swaak-Kragten AT, van den Bent MJ, Taal W. Incidence of pseudoprogression in low-grade gliomas treated with radiotherapy. Neuro-Oncology. 2017;19(5):719–25.
130. Okada H, Kohanbash G, Zhu X, Kastenhuber ER, Hoji A, Ueda R, et al. Immunotherapeutic approaches for glioma. Crit Rev Immunol. 2009;29:1–42.
131. McGinnis GJ, Raber J. CNS side effects of immune checkpoint inhibitors: Preclinical models, genetics, and multimodality therapy. Immunotherapy. 2017;9(11):929–41.

Chapter 5

Multiple System Atrophy, Orthostatic Hypotension, and Autonomic Dysfunction and Cognition

Cecilia Peralta

Introduction

Multiple system atrophy (MSA) is a sporadic and rapidly progressive degenerative disorder of the central and autonomic nervous system, affecting both men and women, primarily in their fifties, with a prevalence rate of 1.0–4.0 individuals per 100,000 population [1].

The complex disorder is characterized by symptoms of autonomic nervous system failure along with parkinsonism, cerebellar ataxia, and pyramidal signs either in a pure form or in any combination.

At the present time, MSA is the name conceived to describe three disorders previously known as Striatonigral degeneration (predominant parkinsonian features, currently MSA-P), sporadic olivopontocerebellar atrophy (predominant cerebellar signs, currently MSA-C), and the Shy–Drager syndrome (predominant autonomic dysfunction).

MSA relentlessly progresses over the years to cause more widespread compromise of different systems within the central nervous system, hence the name of "multiple system atrophy," including cognitive dysfunction and depression.

Clinical Features

In a series of 100 patients (67 men and 33 women), studied by Wenning and coworkers, it was observed that the disease began with autonomic manifestations universally present in 41–74% of patients at later stages [2]. During the course of the disease, orthostatic hypotension (OH) arose in eventually almost all patients. Progressive urogenital dysfunction was the most frequent initial complaint in women, and erectile dysfunction was almost always present in men. Orthostatic hypotension, defined as a reduction of systolic blood pressure (BP) of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 min of standing, was common and occurred in at least 68% of patients, manifesting clinically as light-headedness; dizziness; dimming of vision; head, neck, or shoulder pain; weakness of the legs; fatigue; yawning; and less frequently syncope.

In the autonomic laboratory setting, OH must be distinguished from postural tachycardia syndrome, which is defined as an increase in the heart rate greater than 40 beats/min and maintained BP [3]. In some cases, MSA patients may suffer from a combination of supine hypertension

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Table 5.1 Features supporting (red flags) and not supporting a diagnosis of MSA

Supporting features	Nonsupporting features
Orofacial dystonia	Classic pill-rolling rest tremor
Disproportionate antecollis	Clinically significant neuropathy
Camptocormia (severeanterior flexion of the spine) and/or Pisa syndrome (severe lateralflexion of the spine)	Hallucinations not induced by drugs
	Onset after age 75 years
	Family history of ataxia or parkinsonism
Contractures of hands or feet	Dementia (on DSM-IV)
Inspiratory sighs	White matter lesions suggesting multiple sclerosis
Severe dysarthria	
Severe dysphonia	
New or increased snoring	
Cold hands and feet	
Pathologic laughter or crying	
Jerky, myoclonic postural/action tremor	

and OH, which is sometimes severe (>190/110 mmHg) and complicates the treatment of OH [4].

Parkinsonian features were observed in 46% of patients who presented bradykinesia and rigidity, generally symmetrical. Rest tremor was observed in 29% of patients, although a classical pill-rolling tremor as seen in Parkinson's disease (PD) was not frequently present. Instead, tremor in MSA is usually an irregular jerky postural and action tremor, characterized phenomenologically as myoclonic jerks, which are sometimes touch or stretch sensitive [5]. A particular motor feature of MSA-P is the occurrence of a disproportionate antecollis (cervical dystonia). According to the European MSA Study Group (EMSA-SG), antecollis is a red flag that distinguishes between MSA-P and PD [6] (see Table 5.1).

Another striking feature of parkinsonism in MSA is the tone of the voice, which is typically quivering and strained, as opposed to PD where it is monotonous and hypophonic.

The parkinsonian symptoms are for the most part unchanged by levodopa, and most patients show a poor response (fewer than 30%), although some of them may have a good or even excellent response to levodopa earlier in the course of the disease.

Cerebellar symptoms were encountered in 5% of the patients at the initial stages, in whom gait and limb ataxia or dysmetria, slurred speech, and abnormal eye movements were frequently observed.

In a recent study by Anderson et al., who reviewed the oculomotor findings in 30 patients with probable MSA, square wave jerks were observed in 21 of 30 patients, gaze-evoked nystagmus in 12 of 30 patients, positioning downbeat nystagmus in 10 of 25; mild or moderate saccadic hypometria in 22 of 30; and impaired ("broken up") smooth pursuit in 28 of 30 [7].

In another review of 203 pathologically proven MSA patients by Wenning et al., they found that the compromise of the pyramidal tract included unilateral or bilateral extensor plantar responses together with hyperreflexia and/or spasticity [8]. Other symptoms such as vocal cord paralysis developed less frequently and may lead to hoarseness and stridor.

Recently there has been an increasing interest in describing the sleep disorders associated with MSA. In this line, it has been pointed out that the vocal cord paralysis may also lead to a neurogenic and obstructive mixed form of sleep apnea, reflecting the loss of cholinergic neurons in the arcuate nucleus of the ventral medulla [9]. Other sleep disorders, such as REM behavior disorder (RBD), typically occurring in synucleinopathies (a group of neurodegenerative disorders

characterized by fibrillary aggregates of alpha-synuclein protein in the cytoplasm of selective populations of neurons and glia) such as PD or MSA as a consequence of brainstem involvement, are more accentuated in patients with MSA in contrast to PD according to Iranzo et al. [10].

MSA patients also suffer from a greater periodic leg movement index, and less total sleep time, reflecting the loss of cholinergic mesopontine neurons, in the setting of loss of locus coeruleus neurons and the preservation of rostral raphe neurons [10].

Finally, a majority of them also display abnormalities of the microcirculation with peripheral edema, Raynaud's Syndrome or pericold, dusky, and violaceous extremities [5, 11].

Diagnosis

The diagnosis in life of MSA can be difficult, especially at earlier stages of the disease, where MSA-P and PD share many similarities. The criteria to define MSA were recently reviewed [12]; however, the classification in levels of diagnostic certainty remains as definite, possible, and probable MSA (see Table 5.2).

Table 5.3 Clinical domains

1. Autonomic and urinary dysfunction
Orthostatic hypotension with blood pressure falling by at least 20 mmHg and/or 10 mmHg diastolic within 3 min of standing
Urinary incontinence as persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men
2. Parkinsonism
Bradykinesia – slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions
Rigidity – muscle stiffness
Postural instability not caused by primary visual, vestibular cerebellar, or proprioceptive dysfunction Tremor – postural, resting or both
3. Cerebellar dysfunction
Gait ataxia (wide-based stance with steps of irregular length and direction)
Ataxic dysarthria
Limb ataxia
Sustained gaze-evoked nystagmus

The previous distinction between features (clinical findings) and criteria (features used for diagnosis) was simplified, since this classification was found confounding.

The current criteria require direct description of clinical findings for possible and probable MSA, which include three domains: (1) autonomic

Table 5.2 Diagnostic categories of MSA

Category	Definition
Possible MSA	A sporadic progressive adult (>30 years) onset disease characterized by:
	Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
	A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) *and*
	At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) *and*
	At least one of the features showed in Table 5.5
Probable MSA	A sporadic, progressive, adult (>30 years) onset disease characterized by
	Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic *and*
	Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor or postural instability) *or*
	A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)
Definitive MSA	Pathologically confirmed by presence of high density of GCIs in association with degenerative changes in nigrostriatal and olivopontocerebellar pathways

Table 5.4 Additional features of possible MSA

Possible MSA-P or MSA-C
Babinski sign with hyperreflexia
Stridor
Possible MSA-P
Rapidly progressive parkinsonism
Poor response to levodopa
Postural instability within 3 years of motor onset
Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
Dysphagia within 5 years of motor onset
Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C
Parkinsonism (bradykinesia and rigidity)
Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
Hypometabolism on 18FDG-PET in putamen
Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

and/or urinary dysfunction, (2) parkinsonism, and (3) cerebellar dysfunction (see Table 5.3).

The main differences between the previous and the current set of criteria are for possible MSA, which includes clinical and imaging results to increase the diagnostic accuracy in patients with parkinsonian features or cerebellar dysfunction plus autonomic symptoms that do not meet the level needed for the diagnosis of probable MSA (see Table 5.4).

Neurological tests: There is no single specific test that can help in the diagnosis of MSA, which is made by a neurologist based on the history of symptoms, a physical examination, and by ruling out other causes. However, an assessment of the sympathetic and parasympathetic function may help to detect autonomic dysfunction in the autonomic laboratory setting.

The single most useful measure is an otherwise unexplained drop in systolic blood pressure (BP) of at least 20 mmHg and/or diastolic BP of at least 10 mmHg within 3 min of standing, documenting the existence of OH, one of the most relevant symptoms of dysautonomia. Other tests composing an "autonomic battery," such as the Valsalva maneuver, the isometric exercise (handgrip), or the cold pressor stimuli, are useful. A sphincter electromyography (EMG) may also be helpful showing hyperreflexia of a detrusor in detecting increased voltage, duration, and polyphasia of the motor unit potentials, which may correlate with urinary dysfunction and should ideally be performed by an expert because of the possible diagnostic pitfalls. Moreover, it is remarkable that a normal result should be considered an evidence against MSA diagnose [13].

A functional imaging technique using ([^{123}I] MIBG) cardiac scintigraphy can differentiate between pre- and postsynaptic sympathetic denervation [14]. In MSA, the postsynaptic function is preserved, usually displaying normal results in cardiac MIBG as opposed to PD where there is a presynaptic involvement.

The levodopa challenge is useful to quantify the motor response to levodopa and to differentiate among an excellent, good, or poor dopaminergic effect and, therefore, to classify the parkinsonian syndrome as responsive or unresponsive to levodopa.

Neuroimaging: The initially clinical diagnosis of MSA has been further enhanced by modern imaging techniques, and the recently revised consensus criteria include now neuroimaging criteria for the diagnosis of possible MSA.

MRI can disclose abnormalities of the basal ganglia and brainstem and is useful in excluding cerebrovascular lesions and other etiologies.

Two basic abnormalities have been found in MSA according to Schrag et al.: putaminal and brainstem hyperintensities and infratentorial atrophy [15]. A typical finding of MSA is the hyperintense rim at the lateral putaminal edge, putaminal atrophy, and putaminal hyperintensity, which were observed only in MSA patients out of a series of 47 PD patients and 45 controls.

At an infratentorial level, atrophy of the cerebellum was one of the most consistent changes, along with atrophy of the middle cerebellar peduncles (MCP), which was the single most useful marker to differentiate PD from

MSA. Signal change at the level of the pons, the midbrain, and the middle cerebellar peduncles was also frequently observed. Pontine hyperintensities can be cruciform resembling a "hot cross bun," whereas those of the middle cerebellar peduncles and the cerebellar hemisphere were frequently diffused. However, the absence of any of these changes does not exclude the diagnosis of multiple system atrophy.

Positron emission tomography 2-[fluorine-18] fluoro-2-deoxy-D-glucose PET (FDG-PET) can be used to differentiate MSA and PD, showing that the caudate–putamen index is lower in patients with MSA than in patients with PD, as well as reduced cerebellar glucose metabolism in MSA-C [16].

In conclusion, atrophy on conventional MRI of putamen, MCP, pons, or cerebellum or hypometabolism on FDG-PET in putamen, brainstem, or cerebellum were included as additional features for possible MSA-P; and atrophy on conventional MRI of putamen, MCP, or pons or hypometabolism on FDG-PET in putamen was included as additional features for possible MSA-C [17].

Pathology

The pathology of MSA is characterized by a progressive loss of neuronal and oligodendroglial cells and gliosis in numerous sites in the central nervous system, of unknown etiology, involving the putamen, caudate nucleus, substantia nigra, locus ceruleus, pontine nuclei, inferior olivary nucleus, Purkinje cells, and intermediolateral cell columns [18].

The presence of typical glial cytoplasmic inclusions (GCIs), immunoreactive for ubiquitin and alpha-synuclein, is considered the hallmark of the disease. However, whether the inclusions represent primary lesions or nonspecific secondary markers of cellular injury remains undetermined.

The loss of preganglionic sympathetic neurons in the intermediolateral cell column has been associated with OH [19] and the loss of parasympathetic neurons and motor neurons of the Onuf nucleus at spinal cord levels S2–S4 with the urologic manifestations [9]. For a more detailed correlation between the clinical symptoms and the pathology see Table 5.5.

Table 5.5 Clinicopathologic correlations

Clinical symptom	Pathologic findings and location of cell loss
Orthostatic hypotension	Primary preganglionic damage of intermediolateral cell columns
Urinary incontinence	Preganglionic cell loss in spinal cord (intermediolateral cell columns), related to detrusor hyperreflexia caused mainly by loss of inhibitory input to pontine micturition center (rather than to external urethral sphincter denervation)
Urinary retention	Sacral intermediolateral cell columns
Cerebellar ataxia	Cell loss in inferior olives, pontine nuclei, and cerebellar cortex
Pyramidal signs	Pyramidal tract demyelination
Motor abnormalities	GCIs in cortical motor areas or basal ganglia
Akinesia	Putamen, globus pallidus
Rigidity	Putaminal (not nigral) damage
Limb and gait ataxia	Inferior olives, basis pontis
Decreased or absent levodopa	Striatal cell loss, loss of D1 and D2 receptors in striatum
Nystagmus	Inferior olives, pontine nuclei
Dysarthria	Pontine nuclei
Laryngeal stridor	Severe cell loss in nucleus ambiguous or biochemical defect causing atrophy of posterior cricoarytenoid muscles

Cognition, Attention, and Depression in MSA

Of great interest in the last years has been the relevance of certain aspects of the disease such as cognition, attention, and depression, considering that dementia represents an absolute exclusion criterion for the diagnosis of MSA.

Earlier studies assessing cognitive function in patients with MSA-P encountered deficits in tests evaluating frontal lobe function and attention, somewhat similar to the deficits occurring in PD. In a seminal study of cognition in MSA, Robbins et al. studied MSA-P, PD, and Alzheimer's disease patients using tests of frontal lobe function and a battery sensitive to memory and learning. They observed in MSA patients impairment in spatial working memory and in the speed of thinking, reproducing a pattern of prominent frontal lobe-like component [20].

When other aspects of cognition were also studied in MSA-C patients, it was observed that neither patients nor controls presented dementia and they did not differ with respect to verbal and performance IQ [21]. The analysis of attention did not reveal significant differences between patients and controls, but in contrast, the assessment of verbal memory revealed an impairment not only in the immediate but also in the delayed recall of all types of word lists. Visuospatial function was preserved, but in fronto-executive functions.

MSA-C subjects tended to achieve lower scores and produced more perseverative and random errors than healthy controls, showing that MSA-C as well as MSA-P patients present prefrontal lobe dysfunction.

The prefrontal dysfunction may occur secondary to cerebral cortex degeneration in parallel to the compromise of the pontocerebellar system or may happen as a consequence of the disruption of cerebro-cerebellar connections with the frontal cortex, as shown by imaging studies demonstrating cerebellar activation during the performance of executive and verbal memory tasks [22].

However, the executive deficits may also correlate with the degeneration of subcortical structures, resulting from a disruption of a cortico-striatal thalamocortical circuitry connecting the frontal cortex to the basal ganglia and thalamus, although the frontal lobe was morphologically intact, as occurring in MSA-P patients without cerebellar disease.

Attention is part of the core of the cognitive system. However, attention in MSA has not been extensively investigated until recently. In 2006, Meco et al. reported on the evaluation of attention in MSA and PD patients using tests of attentional set shifting, memory, and conceptual thinking as well as motor and verbal fluency [23].

They observed no differences in verbal fluency and short-term memory, but both groups showed impairment in conceptual thinking and motor function. When attention and the results of the Stroop Test and Trail Making were analyzed, it was observed that the execution time of MSA patients was significantly longer than that of PD patients. MSA patients also made significantly greater number of errors in the Stroop effect and were unable to switch attention from one stimulus attribute to another (alternating condition).

This selective attention impairment in MSA has been related to the depletion of central processing resources and to dysfunction of the supervisory attentional system [24], which is an automatic mechanism of attentional control derived from an information processing model of frontal lobe function, according to Norman and Shallice.

In MSA, the attentional deficits may also be related to the presence of striatal (caudate plus putamen) damage to the dopaminergic pathway. The caudate–thalamus–frontal cortex loop mediates executive functions and motor programming, and it is modulated by the dopaminergic pathway and affected by a more marked dopaminergic deficit in the caudate. Recent studies have localized the attentional impairment in MSA to the mesial and dorsolateral prefrontal regions as the loci of activation during sustained attention and performances in sensitive tests of shifting attention. The slowness of information processing is likely to have its anatomical base at the dorsolateral circuit structures and might thus be responsible for the attentional deficits observed in patients with MSA.

Mood

Recently it has been reported that depression does not appear to be more marked in MSA patients based on Beck Depression Inventory (BDI) scores and Hamilton Depression Rating Scale (HDRS), as opposed to PD patients [22]. Herting et al. studied prefrontal alterations in brain function associated with depression in patients with MSA and progressive supranuclear paralysis (PSP). Patients were screened for the diagnostic criteria of a major depressive episode [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)] and the severity of symptoms was assessed using the HDRS (17-item version). They also underwent measurement of cerebral glucose metabolism applying positron emission tomography with 18FDG-PET. When compared to controls, MSA patients showed significant metabolic decrease in bilateral frontal, parietal, and cerebellar cortex and in the left putamen, and depression severity was significantly associated with dorsolateral prefrontal glucose metabolism, supporting the hypothesis that depressive symptoms in MSA are associated with prefrontal dysfunction.

The North American Multiple System Atrophy Study Group also investigated the relationship of life satisfaction and depressive symptoms in 98 MSA patients [25]. The study revealed low life satisfaction, with a mean of 38.8 on a 100-point visual analogue scale (0 = extremely dissatisfied, 100 = extremely satisfied), with 35% of patients reporting moderate to severe depressive symptoms on the Beck Depression Inventory (BDI $\geq$ 20), highlighting that depressive symptoms may be an important determinant of life satisfaction in addition to disease-related factors.

Another study led by Fetoni et al. evaluated the extent to which psychiatric disturbances (especially mood disorders) were present in patients with MSA-P compared with PD patients at baseline and after receiving levodopa using the Hamilton (HAM-D), brief psychiatric rating scale (BPRS), and Unified Parkinson's disease rating scale (UPDRS) [26]. At baseline PD patients were more depressed and anxious than patients with MSA who showed blunted affect. After levodopa, depression and anxiety improved significantly in patients with PD, while MSA patients showed no change in the affective mood, suggesting that the major neuronal loss in the caudate and ventral striatum, which are part of the lateral orbitofrontal and limbic circuits, may be responsible for the blunted affect unresponsive to levodopa occurring in these patients.

Treatment

Parkinsonism

Parkinsonism is the core motor syndrome which offers a major target for therapeutic interventions, since the other motor features of MSA offer less opportunities to permit an adequate pharmacological management. L-Dopa replacement represents the main strategy of antiparkinsonian therapy in MSA. Open-label studies suggest that a good but transient initial benefit from L-dopa therapy may occur early in the disease, although in the long term most patients fail to recognize a benefit. On the contrary, adverse events or intolerance to L-dopa therapy may occur, i.e., accentuation of OH following L-dopa intake.

When L-dopa intake aggravates OH, the negative impact of this adverse event is frequently perceived by the patient as more relevant than the long-term benefit derived, leading occasionally to discontinuation of the dopaminergic therapy.

The classical generalized choreodystonic L-dopa-induced dyskinesia is rarely seen in MSA patients, as opposed to PD. However, in MSA patients dyskinesias often predominate in the neck or face under the phenomenology of dystonia [27]. As occurring with L-dopa, there are no sufficiently well-designed double-blind trials to specifically assess the efficacy and tolerability of dopamine agonists in the treatment of MSA. In a trial using doses of 10–80 mg daily of bromocriptine, Goetz and colleagues reported benefit in five patients who had responded to L-dopa [28].

There are currently no published series of MSA patients investigating the efficacy of other dopamine agonists such as cabergoline, ropinirole, or pramipexole. Anticholinergics may be usefully employed when sialorrhea (excessive secretion of saliva) is severe, although the side effects such as aggravating constipation or dry mouth may occur. The experience of surgery in MSA is still limited. Case reports of pallidotomy or subthalamic nucleus deep brain stimulation (STN DBS) show that the results are not uniform and in most cases failed to improve parkinsonian motor signs in the long run. In other studies, DBS improved L-dopa responsive upper extremity bradykinesia but aggravated speech, swallowing, and gait [29].

Cerebellar Dysfunction

There are few experience-based observations in treatment of cerebellar dysfunction available in MSA. Drugs such as clonazepam or valproate may be beneficial in ameliorating tremor or myoclonus when they are prominent. Some anecdotal responses to amantadine, 5-hydroxytryptophan, isoniazid, baclofen, or propanolol have been reported, although in the majority of patients these drugs showed no clear benefit [30].

Dysautonomia

Peripherally acting anticholinergics improving the detrusor hyperreflexia is the treatment suggested for urological symptoms [31]. Special attention, however, should be paid to the occurrence of side effects such as urinary retention, dry mouth, constipation, blurred vision, and drowsiness. Drugs such as oxybutynin, trospium chloride, tolterodine for detrusor hyperreflexia or prazosin, moxisylyte, tamsulosin, and alfuzosin for incomplete bladder emptying are suggested. In MSA patients with incomplete bladder emptying, clean intermittent catheterization 3–4 times/day can be helpful in case of failure to initiate micturition. In advanced stages, an urethral or transcutaneous suprapubic catheter may be necessary [30]. The necessity of a specific treatment of sexual dysfunction needs to be evaluated individually in each MSA patient. Anecdotal reports suggest that sildenafil citrate may also be successful in treating erectile failure in MSA patients [32].

Orthostatic Hypotension

Indeed, the treatment of OH is the area of autonomic disorders in which more investigation and effective interventions are available. The objective of the medical treatment is to increase blood volume by increasing sodium intake and the management comprises pharmacological and nonpharmacological measures.

The initial recommendation is to avoid the effects of contributing factors known to aggravate OH such as prolonged recumbency, mealtime, physical exertion, heat, alcohol, coughing, and defecation [33, 34]. Nonpharmacological options include sufficient fluid intake, high-salt diet, more frequent, but smaller meals per day to reduce postprandial hypotension, and the use of elastic body garments. During the night, a head-up tilt increases intravasal volume due to an increase of secretion of renin secondary to a reduced renal perfusion pressure and a reduction of atrial natriuretic hormone [30].

Pharmacological measures include the use of two basic groups of drugs. One of them is the mineralocorticoid fludrocortisone which further increases the sodium retention. The other group is the vasoactive agents like midodrine, an adrenergic agonist activating the 1-receptors on arterioles and veins inducing increase of peripheral resistance, an effect demonstrated in randomized, controlled studies [35, 36]. L-Threo-dihydroxyphenylserine (L-threo-DOPS) is a synthetic catechol amino acid which increases standing blood pressure and improves standing ability in patients with neurogenic orthostatic hypotension by conversion of L-DOPS to norepinephrine [37]. Other

drugs such as the somatostatin analogue octreotide are beneficial in treating postprandial hypotension by inhibiting the release of vasodilatory gastrointestinal peptides [38].

The vasopressin analogue desmopressin, which acts on renal tubular vasopressin-2 receptors, reducing nocturnal polyuria and improving morning postural hypotension, improves nocturnal waking in urination (nocturia) which is a common feature in patients with MSA. The degeneration of arginine vasopressin neurons in the suprachiasmatic nucleus may lead to polyuria [39]. The peptide erythropoietin may be beneficial in increasing the red cell count in selected MSA patients with symptomatic OH and anemia, secondarily improving cerebral oxygenation. The release of erythropoietin is under sympathetic control and in patients with MSA may be associated with normocytic normochromic anemia and erythropoietin deficiency [40].

Constipation can be relieved by increasing the intraluminal volume, using macrogol-water solution. A daily use of dietary fiber, adequate liquid intake, and laxatives is useful. To treat the excessive drooling that may occur in MSA, systemic anticholinergic drugs and the use of botulinum toxin into the parotid and submandibular gland are useful strategies [30].

Conclusions and Future Directions

The management of this disorder includes symptomatic and palliative strategies, as well as family education and support, being the ultimate goal to improve the quality of life of patients and caregivers, to make the patient more comfortable, and to preserve body functions as long as possible.

There is a great need for specific and sensitive tests to earlier and better diagnose MSA. Toward this objective, clinical trials assessing diagnostic and prognostic biomarkers in PD and MSA or SPECT in parkinsonian syndromes are ongoing. Other investigational lines regarding therapeutic interventions, such as management of OH in PD and MSA, or treatment of supine hypertension in autonomic failure, or the effect of riluzole as symptomatic approach in patients with chronic cerebellar ataxia, are under continuous investigation.

Future therapeutic strategies include stereotaxic interventions also. The experience with STN DBS is limited and the response is also limited, suggesting that other targets or procedures are warranted. However, during the past decade, there have been major advances in the understanding of the cellular pathology and the clinical features of MSA.

The knowledge obtained in the clinical and pharmacological field of MSA will permit along with the ongoing research initiatives the possibility of more options to improve the diagnosis and treatment of this rapidly evolving disorder and, even if negative, to stimulate further interest in trials and future venues of investigation in MSA.

References

1. Wenning GK, Geser F. Multiple system atrophy. Rev Neurol (Paris). 2003;159:S31–8.
2. Wenning GK, Ben Shlomo Y, Magalhães M, et al. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain. 1994;117:835–45.
3. Kaufmann H, Biaggioni I. Autonomic failure in neurodegenerative disorders. Semin Neurol. 2003;23:351–63.
4. Goldstein DS, Pechnik S, Holmes C, et al. Association between supine hypertension and orthostatic hypotension in autonomic failure. Hypertension. 2003;42:136–42.
5. Niall P. Quinn, how to diagnose multiple system atrophy. Mov Disord. 2005;20:S5–10.
6. Kollensperger M, Geser F, Seppi K, et al., on behalf of the European MSA Study Group (EMSA-SG). Red flags for multiple system atrophy. Mov Disord. 2008;28:1093–9.
7. Anderson T, Luxon L, Quinn N, et al. Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients. Mov Disord. 2008;28:977–84.
8. Wenning GK, Tison F, Ben Shlomo Y, et al. Multiple system atrophy: a review of 203 pathologically proven cases. Mov Disord. 1997;12:133–47.
9. Eduardo E. Benarroch brainstem in multiple system atrophy: clinicopathological correlations. Cell Mol Neurobiol. 2003;23(4–5):519–26.

10. Iranzo A, Santamaría J, Rye DB, et al. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology. 2005;26:247–52.
11. Reich SG. The cold hands sign in MSA. Multiple system atrophy. Neurology. 2003;60:719.
12. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008;71(9):670–6.
13. Paviour DC, Williams D, Fowler CJ, Quinn NP, Lees AJ. Is sphincter electromyography a helpful investigation in the diagnosis of multiple system atrophy? A retrospective study with pathological diagnosis. Mov Disord. 2005 Nov;;20(11):1425–30..
14. Courbon F, Brefel-Courbon C, Thalamas C, et al. Cardiac MIBG scintigraphy is a sensitive tool for detecting cardiac sympathetic denervation in Parkinson's disease. Mov Disord. 2003;18:890–7.
15. Schrag A, Kingsley D, Phatouros C, et al. Clinical usefulness of magnetic resonance imaging in multiple system atrophy. J Neurol Neurosurg Psychiatry. 1998;65:65–71.
16. Otsuka M, Kuwabara Y, Ichiya Y, et al. Differentiating between multiple system atrophy and Parkinson's disease by positron emission tomography with 18F-dopa and 18F-FDG. Ann Nucl Med. 1997;11:251–7.
17. Brooks DJ, Seppi K. Proposed neuroimaging criteria for the diagnosis of multiple system atrophy. Neuroimaging Working Group on MSA. Mov Disord. 2009;24:949–64.
18. Llantos PL. The definition of multiple system atrophy: a review of recent developments. J Neuropathol Exp Neurol. 1998;57:1099–111.
19. Spokes EG, Bannister R, Oppenheimer DR. Multiple system atrophy with autonomic failure: clinical, histological and neurochemical observations on four cases. J Neurol Sci. 1979;43:59–82.
20. Robbins TW, James M, Lange KW, et al. Cognitive performance in multiple system atrophy. Brain. 1992;115:271–91.
21. Bürk K, Daum I, Rüb U. Cognitive function in multiple system atrophy of the cerebellar type. Mov Disord. 2006;21:772–6.
22. Herting B, Beuthien-Baumann B, Pöttrich K, et al. Prefrontal cortex dysfunction and depression in atypical parkinsonian syndromes. Mov Disord. 2007;15:490–7.
23. Meco G, Gasparini M, Doricchi F. Attentional functions in multiple system atrophy and Parkinson's disease. J Neurol Neurosurg Psychiatry. 1996;60:393–8.
24. Norman D, Shallice T. Attention to action: willed and automatic control of behavior. San Diego, CA: University of California CHIP report 99; 1980.
25. Gilman S, May SJ, Shults CW, et al. The North American multiple system atrophy study group. J Neural Transm. 2005;112:1687–94.
26. Fetoni V, Soliveri P, Monza D, et al. Affective symptoms in multiple system atrophy and Parkinson's disease: response to levodopa therapy. J Neurol Neurosurg Psychiatry. 1999;66:541–4.
27. Boesch SM, Wenning GK, Ransmayr G, et al. Dystonia in multiple system atrophy. J Neurol Neurosurg Psychiatry. 2002;72:300–3.
28. Goetz CG, Tanner CM, Klawans HL. The pharmacology of olivopontocerebellar atrophy. Adv Neurol. 1984;41:143–8.
29. Tarsy D, Apetauerova D, Ryan P, et al. Adverse effects of subthalamic nucleus DBS in a patient with multiple system atrophy. Neurology. 2003;61:247–9.
30. Wenning GK, Geser F, Poewe W. Therapeutic strategies in multiple system atrophy. Mov Disord. 2005;20(Suppl 12):S67–76.
31. Beck RO, Betts CD, Fowler CJ. Genitourinary dysfunction in multiple system atrophy: clinical features and treatment in 62 cases. J Urol. 1994;151:1336–41.
32. Zesiewicz TA, Helal M, Hauser RA. Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. Mov Disord. 2000;15:305–8.
33. Mathias CJ. Orthostatic hypotension: causes, mechanisms, and influencing factors. Neurology. 1995;45: S6–11.
34. Robertson D, Davis TL. Recent advances in the treatment of orthostatic hypotension. Neurology. 1995;45:S26–32.
35. Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. Am J Med. 1993;95:38–48.
36. Low PA, Gilden JL, Freeman R, et al. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA. 1997;277:1046–51.
37. Goldstein DS, Holmes C, Kaufmann H. Clinical pharmacokinetics of the norepinephrine precursor L-threo-DOPS in primary chronic autonomic failure. Freeman RClin Auton Res. 2004;14:363–8.
38. Bordet R, Benhadjali J, Libersa C, et al. Octreotide in the management of orthostatic hypotension in multiple system atrophy: pilot trial of chronic administration. Clin Neuropharmacol. 1994;17:380–3.
39. Sakakibara R, Matsuda S, Uchiyama T, et al. The effect of intranasal desmopressin on nocturnal waking in urination in multiple system atrophy patients with nocturnal polyuria. Clin Auton Res. 2003;13:106–8.
40. Winkler AS, Landau S, Watkins P, et al. Observations on haematological and cardiovascular effects of erythropoietin treatment in multiple system atrophy with sympathetic failure. Clin Auton Res. 2002;12:203–06.

Part II
Vascular System Disease

Chapter 6

Cardiovascular Disease and Neurocognitive Function

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Cardiovascular (CV) diseases are the leading cause of morbidity and mortality in the USA and most Westernized nations [1, 2]. CV risk factors and diseases confer substantial increase in risk for ischemic and hemorrhagic stroke [3]. Yet, outside the context of clinical stroke, the brain is an under-recognized target organ of a spectrum of CV diseases. Although it has long been known that CV risk factors and diseases contribute to the development of vascular (previously known as multi-infarct) dementia, we now know that similar risk is conferred for Alzheimer's disease (AD) [4].

Recent research suggests that the patterns of cognitive impairment associated with vascular dementia (VaD) and AD may not be as etiologically distinct as previously assumed [5, 6]. Indeed, it is likely that most dementia is "mixed," with involvement of both vascular and neurodegenerative pathology [7, 8]. Accordingly, mounting evidence indicates a number of common pathways through which CV risk and protective factors may impact the development of both CV diseases and these major forms of dementia [9–12]. The paths connecting CV risk factors and diseases with dementia are likely multifold. That is, CV risk factors and diseases may directly or indirectly impact dementia pathology or these disease entities may only share similar risk factors.

Importantly, long before clinical manifestations of stroke or dementia are apparent, CV risk factors and diseases negatively impact the brain and neurocognitive function. Consistent with Hachinski's formulation of vascular cognitive impairment and its gradual progression [13], we have proposed that there is a continuum of neurocognitive and neurobiological impairment associated with increasingly severe manifestations of CV disease that, in some individuals, ultimately leads to a dementia and/or stroke [14]. This is a process that occurs across the life span.

In this chapter, we provide a broad overview of current knowledge pertaining to the relation of CV risk factors and diseases to dementia, neurocognitive function, and the brain. Here we are seeking breadth, rather than depth, of coverage in order to highlight complexities with respect to the interrelations among the risk factors and diseases of interest. Whenever possible, we refer to more detailed available reviews. Although we

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acknowledge the presence of mixed findings in most areas reviewed, here we highlight positive associations for ease of presentation. We first briefly review classification of CV risk factors and diseases. Next, in our review of neurocognitive function we follow roughly the natural history of CV disease pathogenesis and its linked treatments. While reading this chapter, it is critical to bear in mind that CV risk factors and diseases tend to aggregate among affected individuals. Further, pathologic alterations in the CV system often co-occur with dysfunction of the metabolic, renal, immune, pulmonary, and other physiological systems. In each section we seek to address the following questions as per our suggested research agenda [15]: (a) What domains of cognitive function are affected? (b) What are relevant vulnerability or resilience factors? (c) What are the mechanisms underlying the noted relations?

Cardiovascular Disease Classification

To help ensure standardization of disease reporting, epidemiologists and clinicians in the USA and elsewhere typically classify CV and other diseases based on the International Classification of Diseases (ICD) codes published by the World Health Organization [16]. CV disease is part of the broadly defined diseases of the circulatory system (ICD-10 I00–I99, Q20–Q28). Many studies use the definitions initially adopted by the Framingham Heart Study which define CV disease as comprised of (1) coronary heart disease (CHD) (coronary death, myocardial infarction (MI), coronary insufficiency, and angina); (2) cerebrovascular disease (ischemic stroke, hemorrhagic stroke, and transient ischemic attack); (3) peripheral artery disease; and (4) heart failure [17, 18].

Using the broad ICD-10 definition, it is estimated that >80 million Americans have one or more types of CV disease, 73 million with hypertension, 16 million with CHD, 5.3 million with heart failure, and 5.8 million with stroke [1]. In addition, there is growing recognition of the importance of subclinical CV disease as assessed by a variety of noninvasive techniques (see below). These numbers quoted for prevalent CHD, stroke, and heart failure severely understate the burden of CV disease in the older adult population because much of the disease is subclinical. For example, electron beam tomography, a noninvasive technique to detect subclinical coronary artery calcification, an indicator of atherosclerotic plaque burden and CHD, showed that 38% of older adults in the Cardiovascular Health Study without any history of clinical CV disease had extensive coronary artery calcification (score >400) and 71% had evidence of subclinical atherosclerotic disease by low ankle–arm blood pressure index (ABI), major abnormalities on resting ECG, or internal carotid intima–media thickening on carotid ultrasound [19].

Cardiovascular Risk Factors and Neurocognitive Function

Traditional biomedical CV risk factors are well recognized, including hypertension, dyslipidemia, obesity, insulin resistance, and glucose intolerance. Newer biomarkers include measures of inflammation and oxidative stress, renal function, and homocysteine. Increased CV risk is conferred by a host of behavioral or lifestyle factors that include smoking, excessive alcohol consumption, poor diet, and physical inactivity. Some of these associations are complex and potentially nonlinear. It is increasingly recognized that various psychosocial and psychophysiological factors may also play a role in increasing CV risk. Here we examine relations of these biomedical (both traditional and new), behavioral, psychosocial, and psychophysiological CV risk factors to the brain, cognitive function, and dementia. However, first we begin with a description of two genetic polymorphisms that may link CV risk and dementia.

Genetics

At least two genotypes are known to be common to both CV disease and dementia. An association

between the apolipoprotein E (*APOE*) *ε4* allele and AD has been widely replicated in the literature [20], and the *APOE* genotype is also a risk factor for dyslipidemia, atherosclerosis, cardiac disease, and stroke [21]. The *APOE* genotype impacts CV risk largely through its role in the modulation of lipid transport. However, the mechanism(s) by which the *APOE* genotype is associated with AD remains unknown. The *APOE* genotype may lead to dementia indirectly via its effects on lipid metabolism and CV disease, but it is likely that other mechanisms operate as well. Possibilities include effects of the *APOE* genotype on beta-amyloid deposition and/or differential antioxidant properties of the various allele combinations [12]. The *APOE ε4* alleles have also been associated with lower levels of cognitive performance, cognitive decline, and changes in brain morphology prior to dementia [22]. Another gene of interest is *MEOX2*, a known cerebrovascular gene. At least one study has identified a relation between low expression of *MEOX2* and AD neuropathology [23].

Traditional Biomedical Risk Factors

To date, the most available literature addresses the relations of traditional biomedical CV risk factors to brain and cognitive outcomes. Here we examine hypertension, lipids, obesity, and glucose-related variables.

Hypertension/Antihypertensives

Hypertension is defined as a systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, taking antihypertensive medicine, or having been told at least twice by a physician or other health professional that one has hypertension [18]. Applying this definition, about one-third of adults have hypertension. More than 90% of those affected have primary or idiopathic hypertension. About 10% have secondary hypertension where there are underlying diseases (such as renovascular disease) that cause hypertension. There is also growing awareness of the health importance of "prehypertension" defined as untreated systolic BP of 120–139 mmHg or untreated diastolic BP of 80– 89 mmHg (and not having been told on two occasions by a health professional that one has hyper-tension) [18]. It is estimated that 37.4% of the US population >20 years of age has prehypertension [1]. Prehypertension markedly increases the risk for the development of overt hypertension and CV disease.

Hypertension has a major impact on morbidity and mortality. It is estimated that hypertension is associated with 5 years reduced overall life expectancy [24]. Yet, awareness of hypertension and adequate treatment and BP control in known hypertensives remains inadequate. Data suggest that perhaps 40% of all hypertensives do not meet their BP goals with resistant or difficult-to-control systolic hypertension being more common in older patients [25]. This is of major clinical importance as patients with poorly controlled hypertension are more likely to develop end-organ damage (e.g., heart failure, stroke, MI, and renal failure) and have a substantially higher long-term CV disease risk than patients with well-controlled BP.

It is well known that hypertension contributes significantly to the pathogenesis of stroke and VaD [1]. A growing literature links hypertension with AD as well [26, 27]. Evidence is strongest for a relation between midlife BP and development of AD, presumably due to the cumulative impact of long-standing hypertension [28]. In fact, several studies have suggested that midlife hypertension confers a similar degree of increased risk (approximately 3–4 times) for both VaD and AD [6, 29]. This heightened risk is thought to be primarily associated with hypertension's role in the pathogenesis of atherosclerosis [12].

Hypertension has been the most extensively studied of the traditional CV risk factors with respect to pre-stroke and pre-dementia cognitive performance (for review see [30]). The preponderance of early studies of the relation of BP to cognitive function contrasted the performance of those with diagnosed hypertension to persons with normal levels of BP (i.e., normotensives). Our review of those studies in 1991 suggested

that hypertensives performed more poorly than normotensives particularly on tests of executive function, learning and memory, and attention [31]. More current case–control studies continue to document lowered levels of cognitive performance in hypertensives in age cohorts ranging from children to the elderly in these and other domains of function such as perceptuo-motor and motor performance and visuospatial abilities [32–34]. Moreover, indices of arterial stiffening, a major factor underlying BP elevation particularly in older adults, have been associated with lowered levels of cognitive function and prospective cognitive decline [35]. Recent work further suggests that the relation of BP to cognitive function is nonlinear and may be "J shaped" such that both high and low levels of BP are associated with lower levels of cognitive performance and cognitive decline [36–38].

Since 1993, a host of epidemiological investigations have shown that higher levels of BP are associated with lowered levels of cognitive function and cognitive decline [33]. The chronicity of lifetime exposure to high levels of BP is a particularly important determinant of poor prospective cognitive outcomes [39]. Further, higher BP at midlife predicts poorer cognitive performance during older age [40]. Although duration of hypertension is likely an important influence on cognitive outcome, this variable is notoriously difficult to capture adequately given that the disease may go undetected for lengthy periods of time [30].

A number of vulnerability and resilience factors may moderate associations of high (or low) blood pressure or hypertension to cognitive function and decline [30]. Vulnerability to the potential cognitive consequences of hypertension is most pronounced at younger ages [41], among those with lower levels of education [42], in women [43], among those with *APOE e4* alleles [44, 45], and in hyperinsulinemic, diabetic, or obese persons [46–48]. The latter findings suggest that the cumulative impact of more than one CV risk factor may be multiplicative rather than additive. In addition, within hypertensives those with uncontrolled BP display the most pronounced cognitive difficulties [49, 50].

Various neurobiological mechanisms may underlie hypertension–cognition relations [30, 51]. These include neurophysiological factors such as reduced regional or global cerebral blood flow or metabolism, disruption of the blood–brain barrier, endothelial dysfunction, or other aspects of cellular dysfunction, all of which have been associated with hypertension. Neuroanatomical findings in hypertension include increased cerebral white matter disease, silent brain infarction, and brain atrophy, in addition to macrovascular disease.

Prospective investigations generally indicate better cognitive outcomes for those taking antihypertensive medication than untreated hypertensives [52]. Results of double-blind, placebo controlled trials of antihypertensives have yielded complex and conflicting findings [53] with similar numbers of studies suggesting positive, negative, or no impact. Our work and results of a recent meta-analysis suggest that whereas select measures of verbal memory appear to benefit from antihypertensive agents, measures of learning and perceptuo-motor speed may show decrement [54, 55].

Lipids/Statins

Dyslipidemia encompasses a range of disorders of lipoprotein lipid metabolism that include both abnormally high and low lipoprotein concentrations and abnormalities in the composition of these lipoprotein particles. Dyslipidemias are clinically important because of their role in the pathogenesis of CV disease. In clinical practice, a lipid or cholesterol panel commonly measures total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Higher levels of LDL-C promote atherosclerosis, whereas higher levels of HDL-C are in part protective against atherosclerosis. Higher levels of TG are associated with increased risk for atherosclerosis, but controversy remains as to whether elevated TG concentrations are independently causal in atherosclerosis. The consensus treatment

guidelines [56] for the management of dyslipidemia are continually being reevaluated and these guidelines have made the target lipoprotein concentrations more stringent for individuals with CV disease.

Epidemiological and clinical trial data suggest that the optimal concentration for LDL-C may be <100 mg/dL or even as low as 70 mg/dL for some high-risk patients with known CHD. The optimal concentration for the protective HDL-C may be >60 mg/dL. Desirable levels for TG are below 150 mg/dL, and perhaps as low as 80 mg/dL. The initial therapy for dyslipidemia usually consists of therapeutic lifestyle interventions that include diets reduced in saturated fat and cholesterol and increased in fiber and complex carbohydrate content, weight loss, and regular aerobic exercise. In many patients with hyperlipidemia at risk for CHD, therapeutic lifestyle intervention does not effectively lower LDL-C to within the target range. Several classes of drugs are available to treat hyperlipidemia. Statins (HMG-CoA reductase inhibitors) are the most commonly used lipid-lowering agents. Other pharmacologic agents include fibrates, niacin, bile acid sequestrants (resins), and ezetimibe.

To date, relatively few studies have examined the relation between lipid levels and dementia [10, 12, 57]. This paucity is surprising, given the established role of the *APOE* genotype in lipid metabolism and its association with dementia [57]. Studies have demonstrated significant and nonsignificant relations of both high levels of total and LDL-C and low levels of HDL-C with increased risk of dementia [58–61]. Similar to hypertension, the evidence is strongest for an effect of midlife dyslipidemia [62, 63]. Proposed mechanisms linking lipid levels with dementia include atherosclerosis, *APOE* genotype, modulation of beta-amyloid protein, and oxidative stress [11, 12].

Among dementia- and stroke-free persons, levels of total serum (or plasma) cholesterol have been examined in relation to cognitive function in cross-sectional and longitudinal investigations [63, 64]. Several cross-sectional studies of young to middle-aged adults have found that lower levels of total cholesterol are associated with higher scores on various indexes of IQ (e.g., the vocabulary subtest of the Wechsler scales). Yet, some have noted worse performance on tests of processing speed and visuoconstructional ability among those with relatively lower levels of cholesterol [64]. These findings led Muldoon and colleagues to hypothesize that higher cholesterol levels may be associated with lower levels of crystallized intelligence, thus perhaps reflecting less exposure to health literacy, whereas higher cholesterol may predict better fluid intelligence. Recent data from the Framingham Heart Study revealed similar relations of lower levels of cholesterol to poorer performance on measures of abstract reasoning, attention/concentration, executive function, and word fluency [65].

In contrast to these findings, a number of epidemiological investigations have revealed associations of higher total or LDL cholesterol with lower levels of performance [63], or relations of higher HDL-cholesterol with better performance [66], on cognitive screening measures. Further, and similar to the BP literature, higher levels of cholesterol during middle age may be predictive of lower levels of cognitive function at older ages [67]. Higher total cholesterol has also been related to cognitive decline or impairment [64, 68]. However, Swan and colleagues reported *less* prospective decline in perceptuo-motor speed as a function of higher cholesterol levels [69]. Further, those with decreasing total cholesterol levels after midlife had greater cognitive difficulty in late life [67]. Elderly subjects with frailty and reduced muscle mass (sarcopenia) often have reduced nutritional parameters, low cholesterol levels, and cognitive impairment further complicating studies on the relation between cholesterol levels and neurocognitive function. As in the BP literature, the possibility of nonlinear relations of cholesterol to neurocognition requires exploration.

Biological mechanisms linking high versus low cholesterol levels to cognitive function may differ. As reviewed by Muldoon and colleagues [64], cholesterol is an important constituent of neuronal and glial membranes and of myelin sheaths. It provides structural integrity, modulates membrane fluidity, and is important for

synaptic function, neurotransmission, and the transport of nutrients to the brain. Brain lipids are indeed vulnerable to serum lipid levels. Cholesterol is also a precursor of steroid hormones (e.g., estrogen) involved in brain function. Therefore, it is possible that lower levels of cholesterol may negatively impact the brain's microstructure and function. Further, cholesterol may act as an antioxidant. Yet, higher levels of cholesterol play a major role in the development of atherosclerosis, which may lead to macrovascular disease and associated structural and functional changes in the brain prior to stroke. In addition, in vitro studies have suggested that increased cholesterol levels may lead to increased formation of beta-amyloid from amyloid-precursor protein [70]. The relation of the *APOE* polymorphism to cholesterol is beyond the scope of this chapter [see 64] but this association could be pertinent to cognitive decline and dementia.

Statin use may be related to lesser prospective decline in cognitive performance [71]. Results of investigations of the impact of statin administration have yielded mixed findings. Whereas most have noted no significant impact on cognitive function, others have found small detrimental relations to performance on tests of attention or a failure to show the practice effects evidenced by a placebo control group [72].

Obesity

Overweight is defined as a body mass index (BMI) of 25–29.9 kg/m ^{2} and obesity as a BMI of ≥ 30 kg/m^2. The degree of obesity is often further broken down into subcategories: a BMI of 30–34.9 kg/m^2 is classified as class 1 obesity, 35–39.9 kg/m^2 is classified as class 2 obesity, and >40 kg/m^2 as morbid obesity. A BMI less than 18.5 kg/m^2 is underweight, and a BMI of 18.5–24.9 kg/m^2 is considered normal. BMI is an easily measurable index of overweight and obesity. Other adiposity measures such as waist circumference, waist to hip ratio, assessment of total body fat by DEXA scan, and measurement of intra-abdominal and subcutaneous fat by CT scan may correlate more strongly with metabolic abnormalities that could mediate the association between obesity and CHD. These findings lead many to advocate the inclusion of measures of body fat distribution such as waist circumference in conjunction with measurement of BMI. An increased waist circumference (>102 cm in men and >88 cm in women) is used as a measure of central obesity and is included in the definition of the metabolic syndrome [73]. Some also advocate use of the waist–hip ratio of >0.95 and >0.88 for men and women, respectively, as index of abdominal obesity [73, 74].

Obesity is associated with increased morbidity and mortality, particularly in younger persons. There may be a "U-" or a "J-shaped" relation between BMI and mortality in older adults [75]. Recent Framingham data demonstrate that greater BMI is predictive of first CHD event (angina, MI, or cardiac death) and first cerebrovascular event (stroke, transient ischemic attack, and stroke-related death) [76]. There is strong evidence that weight loss in overweight and obese individuals reduces risk factors for diabetes and CV disease.

Although the obesity–dementia literature appears mixed at first glance [10], ostensibly conflicting findings are likely explained by the decreased validity of adiposity measurement in the elderly, as well as the increased rate of adiposity decline immediately before dementia onset [77, 78]. Taking these methodological issues into consideration, the bulk of the research supports a relation between obesity and dementia (AD, VaD, and all-cause) [79]. Central obesity at midlife may be an especially potent risk factor [80]. Proposed mechanisms include endocrine dysregulation (e.g., hyperinsulinemia, abnormal leptin levels), inflammation, and enhancement of other CV risk factors.

Results of a rapidly growing number of case–control or cross-sectional investigations have shown relations of obesity (and sometimes overweight) to lower levels of cognitive performance in non-demented, stroke-free cohorts ranging from children to older adults following adjustment for correlated risk factors such as hypertension and diabetes [81, 82]. Affected measures typically

include executive function and memory. Age interactions have been explored but not noted [83]. Examining participants from the Framingham Study [48], Elias and colleagues reported associations of obesity to executive function and memory in men only. These investigators also reported a significant cumulative effect of obesity and hypertension on several memory measures. Our group has reported significant interactions of BMI (or waist circumference) with BP level [47]. Those with higher BMI and BP showed diminished performance on tests of motor speed and manual dexterity, and executive function (i.e., response inhibition). Recent prospective data indicated that midlife central obesity, in conjunction with hypertension, was associated with decreased executive function and visual memory 12 years later [84]. The relation between central obesity and cognitive function is diminished after adjustment for physical activity [85].

In contrast, Kuo [86] recently found that overweight persons performed better than normal weight persons on tests of reasoning and visuospatial speed of processing. Obese persons were also better than normal weight individuals on the latter measure. Leanness has also been related to lower Mini-Mental State Examination (MMSE) scores in the elderly [87]. Sturman [88] reported nonlinear associations of BMI to cognitive function. It has been posited that relations of lower BMI to lesser cognitive performance, particularly among older adults, may in part reflect weight loss that is apparent prior to the diagnosis of AD.

Jagust [89] has reviewed potential mechanisms linking obesity to the brain. These include metabolic, inflammatory, vascular, degenerative, and lifestyle (e.g., exercise) factors. Increased BMI and WHR have been associated with temporal lobe or hippocampal atrophy [89], greater overall brain atrophy [90], and greater white matter disease [89]. There is some suggestion that the frontal lobes may be particularly affected [91].

Central obesity may also negatively affect the brain via neuroendocrine disturbances such as hypercortisolemia and low levels of sex steroid and growth hormones [92]. Both central and total obesity have been associated with other hormonal abnormalities such as hyperleptinemia (i.e., high serum levels of leptin – a hormone that plays a major role in fat metabolism), which has known central effects [93]. These hormonal abnormalities have been related to enhanced sympathetic nervous system activity [92, 93] that may promote silent cerebrovascular disease [78, 80]. Both central and total obesity have also been associated with enhanced proinflammatory factors [79, 80]. Sweat [94] recently found that C-reactive protein was associated with decreased frontal lobe function among overweight or obese women (but not men). Obesity may also operate, in part, via correlated CV risk factors such as the metabolic syndrome.

Diabetes, the Metabolic Syndrome, Glucose, Insulin

CV diseases are highly comorbid with diabetes mellitus. Further, CV risk factors commonly aggregate in a pattern known as the metabolic syndrome which is characterized by glucose intolerance, insulin resistance, central adiposity, dyslipidemia (here characterized by increased TG and decreased HDL-C), and hypertension. There is a strong association between the metabolic syndrome and atherosclerosis. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition has been most commonly used [56, 72]; metabolic syndrome is diagnosed when ≥ 3 of the following five risk factors are present: (1) fasting plasma glucose ≥ 100 mg/dL; (2) HDL-C ≤ 40 mg/dL in men or ≤ 50 mg/dL in women; (3) triglycerides ≥ 150 mg/dL; (4) waist circumference ≥ 102 cm in men or ≥ 88 cm in women; and (5) BP ≥ 130 mmHg systolic or 85 mmHg diastolic or drug therapy for hypertension. Those with the metabolic syndrome are at increased risk of developing diabetes mellitus.

Diabetes is characterized by high levels of glucose in the blood. Approximately 7% of adults in the USA are known to have diabetes, with an additional 6 million people having undiagnosed diabetes [95]. Criteria for diagnosing diabetes

include either a fasting glucose level higher than 126 mg/dL (>7 mmol/L) on two occasions; random (non-fasting) blood glucose level >200 mg/dL (>11 mmol/L) and accompanied by the classic symptoms of increased thirst, urination, and fatigue; or glucose level >200 mg/dL at 2 h during an oral glucose tolerance test [95]. Levels between 100 and 126 mg/dL (6.1–6.9 mmol/L) are referred to as impaired fasting glucose or prediabetes. Diabetes can be caused by too little insulin, resistance to insulin, or both. There are two main forms of diabetes: type 1 diabetes mellitus, previously known as insulin-dependent diabetes, childhood diabetes, or also known as juvenile diabetes, is characterized by loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency in insulin secretion. Type 2 diabetes, previously known as adult-onset diabetes, is the most common type of diabetes and accounts for >90% of all cases of diabetes mellitus and is characterized by variable degrees of insulin deficiency and resistance. Morbidity from diabetes involves both macrovascular (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). The therapeutic goals are the alleviations of symptoms of hyperglycemia and aggressive CV risk factor intervention to reduce end-organ damage.

A number of reviews highlight the evidence linking diabetes with dementia [10, 12, 96, 97]. One comprehensive meta-analysis of 25 prospective studies found a 1.6-fold greater risk of future dementia for individuals with diabetes, compared to those without diabetes [98]. Diabetes-associated cerebrovascular disease may mediate the relation [98]. There is also evidence to support detrimental effects of hyperinsulinemia and glucose intolerance on cerebral structure and function, consistent with dementing processes [99].

Prior to dementia, relations of both type 1 and type 2 diabetes to lower levels of cognitive function are well documented (for reviews, see [99–101]). Type 1 diabetes has been associated with difficulties in attention, learning and memory, visuospatial abilities, and perceptuo-motor and motor speed. Associations are most pronounced among those with an age of onset between 4 and 6 years, perhaps via detrimental effects of hyperglycemic episodes on the developing brain [99, 100]. Among type 1 diabetic adults, poor metabolic control is a critical predictor of cognitive difficulties [99]. Findings have been mixed regarding the impact of episodes of hypoglycemia. Although a recent large prospective study found long-term decline in motor speed and psychomotor efficiency among type 1 diabetics, other cognitive functions were not affected [102].

Case–control studies of type 2 diabetes report the most pronounced impact on tests of learning and memory [99]. Also affected are measures of attention, psychomotor speed, and problem solving. Age interactions suggest a greater impact of type 2 diabetes on cognitive function in older than middle-aged adults [99]. Type 2 diabetes has also been associated with cognitive decline, with duration of disease an important predictive factor [103].

Outside the context of frank diabetes, investigations have shown relations of the metabolic syndrome to cognitive function, often using cognitive screening measures [104]. Impaired or increased fasting glucose has been associated with decreased cognitive performance including memory [105]. Hyperinsulinemia has been related to lower levels of cognitive function [46, 106], and insulin resistance has been associated with cognitive decline [107].

Biological mechanisms linking diabetes to cognitive difficulties are thought to be largely independent of comorbid CV risk factors and diseases. As reviewed by Ryan [99], chronic hyperglycemia may be associated with the development of advanced glycosylated end products – oxidation products that are found in senile plaques and neurofibrillary tangles, which are characteristic of AD pathology. Hyperglycemia may increase aldose reductase activity and protein kinase C activity, each of which may negatively impact basic cellular and neuronal functions. Hyperinsulinemia is also thought to impact brain function perhaps via modulation of synaptic activity. Diabetes may alter blood–brain barrier

structure and function thus allowing the passage of toxic substances [108] and has been associated with cortical brain atrophy [109].

Biomarkers

The use of commonly measured and established risk factors (e.g., cholesterol levels, BP, smoking status) does not fully explain the risk of developing CV disease. Therefore, there is a great deal of interest in whether the measurement of new metabolic parameters (biomarkers), particularly chemicals associated with myocardial cell damage, left ventricular dysfunction, renal failure, endothelial dysfunction, and inflammation, can increase the ability to predict CV disease independently of established risk factors. For example, a recent study demonstrated that the combination of N-terminal pro-brain natriuretic peptide, troponin I, cystatin C, and C-reactive protein (CRP) improved the risk stratification for CV disease death in older men beyond an assessment that was based on the established risk factors of age, systolic BP, use of antihypertensive treatment, total cholesterol, HDL-C, use of lipid-lowering medications, diabetes, smoking status, and BMI [110]. From a clinical prospective, the addition of a combination of biomarkers could add substantial prognostic information on the risk of morbidity and mortality from CV disease, leading to more targeted prevention and intervention approaches. However, caution must be applied to extending the risk of disease at a population level using combinations of biomarkers to predict risk in a given person due to the marked overlap of distribution of values for a given biomarker between those with and without the disease [111].

Inflammation

Blood-based biomarkers of systemic inflammation including CRP, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) have been extensively studied as correlates of CV disease. CRP, an inflammatory marker, is widely regarded as a risk factor for CV disease [112]. In contrast, epidemiologic studies have yielded mixed results about the relations between dementia and inflammatory markers [12]. There is some evidence suggesting that a relation exists between inflammatory markers at midlife and AD. For example, participants with higher midlife CRP in the Honolulu–Asia Aging Study had a twofold increased risk of developing AD over 25 years of follow-up [113]. Taken together, limited findings imply that inflammation causes neuronal dysfunction consistent with enhanced risk of dementia. Inflammation may also be associated indirectly with dementia outcomes because of its role in promoting atherosclerosis and potentially because of effects on brain atrophy, with higher levels of IL-6 correlating with hippocampal gray matter atrophy in middle-aged adults [114].

Studies in various community-based samples of older adults have generally found that higher levels of inflammatory biomarkers predict greater decline in cognition during follow-up, with IL-6 generally a stronger predictor than CRP [115–120]. In those studies where multiple domains of function were assessed, higher levels of inflammation correlated best with declines in nonverbal memory [120], immediate verbal recall, and orientation [118]. Significant interactions of inflammation with the metabolic syndrome [119] and the *APOE ε4* genotype [120] on cognitive decline have also been reported.

Several large population-based studies have examined the cross-sectional and longitudinal association of inflammatory markers with radiographically defined vascular disease of the brain, with some conflicting results. For example, among older community-dwelling stroke-free adults, higher IL-6 levels were associated with a greater likelihood of having MRI-defined brain infarcts or white matter hyperintensities, whereas associations of CRP and these outcomes were modest and generally not significant [121]. Among dementia-free elderly in the Rotterdam Scan Study, CRP was associated with both prevalent periventricular and subcortical white matter lesions and the progression of these lesions over 4 years, but not with prevalent or

incident lacunar infarction [122]. In contrast, no relations between CRP and either silent lacunar infarcts or white matter hyperintensities were found in community-based studies of older [123] or stroke-free middle-aged and elderly subjects [124]; the latter study also reported no significant associations of CRP with progression of white matter lesions over 6 years.

Oxidative Stress

Cellular dysfunction from cumulative free radical-mediated injury may contribute to several conditions of aging; the aging brain may be particularly susceptible. Numerous studies have reported associations between biomarkers of oxidative stress and clinical syndromes of cognitive dysfunction, including primarily mild cognitive impairment (MCI) and AD. The majority of these studies have used a case–control design with healthy age-matched controls. For the most part, these studies have not accounted for differences between subject groups in important comorbidities (CV disease, hypertension) which are also related to oxidative stress and dementia or MCI. However, a link between oxidative stress and dementia is supported by studies in autopsy brain tissue [125], and in experimental animal models where increased tissue expression of peroxidation end products and decreased antioxidant capacity were observed.

Few studies have examined the association between oxidative stress and cognitive function prospectively. For example, among older community-dwelling adults, Berr et al. reported that those with cognitive decline (defined by change in MMSE score) had higher levels of lipid peroxides and lower levels of antioxidants at baseline [126]. Biomarkers of lipid peroxidation have also been associated with MRI-defined white matter disease in older adults [127]. Prior studies have not examined associations of oxidative stress biomarkers with different domains of cognitive function in non-demented individuals.

The association of oxidative stress or reduction– oxidation imbalance with cognitive decline and overt cognitive impairment has implications for potential preventive interventions. If these associations are causal, then increasing antioxidant capacity could potentially protect against cognitive decline. Two large randomized clinical trials testing antioxidant supplementation with beta carotene [128] or vitamin E [129] have yielded conflicting results. Among older women free of CV disease, vitamin E supplementation resulted in no difference in longitudinal decline in general cognition, verbal memory, and language fluency [129]. In contrast, long-term beta-carotene supplementation among older male physicians resulted in modestly higher scores (compared to placebo) on tests of general cognitive function and verbal memory but not category fluency [128]. Because inflammation and oxidative stress are interrelated pathophysiological processes and are also related to established CV risk factors such as dyslipidemia, it is possible that there is a cumulative effect of these factors on neurocognitive dysfunction. However, in most epidemiologic studies, inflammatory and oxidative biomarkers have been considered as "independent" risk factors; few prior studies have examined potential multiplicative effects of these factors on cognition.

Biomarkers of Chronic Kidney Disease (CKD)

Kidney disease is an extremely common comorbidity which affects nearly one in five elderly in the USA [130] and which frequently coexists with other conditions known to affect brain function, namely hypertension, diabetes, and cardiac diseases. Biomarkers of kidney disease include abnormally high urinary protein or albumin excretion, which represents an alteration or injury to the normal filtration barrier, and elevations of circulating small molecules (creatinine, cystatin C, urea nitrogen), which are normally freely filtered by the kidney. Studies in patients with end-stage renal disease on maintenance dialysis showed that nearly one-third had clinically significant cognitive impairment, as defined by a

MMSE score of <24 [131] or by large deficits in two or more domains of cognitive function [132]. In the latter study, one-quarter of dialysis patients had a history of prior stroke as compared to 9% of age-matched controls, suggesting a possible role for cerebrovascular disease in explaining the excess impairment.

More recent studies have examined the cross-sectional associations of mild-to-moderate kidney disease and neurocognitive function, noting poorer performance on various cognitive tests including those assessing executive function and verbal learning and memory [133]. Utilizing large epidemiologic studies, authors have reported cross-sectional associations of decreased neurocognitive function with poorer renal filtration function among older adults [134, 135], younger and middle-aged adults [136], and postmenopausal women [137]. In the latter study, significantly poorer performance in CKD was observed for tests of general cognition (MMSE) and attention/concentration, but not on tests of verbal fluency or verbal recall. Three longitudinal studies have examined the association of kidney disease with incident cognitive dysfunction or dementia. Among community-dwelling older adults in the Cardiovascular Health Cognition Study, elevated serum creatinine and elevated urinary albumin excretion were associated with an increased risk of incident dementia; associations were generally stronger for vascular-type versus Alzheimer's type dementia [138, 139]. In an analysis of data from the Health, Aging, and Body Composition Study, incident cognitive dysfunction [defined by a low or declining Modified Mini-Mental State (3MS) Exam score] was 30 and 80% more likely in older individuals with mild and moderate severity kidney disease, respectively [134].

Homocysteine

Homocysteine (Hcy) is an amino acid that is influenced substantially by diet. In high concentrations, Hcy has direct and indirect neurotoxic effects in vitro. High plasma levels of Hcy have been associated with increased risk of CV disease. Circulating Hcy levels can be reduced by diet and vitamin supplementation (e.g., B_6, B_{12}, folic acid) permitting testing of the hypothesis that Hcy is not simply a correlate of brain disease or dysfunction but rather a causative risk factor. Numerous observational studies conducted in diverse patient populations have found cross-sectional associations between higher Hcy and worse performance on tests involving different cognitive domains; associations have generally been greater among the elderly than among middle-aged individuals [140, 141]. Among prospective studies of Hcy and rate of cognitive decline, most but not all [142] have reported a positive association, and Hcy has also been associated with the risk of incident dementia independent of other known risk factors [143–145].

In contrast to this wealth of observational data, interventional trials have shown inconsistent effects of lowering Hcy on the rate of cognitive decline. Among the two largest randomized clinical trials in older individuals with hyperhomocysteinemia, one study – among healthy elderly – found no effect on the change in cognition over 2 years [146]. Another study – among 850 participants followed for 3 years – found a significantly slower rate of decline for tests of psychomotor speed, information processing speed, and memory [147]. Therefore, although Hcy levels seem to correlate with cognitive function, its role as a causative factor in cognitive decline remains uncertain.

Behavioral Risk Factors

Behavioral or lifestyle risk factors for CV health and brain health may operate in part through their known associations with traditional CV risk factors and biomarkers. Associations of psychosocial and psychophysiological factors with CV disease have also been noted. In general, factors with known associations with stroke [148] have also shown relations to cognitive difficulties prior to stroke (or dementia).

Smoking

Smoking, a significant risk factor for CV disease, has been examined as a correlate of dementia and AD. Early case–control studies revealed inverse relations between tobacco consumption and cognitive impairment, citing nicotine as an agent that protected from cholinergic deficit and subsequently enhanced information processing and attention. However, more recent prospective studies (which appropriately adjusted for confounding variables such as education) found that smoking either was associated with increased risk or had a null effect on dementia outcomes [11, 149]. Results of a recent meta-analysis concluded that smokers have increased risk of dementia and cognitive decline [150]. Selective mortality in which smokers are at increased of dying prematurely from CV disease and cancer may confound studies of the relation between smoking and dementia.

A recent review suggests pre-dementia associations of smoking status with cognitive decline particularly on measures of verbal memory and processing speed [151]. Further, smoking during middle age has been related to poor cognitive outcomes in older age [152]. Potential mechanisms include oxidative stress, inflammation, and other CV risk factors, CAD and CHD [151]. Importantly, prenatal exposure to smoke and sidestream smoke (resulting in higher blood cotinine – a metabolite of nicotine – levels) is related to lowered levels of cognitive performance in children [151]. Neuroimaging findings include increased white matter hyperintensities, silent brain infarction, and brain atrophy among smokers [151].

Alcohol

Numerous observational studies reveal that moderate amounts of alcohol consumption are associated with decreased risk of hypertension, CV events, and dementia [7, 13, 58, 149]. Wine seems to demonstrate especially protective effects [149]. Although alcohol appears to be a protective factor in both CV and cognitive health, it should be noted that excessive drinking has been associated with risk of dementia [12, 149]. Observational studies support consumption of ≤ 1 alcoholic drink per day for women and ≤ 2 for men to reduce the risk of CVD disease and dementia while minimizing adverse affects of alcohol [57].

Reviewed elsewhere [153], alcoholism has well-known and potent negative effects on cognitive function that lead to a particular dementia profile. Outside the context of frank alcoholism, associations between alcohol consumption and cognitive function have been complex and nonlinear (thus paralleling alcohol's relation to stroke [154]). In that regard, U- or J-shaped relations have been noted, with moderate levels of alcohol consumption associated with better cognitive performance [155, 156]. In some studies, this relation has only been noted among women but across measures of complex attention, perceptuo-motor speed, learning and memory, problem solving, and executive function [157, 158]. Moderate alcohol intake in middle age has been associated with better cognitive outcomes in older age [159]. It has been noted that some abstainers may have previously been heavy drinkers.

Diet/Antioxidants

Dietary factors, such as consumption of saturated fats, have been associated consistently with CV disease and insulin resistance [11]. Although this association suggests an indirect link between diet and dementia, little research has examined a direct link [11, 12]. It remains unclear whether antioxidant consumption is effective in the prevention of CV disease [11], but several agents show promise in the delay or prevention of AD [160]. These agents include aged garlic extract, curcumin (a component of turmeric), melatonin, resveratrol (found in the skin of red grapes), *Ginkgo biloba* extract, green tea, β-carotene, vitamin C, and vitamin E [11, 12, 160].

Mechanisms for this relation include decreased oxidative damage to sensitive brain tissue, as well as possible vascular benefit [12]. Although findings are mixed, some studies suggest that higher levels of dietary intake of antioxidants (vitamin E, C, carotene) and supplements of these nutrients have also been associated with less cognitive decline in the elderly [161]. Protective effects of dietary poly- and monounsaturated fatty acids have also been noted [162]. Conversely, diets high in saturated fat have been associated with cognitive decline [163]. Dietary intake of omega-3 fatty acids has been associated with greater corticolimbic gray matter volume [164].

Physical Activity, Exercise

As noted previously, several studies cite relations among obesity, CV disease, and dementia. It is known that physical activity reduces CV disease risk through its impact on numerous CV risk factors, including obesity. Thus, it is intuitive that several studies note an inverse relation between physical activity and dementia [11]. An epidemiologic study revealed that engaging in activity (strenuous enough to cause breathlessness and sweating) 2–3 times/week for 20– 30 min was associated with decreased risk of dementia even after adjustments for risk factors including locomotor disorders, *APOE* genotype, vascular disorders, smoking, and alcohol consumption [165]. These results suggest that mild-to-moderate exercise may reduce risk of dementia even in genetically susceptible individuals.

Prior to dementia, there is compelling evidence for an association between higher levels of aerobic fitness or exercise and better cognitive function [166, 167]. Results of a meta-analysis indicate the most potent association between aerobic fitness training and improvements in executive-control functions such as coordination, inhibition, scheduling, planning, and working memory [168]. Further, exercise has demonstrated associations with neuroplasticity in animal models and in humans [166, 167].

Psychosocial Risk

Various psychosocial factors have demonstrated prospective relations to CV risk factor and disease outcomes [169, 170] including stroke [171, 172]. For example, depression is a potent predictor of CV morbidity and mortality. Anxiety, anger and hostility, and other measures of negative emotionality also predict poor CV outcomes. Stress has been associated (albeit inconsistently) with CV outcomes, social support with better outcomes, and lower socioeconomic (SES) with worse outcomes. Each of these factors may be associated with brain outcomes, in part, by promoting or attenuating CV risk. However, another interesting possibility is that of common genetic and/or neurobiological vulnerability among select factors. For example, McCaffery has reported substantial common genetic comorbidity for depression and coronary artery disease [173].

Relations of depression to diminished cognitive function and dementia are well documented, and these disorders may be linked, in part, via inflammatory mechanisms [174]. There is also some support for the relations of other psychosocial factors like anxiety, hostility, social support, and SES to lower levels of cognitive function. It is an interesting new area of research to examine such "upstream" variables and their potential relations to brain outcomes via CV disease or by promoting the psychophysiological disturbances described below.

Psychophysiological Risk

Autonomic Nervous System

Autonomic nervous system dysregulation, including stress-induced CV responses, has been associated with increased risk of CV disease. Several indices of autonomic (i.e., sympathetic

and parasympathetic) nervous system dysregulation have been examined in relation to cognitive performance and the brain. Increased BP variability (assessed by 24 h ambulatory monitoring) has been associated with poorer performance on several tests of cognitive function in elderly hypertensives [175] and a sample of older adults [176]. In two samples, we have reported that independent of resting clinic BP and other potential confounders, systolic and diastolic BP reactivity was associated with diminished performance on tests of attention, immediate and delayed verbal memory, and/or executive function (i.e., response inhibition) [177, 178]. We therefore suggested that enhanced stress-induced BP reactivity may be a biobehavioral risk factor for decreased cognitive performance.

Stress-induced BP reactivity is a stable dimension of individual differences, and BP responses evoked in laboratory settings show generalizability to daily life [179]. It is possible that repeated episodes of BP reactivity might have a negative impact on the brain and therefore cognitive function. With respect to plausible biological mechanisms, greater stress-induced BP reactivity has been associated with incident stroke [180]. Enhanced BP reactivity has also been related to carotid atherosclerosis and its progression and silent cerebrovascular disease [181, 182]. Similarly, various other BP indexes of autonomic dysregulation have been associated with silent cerebrovascular disease. In elderly hypertensives, both extreme nocturnal dippers (nocturnal BP fall $\geq 20\%$) and non-dippers had significantly greater prevalence of silent brain infarction than did dippers [183]. In addition, older, predominantly normotensive, adults with greater BP variability on ambulatory monitoring had the highest severity ratings of white matter disease [184]. Enhanced BP responses to orthostatic manipulation have been associated with a greater prevalence of silent brain infarction in elderly hypertensives [185]. We have hypothesized that repeated episodes of stress-induced BP responses during daily life may enhance cerebrovascular damage by inducing periods of cerebral hypoperfusion or vasospasm, perhaps due to compromised autoregulatory capacity in older adults [182].

Hypothalamic–Pituitary–Adrenocortical (HPA) Axis

Study of the relation of HPA axis functioning to brain and cognition has focused largely on cortisol – disruption of which is associated with increased CV risk. Numerous investigations have revealed associations between higher resting cortisol levels and lowered levels of cognitive performance, particularly on tests of learning and memory [186–188]. It has also been noted that stress-induced cortisol elevations are associated with decreased learning and memory performance [189]. Consistent with this pattern of association, high levels of cortisol have been associated with hippocampal damage [190]. Results of longitudinal studies suggest that cumulative exposure to high and increasing levels of cortisol is associated with decreased hippocampal volumes and decline in attention, memory, and executive function [186, 187]. This suggests that detrimental effects of cortisol on the brain may extend to the frontal lobes [187]. McEwen and colleagues [191] have more generally hypothesized that repeated perturbations across a number of physiological systems (e.g., neural, endocrine, immune) – known as allostatic load – are associated with decreased cognitive function and cognitive decline.

Functioning of the hypothalamic–pituitary–gonadal (HPG) axis also bears important relations to the brain and cognitive function. Although space limitations preclude us from reviewing this literature here, the reader is referred to reviews by Sherwin on the relations of estrogen, testosterone, and hormone therapy to the brain [192, 193]. These hormones should receive further consideration in studies of CV risk, disease, and cognitive function given their potential protective (e.g.,

estrogen) or risk-promoting (e.g., testosterone) relations to various CV endpoints.

Summary

The preceding sections cite evidence linking numerous CV and stroke risk factors with select cognitive impairment, as well as with both VaD and AD. Cerebral hypoperfusion is thought to be particularly important to the ultimate development of dementia. De la Torre has suggested that CV risk factors may operate through a critically attained threshold of cerebral hypoperfusion which triggers a series of cerebromicrovascular changes including increased oxidative stress and impaired nitric oxide activity, pathogenic processes that then promote AD and VaD [194]. Although further research is necessary, early interventions (both pharmacologic and non-pharmacologic) to address modifiable risk factors may help prevent or delay the onset of dementia [195, 196]. Health-care providers may utilize history of CV risk factor burden as an additional means of identifying individuals at increased risk for all-cause dementia.

Among stroke- and dementia-free samples, relevant literature has also demonstrated relations of a multitude of CV risk factors to lower levels of cognitive function. The risk factors span multiple levels of analysis including traditional biomedical risk factors, newer biomarkers, and behavioral, psychosocial, psychophysiological factors. It is critical to remember the potent interrelations among these variables, and that they may exert a cumulative negative impact on cognitive outcomes. For example, the cumulative negative impact of CV risk factors has been demonstrated in several studies using compilations based on the Framingham Stroke Risk Factor Profile [197]. Variability is noted in terms of the domains of neurocognitive function most affected by different risk factors, and surprisingly little is known about relevant vulnerability and resilience factors.

We and others have discussed that, among persons without stroke or dementia, the effect sizes noted in studies of CV risk and cognitive function range from small to large, thus indicating heterogeneity of effects and the likelihood of effect modification. The clinical significance of the reduced levels of cognitive performance in relation to the CV risk factors is yet to be determined. It is not typical in this body of literature to see reference to frank impairment or dementia. However, we have suggested that even small or subtle differences that fall within the range of "normal" performance, such as the difference between above average and average scores, may be perceived as significant at an individual level and could impact role or daily functioning. This is an area in great need of investigation.

We have further suggested that these subtle associations present the first manifestations of the impact of CV risk on the brain and cognitive function. Because these correlates are seen in children and young adults, and because midlife risk factors predict late-life cognition, it is critical to intervene aggressively with risk factor profiles early in the life course. Otherwise, CV risk factors tend to develop into CV diseases which appear to have an even greater negative impact on cognitive function.

Cardiovascular Diseases and Neurocognitive Function

In contrast to the CV risk factor literature, relatively few studies are available on the relations of CV diseases to neurocognition. Here we discuss cardiac conduction disturbances, subclinical and clinical manifestations of CV disease, heart failure, and several common treatments for these diseases.

Cardiac Arrhythmias, Cardiac Arrest

The cardiac arrhythmias comprise disorders of heart rhythm. Three of the most common and clinically important cardiac arrhythmias are atrial

fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation.

The prevalence of AF is about two million, with a lifetime risk of about 20% [1]. During AF, the heart's two upper chambers (the atria) beat chaotically and irregularly, and their contractions are not coordinated with the contractions of the ventricles. The irregular and often rapid heart rate compromises cardiac output and reduces systemic blood flow. These events can result in symptoms of heart palpitations, shortness of breath, and weakness. AF increases risk of developing blood clots that may lead to stroke. Paroxysmal (transient or episodic), persistent, and permanent AF all increase the risk of stroke by two- to threefold and may be responsible for about 15–20% of all strokes. Treatments for AF include medications and procedures that attempt to either reset the heart rhythm back to normal (cardioversion) or control the rapidity of the cardiac rate. Patients with AF are anticoagulated to prevent blood clots and emboli.

VT is defined as three or more successive beats of ventricular origin at a rate greater than 100 beats/min. VT that lasts more than 30 s is called sustained ventricular tachycardia. The hemodynamic consequences of VT depend largely on the presence or the absence of myocardial dysfunction. VT is also dangerous because it can degenerate and become ventricular fibrillation.

Ventricular fibrillation is the uncoordinated, often very rapid ineffective contractions of the ventricles caused by chaotic electrical impulses. In ventricular fibrillation, no blood is pumped from the heart, so it is a form of cardiac arrest that may be fatal unless treated immediately. Indeed the overwhelming majority of sudden cardiac deaths (estimated at about 325,000 per year) are thought to be from ventricular fibrillation. The most common cause of ventricular fibrillation is inadequate blood flow to the heart muscle due to coronary artery disease, as occurs during a heart attack. Ventricular fibrillation is a medical emergency. Cardiopulmonary resuscitation (CPR) must be started as soon as possible, followed by defibrillation. Antiarrhythmic drugs help maintain the normal heart rhythm.

Reviewed by Mead [198], some studies have found a higher prevalence of AF among patients with diagnosed dementia, whereas others have not. Cross-sectional comparisons of patients with AF and those with normal sinus rhythm suggest decreased performance on tests of memory, attention, cognitive composites, and the Mini-Mental State Examination (MMSE) [198]. A prospective study found no association between AF and future cognitive performance. However, this finding was based on only 17 participants with diagnosed AF.

AF is thought to be related to cognitive dysfunction via correlated CV risk factors, cardiogenic brain embolism, and decreased cerebral blood flow [198, 199]. The presence of silent brain infarction, mainly in cortical regions, is twice as likely among those with AF as those without [198]. Knecht and colleagues reported lower levels of learning and memory, attention, and executive function in conjunction with increased hippocampal atrophy in AF patients [200].

Ventricular fibrillation has been studied in the context of resuscitated cardiac arrest. Early case studies suggested a potent negative impact of cardiac arrest on the brain and neurocognition, with reports of isolated amnesia and extensive damage to the hippocampal regions presumably due to abrupt hypoxia and ischemia [199]. More recent investigations confirm that cognitive deficits may be severe, but suggest that these deficits are not isolated to memory, but rather extend to motor and executive functions [201]. Important predictors of subsequent cognitive difficulties include delay in the start of CPR and the need for advanced cardiopulmonary life support [202]. Some recovery of function has been noted in 3 months following cardiac arrest, but pronounced residual deficits typically remain [201]. The cognitive consequences of cardiac arrest have been attributed to diffuse and sudden ischemic–hypoxic injury [201, 203]. Because these are typically persons with preexisting cardiac disease, the mechanisms discussed in prior and

future CV risk factor and disease sections are also likely operative.

Subclinical Cardiovascular Disease

A growing literature supports associations between subclinical, or presymptomatic, CV disease and cognitive function. Advantages of examining subclinical disease states are multifold [204–206]. Subclinical disease can typically be measured quickly, painlessly, and noninvasively. Numerous confounds in the study of CV disease are also dramatically reduced by examining preclinical disease states. It is well known that CV diseases tend to cluster together, and highly comorbid conditions and risk factors (e.g., CAD, diabetes, obesity) become less difficult to account for adequately in nonclinical populations. Third, subclinical measures allow us to predict future CV (and thereby neurocognitive) risk in currently asymptomatic individuals, providing ample opportunity for early intervention. Lastly, relations between subclinical CV disease and cognition provide support for the idea of a continuum of CV disease-related cognitive impairment. If CV-associated decrements in cognitive function are proportional to the degree of underlying CV disease, relations between subclinical CV disease and cognitive function would be expected to be smaller in magnitude than relations between frank CV disease and cognitive function.

At least four subclinical disease states, including atherosclerosis, arterial stiffness, endothelial dysfunction, and left ventricular hypertrophy, have been linked with decrements in concurrent cognitive function and/or prospective cognitive decline. Each of these subclinical diseases is associated with increased risk of various symptomatic CV diseases and/or mortality, above and beyond standard CV risk factors [204, 207, 208, 209, 210].

Atherosclerosis

Atherosclerosis is a known contributor to the development of VaD because of its involvement in cerebral ischemia and stroke [26, 211]. Evidence also indicates that atherosclerosis, as well as subclinical markers of atherosclerosis, are associated with both current AD and prospective risk for AD [10, 11, 211]. The mechanisms whereby atherosclerosis contributes to AD are unclear, although oxidative stress, inflammation, and immune responses have been suggested as possible players. Further, the atherosclerosis–dementia relation appears to be strongest among *APOE ε4* carriers [212].

The most frequently studied indices of subclinical atherosclerosis are carotid intima–media thickness (IMT) and plaque, a more advanced form of atherosclerotic disease. IMT, a measure of arterial wall thickness, has been used as a surrogate measure for generalized atherosclerotic disease [213–215]. Overall, current evidence supports a cross-sectional association between carotid atherosclerosis and cognitive function across at least seven population-based samples [216–223], two CV disease samples [224, 225], and another sample at risk for CV disease [226]. Specifically, significant associations between increased carotid IMT and diminished cognitive function have been found across a number of cognitive domains, including global cognitive function, attention, psychomotor speed, verbal memory, nonverbal memory, language, verbal fluency, inductive reasoning, and mental flexibility. Importantly, not all cross-sectional studies have identified a relation between carotid atherosclerosis and cognition [217, 227]. Furthermore, conclusions regarding the most affected cognitive domains are currently premature, given that each domain has not been examined with sufficient frequency.

Longitudinal research linking carotid atherosclerosis with prospective cognitive decline

is more limited. Several studies have identified longitudinal relations in population-based samples [228–230], but these associations were largely restricted to performance on brief cognitive screening measures such as the Modified Mini-Mental State (3MS) Examination and the Digit Symbol Substitution Test. One more comprehensive study that examined carotid IMT and cognitive decline found no evidence to support a longitudinal association [231]. In contrast, our group noted decline on several memory tests as a function of greater carotid IMT [232]. Studies have also found evidence for a carotid IMT–cognition relation in AD or stroke patients [233–235], but these findings are limited to highly select populations.

Arterial Stiffness

Two common markers of arterial stiffness, pulse pressure (PP) and pulse wave velocity (PWV), are considered indicators of subclinical CV disease [206, 236]. Pulse pressure, computed as the difference between systolic and diastolic BP values, is viewed as a surrogate marker of arterial disease, whereas PWV is regarded as a direct measure of arterial stiffness [237]. PWV is measured between two locations in the arterial tree; carotid and femoral peripheral sites are typically utilized to provide a measure of aortic stiffness.

Both high and low PP predict incident AD and overall dementia [238]. In an examination of participants in the Maine–Syracuse Study [239], greater PP was associated with lower levels of performance on a global composite of cognitive function and specific measures of verbal concept formation, attention, perceptuo-motor speed, and visuoconstructional ability. In another recent study, high PP was associated with diminished performance on a cognitive screening measure among older adult participants in the Third National Health and Nutrition Examination Survey [240]. Cross-sectional evidence also links high PWV with diminished cognitive function. Individuals with dementia or MCI have been found to have higher PWV values than cognitively intact participants [241], and PWV has been found to correlate inversely with MMSE performance among individuals referred for memory deficit [242], even among those without overt vascular disease [243].

Growing evidence also suggests an association between arterial stiffness and cognitive decline that is independent of BP level. Scuteri and colleagues [244] found an association between higher baseline PWV and MMSE decline among participants with memory complaints. Expanding upon these findings, Waldstein and colleagues [35] examined longitudinal relations of PP and PWV to multiple domains of cognitive function among non-demented, stroke-free participants in the Baltimore Longitudinal Study of Aging. Increasing levels of PP were significantly related to prospective decline on tests of verbal learning, nonverbal memory, working memory, and a cognitive screening measure over up to 11 years of follow-up. Similarly, persons with higher baseline PWV exhibited prospective decline on tests of verbal learning and delayed recall, nonverbal memory, and a cognitive screening measure. In contrast, an examination of Rotterdam Study participants failed to identify a significant association between PWV and incident dementia or cognitive decline over two time points [245].

Endothelial Dysfunction

Endothelial function represents an important component of vascular health and contributes to the maintenance of vascular homeostasis [246]. Disruptions in vascular homeostasis, mediated by endothelial dysfunction, can precipitate atherogenesis and other harmful vascular events such as transient ischemia, plaque rupture, thrombosis, and infarction. Brachial artery flow-mediated dilatation (FMD), measured as the magnitude of arterial dilatation after an induction of forearm ischemia, is a commonly used marker of endothelial function [206, 247]. Specifically, the temporarily high blood flow following forearm ischemia triggers the release of nitric oxide (NO), a powerful vasodilator. NO release is reduced in

the presence of endothelial dysfunction, thereby resulting in a reduced brachial artery FMD. Lower values of brachial artery FMD thus indicate poorer endothelial function.

Relatively little research has directly examined the relation between brachial artery FMD and cognitive function. In a study of geriatric outpatients with CV disease, Cohen and colleagues [225] demonstrated consistent associations between increased brachial artery FMD and lower levels of performance on measures of attention, executive function, and psychomotor speed. Consistent with the pattern of impairment typically observed in vascular disease [248, 249], significant associations were not identified among other domains tested, including language ability, memory, and visual–spatial function. Brachial artery FMD has also been associated with structural brain indices as measured by magnetic resonance imaging (MRI). In the aforementioned study, brachial artery FMD was significantly associated with reduced whole brain volume, but not extent of white matter disease. In contrast, in another sample of older adults with CV disease [250], brachial artery FMD was significantly associated with the latter, but not the former index.

Left Ventricular Hypertrophy

Increased left ventricular mass, or left ventricular hypertrophy (LVH), can be assessed noninvasively via echocardiography. The extent of LVH is often, but not always, a reflection of the cumulative impact of another symptomatic or asymptomatic CV disease, such as hypertension, on the myocardium over time [251]. Despite its recognition as a measure of subclinical CV disease among otherwise healthy individuals [204], limited research has examined LVH in relation to cognitive function. Among elderly participants in the Helsinki Aging Study, LVH was present more often in individuals with cognitive impairment or dementia than cognitively intact participants [252]. Furthermore, baseline LVH predicted decline in MMSE performance over 5-year follow-up. Using data from the Framingham Offspring Study, Elias and colleagues [251] identified a significant cross-sectional relation between LVH and performance on cognitive tests assessing verbal concept formation, verbal memory, and visual–spatial memory and organization. However, these relations were significantly attenuated following statistical adjustment for BP, treatment for hypertension, other vascular risk factors, and prevalent CV disease. These latter covariates may therefore mediate the relation between LVH and cognitive function.

Mechanisms

Researchers have proposed a number of mechanisms through which subclinical CV disease may directly or indirectly affect cognitive function. The subclinical measures described above have been associated with various CV risk factors, including demographic, metabolic, immunologic, and lifestyle factors, which in turn have been associated with lower levels of cognitive function [204, 253, 254, 255, 256]. However, relations of subclinical CV disease to cognition are unlikely to be due solely to these shared risk factors [35, 206]. Other hypothesized mechanisms include a common genetic vulnerability, chronic cerebral hypoperfusion, micro and macro-cerebrovascular diseases, and other associated structural brain changes, such as cortical atrophy [225, 238, 241, 250]. It should be noted that subclinical disease states often co-occur and may act additively or synergistically in the prediction of diminished cognitive function [204]. The possibility thus exists that one subclinical disease may mediate another subclinical disease's effects on the brain and cognition, potentially in combination with other mediating variables.

Coronary Heart Disease (CHD)

CHD is the leading cause of death in the USA [1]. Manifestations include stable angina, acute coronary syndromes, myocardial infarction, heart failure, sudden death, and silent ischemia. More

than one million people have a MI each year, and many more are hospitalized for angina. Of patients with acute MI, based on ECG and biomarkers, approximately two-thirds have a non-ST segment elevation myocardial infarction (MSTEMI) where they have an increase in their cardiac isoenzymes (creatine kinase MB, or tropin) and an absence of persistent ST segment elevation on their ECG, and approximately one-third have ST segment elevation MI (STEMI) accompanied by increase in their cardiac isoenzymes.

Treatment of patients with stable angina is targeted to prevent MI and reduce or relieve symptoms. An "ABCDE" approach is advocated: aspirin and antianginal therapy; beta-adrenergic antagonists and blood pressure control; cholesterol-lowering agents and cigarette-smoking cessation; diet; and exercise. Invasive intervention with coronary angioplasty, stenting, and by coronary artery bypass grafting (CABG) is indicated in subsets of CHD patients.

Reviewed by Vingerhoets [257], a history of MI has been associated with concurrent dementia across several investigations. Non-demented cardiac patients have been described as exhibiting dysfunction on tests of memory, fine motor control, and orientation [258]. Cardiac patients assessed prior to CABG surgery have displayed decreased word fluency, manual dexterity, verbal learning, and psychomotor speed, with performance similar to persons with carotid stenosis [257]. Others have similarly found cognitive impairment in pre-surgical coronary patients [259]. Prospective investigations have reported relations between several diagnoses of vascular disease such as CHD and MI with lower levels of future performance on cognitive screening measures [260, 261].

Vingerhoets [257] has proposed several mechanisms linking MI with cognitive dysfunction. These include the presence of systemic vascular disease that leads to cardiac and cerebrovascular insufficiency, brain infarction due to cardiogenic embolism, acute or chronic hypoxia due to impaired myocardial function that leads to decreased cerebral perfusion, and post-MI depression. CHD has been associated with brain atrophy [262] and white matter lesions on MRI [263].

Coronary Artery Bypass Grafting (CABG)

A common cardiac surgery used to treat advanced coronary artery disease (CAD), CABG surgery involves bypassing diseased portions of the coronary arteries using healthier segments of noncardiac blood vessels [264]. CABG may be performed with or without cardiopulmonary bypass (CPB), in which a pump takes over heart and lung function during the operation to permit surgery on a non-beating heart [265]. Despite its effectiveness for reducing angina, stabilizing ventricular function, and prolonging life, evidence suggests that CABG surgery may have unforeseen adverse effects on the brain and cognition [266–269].

Both short- and long-term changes in cognitive function have been observed following CABG surgery. In a seminal, though highly debated [270, 271, 272, 273, 274, 275] study, Newman and colleagues [276] found incidence of post-surgical cognitive decline from baseline to be 53% of patients at hospital discharge, 24% at 6 months postsurgery, and 42% at 5-year follow-up.

Short-term cognitive deficits (appearing <1 month postoperatively) in post-CABG patients are now well recognized, with reported incidences varying considerably from study to study (33–83%) depending on the patient population studied, number and type of neuropsychological tests utilized, interval between surgery and testing, and criteria used to define cognitive decline [277–279]. These short-term effects may include decrements across a number of domains of cognitive function, including memory, psychomotor speed, executive functions, and visuoconstructional abilities [269]. Memory and concentration complaints are the most frequently self-reported cognitive changes, though these findings are not always corroborated by neuropsychological data [269, 280].

Long-term deficits are less understood. At least two studies have detected an initial cognitive recovery period ensuing the aforementioned early cognitive decline, followed by a later period of cognitive decline up to 5 years postsurgery [264, 281]. Across studies, motor and psychomotor speeds appear to be the most vulnerable cognitive domains, but nonsignificant findings and significant effects for other cognitive domains have also been identified [269, 275, 282, 283, 284, 285]. These discrepancies are likely a function of the numerous methodologic differences across studies; Selnes and colleagues [269] describe the prevailing pattern as consistent with cognitive changes observed in patients with mild subcortical vascular disease.

The presumed neurobiological underpinnings of post-CABG cognitive changes remain a topic of debate [266, 269, 286, 287, 288]. The occurrence of cerebral microemboli (particularly during cannulation, manipulation of the aorta, and cardiotomy suction) and cerebral hypoperfusion during surgery has received the most attention as possible mechanisms linking CABG with its cognitive sequelae. Other potential contributing factors include anesthesia, peri- and postoperative AF, medications, systemic inflammation, depression and/or anxiety, and patient characteristics such as age, genetic factors, other cerebrovascular disease risk factors (e.g., hypertension, diabetes), and preexisting cerebrovascular disease.

Peripheral Arterial Disease

Peripheral arterial occlusive disease (PAD), a subtype of peripheral vascular disease (PVD), results from atherosclerosis of the arteries that supply the lower extremities (i.e., abdominal aorta, iliac, femoral, popliteal, tibial). PAD affects approximately 16% of adults over the age of 55, including 10% asymptomatic PAD (stage I), 5% intermittent claudication (stage II), and 1% chronic leg ischemia (stages III–IV), and is a major cause of disability among older individuals [289]. Revascularization may be utilized in stage III or IV PAD (i.e., necrosis or gangrene), and stage IV disease may necessitate limb amputation. Because it is a diffuse atherosclerotic disease, PAD is associated with comorbid atherosclerosis of the coronary and carotid arteries [290]. Risk for atherosclerotic events such as MI, PAD, and stroke clusters among individuals [291–293].

Reviewed by Phillips [294], several early investigations examined patients with PVD as control subjects in studies of the impact of vascular surgeries (e.g., carotid endarterectomy, CABG surgery) on cognitive function [295–297]. Results of these studies suggested that patients with PVD displayed mild neuropsychological dysfunction [295, 296] or showed similar cognitive function as patients with carotid disease [297].

Comparing PVD amputees and non-amputees with mild to moderate claudication to healthy control subjects and atherothrombotic stroke patients, Phillips et al. [298] found that PVD patients performed more poorly than healthy controls on tests of attention, psychomotor speed, executive functions, visual memory, and visuospatial ability. Furthermore, the performance of the PVD patients was typically quite similar to that of the stroke patients.

Our research group found that PAD patients performed significantly more poorly than hypertensives and normotensives, but better than stroke patients, on seven tests of nonverbal memory, concentration, executive function, perceptuomotor speed, and manual dexterity [14]. These findings were independent of age, education, and depression scores. Eight to sixty-seven percent of PAD patients displayed impaired performance (<5th percentile of normotensive controls) on the seven aforementioned cognitive tests. We concluded that the findings suggested a continuum of cognitive impairment associated with increasingly severe manifestations of cardiovascular disease.

In the population-based Rotterdam Study, Breteler et al. [216] found that individuals having an ankle– brachial index (ABI) <0.90 (diagnostic of PVD) displayed poorer performance on the MMSE than patients with greater ABIs. The presence of PVD, as assessed by ABI, has also been associated with cognitive decline on the MMSE and a test of perceptuo-motor speed

particularly among individuals having an *APOE* e4 allele [228, 231].

Several direct and indirect mechanisms may link PAD to cognitive difficulties and have been reviewed (see [14, 294]). In that regard, risk factors for atherosclerosis are generally the same for all arterial systems and include dyslipidemia, diabetes, hypertension, and smoking. These risk factors have all been related to structural abnormalities on MRI that reflect microvascular disease, macrovascular disease, brain atrophy, and diminished cerebral perfusion. Next, atherosclerosis in the carotid arteries, which is often comorbid with PAD, has been related to decreased cognitive performance perhaps by indirectly reducing cerebral perfusion. Generalized atherosclerosis may also be related to cognitive dysfunction via increased microemboli. Studies that have conducted neuroimaging in patients with PAD have found increased white matter disease and brain atrophy [299, 300]. In the Rotterdam Study, mean ABIs were significantly lower in patients with white matter lesions on MRI [300].

Heart Failure/Heart Transplantation

Heart failure (HF) is a syndrome where there are structural or functional cardiac disorders that impair the ability of the left ventricle to fill with or eject blood. It is characterized by specific clinical symptoms, such as dyspnea and fatigue, and signs on physical examination, such as fluid retention [301]. The prevalence of HF has been increasing and is projected to double within 40 years, despite improvements in CV mortality rates over recent decades [301, 302]. This pattern is a product of the rapidly aging population and the increasing prevalence of HF with advancing age. Heart transplantation is a treatment option considered for patients with end-stage HF [303].

Diminished cognitive function in HF has been the subject of several recent comprehensive reviews [302, 304, 305, 306]. One systematic review and meta-analysis of 2,937 HF patients and 14,848 controls identified a pooled odds ratio for cognitive impairment of 1.62 (CI: 1.48–1.79, $p < 0.0001$) among individuals with HF [302]. The pattern of impairment associated with HF appears to be diffuse; affected domains include attention, concentration, memory, language, psychomotor speed, and executive function [306–308]. These decrements in cognitive function are associated with an increased risk of hospital readmission, disability, and mortality among HF patients [305, 309, 310]. There is mixed, and very limited, evidence regarding the cognitive consequences of heart transplantation [307]. Although some studies show postsurgical improvement in cognition [311, 312], others show evidence to the contrary [313, 314], and numerous methodologic weaknesses preclude strong conclusions [307]. Post-transplant neuropsychological function is thus an important area for future study.

The neuropathological mechanisms underlying cognitive changes associated with heart failure remain unclear, and relevant mechanistic research is lacking [306]. The primary hypotheses involve multiple cardiogenic emboli and cerebral hypoperfusion associated with insufficient cardiac output [302]. Given that the brain receives a large relative proportion of cardiac output [307], the latter hypothesis appears highly plausible as a contributing factor. However, other cardiovascular risk factors and disease states (e.g., ischemic heart disease, cerebrovascular disease, hypertension, hypotension, AF, diabetes, lifestyle factors) are common among HF patients, and these factors may contribute directly to the observed cognitive changes [302, 304, 315]. Furthermore, fatigue, depression, medication side effects, and other neurological complications are prevalent in HF and carry independent neuropsychological implications [307].

Summary

Although relatively few investigations are available, there is compelling evidence of an association between various CV diseases and pronounced neurocognitive dysfunction. Studies in this area frequently refer to frank cognitive impairment (as compared to normative standards or control subjects) or report dementia

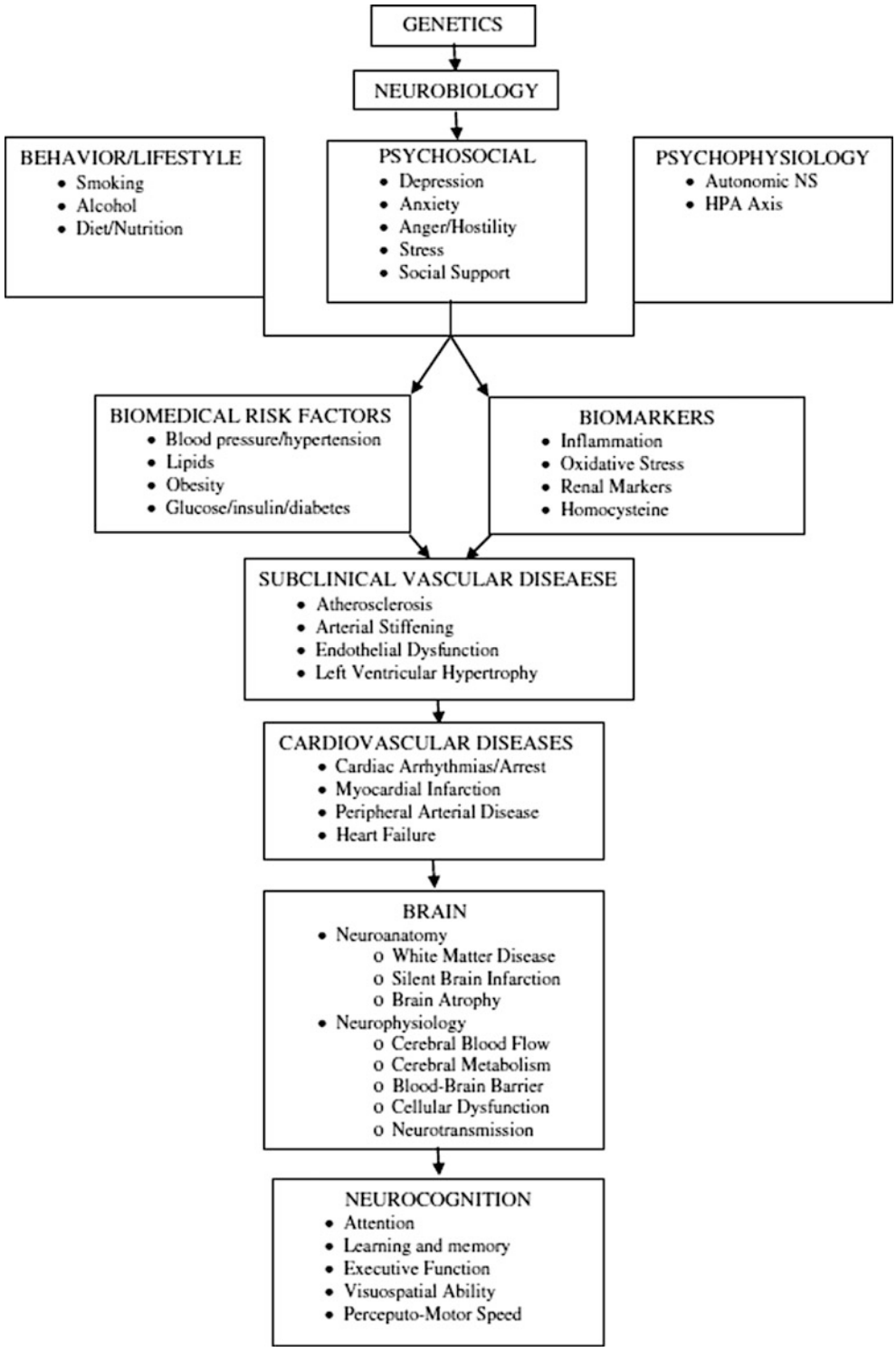

Fig. 6.1 Potential proximal and distal mediators of the relations of CVD risk factors and diseases to neurocognitive function

prevalence. Patterns of performance differ somewhat across the diseases described, but frequently include tests of executive function, motor or perceptuo-motor speed, attention, and memory.

Discussion

CV disease is a complex biopsychosocial phenomenon that likely yields lifelong impact on brain structure and function and, ultimately, cognitive function. We have suggested that there is a multilevel interplay among numerous factors that may serve as proximal and distal mediators of these associations. As noted in Fig. 6.1, genetic risk may operate through any of the subsequent levels to impact brain and cognition. Genetic risk may be expressed in neurobiological manifestations that are present even prior to the appearance of CV risk factors or disease pathology. Genetics and neurobiology may predispose to various behavioral, psychosocial, and psychophysiological factors that have known associations with CV risk factors and diseases. All of these factors may have independent influences on brain structure and function and cognitive performance or may operate through different meditational pathways. Although we have drawn a linear model for the sake of simplicity, it is critical to note the likelihood of multidirectional associations including interrelations among factors at any given level. Although, to our knowledge, tests of this model are unavailable, we have provided reviews of literature that help us to construct possible conceptual linkages.

Here, we have provided brief overviews of the relations of numerous CV risk factors, CV diseases, and their treatments to neurocognitive function. We have highlighted positive findings in order to illustrate possible patterns of associations. Although findings in each area are indeed mixed, we suggest that the preponderance of evidence points to robust associations.

Much more work is needed to clarify the specific neurocognitive tests that are most sensitive to the various CV risk factors and diseases (and associated vulnerability and resilience factors). We have suggested previously that test batteries should provide adequate coverage of major domains of cognitive function. Although there is typically pressure to reduce such data for analysis by factor analysis or conceptual clusters, we prefer to analyze univariate tests to maximize information. Just as it is less informative to interpret a WAIS Verbal or Performance IQ than its individual subscales, there is a substantial loss of information when using factor or composite scores. In clinical neuropsychological assessment, one uses all information available to determine patterns of performance.

In particular, there remains a great need to incorporate more extensive neurocognitive measures into epidemiological investigations, which most commonly use measures such as the MMSE, 3MS, and Short Portable Mental Status Questionnaire to measure "cognitive function." These measures are not optimal in tracking trajectories of domain-specific cognitive decline in healthy individuals and have psychometric limitations [316].

We did not have space to discuss the methodological adequacy of the research in this area. Studies are quite variable with respect to adequacy of design, sample size and characteristics, measurement with respect to both CV and neurocognitive variables, consideration of adjustment variables, and study exclusions. Particularly many studies of CV disease and cognition are fraught with the methodological problems noted above, in addition to the challenges of assessing respective contributions of multiple comorbidities.

There is little research examining the mechanisms underlying relations between CV risk factors or diseases and neurocognition. When possible, investigators should include both cognitive and neuroimaging measures in the same study and examine direct tests of mediation. In addition to traditional MRI and PET methodologies, newer imaging methods such as amyloid and tau imaging should also be employed.

There is generally a paucity of research on the daily life impact of cognitive difficulties related to CV risk factors or diseases. A review is beyond the scope of this chapter. However, work to date suggests associations with quality of life,

physical function (e.g., gait, balance, risk of falls), daily function, disability, and frailty. This is another area in great need of investigation.

Despite the need for further research in each of the areas reviewed, we do have enough evidence to suggest that the relation of CV risk factors and diseases to brain and cognitive outcomes begins very early in life. Further, there appears to be a continuum of cognitive impairment associated with increasingly severe manifestations of cardiovascular disease. Accordingly, early and aggressive efforts at prevention and intervention are critical to the maintenance of "brain health" and cognitive function across the life span.

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References

1. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117:e25–146.
2. Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A. European cardiovascular disease statistics. 3rd ed. Brussels: A European Heart Network; 2008.
3. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L. Risk factors for death from different types of stroke. Multiple Risk Factor Intervention Trial Research Group. Ann Epidemiol. 1993;3:493–9.
4. Meyer JS, Rauch GM, Rauch RA, Anwarul H, Crawford K. Cardiovascular and other risk factors for Alzheimer's disease and vascular dementia. Ann NY Acad Sci. 2000;903:411–23.
5. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004;3:184–90.
6. Roman G. Diagnosis of vascular dementia and Alzheimer's disease. Int J Clin Pract Suppl. 2001; 9–13.
7. White L, Launer L. Relevance of cardiovascular risk factors and ischemic cerebrovascular disease to the pathogenesis of Alzheimer disease: a review of accrued findings from the Honolulu-Asia Aging Study. Alzheimer Dis Assoc Disord. 2006;20:S79–83.
8. Roman GC. Vascular dementia may be the most common form of dementia in the elderly. J Neurol Sci. 2002;203–204:7–10.
9. Roman GC. Vascular dementia prevention: a risk factor analysis. Cerebrovasc Dis. 2005;20(Suppl 2):91–100.
10. Rosano C, Newman AB. Cardiovascular disease and risk of Alzheimer's disease. Neurol Res. 2006;28:612–20.
11. Rosendorff C, Beeri MS, Silverman JM. Cardiovascular risk factors for Alzheimer's disease. Am J Geriatr Cardiol. 2007;16:143–9.
12. Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. J Intern Med. 2006;260:211–23.
13. Hachinski V. Vascular dementia: a radical redefinition. Dementia. 1994;5:130–2.
14. Waldstein SR, Tankard CF, Maier KJ, Pelletier JR, Snow J, Gardner AW, Macko R, Katzel LI. Peripheral arterial disease and cognitive function. Psychosom Med. 2003;65:757–63.
15. Waldstein SR. Health effects on cognitive aging. In: Stern PC, Carstensen LL, editors. The aging mind: opportunities in cognitive research. Committee on future directions for cognitive research on aging. Commission on behavioral and social sciences and education. Washington, DC: National Academy Press; 2000. pp. 189–217.
16. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007. WHO and DMDI 2007 http://www.who.int/classifications/apps/icd/icd10online/
17. Cupples LA, D'Agostino RB. Section 34: some risk factors related to the annual incidence of cardiovascular disease and death in pooled repeated biennial measurements. In: Kannel WB, Wolf PA, Garrison RJ, editors. Framingham Heart Study: 30 year follow-up. Bethesda, MD: US Department of Health and Human Services; 1987.
18. Chobanian AV, Bakris GL, Cushman WC, Green LA, Izzo JLJR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National Heart, Lung and Blood Institute: National High Blood Pressure Education Program Coordinating Committee. Hypertension. 2003;42:1206–52.
19. Newman AB, Naydeck BL, Sutton-Tyrrell K, Edmundowicz D, O'Leary D, Kronmal R, Burke GL, Kuller LH. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. Arterioscler Thromb Vasc Biol. 2002;22:1674.

20. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278: 1349–56.
21. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002;155:487–95.
22. Twamley WE, Legendre Ropacki SA, Bondi MW. Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. J Int Neuropsychol Soc. 2006;12:707–35.
23. de la Torre JC. Cerebrovascular gene linked to Alzheimer's disease pathology. Trends Mol Med. 2005;11:534–6.
24. Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis. Hypertension. 2005;46:280–6.
25. Moser M, Setaro JF. Resistant or difficult-to-control hypertension. NEJM. 2006;355:385–92.
26. Staessen JA, Richart T, Birkenhager WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension. 2007;49:389–400.
27. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. Neurol Res. 2006;28:605–11.
28. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487–99.
29. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000;21:49–55.
30. Waldstein SR, Katzel LI. Hypertension and cognitive function. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 15–36.
31. Waldstein SR, Manuck SB, Ryan CM, Muldoon MF. Neuropsychological correlates of hypertension: review and methodologic considerations. Psychol Bull. 1991;110:451–68.
32. Lande MB, Kaczorowski JM, Auinger P, Schwartz GJ, Weitzman M. Elevated blood pressure and decreased cognitive function among school-age children and adolescents in the United States. J Pediatr. 2003;143:699–700.
33. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. Am J Epidemiol. 1993;138: 353–64.
34. Harrington F, Saxby BK, McKeith IG, Wesnes K, Ford GA. Cognitive performance in hypertensive and normotensive older subjects. Hypertension. 2000;36:1079–82.
35. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension. 2008;51:99–104.
36. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. J Am Med Assoc. 1999;281:438–45.
37. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension. 2005;45:374–9.
38. Tzourio C, Dufouil C, Ducimetiere P, Alperovitch A. Cognitive decline in individuals with high blood pressure. Neurology. 1999;53:1948–52.
39. Elias MF, Robbins MA, Elias PK, Streeten DHP. A longitudinal study of blood pressure in relation to performance on the Wechsler Adult Intelligence Scale. Health Psychol. 1998;17:486–93.
40. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA. 1995;274:1846–51.
41. Waldstein SR, Jennings JR, Ryan CM, et al. Hypertension and neuropsychological performance in men: interactive effects of age. Health Psychol. 1996;15:102–9.
42. Elias MF, Robbins MA, Schultz NR, Streeten DH, Elias PK. Clinical significance of cognitive performance by hypertensive patients. Hypertension. 1987;9:192–7.
43. Waldstein SR, Katzel LI. Gender differences in the relation of hypertension to cognitive function in older adults. Neurol Res. 2004;26:502–6.
44. Pelia R, White LR, Petrovitch H, Masaki K, Ross GW, Havlik RJ, Launer LJ. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu Aging Study. Stroke. 2001;32:2882–9.
45. Kang JH, Logroscino G, De Vivo I, Hunter D, Grodstein F. Apolipoprotein E, cardiovascular disease and cognitive function in aging women. Neurobiol Aging. 2005;26:475–84.
46. Kuusisto J, Koivisto K, Mykkanen L, et al. Essential hypertension and cognitive function: the role of hyperinsulinemia. Hypertension. 1993;22:771–9.
47. Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obesity. 2006;30:201–7.
48. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham Heart study. Int J Obes Relat Metab Disord. 2003;27:260–8.
49. Waldstein SR, Brown JRP, Maier K, Katzel LI. Diagnosis of hypertension and high blood pressure levels negatively affect cognitive function in older adults. Ann Behav Med. 2005;29:174–80.

50. Brady CB, Spiro A 3rd, Gaziano JM. Effects of age and hypertension status on cognition: the Veterans Affairs Normative Aging Study. Neuropsychology. 2005;19:770–7.
51. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. Cell Metab. 2008;7:476–84.
52. Murray MD, Lane KA, Gao S, Evans RM, Unverzagt FW, Hall KS, Hendrie H. Preservation of cognitive function with anithypertensive medications. Arch Intern Med. 2002;162:2090–6.
53. Jonas DL, Blumenthal JA, Madden DJ, Serra M. Cognitive consequences of antihypertensive medications. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 167–88.
54. Birns J, Morris R, Donaldson N, Kalra L. The effects of blood pressure reduction on cognitive function: a review of effects based on pooled data from clinical trials. J Hypertens. 2006;24:1907–14.
55. Muldoon MF, Waldstein SR, Ryan CM, Jennings JR, Polefrone JM, Shapiro AP, Manuck SB. Effects of six antihypertensive medications on cognitive performance. J Hypertens. 2002;20:1643–52.
56. National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
57. Grodstein F. Cardiovascular risk factors and cognitive function. Alzheimers Dement. 2007;3:S16–22.
58. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004;61:705–14.
59. Dufouil C, Richard F, Fievet N, et al. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. Neurology. 2005;64:1531–8.
60. Tan ZS, Seshadri S, Beiser A, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med. 2003;163:1053–7.
61. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu–Asia aging study. Arterioscler Thromb Vasc Biol. 2000;20:2255–60.
62. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62:1556–60.
63. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry. 2008;16:343–54.
64. Muldoon MF, Flory JD, Ryan CM. Serum cholesterol, the brain and cognition. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 37–59.
65. Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham Heart Study. Psychosom Med. 2005;67:24–30.
66. Atzmon G, Gabriely I, Greiner W, Schechter C, Barzilai N. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. J Gerontol A Biol Sci Med Sci. 2002;57:M712–5.
67. Soloman A, Kareholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year-follow-up study. Neurology. 2007;68:751–6.
68. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol. 2002;59:378–84.
69. Swan GE, LaRue A, Carmelli D, et al. Decline in cognitive performance in aging twins: heritability and biobehavioral predictors from the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol. 1992;49:476–81.
70. Kojro E, Gimpl G, Lammich S, et al. Low cholesterol stimulates the nonamylogenic pathway by its effect on the alpha-secretase Alzheimer's Disease AM 10. Proc Natl Acad Sci USA. 2001;98:5814–20.
71. Szwast SJ, Hendrie HC, Lane KA, Gao S, Taylor SE, Unverzagt F, et al. Association of statin use with cog nitive decline in elderly African Americans. Neurology. 2007;69:1873–80.
72. Xiong GL, Benson A, Doraiswamy PM. Statins and cognition: what can we learn from existing randomized trials. CNS Spectr. 2005;867–74.
73. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–52.
74. Després J-P, Lemieux I. Prud'homme D. Treatment of obesity: need to focus on high risk abdominal obesity patients. BMJ. 2001;322:716–20.
75. Calle ED, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med. 1999;341:1097–105.
76. Wilson PW, Bozeman SR, Burton TM, Hoaglin DC, Ben-Joseph R, Pashos CL. Prediction of first events of coronary heart disease and stroke with consideration of adiposity. Circulation. 2008;118:124–30.

77. Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006;5:713–20.
78. Whitmer RA. The epidemiology of adiposity and dementia. Curr Alzheimer Res. 2007;4:117–22.
79. Barrett-Connor E. An introduction to obesity and dementia. Curr Alzheimer Res. 2007;4:97–101.
80. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008; epub, ahead of print.
81. Cserjései R, Molnár D, Luminet O, Lénárd L. Is there any relationship between obesity and mental flexibility in children? Appetite. 2007;49:675–8.
82. Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E. Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord. 2006;11:e15–9.
83. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry. 2007;57–61.
84. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Curr Alzheimer Res. 2007;4:111–6.
85. Dore GA, Elias MF, Robbins MA, Budge MM, Elias PK. Relation between central adiposity and cognitive function in the Maine-Syracuse Study: attenuation by physical activity. Ann Behav Med. 2008;35:341–50.
86. Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, Lipsitz LA. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly Cohort. J Am Geriatr Soc. 2005;54:97–103.
87. Sakakura K, Hoshide S, Ishikawa J, et al. Association of body mass index with cognitive function in elderly hypertensive Japanese. Am J Hypertens. 2008;21:627–32.
88. Sturman MT, de Leon CF, Bienias JL, Morris MC, Wilson RS, Evans DA. Body mass index and cognitive decline in a biracial community population. Neurology. 2008;70:360–7.
89. Jagust W. What can imaging reveal about obesity and the brain? Curr Alzheimer Res. 2007;4:135–9.
90. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle aged adults: a cross sectional study. BMC Neurol. 2005;5:23.
91. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol. 2008;63:652–7.
92. Bjorntorp P, Rosmond R. Neuroendocrine abnormalities in visceral obesity. Int J Obes Relat Metab Disord. 2000;24 Suppl:S80–S85.
93. Ren J. Leptin and hyperleptinemia – from friend to foe for cardiovascular function. J Endocrinol. 2004;18:1–10.
94. Sweat V, Starr V, Bruehl H, Arentoft A, Tirsi A, Javier E, Convit A. C-reactive protein is linked to lower cognitive performance in overweight and obese women. Inflammation. 2008;31:198–207.
95. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183–97.
96. Cechetto DF, Hachinski V, Whitehead SN. Vascular risk factors and Alzheimer's disease. Expert Rev Neurother. 2008;8:743–50.
97. Messier C, Awad N, Gagnon M. The relationships between atherosclerosis, heart disease, type 2 diabetes and dementia. Neurol Res. 2004;26:567–72.
98. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes – systematic overview of prospective observational studies. Diabetologia. 2005;48:2460–9.
99. Ryan CM. Diabetes associated cognitive dysfunction. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 61–82.
100. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol. 2008;7:184–90.
101. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. Endocr Rev. 2008;29:494–511.
102. Diabetes C. Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. Curr Diab Rep. 2008;356: 1842–52.
103. Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, Wolf PA. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes Care. 1997;20:1388–95.
104. Taylor VH, MacQueen GM. Cognitive dysfunction associated with metabolic syndrome. Obes Rev. 2007;8:409–18.
105. Rolandsson O, Backerström A, Eriksson S, Hallmans G, Nilsson LG. Increased glucose levels are associated with episodic memory in nondiabetic women. Diabetes. 2008;57:440–3.
106. Stolk RP, Breteler MM, Ott A, Pols HA, Lamberts SW, Grobbee DE, Hofman A. Insulin and cognitive function in an elderly population. The Rotterdam Study. Diabetes Care. 1997;20:792–5.
107. Young SE, Mainous AG 3rd, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. Diabetes Care. 2006;29:2688–93.
108. Huber JD. Diabetes, cognitive function, and the blood-brain barrier. Curr Pharm Des. 2008;14:1594–600.

109. Schmidt R, Launer LJ, Nilsson LG, et al. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes. 2004;53:687–92.
110. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med. 2008;358:2107–16.
111. Ware JH. The limitations of risk factors as prognostic tools. N Engl J Med. 2006;35:2615–7.
112. Ridker PM, Wilson PWF, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004;109:2818–25.
113. Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol. 2002;52:168–74.
114. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle aged adults. Biol Psychiatry. 2008; epub ahead of print.
115. Rafnsson SB, Deary IJ, Smith FB, et al. Cognitive decline and markers of inflammation and hemostasis: the Edinburgh Artery Study. J Am Geriatr Soc. 2007;55:700–07.
116. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003;61:76–80.
117. Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002;59:371–8.
118. Jordanova V, Stewart R, Davies E, et al. Markers of inflammation and cognitive decline in an African-Caribbean population. Int J Geriatr Psychiatry. 2007;22:966–73.
119. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. J Am Med Assoc. 2004;292:2237–42.
120. Schram MT, Euser SM, de Craen AJM, et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc. 2007;55:708–16.
121. Fornage M, Chiang YA, O'Meara ES, et al. Biomarkers of inflammation and MRI-defined small vessel disease of the brain: the Cardiovascular Health Study. Stroke. 2008;39:1952–9.
122. van Dijk EJ, Prins ND, Vermeer SE, et al. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. Circulation. 2005;112:900–05.
123. Wada M, Nagasawa H, Kurita K, et al. Cerebral small vessel disease and C-reactive protein: results of a cross-sectional study in community-based Japanese elderly. J Neurol Sci. 2008;264:43.
124. Schmidt R, Schmidt H, Pichler M, et al. C-reactive protein, carotid atherosclerosis, and cerebral small-vessel disease: results of the Austrian Stroke Prevention Study. Stroke. 2006;37:2910–6.
125. Marcus DL, Thomas C, Rodriguez C, et al. Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. Exp Neurol. 1998;150:40.
126. Berr C, Balansard B, Arnaud J, et al. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. J Am Geriatr Soc. 2000;48:1285–91.
127. Shibata H, Nabika T, Moriyama H, et al. Correlation of NO metabolites and 8-iso-prostaglandin F2a with periventricular hyperintensity severity. Arterioscler Thromb Vasc Biol. 2004;24:1659–63.
128. Grodstein F, Kang JH, Glynn RJ, et al. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Arch Intern Med. 2007;167:2184–90.
129. Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med. 2006;166:2462–8.
130. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. J Am Med Assoc. 2007;298:2038–47.
131. Sehgal AR, Grey SF, DeOreo PB, et al. Prevalence, recognition, and implications of mental impairment among hemodialysis patients. Am J Kidney Dis. 1997;30:41–9.
132. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006;67:216–23.
133. Elias MF, Elias PK, Seliger SL, et al. Chronic kidney disease, creatinine, and cognitive functioning. Nephrol Dial Transplant 2009;24:24461–52.
134. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the Health, Aging, and Body Composition Study. J Am Soc Nephrol. 2005;16:2127–33.
135. Yaffe K, Lindquist K, Shlipak MG, et al. Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. Ann Neurol. 2008;63:798–802.
136. Hailpern SM, Melamed ML, Cohen HW, et al. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). J Am Soc Nephrol. 2007;18:2205–13.
137. Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. Am J Kidney Dis. 2005;45:66–76.
138. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol. 2004;15:1904–11.

139. Barzilay JI, Fitzpatrick AL, Luchsinger J, et al. Albuminuria and dementia in the elderly: a community study. Am J Kidney Dis. 2008;52:216–26.
140. Elias MF, Sullivan LM, D'Agostino RB, et al. Homocysteine and cognitive performance in the Framingham Offspring Study: age is important. Am J Epidemiol. 2005;162:644–53.
141. Wright CB, Lee HS, Paik MC, et al. Total homocysteine and cognition in a tri-ethnic cohort: the Northern Manhattan Study. Neurology. 2004;63:254–60.
142. Kado DM, Karlamangla AS, Huang M-H, et al. Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. Am J Med. 2005;118:161.
143. Haan MN, Miller JW, Aiello AE, et al. Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging. Am J Clin Nutr. 2007;85:511–7.
144. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002;346:476–83.
145. Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr. 2005;82:636–43.
146. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006;354:2764–72.
147. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369:208–16.
148. Gorelick PB. Cerebrovascular disease in African Americans. Stroke. 1998;29:2656–64.
149. Letenneur L, Larrieu S, Barberger-Gateau P. Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiologic studies. Biomed Pharmacother. 2004;58:95–9.
150. Antsey KJ, Lipnicki DM, Low LF. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166:367–78.
151. Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. Neuropsychol Rev. 2007;17:259–73.
152. Galanis DJ, Petrovitch H, Launer LJ, Harris TB, Foley DJ, White LR. Smoking history in middle age and subsequent cognitive performance in elderly Japanese–American men. The Honolulu–Asia Aging Study. Am J Epidemiol. 1997;145:507–15.
153. Oscar-Berman M, Marinkovic K. Alcohol: effects on neurobehavioral functions and the brain. Neuropsychol Rev. 2007;17:239–57.
154. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. J Am Med Assoc. 2003;289:579–88.
155. Lang I, Wallace RB, Huppert FA, Melzer D. Moderate alcohol consumption in older adults is associated with better cognition and well-being than abstinence. Age Ageing. 2007;36:256–61.
156. Ngandu T, Helkala EL, Soininen H, et al. Alcohol drinking and cognitive functions: findings from the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study. Dement Geriatr Cogn Disord. 2007;23:140–9.
157. Elias PK, Elias MF, D'Agostino RB, Silbershatz H, Wolf PA. Alcohol consumption and cognitive performance in the Framingham Heart Study. Am J Epidemiol. 1999;150:580–9.
158. Dufouil C, Ducimetiere P, Alperovitch A. Sex differences in the association between alcohol consumption and cognitive performance. EVA Study Group: Epidemiology of Vascular Aging. Am J Epidemiol. 1997;146:405–12.
159. Galanis DJ, Joseph C, Masaki KH, Petrovitch H, Ross GW, White L. A longitudinal study of drinking and cognitive performance in elderly Japanese American men: the Honolulu-Asia Aging Study. Am J Public Health. 2000;90:1254–9.
160. Frank B, Gupta S. A review of antioxidants and Alzheimer's disease. Ann Clin Psychiatry. 2005;17:269–86.
161. Wengreen HJ, Munger RG, Corcoran CD, Zandi P, Hayden KM, Fotuhi M, Skoog I, Norton MC, Tschanz J, Breitner JC, Welsh-Bohmer KA. Antioxidant intake and cognitive function of elderly men and women: the Cache County Study. J Nutr Health Aging. 2007;11:230–7.
162. Del Parigi A, Panza F, Capurso C, Solfrizzi V. Nutritional factors, cognitive decline, and dementia. Brain Res Bull. 2006;69:1–19.
163. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology. 2004;62:1573–9.
164. Conklin SM, Gianaros PJ, Brown SM, et al. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in health adults. Neurosci Lett. 2007;421:209–12.
165. Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005;4:705–11.
166. Dishman RK, Berthoud HR, Booth FW, et al. Neurobiology of exercise. Obesity. 2006;14:345–56.
167. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. PNAS. 2004;3316–21.
168. Colcombe SJ, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;125–30.

169. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999;99:2192–217.
170. Kubzansky LD, Davidson KW, Rozanski A. The clinical impact of negative psychological states: expanding the spectrum of risk for coronary artery disease. Psychosom Med. 2005;67:S10–4.
171. Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med. 1998;158:1133–8.
172. Everson SA, Kaplan GA, Goldberg DE, Lakka TA, Sivenius J, Salonen JT. Anger expression and incident stroke: prospective evidence from the Kuopio ischemic heart disease study. Stroke. 1999;30:523–8.
173. McCaffery JM, Frasure-Smith N, Dube MP, et al. Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation an serotonin. Psychosom Med. 2006;68:187–200.
174. Leonard BE. Inflammation, depression and dementia: are they connected? Neurochem Res. 2007;32:1749–56.
175. Bellelli G, Pezzinin A, Bianchetti A, Trabucchi M. Increased blood pressure variability may be associated with cognitive decline in hypertensive elderly subjects with no dementia. Arch Intern Med. 2002;162:483–4.
176. Kanemaru A, Kanemaru K, Kuwajima I. The effects of short-term blood pressure variability and nighttime blood pressure levels on cognitive function. Hypertens Res. 2001;24:19–24.
177. Waldstein SR, Katzel LI. Stress-induced blood pressure reactivity and cognitive function. Neurology. 2005;64:1750–5.
178. Brown JRP, Zonderman AB, Sollers JJ, Thayer JF, Waldstein SR. Blood pressure reactivity and cognitive function in the Baltimore Longitudinal Study of Aging. Health Psychol. 2009;28:641–6.
179. Manuck SB, Kasprowicz AL, Monroe SM, Larkin KT, Kaplan JR. Psychophysiologic reactivity as a dimension of individual differences. In: Schneiderman N, Weiss SM, Kaufmann PG, editors. Handbook of research methods in cardiovascular behavioral medicine. New York, NY: Plenum; 1989. pp. 365–82.
180. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen J. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. Stroke. 2001;32:1263–70.
181. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men. Findings from the Kuopio Ischemic Heart Disease Study. Circulation. 1997;96:3842–8.
182. Waldstein SR, Siegel EL, Lefkowitz D, et al. Stress-induced blood pressure reactivity and silent cerebrovascular disease. Stroke. 2004;35:1294–8.
183. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Relation between nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensives: advanced silent cerebrovascular damage in extreme dippers. Hypertension. 1996;27:130–5.
184. Goldstein IB, Bartzokis G, Hance DB, Shapiro D. Relationship between blood pressure and subcortical lesions in healthy elderly people. Stroke. 1998;29:765–72.
185. Kario K, Eguchi K, Hoshide S, et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives. J Am Coll Cardiol. 2002;40:133–41.
186. Lupien SJ, Schwartz G, Ng YK, et al. The Douglas hospital longitudinal study of normal and pathological aging: summary of findings. J Psychiatry Neurosci. 2005;30:328–34.
187. Li G, Cherrier MM, Tsuang DW, et al. Salivary cortisol and memory function in human aging. Neurobiol Aging. 2006;27:1705–14.
188. Wright CE, Kunz-Ebrecht SR, Iliffe S, Foese O, Steptoe A. Physiological correlates of cognitive functioning in an elderly population. Psychoneuroendocrinology. 2005;30:826–38.
189. Kirschbaum C, Wolf OT, May M, Wippich W, Helhammer DH. Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci. 1996;58:1475–83.
190. Sapolsky RM. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. Exp Gerontol. 1999;34:721–32.
191. McEwen BS. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol Aging. 2002;23:921–39.
192. Sherwin BB. Steroid hormones and cognitive functioning in aging men: a mini-review. J Mol Neurosci. 2003;20:385–93.
193. Sherwin BB. Estrogen and cognitive aging in women. Neuroscience. 2006;138:1021–6.
194. de la Torre JC. How do heart disease and stroke become risk factors for Alzheimer's disease? Neurol Res. 2006;28:637–44.
195. Bergmann C, Sano M. Cardiac risk factors and potential treatments in Alzheimer's disease. Neurol Res. 2006;28:595–604.
196. Korczyn AD, Vakhapova V. The prevention of the dementia epidemic. J Neurol Sci. 2007;257:2–4.
197. Elias MF, Sullivan LM, D'Agostino RB, et al. Framingham stroke risk profile and lowered cognitive performance. Stroke. 2004;35:404–09.

198. Mead GE, Keir S. Association between cognitive impairment and atrial fibrillation: a systematic review. J Stroke Cerebrovasc Dis. 2001;10:35–43.
199. Vingerhoets G. Cognitive consequences of myocardial infarction, cardiac arrhythmias, and cardiac arrest. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 143–63.
200. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J Epub. 2008 Jul;29.
201. Lim C, Alexander MP, LaFleche G, Schnyer DM, Verfaellie M. The neurological and cognitive sequelae of cardiac arrest. Neurology. 2004;63:1774–8.
202. van Alem AP, Waalewijn RA, Koster RW, de Vos R. Assessment of quality of life and cognitive function after out-of-hospital cardiac arrest with successful resuscitation. Am J Cardiol. 2004;93:131–5.
203. Caine D, Watson JD. Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J Int Neuropsychol Soc. 2000;6:86–99.
204. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. Circulation. 1993;88:1444–55.
205. Poredos P. Intima–media thickness: indicator of cardiovascular risk and measure of the extent of atherosclerosis. Vasc Med. 2004;9:46–54.
206. Simon A, Levenson J. May subclinical arterial disease help to better detect and treat high-risk asymptomatic individuals? J Hypertens. 2005;23:1939–45.
207. Chaves PH, Kuller LH, O'Leary DH, Manolio TA, Newman AB. Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. Am J Geriatr Cardiol. 2004;13:137–51.
208. Shechter M, Issachar A, Marai I, et al. Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. Int J Cardiol Epub 2008 May 12.
209. Laurent S, Boutouyrie P. Arterial stiffness: a new surrogate end point for cardiovascular disease? J Nephrol. 2007;20:S45–50.
210. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999;340:14–22.
211. Napoli C, Palinski W. Neurodegenerative diseases: insights into pathogenic mechanisms from atherosclerosis. Neurobiol Aging. 2005;26:293–302.
212. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet. 1997;349:151–4.
213. Grobbee DE, Bots ML. Carotid artery intima–media thickness as an indicator of generalized atherosclerosis. J Intern Med. 1994;236:567–73.
214. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb. 1991;11:1245–9.
215. Wong M, Edelstein J, Wollman J, Bond MG. Ultrasonicpathological comparison of the human arterial wall. Verification of intima–media thickness. Arterioscler Thromb. 1993;13:482–6.
216. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. Br Med J. 1994;308:1604–08.
217. Auperin A, Berr C, Bonithon-Kopp C, et al. Ultra-sonographic assessment of carotid wall characteristics and cognitive functions in a community sample of 59- to 71-year-olds. Stroke. 1996;27:1290–5.
218. Cerhan JR, Folsom AR, Mortimer JA, et al. Correlates of cognitive function in middle-aged adults. Gerontology. 1998;44:95–105.
219. Claus JJ, Breteler MM, Hasan D, et al. Regional cerebral blood flow and cerebrovascular risk factors in the elderly population. Neurobiol Aging. 1998;19:57–64.
220. Kaplan GA, Everson SA, Koivisto K, Salonen R, Salonen JT. Cognitive function and carotid atherosclerosis in Eastern Finnish men. Ann Behav Med. 1996;18:S47.
221. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: the Tromso Study. Neurology. 2004;62:695–701.
222. Muller M, Grobbee DE, Aleman A, Bots M, van der Schouw YT. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis. 2007;190:143–9.
223. Singh-Manoux A, Britton A, Kivimaki M, Gueguen A, Halcox J, Marmot M. Socioeconomic status moderates the association between carotid intima–media thickness and cognition in midlife: evidence from the Whitehall II study. Atherosclerosis. 2008;197:541–8.
224. Haley AP, Forman DE, Poppas A, et al. Carotid artery intima–media thickness and cognition in cardiovascular disease. Int J Cardiol. 2007;121:148–54.
225. Cohen RA, Poppas A, Forman DE, et al. Vascular and cognitive functions associated with cardiovascular disease in the elderly. J Clin Exp Neuropsychol. 2008;1–15.

226. Smith PJ, Blumenthal JA, Babyak MA, et al. Cerebrovascular risk factors, vascular disease, and neuropsychological outcomes in adults with major depression. Psychosom Med. 2007;69:578–86.
227. Yaldizli O, Kastrup O, Obermann M, et al. Carotid intima– media thickness in HIV-infected individuals: relationship of premature atherosclerosis to neuropsychological deficits? Eur Neurol. 2006;55: 166–71.
228. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. J Am Med Assoc. 1999;282:40–6.
229. Johnston SC, O'Meara ES, Manolio TA, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med. 2004;140:237–47.
230. Komulainen P, Kivipelto M, Lakka TA, et al. Carotid intima–media thickness and cognitive function in elderly women: a population-based study. Neuroepidemiology. 2007;28:207–13.
231. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001;56:42–8.
232. Wendell CR, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR. Carotid intimal-medial thickness predicts cognitive decline among adults without clinical vascular disease. Stroke. 2009;40:3180–5.
233. Lee YH, Yeh SJ. Correlation of common carotid artery intima media thickness, intracranial arterial stenosis and post-stroke cognitive impairment. Acta Neurologica Taiwanica. 2007;16:207–13.
234. Silvestrini M, Gobbi B, Pasqualetti P, et al. Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. Neurobiol Aging Epub 2007 Dec 10.
235. Talelli P, Ellul J, Terzis G, et al. Common carotid artery intima media thickness and post-stroke cognitive impairment. J Neurol Sci. 2004;223: 129–34.
236. de Simone G, Roman MJ, Alderman MH, Galderisi M, de Divitiis O, Devereux RB. Is high pulse pressure a marker of preclinical cardiovascular disease? Hypertension. 2005;45:575–9.
237. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588–605.
238. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke. 2003;34:594–9.
239. Robbins MA, Elias MF, Elias PK, Budge MM. Blood pressure and cognitive function in an African-American and a Caucasian-American sample: the Maine-Syracuse Study. Psychosom Med. 2005;67:707–14.
240. Obisesan TO, Obisesan OA, Martins S, et al. High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: the Third National Health and Nutrition Examination Survey. J Am Geriatr Soc. 2008;56:501–09.
241. Hanon O, Haulon S, Lenoir H, et al. Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke. 2005;36:2193–7.
242. Scuteri A, Brancati AM, Gianni W, Assisi A, Volpe M. Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a Pilot Study. J Hypertens. 2005;23:1211–6.
243. Nagai K, Akishita M, Machida A, Sonohara K, Ohni M, Toba K. Correlation between pulse wave velocity and cognitive function in nonvascular dementia. J Am Geriatr Soc. 2004;52:1037–8.
244. Scuteri A, Tesauro M, Appolloni S, Preziosi F, Brancati AM, Volpe M. Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual. J Hypertens. 2007;25:1035–40.
245. Poels MM, van Oijen M, Mattace-Raso FU, et al. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam Study. Stroke. 2007;38: 888–92.
246. Lane HA, Smith JC, Davies JS. Noninvasive assessment of preclinical atherosclerosis. Vasc Health Risk Manag. 2006;2:19–30.
247. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39:257–65.
248. Desmond DW. The neuropsychology of vascular cognitive impairment: is there a specific cognitive deficit? J Neurol Sci. 2004;226:3–7.
249. O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry. 2006;14:724–33.
250. Hoth KF, Tate DF, Poppas A, et al. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. Stroke. 2007;38:308–12.
251. Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. Hypertension. 2007;49:439–45.
252. Kahonen-Vare M, Brunni-Hakala S, Lindroos M, Pitkala K, Strandberg T, Tilvis R. Left ventricular hypertrophy and blood pressure as predictors of cognitive decline in old age. Aging Clin Exp Res. 2004;16:147–52.
253. Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care. 1997;20:935–42.

254. van Exel E, de Craen AJ, Remarque EJ, et al. Interaction of atherosclerosis and inflammation in elderly subjects with poor cognitive function. Neurology. 2003;61:1695–701.
255. Elias MF, Elias PK, Robbins MA, Wolf PA, D'Agostino RB. Cardiovascular risk factors and cognitive functioning: an epidemiological perspective. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 83–104.
256. Scuteri A, Najjar SS, Muller DC, et al. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. J Am Coll Cardiol. 2004;43:1388–95.
257. Vingerhoets G, Van Nooten G, Jannes C. Neuropsychological impairment in candidates for cardiac surgery. J Int Neuropsychol Soc. 1997;3:480–4.
258. Barclay LL, Weiss EM, Mattis S, Bond O, Blass JP. Unrecognized cognitive impairment in cardiac rehabilitation patients. J Am Geriatr Soc. 1988;36:22–8.
259. Hogue CW Jr, Hershey T, Dixon D, et al. Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations. Anesth Analg. 2006;102:1602–08.
260. Singh-Manoux A, Britton AR, Marmot M. Vascular disease and cognitive function: evidence from the Whitehall II Study. J Am Geriatr Soc. 2003;51:1445–50.
261. Elwood PC, Pickering J, Bayer A, Gallacher JE. Vascular disease and cognitive function in older men in the Caerphilly cohort. Age Ageing. 2002;31:43–8.
262. Almeida OP, Garrido GJ, Beer C, et al. Coronary heart disease is associated with regional grey matter volume loss: implications for cognitive function and behavior. Intern Med J. 2008;38:599–606.
263. Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994;44:1246–52.
264. Newman S, Stygall J, Kong R. Neuropsychological consequences of coronary artery bypass surgery. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 189–218.
265. Scarborough JE, White W, Derilus FE, Mathew JP, Newman MF, Landolfo KP. Neurologic outcomes after coronary artery bypass grafting with and without cardiopulmonary bypass. Semin Thorac Cardiovasc Surg. 2003;15:52–62.
266. Gottesman RF, Wityk RJ. Brain injury from cardiac bypass procedures. Semin Neurol. 2006;26:432–9.
267. Hawkes AL, Nowak M, Bidstrup B, Speare R. Outcomes of coronary artery bypass graft surgery. Vasc Health Risk Manag. 2006;2:477–84.
268. Selnes OA, McKhann GM. Neurocognitive complications after coronary artery bypass surgery. Ann Neurol. 2005;57:615–21.
269. Selnes OA, McKhann GM, Borowicz LM Jr, Grega MA. Cognitive and neurobehavioral dysfunction after cardiac bypass procedures. Neurol Clin. 2006;24:133–45.
270. Aklog L. Neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;345:543–4.
271. Mack MJ, Magee MJ, Dewey TM. Neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;345:543.
272. Taggart DP, Browne SM, Halligan PW. Neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;345:544–5.
273. Wilner AP. Neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;345:544.
274. Malphurs JE, Roscoe LA. Neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;345:544.
275. Selnes OA, McKhann GM. Coronary-artery bypass surgery and the brain. N Engl J Med. 2001;344:451–2.
276. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402.
277. Royter V, Bornstein NM, Russell D. Coronary artery bypass grafting (CABG) and cognitive decline: a review. J Neurol Sci. 2005;229–230:65–7.
278. Symes E, Maruff P, Ajani A, Currie J. Issues associated with the identification of cognitive change following coronary artery bypass grafting. Aust N Z J Psychiatry. 2000;34:770–84.
279. Blumenthal JA, Mahanna EP, Madden DJ, White WD, Croughwell ND, Newman MF. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. Ann Thorac Surg. 1995;59:1345–50.
280. Gardner FV, Worwood EV. Psychological effects of cardiac surgery: a review of the literature. J R Soc Health. 1997;117:245–9.
281. Selnes OA, Royall RM, Grega MA, Borowicz LM Jr, Quaskey S, McKhann GM. Cognitive changes 5 years after coronary artery bypass grafting: is there evidence of late decline? Arch Neurol. 2001;58:598–604.
282. Hlatky MA, Bacon C, Boothroyd D, et al. Cognitive function 5 years after randomization to coronary angioplasty or coronary artery bypass graft surgery. Circulation. 1997;96:II-11–14.
283. Mullges W, Babin-Ebell J, Reents W, Toyka KV. Cognitive performance after coronary artery bypass grafting: a Follow-Up Study. Neurology. 2002;59:741–3.

284. Potter GG, Plassman BL, Helms MJ, Steffens DC, Welsh-Bohmer KA. Age effects of coronary artery bypass graft on cognitive status change among elderly male twins. Neurology. 2004;63:2245–9.
285. Stygall J, Newman SP, Fitzgerald G, et al. Cognitive change 5 years after coronary artery bypass surgery. Health Psychol. 2003;22:579–86.
286. Haddock CK, Poston WS, Taylor JE. Neurocognitive sequelae following coronary artery bypass graft. A research agenda for behavioral scientists. Behav Modif. 2003;27:68–82.
287. Taggart DP, Westaby S. Neurological and cognitive disorders after coronary artery bypass grafting. Curr Opin Cardiol. 2001;16:271–6.
288. Reichenberg A, Dahlman KL, Mosovich S, Silverstein JH. Neuropsychiatric consequences of coronary artery bypass grafting and noncardiovascular surgery. Dialogues Clin Neurosci. 2007;9:85–91.
289. Weitz JI, Byrne J, Clagett P, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996;94:3026–49.
290. Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories. J Cardiovasc Risk. 1994;1:333–9.
291. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326:381–6.
292. Sutton KC, Wolfson SK, Kuller LH. Carotid and lower extremity arterial disease in elderly adults with isolated systolic hypertension. Stroke. 1987;18:817–22.
293. Bots ML, Hofman A, Grobbee DE. Common carotid intima–media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. Arterioscler Thromb. 1994;14:1885–91.
294. Phillips NA. Thinking on your feet: a neuropsychological review of peripheral vascular disease. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 121–42.
295. Shaw PJ, Bates D, Cartlidge NEF, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. Stroke. 1987;18:700–07.
296. Hemmingsen R, Mejsholm B, Vorstrup S, Lester J, Engell HC, Boysen G. Carotid surgery, cognitive function, and cerebral blood flow in patients with transient ischemic attacks. Ann Neurol. 1986;20:13–9.
297. Kelly MP, Garron DC, Javid H. Carotid artery disease, carotid endarterectomy and behavior. Arch Neurol. 1980;37:743–8.
298. Phillips NA, Mate-Kole CC. Cognitive deficits in peripheral vascular disease. A comparison of mild stroke patients and normal control subjects. Stroke. 1997;28:777–84.
299. Amar K, Lewis T, Wilcock G, Scott M, Bucks R. The relationship between white matter low attenuation on brain CT and vascular risk factors: a memory clinic study. Aging Ageing. 1995;24:411–5.
300. Bots ML, van Swieten JC, Breteler MM, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet. 1993;341:1232–7.
301. Rich MW. Heart failure in the 21st century: a cardiogeriatric syndrome. J Gerontol A Biol Sci Med Sci. 2001;56:M88–96.
302. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail. 2007;9:440–9.
303. Radovancevic B, Frazier OH. Surgical therapies for heart failure. Curr Opin Cardiol. 2000;15:161–5.
304. Almeida OP, Flicker L. The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. Intern Med J. 2001;31:290–5.
305. Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS. Heart failure and cognitive impairment: challenges and opportunities. Clin Interv Aging. 2007;2:209–18.
306. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature (2002-July 2007). J Cardiovasc Nurs. 2008;23:239–49.
307. Bornstein RA. Neuropsychological function before and after transplantation. In: Waldstein SR, Elias MF, editors. Neuropsychology of cardiovascular disease. Mahwah, NJ: Erlbaum; 2001. pp. 219–28.
308. Vogels RL, Oosterman JM, van Harten B, et al. Profile of cognitive impairment in chronic heart failure. J Am Geriatr Soc. 2007;55:1764–70.
309. Zuccala G, Onder G, Pedone C, et al. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results from a multicentre survey. On behalf of the GIFA (SIGG-ONLUS) Investigators. J Neurol Neurosurg Psychiatry. 2001;70:109–12.
310. Zuccala G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. Am J Med. 2003;115:97–103.
311. Bornstein RA, Starling RC, Myerowitz PD, Haas GJ. Neuropsychological function in patients with end-stage heart failure before and after cardiac transplantation. Acta Neurol Scand. 1995;91:260–5.
312. Roman DD, Kubo SH, Ormaza S, Francis GS, Bank AJ, Shumway SJ. Memory improvement following cardiac transplantation. J Clin Exp Neuropsychol. 1997;19:692–7.
313. Augustine AM, Goldsborough M, McKhann GM, Selnes OA, Baumgartner WA. Neurocognitive deficits pre and one month post transplantation. J Heart Lung Transplant. 1994;13(Suppl):44.

314. Grimm M, Yeganehfar W, Laufer G, et al. Cyclosporine may affect improvement of cognitive brain function after successful cardiac transplantation. Circulation. 1996;94:1339–45.
315. Zuccala G, Onder G, Pedone C, et al. Hypotension and cognitive impairment: selective association in patients with heart failure. Neurology. 2001;57: 1986–92.
316. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40:922–35.

Chapter 7

Cerebrovascular Disease and Disorders

Sabrina E. Smith, Juliana Sanchez Bloom, and Nancy Minniti

Introduction

Brain injury due to cerebrovascular disease is a common cause of cognitive dysfunction in adults and a clinically significant cause of disability in children. Stroke, defined as brain injury due to a disruption of cerebral blood flow, has an incidence of 94/100,000 age-adjusted person-years in high-income countries and 117/100,000 age-adjusted person-years in low-middle income countries [1]. As many as 65% of adults experience new or worsening cognitive deficits following stroke [2], and cognitive deficits occur in up to 50% of children following ischemic or hemorrhagic stroke [3]. Therefore, assessment of neuropsychological function following stroke is an important part of the medical management of these patients.

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Medical Information Regarding Cerebrovascular Disorders

The two main categories of cerebrovascular disease are ischemic and hemorrhagic. Ischemic stroke is due to lack of blood flow to part of the brain. Occlusion of a cerebral artery by a blood clot that travels from the heart or another vessel (embolus) or that develops within a cerebral artery (thrombus) results in an arterial ischemic stroke. Diminished cerebral blood flow due to narrowing of a blood vessel or decreased blood pressure also may result in ischemic brain injury. Less commonly, a blood clot develops within one or more veins that drain the brain, known as cerebral venous sinus thrombosis, and leads to venous infarction. Hemorrhagic stroke occurs when a blood vessel ruptures, leading to brain injury.

Risk Factors for Cerebrovascular Disorders

In adults, arterial ischemic stroke is commonly associated with advancing age, hypertension, atrial fibrillation, smoking, and diabetes mellitus [4]. Other risk factors include obesity, cardiac disease, carotid stenosis, sickle cell anemia, recent infection, and alcohol abuse. In young adults, abnormalities of blood vessel structure such as arterial dissection, noninflammatory vasculopathies, and vasculitis are also associated with stroke [5]. In addition, hematologic abnormalities leading to hypercoagulability may play a

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role in selected cases [6]. Cerebral venous sinus thrombosis, which can result in either ischemic or hemorrhagic infarction, is associated with oral contraceptive use, infections of the head, neck, or central nervous system, malignancy, prothrombotic states, inflammation, and pregnancy [7]. In fact, the risk of both ischemic and hemorrhagic stroke is increased during pregnancy and the postpartum period [8].

A common risk factor for primary intracerebral hemorrhage in adults is hypertension. Other risk factors include amyloid angiopathy, elevated cholesterol, treatment with anticoagulants, heavy alcohol use, smoking, renal dialysis, and use of sympathomimetic drugs such as cocaine and amphetamines [9]. Vascular malformations such as aneurysms and arteriovenous malformations (AVMs) are much less common causes of hemorrhagic stroke in adults [10, 11].

Risk factors for cerebrovascular disorders in children are quite different from adults. Congenital or acquired heart disease, congenital or acquired abnormalities of arterial structure such as arterial dissection, transient cerebral arteriopathy of childhood, moyamoya disease and vasculitis, prothrombotic states, sickle cell anemia, and infection are common risk factors for arterial ischemic stroke in children [12–14]. In neonates, maternal and fetal physiologic factors associated with pregnancy likely contribute to the risk of arterial ischemic stroke, as do congenital heart disease, prothrombotic states, maternal infection, and placental abnormalities [15]. Pediatric cerebral venous sinus thrombosis has been associated with dehydration, prothrombotic states, head and neck infection, trauma, surgery, malignancy, and inflammatory conditions [16]. Hemorrhagic stroke in children is commonly associated with vascular malformations such as AVMs, aneurysms, and cavernous malformations, although hematologic abnormalities and other medical conditions can be precipitants [17]. In contrast, hemorrhagic stroke in term neonates is often secondary to ischemia, but a cause is not always identified [18, 19].

Clinical Presentation of Cerebrovascular Disorders

In the majority of patients, cerebrovascular disease results in a focal neurologic deficit with sudden onset. The nature of the deficit depends on the precise location and the specific mechanism of brain injury. Arterial ischemic stroke affecting a single blood vessel in the anterior circulation (vessels supplied by the carotid arteries) may present with contralateral weakness, numbness or loss of vision, aphasia, or neglect, while ischemic stroke affecting a vessel in the posterior circulation (vessels supplied by the vertebral arteries) may present with cranial nerve abnormalities, ataxia, dysmetria, or altered mental status, as well as contralateral weakness, numbness, or loss of vision. Symptoms are similar in children and adults, although neonates may not exhibit any focal neurologic deficits at the time of an arterial ischemic stroke. Instead, deficits due to perinatal stroke may become apparent over months to years. Seizures occur relatively rarely in adults at the time of an arterial ischemic stroke but are more common in children and very common in neonates. Ischemic stroke due to small vessel vasculitis may be associated with acute motor or sensory deficits but may also have a more indolent presentation with chronic headaches and slowly progressive cognitive or behavioral dysfunction [20]. In patients with sickle cell anemia, symptoms of cerebrovascular disease include those for acute arterial ischemic stroke, as described above. However, these patients are also at high risk for more global neurocognitive deficits as silent infarcts accumulate [21]. Similarly, vascular cognitive impairment or vascular dementia can develop in adults following a clinically apparent episode of acute neurologic dysfunction or may develop in a slowly progressive or stepwise fashion [22]. Vascular dementia is covered in greater detail in a separate chapter in this book.

Patients with cerebral venous sinus thrombosis often come to medical attention after developing severe and unremitting headache, vomiting, altered level of consciousness, seizures, blurry or double

vision. Focal motor or sensory deficits may occur, particularly in the setting of venous infarction. Patients with intracerebral hemorrhage often present with similar symptoms, although the severity of the headache may be greater and deterioration of consciousness may occur more rapidly.

Diagnosis of Cerebrovascular Disorders

Neuroimaging techniques are the mainstay of diagnosis for cerebrovascular disorders [23, 24]; see Fig. 7.1. In the acute setting, non-contrast computed tomography (CT) is used to rapidly assess for intracerebral hemorrhage and to rule out nonvascular causes of an acute neurologic deficit. While CT is quite sensitive for acute hemorrhage, it is rather insensitive for acute ischemic stroke within the first 12–48 h, especially for strokes that are small or affect subcortical structures. Magnetic resonance imaging is the gold standard imaging study for diagnosis of ischemic stroke. In particular, acute ischemia can be detected on the diffusion-weighted imaging (DWI) sequence within minutes to hours of stroke onset [25]. The movement of water in the extracellular space is measured on this sequence. As a consequence of acute ischemia cells begin to swell, which restricts the diffusion of water in the extracellular space. Therefore, this MRI sequence is exceptionally sensitive to acute ischemia since it can detect the earliest effects of ischemia on cell structure. Cerebral perfusion, a quantitative measure of blood flow to particular brain regions, is another parameter that can be assessed. Ischemia and subsequent infarction occur when cerebral perfusion drops below a critical level for some period of time. By measuring cerebral perfusion at the time of acute stroke, either with magnetic resonance perfusion or computed tomography perfusion techniques, one can identify brain tissue that is at risk for infarction but has not yet suffered permanent injury by comparing the areas of abnormal perfusion (tissue at risk for infarction) to the areas of abnormal diffusion (infarcted tissue). The mismatch between these two images reveals the vulnerable brain tissue that may benefit from acute medical interventions and has been the focus of much research in adult stroke treatment.

Venous infarction due to cerebral venous sinus thrombosis is best seen with MRI, and the presence of acute thrombus within the venous system can often be visualized. The extent of parenchymal injury associated with intracerebral hemorrhage and small or chronic areas of hemorrhage are seen better on MRI than CT, so MRI is indicated for the evaluation of intracerebral hemorrhage as well. The high resolution of MRI allows the clinician to distinguish stroke from other conditions that can mimic cerebrovascular disease clinically. This is especially important in the evaluation of children, where stroke is a less common cause of a focal neurologic deficit than in adults [26].

Visualization of cerebral blood vessels is also necessary to characterize the etiology of cerebrovascular disorders. The choice of imaging modality depends on the stroke syndrome, acuity of the patient and local expertise. Arterial and venous structures can be visualized noninvasively with MRI or CT-based techniques. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) provide high-resolution images of the cerebral arteries, while magnetic resonance venography (MRV) and computed tomography venography (CTV) do the same for cerebral veins and venous sinuses. Carotid ultrasound and transcranial Doppler (TCD) are noninvasive techniques that use ultrasound to image flow through arteries, but they do not provide the same anatomic resolution as MRA or CTA. Carotid ultrasound is commonly used to evaluate for carotid stenosis due to atherosclerosis in adults with arterial ischemic stroke, and TCD is routinely used to assess intracranial blood flow at the time of acute stroke as well as to screen for intracranial vasculopathy in patients with sickle cell anemia [27]. The gold standard study for visualization of cerebral vessels is a catheter-based angiogram. This is an invasive test in which a catheter is placed in the femoral artery and advanced into cerebral arteries. Contrast material is then injected and visualized with X-ray images. This study is necessary for the optimal evaluation of vascular malformations such as aneurysms and

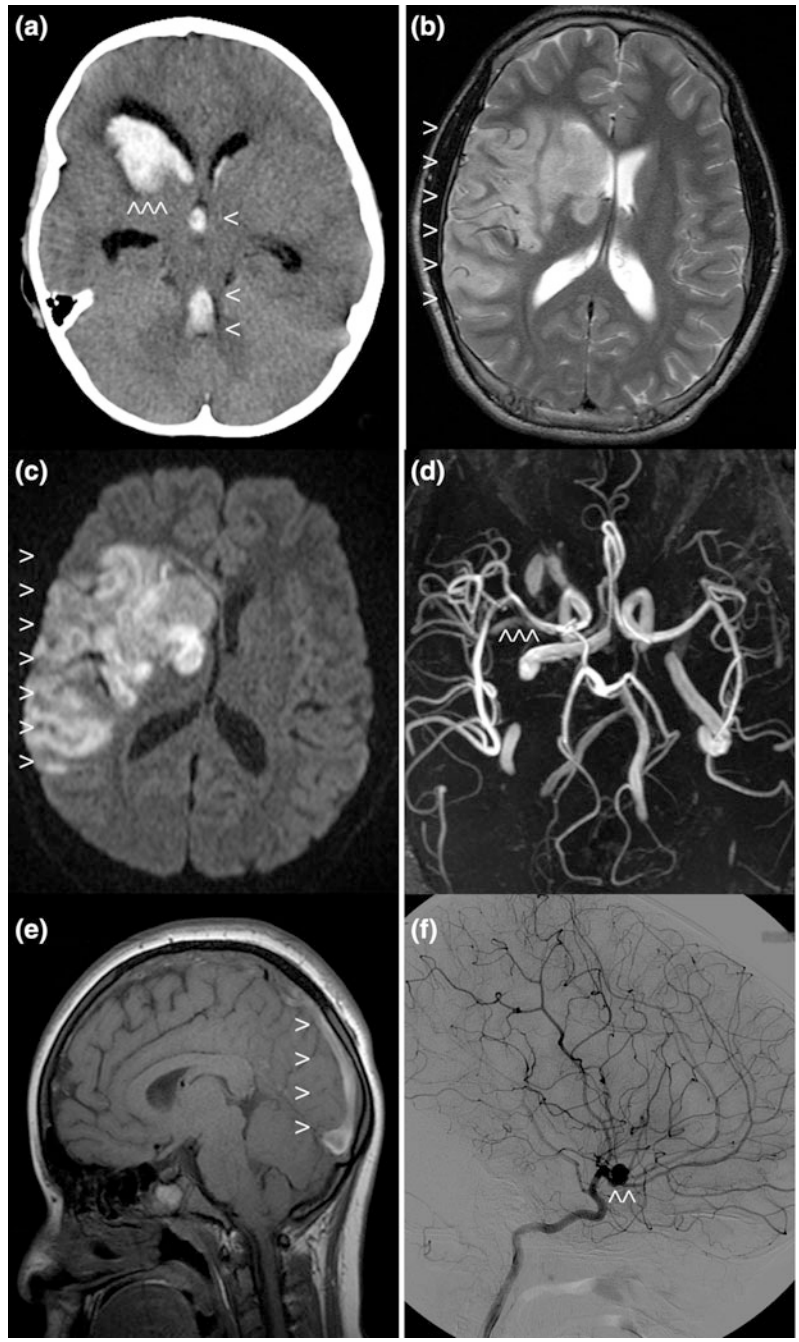

Fig. 7.1 Representative neuroimaging studies from patients with cerebrovascular disease. **a** Head CT from patient with acute intracerebral hemorrhage due to cavernous malformation. Blood is indicated by arrowheads. **b**, **c** Brain MRI from patient with right middle cerebral artery ischemic stroke. Area of infarction is indicated by arrowheads on axial T2 (**b**) and diffusion-weighted (**c**) images. **d** MRA from same patient showing narrowing and irregularity of right middle cerebral artery (arrowheads). **e** Sagittal T1 brain MRI from patient with cerebral venous sinus thrombosis. Blood clot within the superior sagittal sinus and torculum is indicated by arrowheads. **f** Cerebral catheter angiogram from patient with aneurysm affecting right anterior cerebral artery. Aneurysm is marked with arrowheads

AVMs. It is also indicated in selected cases of arterial ischemic stroke, especially when vasculitis is a diagnostic consideration.

Evaluation of heart function with an echocardiogram and electrocardiogram is another critical part of the evaluation for arterial ischemic stroke. Blood tests including serum glucose and cholesterol levels help to identify stroke risk factors in adults, while blood tests to detect a prothrombotic tendency are performed in children with ischemic stroke. In the setting of intracerebral hemorrhage, blood tests to detect a bleeding diathesis may be part of the evaluation, especially in young children.

Treatment of Cerebrovascular Disorders

The acute treatment of stroke depends on the mechanism of injury. In adults with arterial ischemic stroke, intravenous infusion of tissue plasminogen activator (tPA), a drug that lyses blood clots, is the only FDA-approved medical treatment. Widespread use of this drug is limited by the need to administer it within 4.5 h of stroke symptom onset [28], meaning that fewer than 6% of stroke patients benefit from this therapy [29]. Several studies have demonstrated improved outcome compared to medical therapy following mechanical thrombectomy in adults with large vessel occlusion in the anterior circulation. This treatment must be instituted within 6 h of stroke onset, and a greater degree of recanalization correlates with improved outcome [30]. Other acute stroke treatments include aspirin and intra-arterial administration of tPA [31]. Surgical decompression can be beneficial in patients with space-occupying infarction [32]. Ongoing studies are evaluating the optimal use of therapeutic hypothermia in the management of acute stroke [33].

To prevent future strokes, treatment with an antiplatelet or anticoagulant medication is recommended [31], in addition to treatment of stroke risk factors such as hypertension, elevated cholesterol, and diabetes. Stent placement may also be useful for secondary prevention in selected cases of arterial stenosis [34]. None of these treatments have been studied in children, although the use of antiplatelet or anticoagulant medications for secondary prevention is recommended in most cases [35]. Chronic transfusion therapy has been shown to prevent stroke in children with sickle cell anemia [36], and revascularization surgery for moyamoya disease also prevents stroke recurrence [37]. Anticoagulation is the treatment of choice for acute cerebral venous sinus thrombosis in adults and children [35, 38].

Following intracerebral hemorrhage, acute treatment may include surgical evacuation of hemorrhage or placement of a temporary ventriculostomy catheter if obstructive hydrocephalus develops. Preventative treatment of recurrent hemorrhage may include surgical clipping or endovascular coiling in the case of aneurysms, and endovascular embolization, surgical resection or treatment with stereotactic radiosurgery in the case of arteriovenous malformations [39, 40]. Supportive measures following any type of cerebrovascular insult include maintenance of cerebral perfusion pressure with intravenous fluids, avoidance of hypoglycemia or hyperglycemia, and avoidance of fever.

Mechanisms Underlying Cognitive Dysfunction in Cerebrovascular Disorders

Since cerebrovascular disease often results in circumscribed brain injury, the nature of the resulting cognitive deficits in older children and adults is generally related to the specific brain regions injured. In fact, the study of behavior in patients who experienced stroke has been one of the greatest sources of information about the functional organization of brain structure and has contributed immensely to the field of neuropsychology. Patients with focal brain injury, often due to cerebrovascular disease, have provided terrific insights into the biologic basis of behavior [41]. A comprehensive discussion of structure–function relationships in the brain is beyond the scope of this chapter, although numerous books have been devoted to this topic, especially as it relates to cerebrovascular disease (see [42, 43]). One unique aspect of brain injury resulting

from arterial ischemic stroke is that certain patterns of injury are consistently seen in different patients since the artery which supplies a particular brain region is quite consistent across patients. Knowledge of cerebrovascular anatomy allows the clinician to predict which brain regions are most likely to be affected by a stroke in the territory of a specific artery and to anticipate the deficits most likely to be seen. For example, a stroke due to occlusion of the left (language and motor dominant hemisphere) middle cerebral artery, which supplies the frontal, parietal, superior temporal lobes, and the basal ganglia, will generally result in aphasia, right hemiparesis, right hemisensory impairment, and right homonymous hemianopsia, while a stroke in the territory of the right (nondominant) middle cerebral artery will lead to spatial neglect, impaired visuospatial skills, left hemiparesis, left hemisensory disturbance, and left homonymous hemianopsia. Only some of these deficits may occur if the vascular occlusion is confined to smaller branches of the middle cerebral artery. Structure–function relationships are less consistent in patients with multifocal or progressive arterial ischemic disorders such as vasculitis, moyamoya disease, sickle cell anemia, and vascular dementia, which often result in bilateral injury and may affect white matter and subcortical nuclei to a greater degree than cerebral cortex. In patients with intracerebral hemorrhage or infarction due to cerebral venous sinus thrombosis, the deficits are largely determined by the particular brain regions that are injured, but the patterns of brain injury are more variable. In the subsequent sections, the brain regions most often associated with a particular deficit will be mentioned. While many cognitive deficits following stroke relate specifically to lesion location, deficits in attention and concentration, processing speed, and executive functioning are common following brain injury in any location. Another caveat is in the assessment of patients who experienced stroke in the newborn period or early in childhood, as anatomic localization of function and the pattern of cognitive impairment resulting from cerebrovascular disease is more variable in this population [44].

Neuropsychological Assessment Following Stroke

Neuropsychological assessment provides essential information regarding a patient's cognitive, emotional, and behavioral functioning following a stroke. An effective evaluation will provide detailed information on the patient's deficits, but will also highlight areas of strength. It is vital that all participants in the patient's care, including family members, physicians, rehabilitation therapists, and work or school personnel, understand the patient's neuropsychological profile and specifically how functioning may have changed as a result of a stroke. This will enable appropriate interventions and accommodations to be put in place in order to maximize recovery and independence.

Assessment in the Acute Phase

In the acute phases of recovery, the neuropsychologist offers pertinent information regarding patient functioning to an interdisciplinary team on inpatient units, such as establishing reliable communication with the patient (as in cases of aphasia or hemineglect), documenting the degree of cognitive impairment, assessing the patient's own judgment regarding his or her impairment and associated safety concerns (e.g., anosognosia), and contributing to prognosis and rehabilitation planning. The neuropsychologist will assess the patient's cognitive and emotional functioning following a stroke, often at repeated intervals to monitor the course of recovery.

Many challenges are presented to the neuropsychologist when conducting assessments with acutely injured patients or within inpatient settings. Prior to conducting a neuropsychological assessment in the acute period, it must be determined that the patient is oriented, alert, and capable of participating in the evaluation. This can be assessed via a standardized measure such as mini-mental status examinations, the Children's Orientation and Amnesia Test (COAT) [45], or the Galveston Orientation and Amnesia

Test (GOAT) [46]. The neuropsychologist will often need to modify standardized administration procedures to accommodate specific impairments incurred from stroke, such as hemiparesis, visual field cut, aphasia, or fatigue. Testing time may be limited on inpatient units and a comprehensive neuropsychological battery may not be practical. Therefore, a rapid screening instrument is often utilized when working on inpatient units, as they allow for brief assessment of pertinent domains, and are generally highly portable for bedside administration. Examples of these brief screening instruments include the "Cognistat" (formerly known as the *Neurobehavioral Cognitive Status Examination*) [47] and the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) [48] for adults, and the Comprehensive Neuropsychological Screening Instrument for Children (CNSIC) for children ages 6–12 [49][1].

It is important to note that the sensitivity of screening assessments is limited due to the possibility that relevant information may be missed because of the brevity of the evaluation [49]. Therefore, longer neuropsychological batteries may be appropriate for inpatients, depending on the patient's endurance and impairments. Full-length (typically all day) evaluations provide detailed information on a patient's strengths and weaknesses in multiple cognitive domains, assess for emotional or behavioral problems that may impact a patient's functioning, and allow for detailed recommendations. Therefore, after an inpatient stay, most patients who have suffered a stroke should return in 3–12 months for a comprehensive, follow-up neuropsychological evaluation to further identify strengths and weaknesses in their neuropsychological profile, for assessment of change, and for educational, vocational and/or treatment planning. If cognitive deficits are found, ongoing monitoring in the form of repeated neuropsychological evaluations at specified time intervals (one year is commonly recommended) may be appropriate.

It is also important to consult with the patient's neurologist and other specialists that may be involved in the patient's care before and after neuropsychological evaluations. The neurologist may identify neurologic deficits that can inform planning of a neuropsychological evaluation; however, it is important to note that subtle cognitive deficits may be present in a patient with a normal neurologic exam. Speech-language pathologists as well as occupational and physical therapists can also provide valuable information regarding a patient, and may benefit from the neuropsychologist's perspective as well. For example, since therapists work with patients frequently, they can often alert the medical team to possible deficits in attention, memory, or executive functioning, and may enjoy collaborating with the neuropsychologist on strategies to help overcome these deficits in therapy sessions. The team's psychologist and/or social worker are invaluable members of the multidisciplinary team, and can alert the neuropsychologist to psychosocial or emotional factors that may be influencing the patient's functioning and provide or link the patients to appropriate interventions. Finally, an educational or vocational coordinator can assist in re-integrating the patient into home, school, or work with appropriate accommodations and supports as recommended by the medical team as well as information gleaned from the neuropsychological evaluation.

The following sections detail domains of neuropsychological functioning commonly affected by stroke and common methods used to assess those domains. While references to specific tasks or tests are included in this section, a thorough review of assessment measures is beyond the scope of this chapter and can be found elsewhere [49, 50].

Intellectual Functioning

Assessment of intellectual functioning following a stroke is important in order to establish a

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comparison point by which to judge impairments or strengths in other domains and for judging relative performance among domains of intellectual functioning. In addition, performance on scales of intelligence provides clues about other neuropsychological domains that may be impaired and should be assessed further. Finally, the high prevalence rate of cerebrovascular dementia, which has been estimated to affect 25–50% of stroke patients [51], further highlights the need for the assessment of intellectual functioning following a stroke.

It is important to note that there can be a decline in performance on tests of intellectual functioning following stroke due to difficulties with task performance rather than a decline in reasoning skills. For example, hemiparesis of the dominant arm will likely result in lower performance on pencil and paper tasks, such as the Processing Speed subtests from the Wechsler scales (e.g., Wechsler Intelligence Scale for Children—Fourth Edition [52], Wechsler Adult Intelligence Scale, Third Edition [53], among others), and aphasia may result in difficulty understanding task directions and/or expressing oneself through language, as is often required for verbal reasoning tasks. In adults, left hemisphere strokes have been found to impair Verbal IQ more than Performance IQ on the Wechsler scales and the reverse is true for right hemisphere strokes [54]. In addition, brain injury in general and stroke in particular often leads to decline in attentional [54], working memory, and/or processing speed skills [55], which also may impact performance. For this reason, index, factor, and subtests analysis is particularly important when interpreting the scores of patients who have had strokes.

The neuropsychologist may determine that, due to factors that inhibit performance rather than reasoning skills, the composite score of intellectual ability may not accurately reflect the patient's potential. In this case, it may be wise to choose an index or factor score as the most likely representation of underlying cognitive ability, or choose another instrument that may allow the patient to demonstrate their reasoning skills without the need for verbal or motor output. For example, there are a select number of nonverbal tests of intelligence for children and adolescents (e.g., Leiter International Performance Scale-Revised (Leiter-R) [56], Universal Nonverbal Intelligence Test [57] (UNIT), Comprehensive Test of Nonverbal Intelligence [58] (CTONI)) and for children, adolescents, and adults (e.g., Test of Nonverbal Intelligence, Third Edition [59] (TONI-3); Raven's Progressive Matrices [60]). These tests are suitable for patients with aphasia due to lack of language demands; in some cases, even the test directions are communicated nonverbally.

In cases where it is desirable to have an estimate of premorbid intellectual functioning, there are a variety of ways in which this estimate can be obtained. Often, estimates of premorbid functioning are inferred from vocational history, educational attainment, and report from patients and families. It is also inferred with the use of tests on which performance is typically less affected by brain injury; these tests are thought to "hold" the level of premorbid function. For example, measures of crystallized intelligence [61], which is a form of intelligence based on knowledge and experiences, may reflect a patient's pre-injury level of functioning. Examples of tests of crystallized intelligence include the verbal reasoning subtests from intelligence scales, single word reading skills, and receptive vocabulary. Tests specifically developed to determine premorbid intellectual abilities include the North American Adult Reading Test (NAART) [62] and the Wechsler Test of Adult Reading (WTAR) [63] Clearly, due to the verbal aspect of most of these tasks, these tests are not good measures of premorbid functioning in patients with aphasia. It is important to note that although these measures may be good representations of pre-injury functioning, brain injury is extremely diverse and there is no one performance pattern that is diagnostic of brain injury [64].

Language

Aphasia is a common consequence of stroke, particularly left hemisphere stroke, and occurs in approximately one-third of adult stroke patients [65, 66]. Aphasia usually occurs following left

hemisphere strokes that damage the perisylvian regions of the brain, which include Broca's area, Wernicke's area, and the arcuate fasciculus [67]. Left middle cerebral artery ischemic strokes often cause damage to these perisylvian regions and result in aphasia. Damage to Broca's area, which is important for the motor programming of speech, and surrounding structures typically leads to Broca's aphasia. Broca's aphasia is characterized by word-finding difficulty, impaired repetition, agrammatism, hesitations, pauses, phonemic errors, and verbal apraxia (including phonemic errors), but with preserved language comprehension [68]. Agrammatic speech has a telegraphic quality, with omission of articles, prepositions, inflexions, and sometimes even verbs. Damage to Wernicke's area, which is important for comprehension of the spoken word, results in fluent speech characterized by paraphasias and impairment in comprehension, repetition, and naming. Reading and writing are often affected as well [68]. Damage to the arcuate fasciculus results in conduction aphasia, which is defined by poor repetition with relatively fluent speech and intact comprehension [68]. Injury to all of these regions results in global aphasia. Aphasia can also result from damage to non-perisylvian language areas, typically by damaging connections from perisylvian language regions to other brain areas; these disconnection syndromes are referred to as transcortical aphasias [67]. Transcortical motor aphasia is characterized by impaired spontaneous speech and writing with intact repetition and comprehension, while transcortical sensory aphasia is notable for fluent but paraphasic speech, intact repetition, and poor comprehension. A thorough review of aphasia subtypes can be found in Kertesz [68] and in Beeson and Rapcsak [67].

Most patients demonstrate improvement in language skills in the first year following their stroke, though in some patients milder language deficits or even continued aphasia may remain [66, 69]. For this reason, neuropsychologists working with patients who have had strokes should assess for overt aphasia as well as higher level language processing deficits.

There are a number of brief screening tools designed for quick, bedside assessment of adults suspected of having aphasia, of which the Frenchay Aphasia Screening Test (FAST) appears to be the most widely used [70]. Screening tools are designed to identify patients in need of more thorough assessments conducted by speech-language pathologists or neuropsychologists. Further evaluation for aphasia should include formal assessment of speech comprehension, repetition, naming, reading, and writing [50]. There are a number of tests that are designed to provide a comprehensive assessment of aphasia, including the Boston Diagnostic Aphasia Examination [71] and the Multilingual Aphasia Examination [72] (MAE), or the examiner can choose subtests from different tests. In addition, fluency should be assessed by qualitative observation of spontaneous speech, with attention paid to utterance length, language formulation and organization, word-finding problems or paraphasias, grammar, and syntax. Evaluating these areas will allow the examiner to appropriately categorize the subtype of aphasia.

In some stroke patients, overt aphasia improves over time but deficits in higher order language processing remain. Assessment of reading and writing skills is appropriate for children and may be appropriate for adults depending on vocation. In addition to measures of single word reading and spelling, it is useful to assess reading comprehension, fluency of reading and writing, and writing composition. It may also be useful to qualitatively assess the patient's ability to follow written directions, write to dictation, or copy a written passage [50]. Assessment of phonological and rapid naming skills, which are the core cognitive processes underlying reading acquisition [73], is particularly important to assess in children who may be at risk for developing reading problems following a stroke.

Memory

Memory impairment is one of the most common deficits experienced following a stroke.

Prevalence estimates are as high as 50% in the first few weeks following a stroke, with subsequent improvement over the ensuing months. A recent review of poststroke memory dysfunction found that deficits were observed in 13–50% of patients in the initial weeks following stroke, and this number decreased to 11–31% after one year or more [74]. Memory deficits have a negative impact on social and functional independence, can hinder progress in rehabilitation treatment programs, and can adversely impact work and school performance.

There is considerable variability in the presentation of memory deficits following a stroke. While the location of the stroke typically determines the nature of the memory impairment, memory processes are mediated by a broad network of widely distributed subcortical and cortical regions, so damage to any part of the underlying neural circuitry can disrupt memory. Knowledge of the neuroanatomic substrates of memory and acquired memory deficits from focal lesions can help guide assessment procedures in the neuropsychological evaluation. Regions within the medial temporal lobe (MTL), diencephalon, basal forebrain, and frontal lobe, and multimodal association areas of the posterior cortex are associated with memory functioning. Additionally, as memory is a higher order process that is dependent upon the general integrity of more basic perceptual functions (such as visuospatial perception or language comprehension), damage to these lower level functions can result in a memory deficit secondarily. A thorough review of the neuroanatomic underpinnings of memory deficits in stroke is beyond the scope of this chapter, and can be found elsewhere (e.g., [77]). However, a brief overview of amnestic syndromes following stroke will be summarized, with a focus on episodic memory.

Memory involves the ability to encode, store, and retrieve information, and stroke can disrupt these processes at any stage. Memory impairment can manifest in poor immediate or delayed free recall of stimulus material, in a flat learning curve despite repeated presentation of information, and with variable benefit from cueing or recognition. Intrusion errors or confabulation may be prominent. Identifying preserved aspects of memory can facilitate the process of rehabilitation and reintegration into the home or work environment.

It has been well established that damage to MTL structures can result in anterograde amnesia, or a failure to learn new information. The critical region for MTL amnesia is the hippocampal formation, although there are probable contributions from damage to adjacent parahippocampal regions. There is a lateralizing effect, in that damage to the left MTL typically results in verbal memory impairment, whereas damage to the right MTL typically results in nonverbal (visuospatial) memory deficits. MTL damage from stroke is often due to infarction in the posterior cerebral artery (PCA) and to a lesser degree the anterior choroidal artery (AChA) territories [75]. Bilateral PCA infarction involving the MTL can result in severe anterograde amnesia with retrograde amnesia likely as well. However, left PCA infarcts can appear equally severe in the acute phase, as explicit memory is language dependent [55].

Lesions within diencephalic structures have been strongly implicated in anterograde amnesia. Damage to the anterior thalamic nuclei and the mammillary bodies have been repeatedly linked with episodic memory deficits. These regions of the diencephalon have dense connections to the hippocampal formation. Damage to projections between the anterior thalamic nuclei and the mammillary bodies are a strong predictor of memory deficits following stroke. The intralaminar region of the thalamus is a critical junction from MTL structures to the mammillary bodies via the fornix. Infarctions in these regions of the diencephalon are usually from the tuberothalamic or polar arteries that arise from the posterior communicating artery.

Amnestic syndromes resulting from basal forebrain lesions are typically due to anterior communicating artery (ACoA) infarcts and often involve considerable executive impairment. Deficits are usually due to retrieval failure, and patients can benefit from recognition cues. However, both retrograde and anterograde amnesia have been documented in ACoA infarctions.

Confabulation is quite prominent in ACoA strokes, and is often related to poor awareness of memory deficit. Confabulated material can be plausible inventions to fill in gaps of missing material, or can result from intrusion or incorrectly retrieved information from a similar experience. However, confabulations are typically not intentional and tend to dissipate as the person becomes aware of memory problems. Damage to the septal nuclei in the basal forebrain can result in amnesia, due to their cholinergic connection to the hippocampus. Executive dysfunction arising from damaged frontal and subcortical regions can result in memory deficits secondarily, via impaired working memory and poor self-monitoring. Dysfunction of this nature can have considerable impact on memory formation and retrieval.

Thorough assessment of memory necessitates a comprehensive evaluation of other cognitive functions that can impact performance on standardized tests of memory, such as attention, concentration, processing speed, language, and visual-constructional abilities, all quite commonly impaired in stroke. When evaluating subjective complaints of memory deficits, it is important to ask for examples, as patients and families will often confuse dysnomia or attentional problems with memory deficits. Lezak [46] provides the following guidelines for a comprehensive memory assessment: (1) orientation to time and place (2) prose recall to determine if the patient can learn and recall meaningful information (3) rote learning ability (4) visuospatial memory (5) remote memory (6) personal-autobiographical memory. Test selection should allow the patient to engage in immediate and delayed recall trials, with both free and cued recall, recognition trials, and repetition of stimuli to facilitate learning.

Attention and Neglect

Assessment of attention is fundamental to the neuropsychological exam, as attentional deficits can mask a person's abilities in most other cognitive domains. Attention is commonly impaired in stroke, and determination of level of functioning is paramount. Furthermore, a disorder of attention (Attention-Deficit/Hyperactivity Disorder, or ADHD) is the most common psychiatric disorder following childhood stroke [76]. Deficits in attention can be expressed globally or in a limited number of areas, and can result from damage to a variety of cortical and subcortical brain systems. Subtypes of attention that can be impacted include orienting, vigilance, capacity, sustained, selective, and alternating attention. Focal lesions due to stroke may manifest in a striking attentional disturbance of neglect of stimuli contralateral to the lesion side, termed *hemineglect* or *hemi-inattention* (see below). Assessment of neglect has practical significance for treating rehabilitation professionals and caregivers, as neglect has been shown to negatively impact activities of daily living, rehabilitation success, length of hospitalization, and functional outcome [77] It is important to assess early for the presence of neglect, as it poses significant safety concerns (e.g., burns to an affected limb or falls due to neglect of surrounding space).

Assessment of attention in the neuropsychological exam should come from both behavioral observations throughout testing procedures, and from standardized measures designed to assess attention specifically or in conjunction with other cognitive skills. A multifactorial approach is necessary, as attentional impairments can occur in some domains, but not others. It is important to quantify different types of attention in stroke assessment. Sustained attention and vigilance are often assessed using a computerized continuous performance task (e.g., Conners' Continuous Performance Test-II [78] or Conners' Kiddie Continuous Performance Test [79]) or other tests of sustained attention. Attentional capacity is commonly assessed using span tests, such as Digit Span and Spatial Span from the Wechsler batteries [53].

Unilateral spatial hemineglect, characterized by decreased attention or action to stimuli in the contralesional hemifield that cannot be accounted for by sensory or motor deficits, is a well-documented phenomenon in adults with focal brain injury [80]. In adults neglect is more persistent and severe following right hemisphere injury, although it occurs with injury to either hemisphere [81]. It most commonly presents after posterior right hemisphere stroke with neglect of stimulus occurrence in the left field. Neglect can

range in severity, can vary from testing session to testing session and may be specific to a particular region of space. For example, patients may show neglect of stimuli in personal space (stimuli in contact with the body), peripersonal space (items within arm's reach) or extrapersonal space (objects beyond arm's reach) [82]. The presence of neglect may vary across spatial reference frames. Neglect can occur for objects in contralesional space with respect to the viewer (egocentric), to a stimulus (allocentric) or the environment [83]. Neglect may also be specific to a type of task (perceptual versus motor) or sensory modality (visual, tactile, auditory), and may be apparent on some tasks but not others within a given sensory modality [84].

A number of investigators have proposed theories to account for neglect in adult patients with brain injury. Neglect could result from excessive attention to one side of the world or failure to direct attention away from that side of the world. While the final result might appear the same, these are theoretically distinct possibilities and both have been suggested as the mechanism for neglect. Mesulam proposed that spatial attention relies upon a distributed network within each hemisphere, centered in the inferior parietal lobule but receiving polymodal sensory input from other parietal regions as well as information about motivational valence from cingulate cortex and basal forebrain, motor information from frontal eye fields, and general arousal modulation from the reticular activating formation. However, he suggested that the two hemispheres are not equally involved in spatial attention. Rather, the right hemisphere is more active in attentional tasks and may attend to all of extrapersonal space, while the left hemisphere only attends to right space [85]. Heilman also supported the right hemisphere as being dominant for attention, demonstrating that the right parietal lobe is active in attention to either hemifield, while the left parietal lobe only responds to stimuli in the contralateral hemifield [86]. In their views, this accounts for the greater persistence and severity of neglect following right hemisphere injury as compared to left hemisphere insults. Kinsbourne proposed asymmetric involvement of the hemispheres in attention, although he suggested that each hemisphere generates a vector of spatial attention directed contralaterally and inhibits the opposite hemisphere [87]. He accounted for the frequency of neglect after right hemisphere injury by claiming left hemisphere dominance for attention. If the right hemisphere's vector is weaker than the left, then right hemisphere injury unmasks the dominance of the left hemispheric vector.

Another way of conceptualizing neglect is a failure to disengage attention from one part of the visual world. Using this framework Posner and colleagues argued that three steps must occur, "disengaging from the current focus of attention, moving attention to the location of the target and engaging the target," and that parietal lobe injury impairs the disengage function in the contralesional visual field [88]. Numerous studies have provided support for this account of neglect using a cuing paradigm [89]. In this paradigm a subject looks at a fixation point. A highlighted cue then appears on one side, followed by a target. A valid cue appears on the same side as the target and an invalid cue appears on the side opposite the target. Subjects are consistently slower to respond to targets preceded by an invalid cue than a valid cue, and this is interpreted as a measure of the difficulty in disengaging attention from the location to which it was initially cued. However, subjects with neglect are much slower to respond to targets when the invalid cue is presented in contralesional space than ipsilesional space (for example, in left hemifield when the lesion is in the right parietal lobe), suggesting that the asymmetric disengage deficit accounts for the behavior of neglect. Overt cases of neglect can be readily observed in the patient's behaviors, such as eating food from only one side of their plate, reading only portions of a page or part of a word, or addressing persons standing in one visual field. It is important to note, however, that neglect can be subtle, and can require close observation as well as formal testing to be identified. Qualitative assessment in the neuropsychological evaluation is often obtained through object copying tasks or drawing of symmetrical figures (e.g., Clock Drawing Test [90]), in which the patient may omit details on one side of the page. Quantitative assessments of visual neglect include line bisection tests in which the patient is asked to indicate

the midpoint of a line, and cancelation tasks in which the patient is provided a page with numerous small targets and are asked to mark out a particular target stimulus.

Assessment of sensory neglect begins with unilateral presentation of stimuli and asking the patient to state the presence and location of the stimulus. For example, the examiner asks the patient to close his eyes and subsequently touches one hand or the other. Failure to detect stimulation on one side may indicate neglect or may be due to a primary sensory disturbance. For auditory modalities, the examiner stands behind the patient and provides gentle auditory stimulation (e.g., snapping or rubbing fingertips) to one ear and then another. If the patient detects unilateral stimulation accurately, the examiner should also assess for *extinction*, in which the

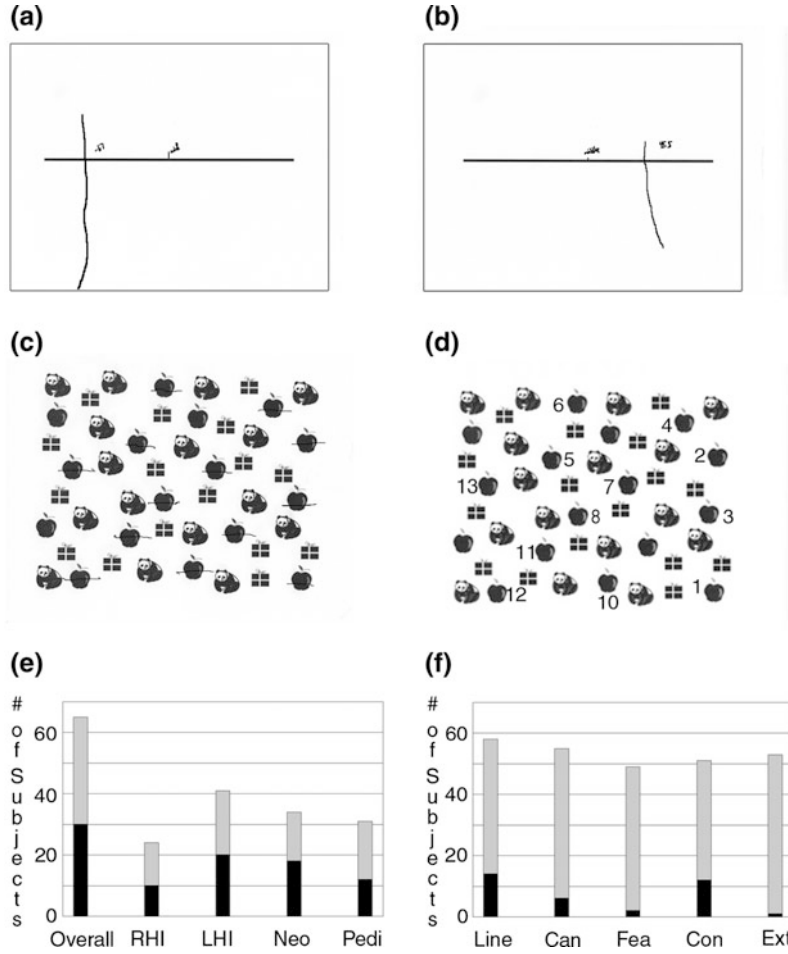

Fig. 7.2 Data from study of visuospatial neglect in children following unilateral neonatal or pediatric arterial ischemic stroke or parenchymal hemorrhage [88]. Presence of neglect was determined by comparison to normal distribution of performance by age-matched controls. **a**, **b** Examples of neglect on line bisection task from subject with left hemisphere stroke (**a**) and right hemisphere stroke (**b**). **c**, **d** Examples of neglect on cancelation task from subject with right hemisphere stroke. Subject omitted more targets from the left hemifield than the right (**c**) and canceled left-sided targets significantly later than right-sided targets (**d**). Numbers depict order in which targets were canceled. **e**, **f** Summary of performance of 65 pediatric subjects ages 2–18 years on tasks assessing for visuospatial neglect. Subjects with neglect are depicted in black and subjects without neglect are shown in gray. **e** Number of subjects showing neglect on at least one task. There was no difference in the proportion of subjects showing neglect with right hemisphere injury (RHI) as compared to left hemisphere injury (LHI), or in subjects with stroke occurring prior to one month of age (Neo) as compared to later in childhood (Pedi). **f** Number of subjects showing neglect on each of 5 tasks: line bisection (Line), cancelation (Can), featural visual search (Fea), conjunctive visual search (Con), and visual extinction (Ext)

patient fails to detect simultaneous stimulation on the side contralateral to his or her lesion but will report perception of the ipsilateral stimulus.

Visuospatial neglect has been reported in children following neonatal or pediatric stroke, but few studies have characterized this phenomenon in detail [91, 92]. In a study of 65 children who experienced unilateral arterial ischemic stroke or parenchymal hemorrhage in the neonatal period or later in childhood, chronic visuospatial neglect was assessed using 5 tasks: line bisection (Fig. 7.2a, b), cancelation (Fig. 7.2c, d), featural visual search, conjunctive visual search, and visual extinction. Almost half (30/65) of the children exhibited mild spatial neglect on at least one task, and the frequency of neglect did not differ significantly between children with right hemisphere injury as compared to left hemisphere injury, or between children with neonatal brain injury as compared to children who experienced brain injury later in childhood (Fig. 7.2e). Line bisection and conjunction search were the most sensitive tasks for the detection of neglect but did not detect neglect in all subjects (Fig. 7.2f) [93]. Overall, this study demonstrates that mild chronic visuospatial neglect is common following stroke in children and suggests that the right hemispheric dominance for visuospatial attention seen in adults is not yet consolidated in children.

Executive Functioning

Executive functions refer to a collection of higher order cognitive abilities that coordinate and regulate other mental activities. Examples of executive functions include deciding on a plan of action, sequencing steps towards a goal, regulating behaviors, selective inhibition of responding, response preparation, cognitive flexibility, set maintenance, and organizing time and space. Executive functions allow us to start and stop behaviors, monitor our performance, adapt to changing conditions and develop new strategies as needed. These functions allow an individual to engage in purposeful, goal-directed, independent behavior [50]. Aspects of attention and working memory are related to executive functioning, and successful performance of these tasks is often dependent upon these abilities.

Executive dysfunction is quite common in patients who have sustained strokes, and is considered to be a core neuropsychological deficit following cerebrovascular injury [55]. Although often described as "frontal functions," executive deficits can occur as a result of injury to non-frontal brain regions. In fact, executive dysfunction is common even in individuals whose strokes did not cause damage to the frontal lobes [55].

Behavioral manifestations of executive dysfunction can present as hypoactivity (e.g., abulia, apathy, loss of motivation, and blunted affect) or hyperactivity (e.g., distractibility, impulsivity, disinhibition, irritability, and emotional lability). Executive dysfunction can manifest cognitively as impaired response initiation and/or suppression, poor rule deduction, poor set maintenance and/or set shifting, difficulty with self-monitoring, and impaired concept formation, problem-solving, or planning abilities (see [55] for a review of these syndromes in stroke). Deficits in response rapidity are particularly common following stroke [55]. Impairments in executive functioning can be the most crippling and intractable cognitive injury, severely impacting an individual's successful reintegration at home, in the workplace, and within the community, despite relatively intact cognitive capacities in other domains. Executive functioning deficits can severely impede progress in rehabilitation of stroke, if the patient cannot benefit from feedback or generalize rehabilitation strategies into their daily living. A recent study demonstrated that executive functioning deficits are prevalent in the early phases of stroke and an excellent predictor of long-term impairment [94]. Therefore, assessment of these skills should be included in the early phases of stroke recovery.

Assessment of executive functioning should be multifaceted, and should include standardized assessment measures and qualitative observations on test-taking strategies. As Lezak notes, "A major obstacle to examining the executive functions is the paradoxical need to structure a situation in which patients can show whether and how well they can structure themselves" ([50]

p. 611). Behavioral questionnaires completed by family members can be critical in identifying poststroke behavioral change, such as the Frontal Systems Behavior Scale (FrSBe) [95]. Similarly, the Behavior Rating Inventory of Executive Function (BRIEF), which has parent, teacher, and self-report forms for children and adolescents [96], can also be useful in the assessment of executive functioning.

Formal testing of executive dysfunction following stroke can vary depending on presenting symptomatology and concerns. If possible and necessary, evaluation should include formal assessment of attention, working memory, speed of processing, response time, impulse control, planning, organization, problem solving, mental flexibility, concept formation, cognitive set maintenance, and generativity. Tests like the Rey Complex Figure Test (RCFT) [97], the Tower of London [98], and the Wisconsin Card Sorting Test (WCST) [99] can be particularly helpful in elucidating deficits in executive functioning following stroke.

Higher Order Visual Processing Skills

Stroke can impact visual processing in a variety of ways, ranging from very subtle to gross impairment. Damage to the visual cortex or portions of the visual pathway beginning at the optic nerve can lead to visual field defects or, in severe cases, cortical blindness. Higher level visual processing deficits can also occur in the absence of gross visual impairment. Impairment on higher order visual tasks is common following stroke, affecting between 34 and 75% of patients [94, 100], underscoring the need to evaluate these functions. Therefore, the neuropsychological assessment of stroke should include measurement of higher order visual processing skills.

Deficits in higher order visual processing skills are often due to posterior right hemisphere lesions; however, damage to other regions can also have an impact. Deficits can occur in the identification and localization of objects within the visual field, defined by anatomically distinct visual systems often referred to as the "what" (i.e., *visuoperception*) and the "where" (i.e., *visuospatial ability*) of higher level visual function. Object recognition ("what") is mediated by occipitotemporal structures (ventral stream), while object location ("where") is mediated by occipitoparietal structures (dorsal stream) [101]. Arterial ischemic strokes affecting the posterior cerebral artery territory can lead to visuoperceptual deficits, while strokes affecting the posterior division of the middle cerebral artery territory may also result in visuospatial deficits. Visual-constructional ability relies on these functions with a combined motor component, and is frequently included in the neuropsychological evaluation of stroke.

Cortical blindness, or complete loss of vision in both hemifields due to brain injury, is the most severe form of visual disturbance that can occur following stroke. Bilateral injury to striate cortex in the occipital lobes, as may occur with bilateral posterior cerebral artery ischemic strokes, may result in cortical blindness. Especially in the acute phase, patients may have a lack of awareness of their visual deficit and may confabulate when asked to describe their visual world, known as Anton syndrome. The mechanisms underlying this syndrome are not well understood, but the disruption of connections from primary visual cortex to brain regions necessary for conscious awareness is one possibility [102].

Visuoperceptual ability in the neuropsychological exam is often assessed through form or pattern discrimination tasks. Visual organization tests require an individual to perceive a stimulus that is fragmented, distorted or incomplete. Hierarchical form stimuli, in which a global level shape is made up of individual local level elements that differ from the global shape (e.g., the letter "M" made up of numerous "Z"s), have been used to detect hemisphere-specific visuoperceptual deficits. In adults with stroke, left hemispheric lesions have been associated with impaired local level processing while right hemispheric lesions have been associated with deficits in global processing [103]. A similar pattern of performance has also been found in children who experienced perinatal brain injury such as stroke [44].

Visual agnosia is a subtype of visuoperceptual disorders in which patients can no longer access semantic knowledge about an object in the visual field, despite intact perceptual processes. This can be further divided into *apperceptive* (impaired higher level perceptual processing) and *associative* agnosia (impaired conceptual knowledge). Modality-specific agnosia syndromes can also occur, such as *prosopagnosia* (impaired recognition of faces) and color agnosia. For a thorough description of agnosia subtypes, please refer to Bauer and Demery [104].

Visuospatial ability refers to perception of an object's orientation or location in space. Spatial neglect (discussed previously) is a common cause of impaired visuospatial skills following stroke. The inability to perform an efficient visual search is another mechanism by which stroke can impair visuospatial function [105]. Deficits in visuospatial ability can be assessed through line orientation measures (e.g., Judgment of Line Orientation; [106]).

Constructional ability, or the ability to draw or assemble an object, is a higher order visual task that requires intact perceptual/spatial skills with an additional requirement of fine motor ability. Tests of constructional ability typically involve graphomotor tasks, such as copying of figures. A popular graphomotor copying task is the Rey Complex Figure Test (RCFT) [97], which requires both visual-constructional and visual organizational skills. Tests requiring assembling and building are also somewhat common and incorporate the use of items, such as blocks or puzzle pieces. Deficits attributed to fine motor coordination in stroke patients should be considered, as they frequently confound the results of constructional tasks.

Fine Motor and Sensory Functioning

Fine motor functioning is commonly impaired following a stroke, typically on the side contralateral to the stroke [54]. It is important to assess fine motor functioning for use as an indicator of the lateralization of lesions or dysfunction [50], to aid in interpretation of other tests in a neuropsychological battery, and for treatment recommendations, such as the need for occupational therapy, school accommodations, or vocational planning.

Neuropsychologists can assess many aspects of fine motor functioning through observation, informal testing, or formal testing. Aspects of fine motor functioning to assess following stroke include apraxia, motor sequencing, assessment of motor soft signs, right–left orientation, handedness, speed, dexterity, and strength [49, 50]. Apraxia refers to the inability to understand or perform a learned skilled movement that cannot be accounted for by a primary motor or sensory deficit (for review, see [107]). While most common following strokes affecting the left parietal lobe, apraxia can occur following damage to extraparietal structures and following right hemispheric injury. Numerous subtypes of apraxia have been described, including ideomotor apraxia, characterized by impaired performance of skilled movements in response to verbal command, or pantomime and ideational apraxia, characterized by impaired use of objects. Both arms are usually affected in these apraxia subtypes, while limb-kinetic apraxia, characterized by slow, stiff, imprecise movements, affects the contralesional arm.

Handedness is particularly important to assess as many strokes, particularly those involving the distribution of the middle cerebral artery, result in hemiparesis [51]. If the dominant hand and arm are affected by the hemiparesis, handedness may be forced to shift. In some cases, a dominant hand advantage may not be present on fine motor tasks, which is another indicator of neurologic impairment. Fine motor speed, dexterity, and strength are also commonly impaired following a stroke. Speed can be assessed via a tapping test (e.g., Finger Tapping Test [108]), speed and dexterity via a pegboard test (e.g., Purdue Pegboard Test [109], Grooved Pegboard Test [110], among others), and strength via a hand dynamometer test. Difficulty with these tasks may suggest deficits in fine motor functioning, which can affect handwriting and typing – and therefore school and work performance – among other tasks. It is

important to note, however, that poor performance on speeded fine motor tasks may represent slow processing common in stroke patients rather than deficits in fine motor dexterity. For this reason, it is important to interpret the results of tests of fine motor functioning within the context of the patient's whole neuropsychological profile. Testing higher level movement control and coordination is particularly important in pediatric evaluations.

Although there is an abundance of formal tests of fine motor functioning, it is also important to observe the patient's fine motor skills during the neuropsychological evaluation. Notation should be made regarding the hand used for writing and drawing, the presence of tremors, the ability to perform skilled movements (praxis) spontaneously and during formal testing, poor coordination, mirror movements, or motor overflow.

In addition to sensory neglect discussed in a previous section, primary somatosensory functioning can be affected by a stroke [54]. Tests of tactile form recognition, graphesthesia (fingertip number writing), and finger recognition perception, among others, may be particularly useful in assessing for higher order sensory deficits [49].

Emotional and Behavioral Functioning

Emotional and behavioral changes are common occurrences following stroke [76, 111], with both neurologic and situational factors likely influencing the development of symptoms. In adults, poststroke depression is common (10–40% of stroke survivors) and is associated with impairments in executive functioning [111], poor affective modulation, and anterior lesion location [112]. Anxiety disorders, and symptoms of Post-Traumatic Stress Disorder in particular, are also common in adults following stroke [112]. Mania, associated with right hemisphere lesions, and psychosis following stroke have been documented but are rare [112]. In children, ADHD is the most common psychiatric disorder following stroke, with anxiety disorders and mood disorders also occurring at a rate higher than orthopedic controls [76].

Considering the relatively high incidence of depression and anxiety following stroke and the possibility that cognition can be impacted by the presence of psychological disturbance [113], evaluation of emotional functioning is an essential part of the neuropsychological evaluation of stroke survivors. Evaluation of behavior is also very important, particularly in light of the high rate of acquired ADHD symptomatology in children following stroke. A comprehensive evaluation of emotional and behavioral functioning requires integration of information from a variety of sources, including direct observation and the clinical interview, and may also include self-report scales, behavioral rating scales, and projective tests [113]. The patient's functional limitations following stroke should be considered in assessment choices. For example, an aphasic patient may not be able to adequately describe their emotional symptoms in a clinical interview or reliably read and comprehend questions on a self-report form. In that case, information provided by caregivers and direct observation will provide the most reliable information. Or, a patient with a new dominant arm hemiparesis may not have the motor skills to fill in answer choices on self-report questionnaires, and a clinical interview may be a better assessment choice. Interpretation of any self-report or rating scale should take into consideration the fact that some scales on these measures may be elevated due to physical symptoms related to the stroke rather than emotional factors [113].

There are a number of rating scales that may be useful in assessing the emotional and behavioral functioning of patients who have had strokes. Broad rating scales that screen a wide range of symptoms can be helpful in pinpointing domains of emotional and behavioral functioning that should be further assessed. The use of additional rating scales that specifically assess for depression, anxiety, and ADHD symptomatology may be indicated based on results of broad rating scales or on presenting concerns. When assessing for depression or anxiety following a stroke, the

clinician should consider adjustment disorder, acute stress disorder, and post-traumatic stress disorder among possible differential diagnoses. Assessment of ADHD in children following strokes should include ratings from parents, teachers, and the child if appropriate.

Long-Term Neuropsychological Outcome

The presence and degree of persistent, long-term cognitive deficits following stroke depends on a number of factors. Premorbid functioning, the age of the patient, the location and volume of the stroke, and the development of epilepsy all influence the eventual degree of cognitive impairment [114–116]. In children with ischemic or hemorrhagic stroke, parent-reported and self-reported health status were also worse in children with epilepsy or persistent hemiparesis [117]. Additionally, long-term cognitive outcome is influenced by the underlying cause of the stroke, which may independently influence neuropsychological functioning or increase the risk of future strokes, which can potentially degrade cognition. Cognitive deficits generally follow a U-shaped curve in relation to age at time of stroke, with the more persistent and severe deficits occurring in very young children and the elderly [118, 119].

Long-term outcome of stroke in adults depends on a variety of factors, such as premorbid health of the patient, demographics, comorbid conditions, and vascular risk factors. A recent literature review of stroke outcomes estimated that 70% of stroke survivors will live in rest homes or institutional care, with only 30% able to perform daily living activities independently [120]. According to this review, neuropsychological impairment in sustained attention, apraxia, pathological emotional reactions, and language deficits have been shown to be predictive of functioning and independence following discharge from the hospital. Memory impairment in the elderly significantly predicts loss of functional independence. Furthermore, recent studies have demonstrated that functional status in the months following stroke have prognostic value for long-term outcome. One study with a large cohort of patients three months post ischemic stroke found that medical and psychiatric comorbidities predicted mortality at three months, and factors such as nonwhite race, older age, not being partnered, and having periventricular white matter disease were predictive of mortality or worse functional outcomes for those that survived beyond three months [121]. Similarly, a second study demonstrated that functional status (such as dependence for ADLs) six months post stroke predicted long-term survival, with fewer than half of patients with severe disability surviving five years [122].

In children who survived ischemic stroke, the majority experience persistent neuropsychological deficits, specifically with regard to attention, concentration, and processing speed [116, 123]. In one study of children who survived hemorrhagic stroke, approximately half of the patients presented with cognitive deficits [124]. Furthermore, the majority of these patients presented with low self-esteem and/or difficulties with mood and behavior [124]. Pediatric stroke survivors are also likely to have academic difficulties and require special education services [116, 125], with one study finding that only fifty percent of patients were able to return to a regular classroom [126].

The effects of stroke on neuropsychological functioning are, in general, more extensive than the typically expected deficits associated with the specific lesion [54]. In fact, deficits in attention and concentration, processing speed, and executive functioning are common following stroke and may be somewhat independent of the location of the cerebral damage, as these functions may require integration of multiple brain regions [54, 127]. This may be particularly true for children who have had strokes, as the developing brain's plasticity allows for reorganization and the potential for "crowding" of functions. For this reason, special considerations must be made when working with children who have had strokes and their families. While cognitive deficits in adulthood are readily apparent, the effects of brain injury on young children may go unrecognized as there may not be an immediate functional loss [128]. Instead, children who have had strokes may fail to develop skills as they grow older.

Reintegration into the home, school, or work setting can be very challenging for patients following a stroke [129]. Motor, cognitive, or sensory deficits may severely limit the patient's abilities and may represent a significant change from prior functioning. Patients may no longer be able to work, drive, take care of their dependents, participate in their educational curriculum, or live independently without assistance. At the same time as their functioning decreases, demands – such as attending frequent doctors or therapy appointments or paying medical bills – may increase. The burden on family members to care for the patient can be great, and there can be significant disruptions in family life. In addition to practical demands, family members may also be emotionally affected by the changes in their loved one's functioning. Caregiver strain is considerable, with depression being a common occurrence [130]. Family-based interventions are recommended to improve these outcomes.

Treatment Approaches to Cognitive Impairment Due to Cerebrovascular Disease

For patients who develop cognitive impairment following an acute stroke, therapy targeted toward these deficits should be one part of a rehabilitation plan that may occur in an inpatient rehabilitation unit or in an outpatient setting. The benefits of cognitive therapy have been demonstrated in adults with language impairment or apraxia following left hemisphere stroke and for visuospatial neglect following right hemisphere stroke [131, 132]. The literature supporting specific cognitive interventions is described in the review by Cicerone and colleagues [131], and is treated in this volume in Sarah Raskin's chapter, "Current Approaches to Cognitive Rehabilitation". Another promising therapy is noninvasive brain stimulation. Numerous small studies have evaluated the effects of transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) to treat deficits following stroke [133, 134].

The intensity of therapy is one factor that influences recovery from aphasia. Numerous approaches have been associated with improved function, including group communication treatment. A form of "constraint-induced" therapy, in which patients participate in massed–practice of language tasks that are particularly difficult, has been shown to improve communication skills to a greater degree than traditional therapy [135]. Small studies of medication and noninvasive brain stimulation show promise for the treatment of aphasia, but additional randomized controlled trials are needed [136]. Specific techniques for amelioration of apraxia include targeted gestural and object use therapy or strategy training (using compensations for apraxia during performance of activities of daily living as part of occupational therapy sessions) [131]. Preliminary studies suggest that noninvasive brain stimulation may have a role in the treatment of apraxia [137]. Noninvasive brain stimulation also has been used successfully to decrease neglect [138]. Visual scanning training has been used successfully in patients with neglect, although it is somewhat surprising that this top-down approach can modulate a deficit characterized by a lack of conscious awareness of stimuli [139]. As the neural mechanisms underlying cognitive dysfunction due to cerebrovascular disease are further elucidated, treatment strategies will continue to evolve. Further advances in cognitive rehabilitation will make the need for accurate neurocognitive assessment even more important, highlighting the critical role that neuropsychologists will continue to play in the rehabilitation of patients with cerebrovascular disease.

References

1. Feigin VL, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
2. Donovan NJ, et al. Conceptualizing functional cognition in stroke. Neurorehabil Neural Repair. 2008;22(2):122–35.
3. Greenham M, Anderson V, Mackay MT. Improving cognitive outcomes for pediatric stroke. Curr Opin Neurol. 2017;30(2):127–32.

4. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics and prevention. Circ Res. 2017;120 (3):472–95.
5. Vilela P, Goulao A. Ischemic stroke: carotid and vertebral artery disease. Eur Radiol. 2005;15(3): 427–33.
6. Waddy SP. Disorders of coagulation in stroke. Semin Neurol. 2006;26(1):57–64.
7. Silvis SM, et al. Cerebral venous thrombosis. Nat Rev Neurol. 2017;13(9):555–65.
8. Swartz RH, et al. The incidence of pregnancy-related stroke: A systematic review and meta-analysis. Int J Stroke. 2017;12(7):687–97.
9. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin. 2008;26(4):871–95, vii.
10. Lawton MT, Vates GE. Subarachnoid hemorrhage. N Engl J Med. 2017;377(3):257–66.
11. Barreau X, et al. Intracranial arteriovenous malformations. Diagn Interv Imaging. 2014;95(12): 1175–86.
12. Bernard TJ, Goldenberg NA. Pediatric arterial ischemic stroke. Pediatr Clin North Am. 2008;55 (2): 323–38, viii.
13. Numis AL, Fox CK. Arterial ischemic stroke in children: risk factors and etiologies. Curr Neurol Neurosci Rep. 2014;14(1):422.
14. Amlie-Lefond C, Sebire G, Fullerton HJ. Recent developments in childhood arterial ischaemic stroke. Lancet Neurol. 2008;7(5):425–35.
15. Wu YW, Lynch JK, Nelson KB. Perinatal arterial stroke: understanding mechanisms and outcomes. Semin Neurol. 2005;25(4):424–34.
16. Ichord R. Cerebral sinovenous thrombosis. Front Pediatr. 2017;5:163.
17. Jordan LC, et al. The importance of cerebral aneurysms in childhood hemorrhagic stroke: a population-based study. Stroke. 2009;40(2):400–5.
18. Bruno CJ, et al. Haemorrhagic stroke in term and late preterm neonates. Arch Dis Child Fetal Neonatal Ed. 2014;99(1):F48–53.
19. Armstrong-Wells J, et al. Prevalence and predictors of perinatal hemorrhagic stroke: results from the kaiser pediatric stroke study. Pediatrics. 2009;123(3): 823–8.
20. Hajj-Ali RA, Calabrese LH. Central nervous system vasculitis. Curr Opin Rheumatol. 2009;21(1):10–8.
21. Berkelhammer LD, et al. Neurocognitive sequelae of pediatric sickle cell disease: a review of the literature. Child Neuropsychol. 2007;13(2):120–31.
22. Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg Psychiatry. 2005;76(Suppl 5):v35–44.
23. Thurnher MM, Castillo M. Imaging in acute stroke. Eur Radiol. 2005;15(3):408–15.
24. Srinivasan A, et al. State-of-the-art imaging of acute stroke. Radiographics. 2006;26(Suppl 1):S75–95.
25. van Everdingen KJ, et al. Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke. 1998;29(9):1783–90.
26. Shellhaas RA, et al. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics. 2006;118(2):704–9.
27. Tsivgoulis G, Alexandrov AV, Sloan MA. Advances in transcranial Doppler ultrasonography. Curr Neurol Neurosci Rep. 2009;9(1):46–54.
28. Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3- to 4.5-hours after acute ischemic stroke: a Metaanalysis. Stroke;2009.
29. Adeoye O, et al. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatement rates over the course of 5 years. Stroke. 2011;42(7):1952–5.
30. Powers WJ, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascualr treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46(10):3020–35.
31. Albers GW, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: american college of chest physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133(6 Suppl):630S–69S.
32. Mohan Rajwani K, Crocker M, Moynihan B, Decompressive craniectomy for the treatment of malignant middle cerebral artery infarction. Br J Neurosurg. 2017;31(4):401–9.
33. Lee JH, Zhang J, Yu SP. Neuroprotective mechanisms and translational potential of therapeutic hypothermia in the treatment of ischemic stroke. Neural Regen Res. 2017;12(3):341–50.
34. Wakhloo AK, Deleo MJ, Brown MM. Advances in interventional neuroradiology. Stroke. 2009;40(5): e305–12.
35. Roach ES, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008;39(9):2644–91.
36. Mehta SH, Adams RJ. Treatment and prevention of stroke in children with sickle cell disease. Curr Treat Options Neurol. 2006;8(6):503–12.
37. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med. 2009;360 (12):1226–37.
38. Saposnik G, et al. Diagnosis and management of cerebral venous thrombosis. Stroke. 2011;42 (4):1158–92.
39. Choi JH, Mohr JP. Brain arteriovenous malformations in adults. Lancet Neurol. 2005;4(5):299–308.

40. Linfante I, Wakhloo AK. Brain aneurysms and arteriovenous malformations: advancements and emerging treatments in endovascular embolization. Stroke. 2007;38(4):1411–7.
41. McCarthy RA, Warrington EK. Cognitive neuropsychology: a clinical introduction. San Diego: Academic Press; 1990. p. 428.
42. Bornstein RA, Brown G, editors. Neurobehavioral aspects of cerebrovascular disease. New York: Oxford University Press;1991. p. 367.
43. Godefroy O, Bogousslavsky J, editors. The behavioral and cognitive neurology of stroke. New York: Cambridge University Press;2007. P. 648.
44. Stiles J, et al. Cognitive development following early brain injury: evidence for neural adaptation. Trends Cogn Sci. 2005;9(3):136–43.
45. Ewing-Cobbs L, et al. The children's orientation and amnesia test: relationship to severity of acute head injury and to recovery of memory. Neurosurgery. 1990;27(5):683–91.
46. Levin HS, O'Donnell VM, Grossman RG. The Galveston orientation and amnesia test: a practical scale to assess cognition after head injury. J Nerv Mental Dis 1979;167(11):675–84.
47. Kiernan RJ, Mueller J, Langston JW. Cognistat (Neurobehavioral Cognitive Status Exam). 1995; Lutz, FL: Psychological Assessment Resources.
48. Randolph C. RBANS manual: repeatable battery for the assessment of neuropsychological status. San Antonio: PSychol Corporat; 1998.
49. Baron IS, Neuropsychological evaluation of the child. 2004;New York, NY: Oxford University Press
50. Lezak M, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.
51. Cummings, J.L. and M.E. Mahler, *Cerebrovascular Dementia*, in *Neurobehavioral aspects of cerebrovascular disease*, R.A. Bornstein and G. Brown, Editors. 1991, Oxford University Press: New York, NY.
52. Wechsler, D., *Administration and scoring manual for the Wechsler Intelligence Scale for Children, Fourth Edition*. 2003a, San Antonio, TX: Psychological Corporation.
53. Wechsler D. Wechsler Adult Intelligence Scale-III. San Antonio: The Psychological Corporation; 1997.
54. Hom, J., *Contributions of the Healstead-Reitan Batter in the Neuropsychological Investigation of Stroke*, in *Neurobehavioral Aspects of Cerebrovascular Disease*, R.A. Bornstein and G. Brown, Editors. 1991, Oxford University Press: New York, NY.
55. Godefroy, O. and D. Stuss, *Dysexecutive syndromes*, in *The Behavioral and Cogntive Neurology of Stroke*, O. Godefroy and J. Bogousslavsky, Editors. 2007, Cambridge University Press: New York.
56. Roid, G.H. and L. Miller, Leiter International Performance Scale - Revised. Wood Dale. IL: Stoelting; 1997.
57. Bracken, B.A. and R.S. McCallum, *Examiner's Manual: Universal Nonverbal Intelligence Test (UNIT)*. 1998, Itasca, IL: Riverside Publishing.
58. Hammill DD, Pearson NA, Wiederholt JL. *Examiner's Manuals: Comprehensive Test of Nonverbal Intelligence*. Pro-Ed: Austin; 1997.
59. Brown L, Sherbenou RJ, Johnsen SK. Test of Nonverbal Intelligence -. 3rd ed. San Antonio: The Pyschological Corporation; 1997.
60. Raven, J., J.C. Raven, and J.H. Court, *Manual for Raven's Progressive Matrices and Vocabulary Scales. Section 1: General Overview*. 2003, San Antonio: Harcourt Assessment.
61. Cattell RB. Abilities: their structure, growth, and action. New York: Houghton Mifflin; 1971.
62. Blair J, Spreen O. Predicting premorbid IQ: A revision of the National Adult Reading Test. Clinical Neuropsychologist. 1989;3:129–36.
63. Wechsler D. Wechsler Test of Adult Reading (WTAR). San Antonio: The Psychological Corporation; 1999.
64. Groth-Marnet, G., ed. *Neuropsychological Assessment in Clinical Practice: A Guide to Test Interpretation and Integration*. 2000, John Wiley & Sons, Inc.: New York.
65. Pedersen, P.M., et al., *Aphasia in acute stroke: incidence, determinants, and recovery* Annals of Neurology, 1995. **38.**: p. 659-666.
66. Laska AC, et al. Aphasia in acute stroke and relation to outcome. Journal of Internal Medicine. 2001;249(5):413–22.
67. Beeson, P.A. and S.Z. Rapcsak, *The Aphasias*, in *Clinical Neuropsychology: A Pocket Handbook for Assessment*, P.J. Snyder and P.D. Nussbaum, Editors. 1998, American Psychological Association: Washington, DC.
68. Kertesz, A., *Aphasia in Stroke*, in *The Behavioral and Cognitive Neurology of Stroke*, O. Godefroy and J. Bogousslavsky, Editors. 2007, Cambridge University Press: New York. p. 53-74.
69. Pedersen P, Vinter K, Olsen TS. *Aphasia after stroke: type, severity and prognosis*. Cerebrovascular Diseases. 2004;17(1):35–43.
70. Salter K, et al. *Identification of aphasia post stroke: A review of screening assessment tools*. Brain Injury. 2006;20(6):559–68.
71. Goodglass, H., E. Kaplan, and B. Barresi, *Boston Diagnostic Aphasia Examination, Third Edition*. 2000, San Antonio: The Psychological Corporation.
72. Benton A, Hamsher K, Examination Multilingual Aphasia. Iowa City. IO: University of Iowa; 1976.
73. Wolf M, Bower PG. *The double-deficit hypothesis for developmental dyslexia*. Journal of Educational Psychology. 1999;91:425–38.
74. Snaphaan L, de Leeuw F. *Poststroke memory dysfunction in nondemented patients: A systematic review on frequency and neuroimaging correlates*. Stroke. 2007;38:198–203.

75. Szabo K, et al. *Hippocampal lesion patterns in acute posterior cerebral artery stroke*. Stroke. 2009;40:2042–5.
76. Max, J.E., et al., *Psychiatric disorders after childhood stroke.* Journal of the American Academy of Child and Adolescent Psychiatry, 2002. **41**(5).
77. Katz N, et al. *Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect*. Arch Phys Med Rehabil. 1999;80(4):379–84.
78. Connors CK. *Conners' Continuous Performance Test II*. Toronto: Multi-Health Systems; 1992.
79. Conners, C.K., *Conners' Kiddie Continuous Performance Test Version 5* 2004, North Tonawanda, NY: Multi-Health Systems, Inc.
80. Heilman, K.M., Watson, R.T., & Valenstein, E., *Neglect and Related Disorders*. Fourth ed. Clinical Neuropsychology, ed. K.M.V. Heilman, E. 2003, New York: Oxford University Press.
81. Ringman JM, et al. *Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort*. Neurology. 2004;63(3): 468–74.
82. Halligan PW, et al. *Spatial cognition: evidence from visual neglect*. Trends Cogn Sci. 2003;7(3):125–33.
83. Marsh EB, Hillis AE. *Dissociation between egocentric and allocentric visuospatial and tactile neglect in acute stroke*. Cortex. 2008;44(9): 1215–20.
84. Buxbaum LJ, et al. *Hemispatial neglect: Subtypes, neuroanatomy, and disability*. Neurology. 2004;62 (5):749–56.
85. Mesulam MM. *A cortical network for directed attention and unilateral neglect*. Ann Neurol. 1981;10(4):309–25.
86. Heilman KM, Van Den Abell T. *Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect).* Neurology. 1980;30(3):327–30.
87. Reuter-Lorenz PA, Kinsbourne M, Moscovitch M. *Hemispheric control of spatial attention*. Brain Cogn. 1990;12(2):240–66.
88. Posner MI, et al. *Effects of parietal injury on covert orienting of attention*. J Neurosci. 1984;4(7): 1863–74.
89. Losier BJ, Klein RM. *A review of the evidence for a disengage deficit following parietal lobe damage*. Neurosci Biobehav Rev. 2001;25(1):1–13.
90. Goodglass H, Kaplan E. *The assessment of aphasias and related disorders*. Philadelphia: Lea and Febiger; 1972.
91. Trauner DA. *Hemispatial neglect in young children with early unilateral brain damage*. Dev Med Child Neurol. 2003;45(3):160–6.
92. Ferro JM, Martins IP, Tavora L. *Neglect in children*. Ann Neurol. 1984;15(3):281–4.
93. Smith SE, Vargas G, Chatterjee A. *Mild visuospatial neglect occurs in children following stroke*. Ann Neurol. 2007;62(S11):S127–8.
94. Nys GMS, et al. *The prognostic value of domain-specific cognitive abilities in acute first-ever stroke*. Neurology. 2005;64:821–7.
95. Grace, J. and P.F. Malloy, *Frontal Systems Behavior Scale Professional Manual*. 2001, Lutz, FL: Psychological Assessment Resources.
96. Gioia, G.A., et al., *Behavior Rating Inventory of Executive Function*. 2000, Odessa, FL: Psychological Assessment Resources, Inc.
97. Osterrieth, P.A., Le test de copie d'une figure complexe. Archives de Psychologie, 1944. **30**: p. 206-356.
98. Culbertson, W.C. and E.A. Zilmer, Tower of London: Drexel University (TOLDX). North Tonawanda. NY: Multi-Health Systems; 2001.
99. Berg EA. *A simple objective treatment for measuring flexibility in thinking*. Journal of General Psychology. 1948;39:15–22.
100. Hochstenbach J, Mulder T, van Limbeek J, Donders R, Schoonderwaldt H. Cogntive decline following stroke: a comprehensive study of cognitive decline following stroke. Journal of Clinical and Experimental Neuropsychology. 1998;20(4):503–17.
101. Ungerleider LG, Haxby JV. 'What' and 'where' in the human brain. Curr Opin Neurobiol. 1994;4 (2):157–65.
102. Girkin CA, Miller NR. Central disorders of vision in humans. Surv Ophthalmol. 2001;45(5):379–405.
103. Delis DC, Robertson LC, Efron R. Hemispheric specialization of memory for visual hierarchical stimuli. Neuropsychologia. 1986;24(2):205–14.
104. Bauer, R.M. and J.A. Demery, *Agnosia*. Fourth ed. Clinical Neuropsychology, ed. K.M.V. Heilman, E. 2003, New York: Oxford University Press.
105. Mort DJ, Kennard C. *Visual search and its disorders*. Curr Opin Neurol. 2003;16(1):51–7.
106. Benton AL, Hannay HJ, Varney NR. *Visual perception of line direction in patients with unilateral brain disease*. Neurology. 1975;25:907–10.
107. Koski L, Iacoboni M, Mazziotta JC. *Deconstructing apraxia: understanding disorders of intentional movement after stroke*. Curr Opin Neurol. 2002;15(1):71–7.
108. Halstead WC. *Brain and Intelligence*. Chicago: University of Chicago Press; 1947.
109. Foundation PR, Test Purdue Pegboard. Lafayette. IN: Lafayette Instrument Company; 1948.
110. Klove, H., *Clinical Neuropsychology*, in *The medical clinics of North America*, F.M. Forster, Editor. 1963, Saunders Press: New York, NY.
111. Haroon E, Kumar A. *The clinical neuroscience of post-stroke depression*. Current Neuropharmacology. 2004;2:353–62.
112. Annoni J-M, et al. *Emotional disturbances after stroke*. Clinical and Experimental Hypertension. 2006;28:243–9.
113. Gass, C.S., *Assessment of Emotional Functioning with the MMPI-2*, in *Neuropsychological Assessment in Clinical Practice*, G. Groth-Marnet, Editor. 2000, John Wiley & Sons: New York.

114. Sachdev PS, et al. *Clinical Determinants of Dementia and Mild Cognitive Impairment following Ischaemic Stroke: The Sydney Stroke Study*. Dementia & Geriatric Cognitive Disorders. 2006;21(5/6):275–83.
115. Jokinen H, et al. *White matter hyperintensities as a predictor of neuropsychological deficits post-stroke*. Journal of Neurology, Neurosurgery & Psychiatry. 2005;76(9):1229–33.
116. Steinlin M, Roellin K, Schroth G. *Long term follow-up after stroke in childhood*. European Journal of Pediatrics. 2004;163:245–50.
117. Smith SE, et al. *Hemiparesis and epilepsy are associated with worse reported health status following unilateral stroke in children*. Pediatr Neurol. 2015;52(4):428–34.
118. Duval J, et al. *Brain lesions and IQ: recovery versus decline depends on age of onset*. J Child Neurol. 2008;23(6):663–8.
119. Ballard C, et al. *Neuropsychological deficits in older stroke patients*. Ann N Y Acad Sci. 2002;977:179–82.
120. Barker-Collo S, Feigin V. The impact of neuropsychological deficits on functional stroke outcomes. Neuropsychology Review. 2006;16(2):53–64.
121. Kissela B, et al. Clinical prediction of functional outcome after ischemic stroke: The surprising importance of periventricular white matter disease and race. Stroke. 2009;40:530–6.
122. Slot KB, et al. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. British Medical Journal. 2008;336(7640):376–9.
123. Williams TS, et al. Prevalence and predictors of learning and psychological diagnoses following pediatric arterial ischemic stroke. Dev Neuropsychol. 2017;42(5):309–22.
124. Blom I, et al. Prognosis of haemorrhagic stroke in childhood: a long term follow-up study. Developmental Medicine and Child Neurology. 2003; 45:233–9.
125. De Schryver ELLM, et al. Prognosis of inschemic stroke in childhood: a long-term follow-up study. Developmental Medicine and Child Neurology. 2000;42:313–8.
126. Hurvitz EA, et al. Functional outcome of paediatric stroke survivors. Pediatric Rehabilitation. 1999;3 (2):43–51.
127. Ballard C, et al. Profile of neuropsychological deficits in older stroke survivors without dementia. Dementia & Geriatric Cognitive Disorders. 2003;16:52–6.
128. Baron, I.S., E.B. Fennell, and K.K.S. Voeller, Pediatric Neuropsychology in the Medical Setting. 1995, New York, NY: Oxford University Press.
129. Clarke PJ, et al. Handicap in stroke survivors. Disabil Rehabilitat. 1999;21(3):116–23.
130. Forster A. Caregiver Burden in Stroke. Current Medical Literature: Stroke Review. 2005;9(1): 127–31.
131. Cicerone KD, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil. 2005;86(8):1681–92.
132. Rohling, M.L., et al., Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Cicerone et al.'s (2000, 2005) systematic reviews. Neuropsychology, 2009. **23**(1): p. 20-39.
133. Elsner, B., et al., Transcranial direct current stimulation (tDCS) for improving activities of daily living, amd physical and cognitrive function, in people after stroke. Cochrane Database Syst Rev, 2016(3).
134. Lefaucheur JP, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125(11):2150–206.
135. Pulvermuller F, et al. Constraint-induced therapy of chronic aphasia after stroke. Stroke. 2001;32 (7):1621–6.
136. Saxena A, Hillis AE. An update on medications and noninvasive brain stimulation to augment language rehabilitation in post-stroke aphasia. Expert Rev Neurother. 2017;17(11):1091–107.
137. Park JE. Apraxia: review and update. J Clin Neurol. 2017;13(4):317–24.
138. Salazar, A.P.S., et al. Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil, 2017.
139. Barrett AM, et al. Cognitive rehabilitation interventions for neglect and related disorders: moving from bench to bedside in stroke patients. J Cogn Neurosci. 2006;18(7):1223–36.

Chapter 8

Cognitive Declines During Migraine and Cluster Headaches are Caused by Cerebral 5HT Neurotransmitter Dysfunction

John Stirling Meyer

Introduction and Neurological Mechanisms of Headaches

During the 1990s, 26 million US citizens (majority women) suffered recurrent migraine headaches [1]. Migraine is debilitating and incapacitating, resulting in poor performance at workplace or in school [2, 3].

If cluster headaches (CHs) and chronic daily headaches (CDHs) are included among the types of vascular headaches classified by the International Headache Society (IHS) [4], numbers of US headache sufferers will increase further. By definition, migraine headaches that increase in frequency to more than 15 per month become transformed into CDH.

Recurrent CHs are rarer but in some ways similar to migraine. Men are affected more than women, and cephalalgia is often said to be more severe [5, 6]. CHs are more strictly unilateral than in migraine and are pathognomonically associated with tearing, pupillary changes, and conjunctival injection with redness of ipsilateral eye. Since lacrimation drains into ipsilateral nostril, unilateral nasal dripping results. Like recurrent migraine, CHs are intermittent but may increase in frequency until 15 days of headache per month are exceeded and then by definition are transformed into chronic CH.

Migraine, with and without aura, with other variants of vascular headache which include CH and CDH, appears to be initiated by neuronal discharges releasing neurotransmitters from the upper brain stem – trigeminal system, resulting in unilateral cerebral vasoconstriction, causing auras, followed by vasodilatation of intracranial and extracranial blood vessels, causing the ipsilateral headaches and has provoked cortical spreading depression [7, 8] and changes in posterior cerebral cortical excitability predisposing to photopsias [9]. Other symptoms accompanying migraine headache include nausea, vomiting, visual auras followed by cephalalgia due to cerebral hyperemia which are promptly terminated by sumatriptan administration (or other similar triptans) administered by injection, inhalation, mucus membrane absorption under the tongue, or ingestion.

Cerebral blood flow and metabolism are both reduced during auras of migraine [10] followed by increased cerebral perfusion during headache, which are promptly relieved by sumatriptan injection. It is generally considered that during the aura phase of migraine, cerebral metabolism and perfusion are reduced, to be followed later by cerebral hyperemia in the headache phase. Both are caused by release of neurotransmitters initiated by discharges arising from the upper brain stem and trigeminal system. The headache phase is accompanied by painful cerebral vasodilatation.

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The aura phase and later headache *with mental confusion and difficulty thinking* are due to temporary imbalance of cerebral neurotransmitter and serotoninergic systems. With injection or oral administration of sumatriptan, 5HT (serotonin) receptors of both neurons and blood vessels are stimulated: promptly correcting the neuronal and cerebro-vascular transmitter disorders, with restoration of neuronal 5HT function to normal.

Headache-related transient cognitive impairments last for about an hour, making it difficult for students to complete homework resulting in declines in academic performance. Similar headache-related problems occur among adults resulting in poor work performance or housewives who report difficulty completing their household chores.

Vascular headaches affect all ages, usually beginning around age 5, deteriorating family and interpersonal relationships. Headache-related cognitive impairments persist until headaches subside, following natural or drug-induced sleep or following administration of serotoninergic receptor agonists including sumatriptan and other triptans.

Possible influences of vascular headaches on psychometric test scores – mini-mental status examinations (MMSE), cognitive capacity status examinations (CCSE), and Hamilton Depression Rating Scales (HDRS) scores – across time were evaluated among 182 vascular headache subjects. When headache-free subjects established stability of the "mini" test battery. Confounding effects of depression were not found to influence cognitive test scores when subjects were headache free.

The vascular headaches, when "headache present," induced cognitive declines which were analyzed. Stability of CCSE, MMSE, and HDRS scores across time was evaluated among 182 subjects who made at least two clinic visits labeled "headachepresent" or "headache-absent." There were no significant changes in MMSE, CCSE, and HDRS test scores at different time intervals measured across many different clinic visits labeled "headache-absent" which confirmed stability of "mini" test battery scoring.

History

Early investigations concerning cognitive declines during migraine attacks are as follows:

The first study to utilize standardized, documented measures for testing cognitive performance among sufferers from migraine during headache intervals and later when headache free was reported by Black et al. in 1997 [11]. These authors tested 30 migraineurs utilizing standard, structured interviews of their own design. Subjects were tested when headache free, and the same tests were repeated during confirmed migraine headache intervals. Impairments of immediate attention, sustained attention, and recall of test materials were evaluated by comparing serial testing of each subjects' responses to verbal conversation scoring recent and remote recall of events.

In 1999, Mulder et al. [12] reported comparable results utilizing self-administered mechanical evaluation systems with timed responses obtained by standardized questions. Responses were graded for accuracy including neurobehavioral assessments which were tested among the migraineurs, with and without aura. These standard tests were administered during headache intervals and repeated 30 h later when headache free after completion of a good night's sleep. Migraineurs with aura showed residual slowing of response times when headache free but all subjects recovered completely or improved to near-normal status when tested 30 h later, when severe headaches had subsided.

Experimental Studies of Treatments

Review of earlier studies including descriptions of new insights and causal interpretations:

The present report summarizes and expands earlier investigations by the author, when he was working with different co-workers before his retirement and closing his Cerebrovascular Research and Headache Clinic. In his clinical investigations his standard "mini"

neuropsychometric test batteries were serially administered. These studies included large series of prospective, clinical trials among the author's practice with patients suffering from different types of headaches. Results were compared with a selected group of normal volunteers who were also being treated for different degrees of organic cognitive impairments varying from mild cognitive impairment to dementia. All long-term studies included serial neurological and physical examinations combined with the serial "mini" neuropsychometric test batteries as described. Results were correlated at intervals, among all subjects but particularly among vascular headache patients when they reported headaches to be present or absent. Headache sufferers were of four different types: (1) migraine with aura, (2) migraine without aura, (3) migraine converted to chronic daily headaches (CDHs) and cluster headaches (CHs). Tension-type headaches were excluded.

Earlier publications validated the "mini" test battery according to reliability, stability, and specificity for each of three test instruments utilized [13–17], among headache sufferers. Test instruments used proved to be highly reproducible [13–15] as the "mini" test battery was used among the headache sufferers when headaches were present or absent. One article on methods identified and described domains of cognitive impairments found to be present during vascular headaches [14]. Domains most affected included "deficits in attention," "digit span," "learning new words," "immediate recall," "calculation," "abstraction," and "overall cognitive functioning."

Mini-mental state examination (MMSE) [18, 19] and cognitive capacity screening examination (CCSE) [20–22] were combined when utilized for testing cognition. The two tests take 20–30 min or less to administer. Both quantify general cognitive test performance and identify different cognitive domains that may be affected [19–25]. The Hamilton Depression Rating Scale (HDRS) was included which quantitates changes pertaining to mood and affect. HDRS is sensitive for detecting episodes of depression which sometimes accompany vascular headaches. The HDRS scale was scored, at each visit, to exclude confounding depression, since severe depression may decrease cognitive test performance.

Experimental designs were longitudinal over 15 years. Subjects returned every 3–12 months to clinic so that mood and cognition were tested at each visit. Whenever possible, test performances were compared during different intervals, labeled "headache-absent" and "headache-present."

All subjects tested were neurologically and psychometrically normal when headache-absent. Volunteers with history of severe head injury or psychiatric disorders, drug, alcohol, or substance abuse were excluded.

"Mini-cognitive test battery" was administered during structured neurobehavioral interviews at each clinic visit. During headache-present intervals, volunteers were administered oral sumatriptan (Imitrex), 100 mg, or other "tailored" triptans including zolmitriptan, 5 mg, or as orally disintegrating tablets of Maxalt MLT, 10 mg, by sublingual administration. Subjects could thus be re-tested shortly after triptan-induced headache-free intervals. By these means cognitive testing was repeated during intervals with headache present, or headache free, after headaches subsided, either spontaneously or by pharmacologically induced triptan administration.

Presence or absence of vascular headaches was noted during interviews that were made to correlate clinical observations with changes in the "mini" cognitive test battery. When headache absent, all participants had normal neurological examinations, normal CT and MRI brain scans.

Participants

Patients with headaches were classified according to IHS into four types [4] displayed in Table 8.1.

In the first IHS headache classification, chronic daily headaches (CDHs) and transformed migraines were omitted but later, CDHs were still shown to have headache intervals similar to migraine and thus met IHS criteria, although

Table 8.1 Different types of vascular headaches classified according to IHS criteria

	Numbers of subjects ratios (women:men)	Age, years (mean ± SD)
Migraine with aura	39 (32:7)	47 ± 13
Migraine without aura	133 (95:38)	45 ± 11
Cluster headaches	11 (2:9)	51 ± 10
Chronic daily headaches	13 (4:9)	50 ± 17
Total	196 (133:63)	46 ± 2

Modified from Meyer et al. [13]

migraine headaches had become many times more frequent, exceeding 15 or more headache days each month [7, 26]. Table 8.1 lists participants classified into four headache types, according to IHS criteria [4] modified to include subjects with CDH, as follows: (1) migraine with aura; (2) migraine without aura; (3) periodic cluster headaches; and (4) migraine transformed to CDH. Subjects with tension-type headaches were excluded, since they did not exhibit cognitive impairments when headaches present. Furthermore, tension-type headaches are clinically milder, diffuse, bilateral, and with "constricting" or "band-like" features. Subjects with chronic cluster were excluded because they were seldom headache free.

After signing informed consent, 196 subjects were admitted to a prospective trial. Total cohort of vascular headaches consisted of 136 women and 63 men. Mean age was 46 ± 2 years. One hundred thirty-three suffered from migraine without aura; 39 suffered from migraine with aura, 11 had periodic CH, and 13 had CDH. Subjects spoke fluent English and had completed high school and the majority received higher education by attending colleges, universities, or advanced technical or administrative training programs.

At clinic visits, medical and neurological examinations, MMSE combined with CCSE and HDRS were completed. Normative CCSE and MMSE values among these highly educated subjects fell between 27 and 30. Interrater reproducibility was excellent, with high specificity and sensitivity of cognitive testing. CCSE has less ceiling effects than MMSE, with retesting reliability of ±2.

Hypotheses to Be Tested

Trials were designed to measure cognitive declines liable to occur among a large group of volunteers with different types of vascular headaches, with headaches present, during clinic visits. Additional hypotheses analyzed were whether or not cognitive declines during headache-present intervals were influenced by subjects' age, gender, or type of headache.

Ethical Treatment

Prophylactic therapy was continued as prescribed for prevention of vascular headaches during the trial. These included calcium channel blockers (principally verapamil), beta blockers (principally propranalol), and anti-depressant and anxiolytic agents (principally amitriptyline). Abortive therapy initiated at headache onset included serotonin (5HT) receptor agonists such as sumatriptan (Imitrex) and similar "tailored" serotonin receptor agonists, i.e., zomig and maxalt.

Results

Accumulated data were analyzed from all clinic visits among 77 eligible subjects who had, at least, one clinic visit with headache present and one visit with headache absent. These 77 subjects had a total of 436 visits, 112 with headache present and 324 visits with headache absent (Table 8.2). As shown in Table 8.2, there were significant declines in CCSE and MMSE test scores during intervals with "headache present" when compared with intervals with "headache absent."

There were no significant changes in MMSE, CCSE, and HDRS test scores at different time intervals measured across different clinic visits labeled "headache-absent," confirming stability of test battery. There were no significant changes

Table 8.2 Mean CCSE, MMSE, and HDRS test score changes during visits with headache absent or headache present according to headache types

Headache type	Patients	Headache status at clinic visit	CCSE*	MMSE**	HDRS
Chronic daily headache (CDH)	5	Absent headache	28.9 ± 1.3	29.2 ± 0.8	1.5 ± 3.2
		Present headache	24.2 ± 2.2	27.8 ± 2.8	4.5 ± 5.7
Cluster headache (CH)	7	Absent headache	27.7 ± 4.1	28.4 ± 1.5	5.1 ± 4.7
		Present headache	25.3 ± 3.1	26.5 ± 0.18	3.7 ± 3.7
Migraine with aura (MA)	17	Absent headache	29.5 ± 2.0	28.6 ± 2.0	5.9 ± 4.5
		Present headache	24.8 ± 3.6	26.4 ± 2.2	5.3 ± 5.2
Migraine without aura (MO)	48	Absent headache	29.5 ± 1.1	29.0 ± 1.5	6.8 ± 5.6
		Present headache	25.0 ± 1.7	26.7 ± 1.5	7.1 ± 6.8

Both CCSE and MMSE values declined significantly when pooled vascular headaches present were compared to headache absent. HDRS scores did not change significantly.
*$p < 0.0001$; **$p < 0.001$.

measured by the same or two different raters, among headache-free subjects. There were also no discernible age-related declines between ages 45 and 51 years for cognitive test scores, among subjects labeled "headache-absent." Confirming that, in this study, age alone did not influence "mini" cognitive battery test scores when headache free. No confounding effects of depression, measured by HDRS test scores, influenced cognitive test scores when headache free. As shown in Table 8.2, there were significant declines in CCSE and MMSE test scores when "headache-present" intervals were compared with "headache-absent" intervals.

HDRS showed no significant changes at intervals with headaches absent or headaches present so that depression was not a confound. Both CCSE and MMSE declined significantly during headache-present intervals; CCSE declined to a greater, more significant degree than MMSE measured during same headache-present intervals.

Possible influences of headache type, according to IHS classification into types 1, 2, 3, and 4, or any possible effects of gender or advancing age, on headache-present-induced cognitive declines were analyzed next.

Gender, and advancing age of subjects tested, exerted significantly different effects on severity of cognitive declines during headaches. Among women, mean CCSE scores decreased more during headache-present intervals ($p < 0.02$) showing mean declines of –4.8 points. Among men, mean CCSE scores declined less than women, during headache-present intervals showing a mean decline of –3.6 points. Likewise, among younger subjects CCSE scores declined more during headache-present intervals, than among the older subjects ($p < 0.2$). In younger subjects during headache-present intervals, mean scores declined greatly by –4.8 points, compared to –3.7 among older subjects. No significant differences of CCSE declines during headache-present intervals were noted among the four different headache types according to IHS classifications.

McNemar analysis revealed no significant differences in specificity between overall MMSE and cognitive capacity screening examination (CCSE) testing. During headache intervals, however, 85.7% of subjects registered below normal scores, but CCSE declines during the same headache intervals; only 49.4% subjects registered MMSE scores below normal. During the same headache-present intervals CCSE scores showed greater sensitivity ($p < 0.0001$) in recording the declines compared to concurrent MMSE scores. CCSE scoring is more reliable and more sensitive than MMSE scoring for registering cognitive declines among a highly educated cohort of volunteers.

During headache intervals among all four types of vascular headaches migraine with aura,

migraine without aura, CDH, and CH, all showed significant declines occurred in cognitive test performance ($p > 0.0005$) consonant with their subjective complaints. These cognitive declines were best measured by CCSE compared with MMSE. During headache intervals women showed greater cognitive declines than men. Likewise, during headaches younger subjects showed greater cognitive declines than older. Headache-related cognitive declines involved attention, but also all other cognitive domains tested: including immediate recall, digit retention, arithmetic, calculation, acquisition of new words, and abstract thinking.

Among these highly educated volunteers, CCSE proved more sensitive than MMSE for detecting cognitive declines, among all types of vascular headaches. Results provide pharmacological and physiological evidence that vascular headache sufferers have justifiable reason to be unable to function normally in workplace, home, school, university, or college and may be responsible for marital discord, impaired social functioning, and neurobehavioral problems.

Results indicate that pharmacologic stimulation of serotoninergic (5HT) receptors of brain and cerebral blood vessels plays key parts in terminating vascular headaches and restoring cognitive performance. Recent PET studies of cerebral serotonin synthesis confirm widespread increases in brain serotonin (5HT) synthesis at the onset of each migraine attack. Sumatriptan administration promptly restores cerebral 5HT metabolism to normal. Regional cerebral blood flow measures by PET confirm that upper brain stem neurones, including trigeminal nuclei, become activated and initiate migraine attacks. Results described show 5HT cerebral receptors are better developed among women with vascular headaches than among men, although both genders show cerebral 5HT receptor declines during advancing age. Such observations support clinical experience that migraine headaches decline in frequency and severity during aging, particularly among women. This clarifies why migraine headaches decrease during aging, and after age 70, with few exceptions, often cease.

References

1. Durham CF, Alden RR, Dalton JA, et al. Quality of life and productivity in nurses reporting migraine headache. Headache. 1998;38:427–35.
2. Stewart WF, Lipton RB. Simon D work related disability: results from the American migraine study. Cephalalgia. 1996;16:231–9.
3. Linet MS, Stewart WF, Celantano DD, Ziegler D. An epidemiological study of headache among adolescents and young adults. JAMA. 1989;261:2211–6.
4. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia. 1988;8(Suppl 7):1–96.
5. Kudrow L. Cluster headache. Mechanism and management. New York, NY: Oxford University Press; 1980.
6. Kudrow L. Cluster headache. In: Blau JN, editor. Migraine, clinical, therapeutic, conceptual and research aspects. London: Chapman and Hall; 1987. pp. 113–33.
7. Mathew N, Reaveni U, Perez F. Transformed or evolutive migraine. Headache. 1987;27:102–6.
8. Lauritzen M, Olsen J. Spreading depression. In: Blau JN, editor. Migraine, clinical, therapeutic, conceptual and research aspects. London: Chapman and Hall; 1987. pp. 387–402.
9. Aurora SK, Cao Y, Browyer SM, Welch KM. The occipital cortex is hyper excitable in migraine: experimental evidence. Headache. 1999;39:469–76.
10. Woods RP, Jacoboni M, Mazziotta JC. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med. 1994;331: 1689–92.
11. Black LK, Horn GJ, Miller DW, Logue PE. Migraine headache disorder and cognitive ability. Headache. 1997;37:301–02.
12. Mulder EJM, Liassen WHP, Passchier J, Orlebeke JF, DeGeus EJ. Interictal and postictal cognitive changes in migraine. Cephalagia. 1999;19: 557–65.
13. Meyer JS, Thornby J, Crawford K, Rauch G. Reversible cognitive decline accompanies migraine and cluster headache. Headache. 2000;403:638–46.
14. Li YS, Meyer JS, Thornby J, Minh P. Transient domains of cognitive impairment during intervals of migraine headache. Headache Quarterly. 2004;12:21–6.
15. Meyer JS, Li YS, Thornby J. Validating mini-mental state, cognitive capacity screening and Hamilton depression scales utilizing subjects with vascular headaches. J Geriatr Psychiatry. 2001;16:430–5.
16. Meyer JS, Thornby J, Li YS, Rauche GM. Migraine, cluster and chronic daily headaches are often accompanied by reversible cognitive decline. In Advanced Studies in Medicine, vol 1. Johns Hopkins University School of Medicine. 2001. pp. 97–100.

17. Meyer JS, Thornby J, Crawford K, Rauch GM, Li Y. Migraine and cluster headaches cause temporary cognitive impairments. Cephalalgia. 2000;20:381.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res. 1975;12:189–98.
19. Grigoletto F, Zappala G, Anderson DW, Lebowitz BD. Norms for the Mini-Mental State Examination in a healthy population. Neurology. 1999;53:315–20.
20. Jacobs JW, Bernhard MR, Delgado A, Strain JJ. Screening for organic mental syndromes in the medically ill. Ann Intern Med. 1977;86:40–6.
21. Kaufman DM, Weinberger GM, Strain JJ. Detection of cognitive decline by a brief mental state examination. The cognitive capacity screening examination, a reappraisal and a review. Gen Hosp Psychiatry. 1979;1:247–55.
22. Walker ML. Performance of older normal subjects on a brief test of cognitive functions. The cognitive capacity screening examination [Master's Thesis], University of Houston, Houston, TX, 1988.
23. Hamilton MA. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
24. Sakai Y, Dobson L, Diksic M, Aube M, Hamel E. Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis. Neurology. 2008;70:431–9.
25. Weiller C, May A, Limroth V. Brainstem activation in spontaneous human migraine attacks. Nat Med. 1995;1:658–60.
26. Spierings EL, Shroevent M, Houkoop PC, Sorbi M. Presentation of chronic daily headache: a clinical study. Headache. 1998;38:191–6.

Chapter 9

Respiratory Disorders: Effects on Neurocognitive and Brain Function

Ramona O. Hopkins

Introduction

Diseases and/or disorders of the pulmonary system may affect brain behavior relationships due to impaired oxygen delivery (i.e., anoxia, hypoxia). Neurons are dependent on oxygen and without oxygen cellular function is disrupted and damage to cell structure leading to neuronal death may follow. A variety of respiratory disorders such as cardiac or respiratory arrest, carbon monoxide poisoning, obstructive sleep apnea, chronic obstructive pulmonary disease, and acute respiratory distress syndrome result in anoxia or hypoxia which can result in anoxic brain injury. The neuronal injury is manifest structurally by lesions and neuronal atrophy and functionally as neurocognitive and neuropsychiatric impairments.

The incidence of cardiac arrest with anoxia and cerebral ischemia occurs in more than 400,000 cases per year, of which more than 80% of these patients are likely to have poor neurological outcomes [1, 2]. Improvements in emergency and critical care medicine have resulted in approximately 200,000 cardiac resuscitations per year of which over 70,000 patients survive but constitute only 1% of those admitted to brain injury rehabilitation centers [3]. Other respiratory disorders associated with anoxia or hypoxia may also cause anoxic brain injury. The severity of anoxia/hypoxia does not appear to be related to development of neuropsychological impairments. However, the degree of neuropsychological impairment appears parallel to the degree of morphologic abnormalities as demonstrated by quantitative MRI image analysis [4, 5]. Neuropsychological deficits are common in respiratory disorders with concomitant hypoxia including impaired memory [6–8], executive function [9, 10], apperceptive agnosia [11], visual–spatial deficits [12], and generalized neurocognitive decline [6, 13, 14].

Effects of Hypoxia

The human brain constitutes approximately 2% of the total body mass but utilizes 20% of the total oxygen consumption [15]. The brain requires oxygen to produce energy and uses aerobic glucose oxidation to produce 95% of the brain's adenosine triphosphate (ATP). ATP serves as a source of energy for many metabolic processes including neural function. ATP releases energy when it is broken down into ADP by hydrolysis during cell metabolism. Neocortical and subcortical functions depend upon continuous supply of

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oxygen, as neurons are not able to store oxygen and glucose for later use [16]. Hypoxia or anoxia damages multiple organ systems especially those with high oxygen utilization such as the central nervous system. Oxygen and glucose are required to maintain the function of the central nervous system (CNS) and reduction or depletion of oxygen and glucose results in neuronal injury. Slight decreases in oxygen delivery may cause permanent biochemical and morphological changes. Anoxia is defined as absence of oxygen in arterial blood or tissues, hypoxia as tissue oxygen deprivation, and hypoxemia as reduced oxygenation of the blood [17, 18]. Hypoxia and anoxia are often used interchangeably as anoxia is severe hypoxia.

Regional brain oxygen utilization is not homogeneous with some brain regions more vulnerable to the effects of anoxia/hypoxia, particularly structures at the end of the vascular supply or with high metabolic rates [19]. Selective vulnerability of some brain regions has been attributed to vascular or hemodynamic specificity [19], increased regional metabolism of glucose [20], and/or proximity to structures with high levels of excitatory amino acids such as glutamate [21, 22]. Vulnerable brain regions include the neocortex, hippocampus, basal ganglia, cerebellar Purkinje cells, primary visual cortex, frontal regions, and thalamus [23–25].

Mechanisms of Brain Injury

Anoxia or ischemia causes a pathophysiological cascade that leads to neuronal damage and death (for reviews of the mechanisms see [17, 26]). Mechanisms of anoxia-induced neuronal injury include the following: (1) Decreased ATP production without decreasing ATP utilization, resulting in energy depletion, ionic pump failure, K^+ outflow, and inflow of Ca^{2+} [27]; (2) lactic acidosis due to anaerobic metabolism [28]; (3) excitotoxic damage due to excessive glutamate release leading to increased neuronal firing, calcium influx, and neuronal death [26]; (4) increased calcium influx and intracellular accumulation of calcium due to ionic pump failure [29]; (5) the formation of oxygen radicals during reperfusion or reoxygenation [17]; (6) nitric oxide synthase leading to impaired neurotransmission, protein synthesis, and membrane peroxidation [17]; and (7) anoxia or ischemia resulting in neuronal necrosis and/or apoptosis or programmed cell death [30, 31]. Controversy exists in the literature regarding whether hypoxia in the absence of ischemia can result in brain injury [32]. Neuropsychological sequelae following hypoxia without ischemia occurred in 22 patients with hypoxia without hypotension, all were comatose and recovery to the premorbid level of function occurred in only 50% of the patients [33]. In fact three patients with hypoxia (PO_2 less than 45 mmHg) without hypotension died of cardiac failure, indicating that factors other than ischemia contributed to poor outcome [34]. Further, neuropsychological impairments are common in patients with pulmonary disorders in which continuous or intermittent hypoxia or hypoxemia occur without ischemia. For example, patients with pulmonary disorders including chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) with concomitant hypoxia have neuropsychological deficits similar to patients with anoxia due to cardiac or respiratory arrest.

Neuroimaging Findings

As stated previously, some brain regions are more vulnerable to the effects of anoxia/ischemia, particularly structures at the end of the vascular supply, with high metabolic rates [19], and/or proximity to structures that contain excitatory amino acids such as glutamate [21, 22]. Anoxic brain injury results in focal and diffuse neuropathologic lesions and atrophy [7, 35–37] including lesions in the hippocampus [38, 39], basal ganglia, cerebellum [40], subcortical and periventricular white matter lesions [41], and atrophy of the corpus callosum [42]. Generalized brain volume loss leading to ventricular enlargement and sulcal widening [36] and hippocampal atrophy are also common [7, 43]. A review of anoxic brain injury (N = 90) found that 44% of

individuals had cortical edema or atrophy, 33% had cerebellar lesions, 22% had basal ganglia lesions, 21% had hippocampal atrophy, and 3% had thalamic lesions [36]. Hippocampal damage, including lesions and atrophy [38, 39], has long been established as a common consequence of anoxia. Hippocampal atrophy can be identified on magnetic resonance scans as volume reduction. Previous research has suggested that the hippocampus may be more vulnerable to hypoxic injury than adjacent medial temporal lobe structures such as the parahippocampal gyrus or temporal lobes [44].

Neurological and Neuropsychological Sequelae

Poor neurological outcomes after brain injury include death, coma, vegetative state, severe neurologic disability [45], neurocognitive sequelae, and development of new psychiatric disorders [35, 36]. Neuropsychological deficits following anoxia brain injury are heterogeneous and include agnosia [11], impaired memory [8, 39, 46], executive dysfunction [9, 10], impaired visual–spatial skills [12], generalized neurocognitive impairments [14], and motor disturbances [47]. Psychological and behavioral changes include euphoria, irritability, emotional volatility, depression, and anxiety [48, 49]. This chapter will review some common respiratory disorders and associated neurocognitive and neuropsychiatric sequelae.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) refers to a group of pulmonary diseases with airflow limitation that is not fully reversible including chronic bronchitis and emphysema, which occur without an asthmatic component. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs [50]. Both chronic bronchitis and emphysema are characterized by airway obstruction that may be partially reversible. COPD is the fourth leading cause of death in the United States and leads to serious, long-term disability [51]. The estimated prevalence of COPD in the United States in the adult population is 5–10% [52]. Chronic obstructive pulmonary disease (COPD) is a growing cause of morbidity and mortality worldwide and the prevalence of stage II (forced expiratory volume of 30 to <50% predicted) or higher COPD was 10.1% overall, 11.8% for men, and 8.5% for women [53]. More than 14 million people are currently diagnosed with COPD and an additional 12 million likely have COPD that has not been diagnosed [54]. COPD is a progressive, degenerative disease process that results in airflow obstruction, air trapping, hyperinflation of the lungs, and impaired gas exchange. The most important risk factor for development of COPD is cigarette smoking [55]. Other risk factors include family history of pulmonary disease, exposure to allergies and/or irritants, and pulmonary infection [56]. Symptoms include shortness of breath, dyspnea, cough, increased sputum production, and wheezing. As the disease process advances, the pulmonary changes lead to abnormal sleep structure, sleeplessness, poor physical and neurocognitive function, poor exercise tolerance, lack of appetite, weight change, fatigue, and dyspnea [57]. Dyspnea or air hunger, manifest as difficult or labored breathing [58], can lead to hypoxia/hypoxemia, which, as noted above, is linked to brain injury and development of neurocognitive impairments [59], depression, and anxiety [56].

Neurocognitive Morbidity

Neurocognitive impairments are common in patients with chronic obstructive pulmonary disease (COPD) [60]. The pattern, extent, and severity of neurocognitive impairments in COPD patients are variable, but are associated with hypoxemia [61, 62]. Patients with COPD have impaired memory, executive function [63], flexible thinking [61], attention, and slow mental processing speed [64]. In general, neurocognitive impairments correlate with the

duration and severity of the hypoxia [62, 65]. However, even patients with mild hypoxemia have neurocognitive impairments in a variety of cognitive domains [61, 62]. The severity of the neurocognitive impairments is also associated with older age and duration of COPD [66]. Further, older age, poorer aerobic fitness, and reduced pulmonary function predict worse neurocognitive performance [67]. Frequently reported neurocognitive impairments include executive dysfunction; reduced perceptual motor speed, impaired memory, and attention; and reduced intellectual function [68]. Investigations to date find great inter-individual variability in neurocognitive impairments in COPD patients. Memory is one of the most commonly affected neurocognitive domains in COPD. For example, impaired verbal memory is associated with poor adherence to the patients' medication regimen [69].

As noted above, neurocognitive impairments in COPD patients correlate with hypoxia/hypoxemia [61, 62]. Moderate to severe hypoxemia deficits lead to poor motor skills, abstract reasoning, attention learning, and memory and language skills [70]. Prigatano et al. [60] found that COPD patients with mild hypoxemia had mild impairments in "higher cerebral problem-solving skills." Other studies find impaired memory, problems forming new concepts, problems with flexible thinking [61], impaired attention, and slow mental processing speed [64] correlate with the severity of hypoxia [62, 65]. In fact COPD patients with mild hypoxia, the majority of who were treated with supplemental oxygen, had neurocognitive impairments [63]. Several studies suggest that long-term oxygen treatment improves cognitive functioning [62, 65]. Alternatively, acute oxygen treatment may not improve cognitive functioning in some COPD patients [71]. One study found that COPD patients had significantly worse intellectual function and attention than controls and the neurocognitive impairments did not correlate with disease severity (i.e., lung function, blood gas analysis, nocturnal oxygen saturation) [72]. Current data suggest the ability to predict neurocognitive impairments on the basis of the severity of the disease or hypoxemia is poor and the effectiveness of oxygen therapy for improving cognitive functioning of COPD patients is unclear.

Potential reasons for the lack of relationship between hypoxemia and neurocognitive impairments may due to non-compliance with oxygen therapy or other factors such as variable duration of illness and illness severity (such as variable duration and severity of hypoxemia), comorbid disorders, poor medication adherence, and reduced functional capacity and physiologic reserve to name a few [73]. For example, COPD patients that have impaired global cognitive performance and memory had poor adherence to medication regimes [69]. Physical exercise may improve cognitive function in healthy individuals through improved cerebral metabolism and oxygenation [74]. Pulmonary rehabilitation consisting of exercise, education, and psychosocial counseling improved psychomotor speed and mental flexibility [75]. However, memory and concentration did not improve [75], neurocognitive impairments that are associated with hypoxia/hypoxemia induced hippocampal damage rather than those associated with fatigue. Risk factors and mechanisms of neurocognitive impairments, as well as interventions that may lead to improved cognitive functioning in COPD patients, remain to be determined.

In addition to neurocognitive impairments COPD patients have impaired physical function, health status, and reduced quality of life. These patients often are impaired in their ability to perform activities of daily living (i.e., bathing, dressing, toileting, transfer, continence, and feeding) which are related to their pulmonary function, cough, wheezing, and dyspnea [76]. COPD patients report poor physical function that contributed to reduced quality of life compared to healthy control subjects [60]. Further, the degree of physical limitations paralleled the severity of the COPD. Decreased exercise tolerance and dyspnea are related to poor health status and functional abilities [77]. Even COPD patients with mild hypoxemia have significantly lower quality of life (measured using the Medical Outcome Survey short form-36; SF-36) compared to healthy controls [78]. Higher levels of depression and anxiety symptoms are also associated with reduced quality of life in COPD patients [79].

Neuropsychiatric Morbidity

Neuropsychiatric disorders, especially depression and anxiety, are common in patients with COPD. The prevalence of neuropsychiatric disorders is as high as 30–58% of COPD patients [80]. Other studies note the prevalence of depression is as high as 42% [81] and 37% of patients have anxiety disorder [82]. Depression increases with increased hypoxemia, carbon dioxide levels, or dyspnea [83]. Hypoxia may be a cause factor in the development of depression and anxiety in COPD due to brain injury (see section "Mechanism of Brain Injury") [84]; however, treatment with oxygen results in little or no improvement in the severity of the depression [85]. Even patients who undergo long-term oxygen therapy have severe depression [86]. It is unclear why oxygen treatment improves neurocognitive function but not neuropsychiatric function, but may be due to physical or psychological responses. Another possible cause of neuropsychiatric morbidity may be negative self-perception and restrictions in behavioral functioning due to reduced physical capacity [75]. Exercise rehabilitation in COPD patients improves depression and anxiety [75].

Anxiety is also common in patients with pulmonary disorders such as COPD. Vögele et al. found 55% of COPD had a diagnosis of an anxiety disorder compared to 30% of controls [87]. Vögele and colleagues found no associations between anxiety levels and respiratory function in the COPD group, but there was positive association between anxiety levels and physical symptoms, as well as negative cognition in COPD patients with anxiety disorders. The above findings confirm the high prevalence rate of neurocognitive and neuropsychiatric disorders in patients with COPD [87].

COPD Summary

COPD is a chronic obstructive pulmonary disorder associated with poor physical health, reduced physical function, neurocognitive impairments, and neuropsychiatric manifestations including depression and anxiety. Oxygen treatment may improve neurocognitive function in some patients. Studies using exercise rehabilitation show improvements in physical functioning, endurance, neurocognitive functioning, and improved neuropsychiatric well-being [70, 75].

Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a common cause of mortality and morbidity and affects 150,000 people per year [88] or more [89] in the United States. Patients are critically ill and survival has improved from less than 50% to approximately 70% [90–92] resulting in approximately 100,000 ARDS survivors per year. Acute respiratory distress syndrome is characterized by acute lung injury, hypoxemia, reduced total thoracic compliance, and diffuse bilateral infiltrates [93, 94]. Although the pathophysiology of ARDS is unclear it occurs in response to a variety of insults including sepsis, shock, trauma, pneumonia, massive transfusion, and other medical/surgical conditions. ARDS is frequently accompanied by organ dysfunction, which includes central nervous system dysfunction. Treatment of ARDS requires aggressive supportive care including positive pressure ventilation [92] and increased oxygen concentration with risks of barotrauma, oxygen toxicity, and nosocomial infection. Survivors of ARDS are often left with pulmonary function abnormalities, neuromuscular weakness, diminished health-related quality of life, neuropsychiatric and neurocognitive deficits [95–97].

Investigations of the neurologic dysfunction in ARDS survivors have been relatively neglected compared to other organ systems. A study that assessed CNS dysfunction using the Glasgow Coma Scale score found that greater severity of the initial neurologic dysfunction (lower Glasgow Coma Scale scores) and no change or worsening of the neurologic dysfunction were associated with higher 30-day mortality [98]. Neurologic complications of ARDS involve the central and peripheral nervous systems and contribute to significant

mortality and morbidity. Brain imaging data in 15 ARDS patients suggest that neurologic morbidity includes neuropathologic changes including generalized brain atrophy and structural lesions [99]. The patients with ARDS and brain CT scans had a longer hospital and ICU length of stays, duration of mechanical ventilation, and lower FiO_2 compared to ARDS patients without brain imaging. The patients who underwent brain CT imaging had significantly larger ventricular volumes for the lateral ventricles, III ventricle, temporal horns of the lateral ventricles, total ventricular volume, and ventricle-to-brain ratio (a measure of diffuse atrophic change and a general index of white matter integrity; *p* values 0.02–0.008) compared to the normal control subjects [99]. Clinical radiological brain CT reports identified seven patients with atrophy that support the finding of ventricular enlargement and brain atrophy. Six of the 15 ARDS patients had mild to moderate cerebral atrophy or ventricular enlargement including hippocampal atrophy in one patient and one patient had increased temporal horn size [99]. The observed brain atrophy may be due to hypoxia during critical illness [96, 100]. The nonspecific brain injury manifested by reduced gyral volume, increased sulcal space, passive increase in ventricular volume, and increased cerebrospinal fluid is common following hypoxic brain injury [101]. While the sample size is small, the data suggest that longer ICU and hospital length of stays, longer duration of mechanical ventilation and lower FiO_2 may be risk factors for brain injury [99]. Both the patients with ARDS with and without CT scans had significant cognitive impairments including impaired memory, attention, mental processing speed, and executive function at hospital discharge and 1 year post-hospital discharge. These findings suggest that ARDS may result in neuropathologic injury and concomitant neuropsychological impairments.

Mechanisms of Injury

The mechanisms of ARDS-induced brain injury are just beginning to be elucidated, but hypoxemia is undoubtedly implicated [96, 100]. Hopkins et al. measured pulse oximetry in a prospective cohort of mechanically ventilated ARDS survivors and assessed the relationship between the duration and severity of mean oxygen saturation below 90, with neurocognitive outcome [96] (pulse oximetry: SpO_2 level <90 is approximately a PaO_2 of 50% or severe hypoxia). The pulse oximetry was measured for a total of 31,665 h, excluding data without a good pulse waveform. Patients' mean saturations were below 90% for 122 ± 144 h per patient. The degree of hypoxemia correlated significantly with neurocognitive sequelae [96]. Supportive evidence for the role of hypoxia in brain injury includes CA1 neuronal in the hippocampus due to hypoxia and increased S-100B protein serum levels in pigs with acute lung injury [102]. Other mechanisms of brain injury following ARDS include hyperglycemia [103], delirium [104], hypotension [105], and the use of sedatives or analgesics [106]. The mechanisms of neurologic dysfunction are likely multi-factorial in nature. Thus, ARDS may result in significant long-term brain-related morbidity manifest by neurocognitive impairments, neuropsychiatric morbidity, and decreased quality of life.

Neurocognitive Morbidity

Neurocognitive impairments in ARDS patients are long lasting and are reported at 6 months [107], 1 year [96, 105, 108], 2 years [100], and 6 years following hospital discharge [109, 110]. Hopkins and colleagues found ARDS survivors had global neurocognitive decline and impaired memory, attention, concentration, mental processing speed, and global neurocognitive decline [96]. At 1-year follow-up, 30% of the 55 patients had lower intellectual function and 78% had impaired memory, attention, concentration, and/or mental processing speed. In other studies of ARDS survivors neurocognitive sequelae occurred in 73% (54 of 74) of survivors at hospital discharge, 46% (30 of 66) at 1 year, and 47% (29 of 62) at 2 years [100, 105]. Regarding global intellectual function, Hopkins et al. showed that ARDS patients' estimated premorbid IQ was significantly higher than their measured IQ at hospital discharge but improved to their premorbid level

by 1-year follow-up [100]. The finding that patients recovered over time with regard to IQ does not necessarily suggest a comparable recovery in all cognitive domains, as data from traumatic and anoxic brain injury literature suggest that some cognitive abilities are more likely to improve.

The neurocognitive impairments appear to improve during the first 12 months post-hospital discharge [100]. For example, at hospital discharge 70% of ARDS survivors had neurocognitive impairments whereas only 45% had neurocognitive impairments at 1 and 2 years following hospital discharge [100]. While highly prevalent, cognitive impairment demonstrated by ICU survivors is also often quite severe. The aforementioned ARDS patients with cognitive sequelae all fell below the sixth percentile of the normal distribution of cognitive functioning, displaying marked neuropsychological deficits in memory, executive functioning, attention, and mental processing abilities. Impairment does not impact all domains equally – and deficits in some areas rebound relatively more completely than others. The duration of the neurocognitive impairments in at-risk ARDS survivors lasts years and may be permanent. Two studies found that 25–33% of ARDS survivors have neurocognitive impairments 6 years after ARDS [109, 110]. The observed neurocognitive impairments are similar to those reported in other ARDS survivors [108, 109, 111], medical ICU survivors [112], following carbon monoxide poisoning [113], and several years after elective coronary artery bypass surgery [114]. Risk factors for acute and chronic neurocognitive impairments following ARDS are unknown and should be the subject of future studies.

Neuropsychiatric Morbidity

Psychiatric or neurobehavioral morbidity following ARDS is common and includes depression, anxiety, and posttraumatic stress disorder (PTSD). It is unclear whether psychiatric disorders are a psychological reaction to extraordinary emotional and physiologic stress, sequelae of brain injury sustained due to ARDS and its treatment, or all of the above. The combination of medications (e.g., sedatives, narcotics, atypical antipsychotic medications, physiological changes, pain, altered sensory inputs, and an unfamiliar environment may contribute to emotional changes) [115–117]. The prevalence and severity of depression, anxiety, and PTSD in survivors of critical illness are variable [109, 117–119]. Depression occurs in a quarter [100] to over half of ARDS survivors [118]. For example, one study found 43% of ARDS patients had depression [120] and another study reported that over 50% of ARDS survivors had depression 1 year after intensive care unit treatment [118]. A longitudinal study found that ARDS survivors have moderate to severe depression (16 and 23%) and anxiety (24 and 23%) at 1 and 2 years, respectively [100, 105]. While data are accumulating regarding depression following ARDS, less is known regarding anxiety. Anxiety occurs in as many as 41% of ARDS survivors [121, 122]. A longitudinal ARDS study found that anxiety occurred in 24% at 1 and 2 years [100, 105].

The most commonly reported anxiety disorder in ARDS populations is posttraumatic stress disorder (PTSD). Posttraumatic stress disorder is the development of characteristic symptoms that occur following a traumatic event(s) where triggers include a serious personal threat experienced with helplessness and intense fear [123]. Schelling and colleagues were the first to report PTSD following ARDS and intensive care unit treatment [124]. Almost a third of the ARDS survivors reported impaired memory, bad dreams, anxiety, and sleeping difficulties after ICU discharge, with a prevalence rate of PTSD of 28%. Others have reported high rates of PTSD in ARDS survivors [125]. The prevalence of PTSD is as high as 38% [126] and persists years after intensive care unit discharge [109]. For example, PTSD has been reported at hospital discharge and 8 years after discharge [124]. One treatment study found that ARDS patients treated with hydrocortisone had a significant reduction in the development of PTSD compared to patients without treatment (19 vs. 59%).

ARDS Summary

The significant and sometimes permanent effects of ARDS on neurocognitive and neuropsychiatric functioning are increasingly recognized in the intensive care community regarding the importance of this issue; however, it is less recognized in the psychological or neuropsychological communities. Since the presence of cognitive impairment among ARDS survivors was first systematically identified a decade or so ago, progress has been made to study and better characterize this phenomenon. Neurocognitive impairments following ARDS are prevalent, occur in wide-ranging cognitive domains, and are functionally disruptive. Key questions remain unanswered with regard to determining mechanisms, risk factors, and the degree to which brain injuries associated with ARDS are amenable to rehabilitation.

Carbon Monoxide Poisoning

Carbon monoxide is a colorless, odorless gas produced as a by-product of combustion. Common sources of CO are internal combustion engines and faulty furnaces [127]. Carbon monoxide is the leading cause of poisoning injury and death worldwide [128] and the most common cause of accidental and intentional poisoning in the United States. Carbon monoxide results in approximately 40,000 emergency department visits [129] and 800 deaths per year in the United States [130]. The acute symptoms of CO poisoning are nonspecific and are similar to those associated with flu-like illness, which can make diagnosis of CO poisoning difficult. The brain and heart are particularly vulnerable to the pathological effects of CO [128].

Carbon monoxide poisoning results in focal and generalized neuroanatomical abnormalities observed on magnetic resonance (MR) and computed tomography (CT) imaging. Brain lesions following CO poisoning occur in the cortex [131], cerebellum [132], thalamus [133], and substantia nigra [134]. Lesions also occur in subcortical structures including white matter [135] and basal ganglia including the globus pallidus [136], caudate, and putamen [137, 138]. White matter hyperintensities occur in the periventricular and centrum semiovale or deep white matter regions [41]. In addition to neural lesions, carbon monoxide poisoning may cause neuronal cell loss and concomitant structural atrophy. Atrophy occurs in the fornix [139], hippocampus [37], and corpus callosum [42]. Generalized atrophy is also reported with brain volume reduction manifested by reduced gyral volume, increased sulcal space, and passive ventricular enlargement [37]. One study found CO-poisoned patients had atrophy in the putamen, caudate, and globus pallidus [140].

Neurocognitive Morbidity

Neurocognitive impairments commonly occur following CO poisoning in previously healthy individuals [113]. It is estimated that between 15 and 49% of individuals diagnosed with acute CO poisoning will develop neurocognitive sequelae [141]. A recent review of 18 group studies (N = 979) and 16 case studies (N = 35) found that 94% of the case studies and 33.9% of patients in the group studies had cognitive impairments [142]. Neurocognitive sequelae of CO poisoning are heterogeneous regarding onset, severity, neurocognitive domain affected, and the pattern of neurocognitive deficits is variable [37]. Carbon monoxide-related neurocognitive impairments include impaired memory [143], executive function [144], slow mental processing speed, decreased intellectual function [37], apraxia, aphasia, and agnosia [145]. Neurocognitive sequelae lasting 1 month [146, 147], or more [113, 148], occur in 25–50% of patients with loss of consciousness or COHb levels greater than 25% [147, 149].

Weaver and colleagues studied individuals with acute carbon monoxide poisoning who were compared for neurocognitive outcome following either hyperbaric oxygen or normobaric oxygen treatment in a randomized double blind clinical trial. The neurocognitive impairments were

significantly more frequent in the normobaric oxygen group (14.5%) as compared with the hyperbaric oxygen group (3.9%; $p = 0.03$) [113]. Hyperbaric oxygen therapy reduced neurocognitive impairments by 46% at 6-week outcome. Both groups improved with time, but the difference in neurocognitive impairments between the groups was maintained at 12 months [113]. Thus, treatments such as hyperbaric oxygen may potentially prevent or reduce the neurocognitive impairments that occur following CO poisoning. Risk factors for development of neurocognitive sequelae following acute CO poisoning were assessed using multivariable logistic regression in 163 CO-poisoned patients not treated with hyperbaric oxygen [150]. Of the 163 patients, 68 (42%) manifested neurocognitive sequelae [150]. The risk factors for development of neurocognitive sequelae were aged ≥ 36 years (odds ratio 2.6; $p = 0.005$) and CO exposure intervals ≥ 24 h (odds ratio 2.4; $p = 0.019$).

Neuropsychiatric Morbidity

Neuropsychiatric morbidity following CO poisoning are common and include depression, anxiety [151], obsessive and compulsive behavior, hallucinations [152], violent outbursts [145], elated mood [146], irritability, and decreased frustration tolerance [153]. The prevalence of CO-related neuropsychiatric morbidity ranges from 33 to 100% [37, 146, 154]. For example, a study by Jasper et al. found significant depression and anxiety in CO-poisoned patients: 45% at 6 weeks, 44% at 6 months, and 43% at 12 months [151]. Accidentally CO-poisoned patients are as likely as individuals with intentional CO poisoning to have depression and anxiety at 6 and 12 months. Patients with neurocognitive sequelae had a higher rate of depression and anxiety at 6 weeks compared to those with no neurocognitive sequelae, but not at 12 months. Patients with intentional CO poisoning have a higher rate of depression and anxiety at 6 weeks compared to accidental CO-poisoned patients, but not at 6 and 12 months. Although there was some subgroup improvement in depression and anxiety over time, the overall prevalence did not change. Hyperbaric oxygen therapy did not reduce the rate of depression and anxiety, but did reduce neurocognitive sequelae [151]. Consistent findings across CO studies to date are the high rate of depression and anxiety following CO poisoning. Similar prevalence rates of depression and anxiety occur in patients with traumatic brain injury and stroke [155], chronic obstructive pulmonary disease [156], acute respiratory distress syndrome [118], and acute myocardial infarction [157].

Accurately predicting outcomes in CO poisoning is difficult as markers of poisoning severity do not appear to predict outcomes. The severity of CO poisoning (measured by COHb level <15% without loss of consciousness) did not result in lower rates of neurocognitive sequelae in less severe CO-poisoned patients compared to patients with more severe poisoning (COHb >15% or loss of consciousness) [158]. Other studies have similarly found COHb levels are not related to neurocognitive deficits [139, 148, 159]. Furthermore, COHb levels and loss of consciousness are neither associated with nor predict clinical outcome [148, 160]. Neither symptoms of poisoning, neurocognitive impairment [37, 148], white matter hyperintensities [41], fornix atrophy [139] nor corpus callosum atrophy [42] is related to CO poisoning severity (e.g., loss of consciousness or COHb level).

CO Summary

Carbon monoxide poisoning may result in significant neurocognitive and neuropsychiatric sequelae which persist 12 months or more post-CO poisoning. Patients with neurocognitive sequelae have a higher rate of depression and anxiety at 6 weeks compared to those with no neurocognitive sequelae, but not at 12 months. Patients with intentional CO poisoning have a higher rate of depression and anxiety at 6 weeks compared to accidental CO-poisoned patients, but not at 6 and 12 months for those with intentional vs. accidental CO poisoning.

Hyperbaric oxygen therapy did not reduce the rate of depression and anxiety, but does reduce neurocognitive sequelae. Clinicians need to be aware of neurocognitive and neuropsychiatric morbidity following CO poisoning and remain vigilant about CO prevention.

Obstructive Sleep Apnea

As many as 18 million Americans suffer from obstructive sleep apnea (OSA). Obstructive sleep apnea is more common among men and individuals who snore, are overweight, have high blood pressure, or have physical abnormalities in their upper airways [161, 162]. The incidence of obstructive sleep apnea in this patient population is greater than 70% and increases in incidence as the body mass index increases [163]. Obstructive sleep apnea is a sleep disorder that results in the absence (apnea) or reduction (hypopnea) of airflow lasting at least 10 s despite normal respiratory efforts [164, 165]. Apnea and hypopnea result in hypoxemia and disrupt or fragment the sleep cycle. OSA affects an estimated 2–4% of the middle-aged population and the prevalence increases with age [166, 167]. Common symptoms include excessive daytime sleepiness (EDS), snoring, gasping or choking during sleep, headaches (especially upon waking), irritability, mood disturbance, personality change, motor restlessness, and neurocognitive complaints [168, 169]. OSA is associated with development of pulmonary hypertension, cardiovascular and cerebrovascular disease, hypertension, arrhythmias, and hormonal abnormalities in adults [170–172]. Although OSA is associated with medical morbidity such as cardiovascular disease, its most functionally disruptive effects in adults appear to be neurocognitive and neuropsychiatric in nature [173].

Neurocognitive Morbidity

Patients with OSA may exhibit impairments in vigilance, attention, memory, general intellectual functioning, problem solving [174], executive dysfunction, visuospatial abilities [175], and psychomotor speed [174, 176]. Impairments in memory and attention are the most commonly reported [174]. The neurocognitive and neuropsychiatric morbidities associated with OSA are associated with both intermittent hypoxia and sleep fragmentation [176–178]. Further, neurocognitive impairments appear to be exacerbated by the severity and duration of hypoxemia [176, 179], higher apnea hypopnea index scores [180], and sleep arousals [180]. There is continued discussion regarding which of the above aspects of OSA are associated with neurocognitive impairments. Previous research has reported both improvement [181] and no change in cognitive function following nCPAP [182].

A study comparing neuroimaging and neuropsychological findings in 14 patients with OSA and 20 CO-poisoned patients found hippocampal and generalized atrophy and neuropsychological impairments in CO poisoning and OSA [144]. Hippocampal atrophy occurred in both groups; however, increased VBR due to generalized cerebral atrophy (i.e., whole brain volume loss) was greater in the CO group [144]. The groups may differ due to moderation of tissue damage from intermittent hypoxia observed on OSA instead of a single episode of longer duration as occurs in CO poisoning. Therefore, the duration of hypoxia may account for the more severe generalized brain atrophy observed in the CO patients. Alternatively, the long-term effects of chronic intermittent hypoxia, such as occurs in OSA, may result in cerebral vascular problems, neurodegeneration, and neurocognitive deficits due to the cumulative effects of the hypoxia [183]. The CO group consistently performed worse on most neurocognitive measures while the OSA group had more selective neurocognitive impairments (predominately executive dysfunction and impaired memory). Improvement in neurocognitive function in OSA patients following 6 months of nasal continuous positive airway pressure (nCPAP) treatment was limited to executive function. Differences in test performance between the CO and OSA groups were more pronounced after the OSA group had received 6 months of nCPAP treatment [144]. Previous research has suggested that the hippocampus is more vulnerable to hypoxic injury than adjacent structures such as the parahippocampal gyrus or

temporal lobes [44]. Alternatively, injury to the prefrontal cortex, rather than medial temporal lobe structures may be responsible for the neurocognitive and neuropsychiatric morbidity associated with OSA [173].

Neuropsychiatric Morbidity

Neuropsychiatric morbidity including depression and anxiety are common in patients with OSA [164, 177]. The prevalence of depression is 24% [184] to as high as 45% of individual with OSA [185]. Depression is associated with fatigue, feeling tired, sleepiness, and reduced motivation in OSA patients [186]. A study that assessed the prevalence of neuropsychiatric disorders in 171 patients with sleep disorders (83% with OSA) found that 11% of patients had major depression, 7% minor depression, 3% panic disorder, and 12% anxiety [187]. The rate of depression and anxiety in OSA is higher than population norms [188]. Gender differences in neuropsychiatric disorders appear to be more common in women than men with OSA, similar to that observed in the general population. While the prevalence of OSA is higher in men, McCall et al. [189] found women with OSA had more common and more severe symptoms of depression and milder hypoxemia was associated with worse depression [189]. Nasal CPAP does not appear to improve depression or anxiety [190]. However, one study noted some improvement after long-term nCPAP therapy (approximately 1 year) [191]. In addition uvulopalatal flap surgery improved depression and anxiety in OSA patients [188].

OSA Summary

The neurocognitive and neuropsychiatric impairments are common in individuals with OSA with intermittent hypoxia. The neurocognitive and neuropsychiatric sequelae are similar to those observed in CO poisoning and other pulmonary disorders and are associated with acute hypoxia. Research is needed to determine mechanisms, risk factors, and treatment for OSA-associated neuropsychiatric morbidity.

Rehabilitation Outcomes Following Anoxia

Outcome following severe anoxia is variable, however, the majority of patients have poor outcome [3]. Information regarding the effects of rehabilitation on neurocognitive outcome following anoxic brain injury is limited. Survival rates following post-anoxic coma range from 9 to 40% [192, 193]. Patients who survived anoxic coma regain mobility and ability to perform activities of daily living but not neurocognitive [194]. Outcome following anoxic coma was not predicted by age, sex, site of resuscitation, cause of anoxia, nor presence of post-anoxic seizures [193]. A single case suggested that "relatively" good neurocognitive function 1 month post-anoxic coma suggesting some recovery and benefit of rehabilitation [194]; however, this finding is not generally reported.

Groswasser et al. [195] followed a group of 31 comatose patients following anoxic brain injury, 13 were independent in activities of daily living, 2 regained premorbid neurocognitive functioning, and 4 returned to work, but only 1 to the same job. Patients who were younger with shorter coma had "relatively better outcomes". The differences in recovery may be due to the interaction of the diffuse damage and delayed cell death, but not the etiology of the anoxic brain injury. Armengol [195] reported eight individuals with severe anoxia who were treated in a long-term neurobehavioral rehabilitation program. Six of the eight individuals had poor outcome with significant impairments in attention, executive function, memory, reasoning, language, visuospatial, and motor skills, while two patients exhibited mild neurocognitive impairments. In-patient rehabilitation appears to improve functional status, with individuals who had higher Functional Independence Measure scores on admission had the best outcome;

however, few resumed their previous jobs and level of function [196].

Little is known regarding rehabilitation outcomes in many hypoxic disorders. Further, it is unknown if the severity of hypoxia/hypoxemia is related to rehabilitation outcomes. For example, there are no studies that assess rehabilitation after ARDS. A few studies assess rehabilitation following COPD and OSA. As noted above, pulmonary rehabilitation consisting of exercise, education, and psychosocial counseling improved psychomotor speed and mental flexibility but not memory and concentration in COPD patients [75]. One study found lung volume reduction surgery plus pulmonary rehabilitation (exercise and education) compared to pulmonary rehabilitation alone and found improved neurocognitive and neuropsychiatric function in the lung volume reduction group [197]. It remains to be determined if rehabilitation on neurocognitive and neuropsychiatric morbidity in patients with hypoxia/hypoxemic disorders is effective.

Conclusions

Patients with respiratory disorders and concomitant brain injury exhibit both diffuse and focal brain injury and concomitant neurocognitive and neuropsychiatric sequelae. Respiratory disorders are heterogeneous and include cardiac or respiratory arrest, COPD, CO poisoning, OSA, and ARDS. The associated hypoxic or anoxic brain injury results in focal and diffuse neuropathologic lesions and atrophy including hippocampal, basal ganglia, cerebellar, and white matter abnormalities. Neuropsychological impairments include generalized intellectual decline, memory deficits, decreased attention, visuo-perceptual, problem solving, executive dysfunction, and decreased mental processing speed. Further, these individual may experience a high rate of neurobehavioral disorders including euphoria, irritability, hostility, depression, and anxiety and personality changes. Thus, respiratory disorders and their associated hypoxia and ischemia result in significant neurological structural and functional abnormalities, and neuropsychological impairments.

Questions remain regarding risk factors for development of neurocognitive and neuropsychiatric sequelae, precise mechanisms of brain injury, and whether there are treatments that will prevent or ameliorate these sequelae. Further, physicians and other health-care providers often are unaware and do not assess for the presence of neurocognitive impairments. A recent study found 42% of ARDS survivors underwent rehabilitation therapy, but most were not evaluated for neurocognitive impairments, with only 12% identified as having neurocognitive impairments by the clinical rehabilitation team [100]. Neurocognitive impairments appear to be under recognized by both intensivists and rehabilitation providers. Studies suggest that in non-critical care clinical settings many physicians fail to recognize (or assess) neurocognitive impairment in 35–90% of patients [198]. Increased identification of neurocognitive impairments patients with respiratory disorders may benefit patients by raising physician awareness potentially leading to increased referrals to rehabilitation specialists, neuropsychologists, speech and language therapists, and other health-care providers who can provide interventions such as cognitive remediation. It should be noted that there is a paucity of data regarding interventions for neurocognitive impairments or the potential benefit of such interventions in critically ill patients.

Today, it is recognized that neurocognitive sequelae are common in patients with respiratory disorders, especially those with concomitant hypoxia. The neurocognitive impairments are long lasting, and may be permanent, although substantial research needs to be done to fully understand the prevalence, nature, risk factors, etiology, and nuances of the neurocognitive and neuropsychiatric impairments in this population. Referrals to colleagues in rehabilitation medicine, psychiatric, neurology, or psychology would facilitate evaluation of potential areas of concern. Attention to proximal determinants and possible interventions to prevent neurocognitive morbidity are warranted and should be an

emphasis in outcomes research. Such research will likely yield valuable insights into identification, the natural history, prognosis, and potential mechanisms of the neurocognitive deficits and guide the development, implementation, and fine-tuning of intervention programs.

References

1. Geocadin RG, Buitrago MM, Torbey MT, et al. Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. Neurology. 2006;67:105–08.
2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation. 2001;104:2158–63.
3. Bachman D, Katz DI. Anoxic-hypotensive brain injury and encephalitis. In: Mills VM, Cassidy JW, Katz DI, editors. Neurologic rehabilitation: a guide to diagnosis, prognosis, and treatment planning. Malden, MA: Blackwell Science Ltd; 1997. pp. 145–76.
4. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. J Int Neuropsychol Soc. 1995;1:501–09.
5. Johnson SC, Bigler ED, Burr RB, Blatter DD. White matter atrophy, ventricular dilation, and intellectual functioning following traumatic brain injury. Neuropsychology. 1994;8:307–15.
6. Bigler ED, Alfano M. Anoxic encephalopathy: neuroradiological and neuropsychological findings. Arch Clini Neuropsychol. 1988;3:383–96.
7. Hopkins RO, Kesner RP, Goldstein M. Item and order recognition memory in subjects with hypoxic brain injury. Brain Cogn. 1995;27:180–201.
8. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 1986;6:2950–67.
9. Lezak MD. Neuropsychological assessment. 3rd ed. New York, NY: Oxford University Press; 1995.
10. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. J Int Neuropsychol Soc. 1995;1:501–09.
11. Farah M. Visual agnosia. Cambridge, MA: MIT Press; 1990.
12. Barat M, Blanchard J, Carriet D. Les troubles neuropsychologiques des anozies cerebrales prolongees. Ann Readapt Med Phys. 1989;32:657–68.
13. Parkin AJ, Miller J, Vincent R. Multiple neuropsychological deficits due to anoxic encephalopathy: a case study. Cortex. 1987;23:655–65.
14. Wilson BA. Cognitive functioning of adult survivors of cerebral hypoxia. Brain Inj. 1996;10:863–74.
15. Ganong WF. Review of medical physiology. 10th ed. Los Altos, CA: Lange Medical Publications; 1981.
16. Hicks SP. Vascular pathophysiology and acute and chronic oxygen deprivation. In: Minckler J, editor. Pathology of the nervous system, vol.0 1. New York, NY: McGraw-Hill; 1968. pp. 341–50.
17. Biagas K. Hypoxic-ischemic brain injury: advancements in the understanding of mechanisms and potential avenues for therapy. Curr Opin Pediatr. 1999;11:223–8.
18. Kuroiwa T, Okeda R. Neuropathology of cerebral ischemia and hypoxia: recent advances in experimental studies on its pathogenesis. Pathol Int. 1994;44:171–81.
19. Brierley JB, Graham DI. Cerebral complications of hypotensive anaesthesia in a healthy adult. J Neurol Neurosurg Psychiatr. 1984;25:24–30.
20. Blennow M, Ingvar M, Lagercrantz H, et al. Early [18F] FDG positron emission tomography in infants with hypoxic-ischaemic encephalopathy shows hypermetabolism during the postasphyctic period. Acta Paediatr. 1995;84:1289–95.
21. Martin RL, Lloyd HG, Cowan AI. The early events of oxygen and glucose deprivation: setting the scene for neuronal death? Trends Neurosci. 1994;17:251–7.
22. Siesjo BK, Bengtsson F, Grampp W, Theander S. Calcium, excitotoxins, and neuronal death in the brain. Ann N Y Acad Sci. 1989;568:234–51.
23. Chalela JA, Wolf RL, Maldjian JA, Kasner SE. MRI identification of early white matter injury in anoxic-ischemic encephalopathy. Neurology. 2001;56:481–5.
24. Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. Neuroscience. 1991;40:599–636.
25. Schurr A, Rigor BM. The mechanism of cerebral hypoxic-ischemic damage. Hippocampus. 1992;2:221–8.
26. Johnston MV, Nakajima W, Hagberg H. Mechanisms of hypoxic neurodegeneration in the developing brain. Neuroscientist. 2002;8:212–20.
27. Lutz PL, Nilsson GE. The brain without oxygen causes of failure and mechanisms for survival. Austin, TX: R.G. Landes Company; 1994.
28. Siesjo BK. Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab. 1981;1:155–85.
29. Schurr A, Lipton P, West CA, Rigor BM. The role of energy in metabolism and divalent cations in the neurotoxicity of excitatory amino acids in vitro. In: Krieglstein J, editor. Pharmacology of cerebral ischemia. Boca Raton, FL: CRC Press; 1990. pp. 217–26.
30. Steller H. Mechanisms and genes of cellular suicide. Science. 1995;267:1445–9.

31. Beilharz EJ, Williams CE, Dragunow M, et al. Mechanisms of delayed cell death following hypoxic-ischemic injury in the immature rat: evidence for apoptosis during selective neuronal loss. Brain Res Mol Brain Res. 1995;29:1–14.
32. Miyamoto O, Auer RN. Hypoxia, hyperoxia, ischemia, and brain necrosis. Neurology. 2000;54:362–71.
33. Gray FD Jr, Horner GJ. Survival following extreme hypoxemia. J Am Med Assoc. 1970;211:1815–17.
34. Rie MA, Bernad PG. Prolonged hypoxia in man without circulatory compromise fail to demonstrate cerebral pathology. Neurology. 1980;30:433.
35. Bachevalier J, Meunier M. Cerebral ischemia: are the memory deficits associated with hippocampal cell loss? Hippocampus. 1996;6:553–60.
36. Caine D, Watson JD. Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J Int Neuropsychol Soc. 2000;6:86–99.
37. Gale SD, Hopkins RO, Weaver LK, et al. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj. 1999;13:229–43.
38. Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. Neuron. 2003;38:127–33.
39. Manns JR, Hopkins RO, Reed JM, et al. Recognition memory and the human hippocampus. Neuron. 2003;37:171–80.
40. Mascalchi M, Petruzzi P, Zampa V. MRI of cerebellar white matter damage due to carbon monoxide poisoning: case report. Neuroradiology. 1996;38:S.
41. Parkinson RB, Hopkins RO, Cleavinger HB, et al. White matter hyperintensities and neuropsychological outcome following carbon monoxide poisoning. Neurology. 2002;58:1525–32.
42. Porter SS, Hopkins RO, Weaver LK, et al. Corpus callosum atrophy and neuropsychological outcome following carbon monoxide poisoning. Arch Clin Neuropsychol. 2002;17:195–204.
43. Press GA, Amaral DG, Squire LR. Hippocampal abnormalities in amnesic patients revealed by high-resolution magnetic resonance imaging. Nature. 1989;341:54–7.
44. Hopkins RO, Tate DF, Bigler ED. Anoxic versus traumatic brain injury: amount of tissue loss, not etiology, alters cognitive and emotional function. Neuropsychology. 2005;19:233–42.
45. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1:480–4.
46. Hopkins RO, Myers CE, Shohamy D, et al. Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. Neuropsychologia. 2004;42:524–35.
47. Lishman WA. Organic psychiatry: the psychological consequences of cerebral disorder. 3rd ed. Oxford: Blackwell Science Ltd.; 1998.
48. Bahrke MS, Schukitt-Hale B. Effects of altitude on mood, behaviour, and cognitive functioning. A review. J Sports Med. 1993;16:97–125.
49. Li XY, Wu XY, Fu C, et al. Effects of acute mild and moderate hypoxia on human mood state. Space Med Med Eng (Beijing). 2000;13:1–5.
50. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2007;4:502–06.
51. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970–2002. J Am Med Assoc. 2005;294:1255–9.
52. Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? Chest. 2003;123:1684–92.
53. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370:741–50.
54. Tirimanna PR, van Schayck CP, den Otter JJ, et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract. 1996;46:277–81.
55. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. Chest. 2002;121:121S–6S.
56. Leidy NK. Functional performance in people with chronic obstructive pulmonary disease. Image J Nurs Sch. 1995;27:23–34.
57. Hodgkin JE, Petty TL. Chronic obstructive pulmonary disease: current concepts. Philadelphia, PA: W.B. Saunders Company; 1987.
58. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85:751–8.
59. Prigatano GP, Parsons O, Wright E, et al. Neuropsychological test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease. J Consult Clin Psychol. 1983;51:108–16.
60. Prigatano GP, Wright EC, Levin D. Quality of life and its predictors in patients with mild hypoxemia and chronic obstructive pulmonary disease. Arch Intern Med. 1984;144:1613–9.
61. Grant I, Heaton R, McSweeny A, et al. Neuropsychological findings in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1982;142:1470–6.
62. Heaton RK, Grant I, McSweeny AJ, et al. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med. 1983;143:1941–7.
63. Kozora E, Filley CM, Julian LJ, Cullum CM. Cognitive functioning in patients with chronic obstructive pulmonary disease and mild hypoxemia compared with patients with mild Alzheimer disease and normal controls. Neuropsychiatry Neuropsychol Behav Neurol. 1999;12:178–83.

64. Fix AJ, Golden CJ, Daughton D, et al. Neuropsychological deficits among patients with chronic obstructive pulmonary disease. Int J Neurosci. 1982;16:99–105.
65. Krop HD, Block AJ, Cohen E. Neuropsychologic effects of continuous oxygen therapy in chronic obstructive pulmonary disease. Chest. 1973;64:317–22.
66. Incalzi RA, Gemma A, Marra C, et al. Chronic obstructive pulmonary disease. An original model of cognitive decline. Am Rev Respir Dis. 1993;148:418–24.
67. Etnier J, Johnston R, Dagenbach D, et al. The relationships among pulmonary function, aerobic fitness, and cognitive functioning in older COPD patients. Chest. 1999;116:953–60.
68. Grant I, Prigatano GP, Heaton RK, et al. Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. Arch Gen Psychiatry. 1987;44:999–1006.
69. Incalzi RA, Gemma A, Marra C, et al. Verbal memory impairment in COPD: its mechanisms and clinical relevance. Chest. 1997;112:1506–13.
70. Kozora E, Emery C, Kaplan RM, et al. Cognitive and psychological issues in emphysema. Proc Am Thorac Soc. 2008;5:556–60.
71. Wilson DK, Kaplan RM, Timms RM, Dawson A. Acute effects of oxygen treatment upon information processing in hypoxemic COPD patients. Chest. 1985;88:239–43.
72. Orth M, Kotterba S, Duchna K, et al. [Cognitive deficits in patients with chronic obstructive pulmonary disease (COPD)]. Pneumologie. 2006;60:593–9.
73. Carter R, Nicotra B, Clark L, et al. Exercise conditioning in the rehabilitation of patients with chronic obstructive pulmonary disease. Arch Phys Med Rehabil. 1988;69:118–22.
74. Dustman RE, Ruhling RO, Russell EM, et al. Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiol Aging. 1984;5:35–42.
75. Emery CF, Leatherman NE, Burker EJ, MacIntyre NR. Psychological outcomes of a pulmonary rehabilitation program. Chest. 1991;100:613–7.
76. Kaptein AA, Brand PL, Dekker FW, et al. Quality-of-life in a long-term multicentre trial in chronic nonspecific lung disease: assessment at baseline. The Dutch CNSLD Study Group. Eur Respir J. 1993;6:1479–84.
77. Graydon J, Ross E. Patients with chronic respiratory disease: what influences level of functioning? Proceedings of the 12th work group meeting and international nursing research conference. Frankfurt, Germany: WENR; 1989. pp. 276–80.
78. Salik Y, Ozalevli S, Cimrin AH. Cognitive function and its effects on the quality of life status in the patients with chronic obstructive pulmonary disease (COPD). Arch Gerontol Geriatr. 2007;45:273–80.
79. Cully JA, Graham DP, Stanley MA, et al. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. Psychosomatics. 2006;47:312–9.
80. Hynninen KM, Breitve MH, Wiborg AB, et al. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. J Psychosom Res. 2005;59:429–43.
81. Gift AG, McCrone SH. Depression in patients with COPD. Heart Lung. 1993;22:289–97.
82. Porzelius J, Vest M, Nochomovitz M. Respiratory function, cognitions, and panic in chronic obstructive pulmonary patients. Behav Res Ther. 1992;30:75–7.
83. Gift AG, Cahill CA. Psychophysiologic aspects of dyspnea in chronic obstructive pulmonary disease: a pilot study. Heart Lung. 1990;19:252–7.
84. McSweeney AJ, Heaton RK, Grant I, et al. Chronic obstructive pulmonary disease; socioemotional adjustment and life quality. Chest. 1980;77:309–11.
85. Lahdensuo A, Ojanen M, Ahonen A, et al. Psychosocial effects of continuous oxygen therapy in hypoxaemic chronic obstructive pulmonary disease patients. Eur Respir J. 1989;2:977–80.
86. Borak J, Sliwinski P, Piasecki Z, Zielinski J. Psychological status of COPD patients on long term oxygen therapy. Eur Respir J. 1991;4:59–62.
87. Vögele C, von Leupoldt A. Mental disorders in chronic obstructive pulmonary disease (COPD). Respir Med. 2008;102:764–73.
88. Rubenfeld GD, Doyle RL, Matthay MA. Evaluation of definitions of ARDS. Am J Respir Crit Care Med. 1995;151:1270–1.
89. Rubenfeld GD. Epidemiology of acute lung injury. Crit Care Med. 2003;31:S276–84.
90. Abel SJ, Finney SJ, Brett SJ, et al. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). Thorax. 1998;53:292–4.
91. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS):1983–1993. J Am Med Assoc. 1995;273:306–9.
92. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
93. Petty TL, Ashbaugh DG. The adult respiratory distress syndrome: clinical features and factors influencing prognosis and principles of management. Chest. 1971;60:233–9.
94. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial

coordination. Consensus Committee. J Crit Care. 1994;9:72–81.
95. Davidson TA, Caldwell ES, Curtis JR, et al. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. J Am Med Assoc. 1999;281:354–60.
96. Hopkins RO, Weaver LK, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160:50–6.
97. Weinert CR, Gross CR, Kangas JR, et al. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med. 1997;156:1120–8.
98. Russell JA, Singer J, Bernard GR, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. Crit Care Med. 2000;28:3405–11.
99. Hopkins RO, Gale SD, Weaver LK. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. Brain Inj. 2006;20:263–71.
100. Hopkins RO, Weaver LK, Collingridge D, et al. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171:340–7.
101. Graham DI, Gennarelli TA, McIntosh TK. Trauma. In: Graham DI, Lantos PI, editors. Greenfield's neuropathology, vol. 2. 7th ed. London: Edward Arnold; Hodder Headline Group; 2002. pp. 823–82.
102. Fries M, Dembinski R, Bickenbach J, et al. Brain damage in a porcine model of acute lung injury. Am J Respir Crit Care Med. 2004;169:A350.
103. Hopkins RO, Suchyta MR, Jephson A, et al. Hyperglycemia and neurocognitive outcome in ARDS survivors. Proc Am Thorac Soc. 2005; Abstracts 2:A36.
104. Jackson JC, Gordon SM, Hart RP, et al. The association between delirium and cognitive decline: a review of the empirical literature. Neuropsychol Rev. 2004;14:87–98.
105. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. J Int Neuropsychol Soc. 2004;10:1005–17.
106. Starr JL, Whalley LJ. Drug induced dementia. Drug Saf. 1994;11:310–7.
107. Hopkins RO, Jackson JC, Wallace CJ. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation. International Neuropsychological Society, 33rd Annual Meeting Program and Abstract Book. St. Louis, MO, 2005:61.
108. Al-Saidi F, McAndrews MP, Cheung AM, et al. Neuropsychological sequelae in ARDS survivors. Am J Respir Crit Care Med. 2003;167:A737.
109. Rothenhäusler HB, Ehrentraut S, Stoll C, et al. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen Hosp Psychiatry. 2001;23:90–6.
110. Suchyta MR, Hopkins RO, White J, et al. The incidence of cognitive dysfunction after ARDS. Am J Respir Crit Care Med. 2004;169:A18.
111. Marquis K, Curtis J, Caldwell E, et al. Neuropsychological sequelae in survivors of ARDS compared with critically ill control patients. Am J Respir Crit Care Med. 2000;161:A383.
112. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 2003;31:1226–34.
113. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002;347:1057–67.
114. Newman M, Kirchner J, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402.
115. McCartney JR, Boland RJ. Anxiety and delirium in the intensive care unit. Crit Care Clin. 1994;10:673–80.
116. Skodol AE. Anxiety in the medically ill: nosology and principles of differential diagnosis. Semin Clin Neuropsychiatry. 1999;4:64–71.
117. Szokol JW, Vender JS. Anxiety, delirium, and pain in the intensive care unit. Crit Care Clin. 2001;17:821–42.
118. Angus DC, Musthafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med. 2001;163:1389–94.
119. Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med. 2003;168:1457–61.
120. Weinert CR, Gross CR, Kangas JR, et al. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med. 1997;156:1120–8.
121. Granja C, Teixeira-Pinto A, Costa-Pereira A. Quality of life after intensive care – evaluation with EQ-5D questionnaire. Intensive Care Med. 2002;28:898–907.
122. Kapfhammer HP, Rothenhäusler HB, Krauseneck T, et al. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. Am J Psychiatry. 2004;161:45–52.
123. Gersons BP, Carlier IV. Post-traumatic stress disorder: the history of a recent concept. Br J Psychiatry. 1992;161:742–8.
124. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med. 1998;26:651–9.
125. Stoll C, Kapfhammer HP, Rothenhäusler HB, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose posttraumatic stress disorder in ARDS patients after

intensive care treatment. Intensive Care Med. 1999;25:697–704.
126. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med. 2001;29:573–80.
127. Weaver LK. Carbon monoxide poisoning. Crit Care Clin. 1999;15:297–317.
128. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning – a public health perspective. Toxicology. 2000;145:1–14.
129. Hampson NB, editor. Hyperbaric oxygen therapy: 1999 committee report revised. Kensington, MD: Undersea and Hyperbaric Medical Society; 1999.
130. Piantadosi CA. Carbon monoxide poisoning. N Engl J Med. 2002;347:1054–5.
131. Uchino A, Hasuo K, Shida K, et al. MRI of the brain in chronic carbon monoxide poisoning. Neuroradiology. 1994;36:399–401.
132. Bruno A, Wagner W, Orrison WW. Clinical outcome and brain MRI four years after carbon monoxide intoxication. Acta Neurol Scand. 1993;87:205–9.
133. Chang KH, Han MH, Kim HS, et al. Delayed encephalopathy after acute carbon monoxide intoxication: MR imaging features and distribution of cerebral white matter lesions. Radiology. 1992;184:117–22.
134. Kawanami T, Kato T, Kurita K, Sasaki H. The pallidoreticular pattern of brain damage on MRI in a patient with carbon monoxide poisoning. J Neurol Neurosurg Psychiatr. 1998;64:282.
135. Watanabe N, Nohara S, Matsuda H, et al. Statistical parametric mapping in brain single photon computed emission tomography after carbon monoxide intoxication. Nucl Med Commun. 2002;23:355–66.
136. Mori E, Yamashita H, Takauchi S, Kondo K. Isolated athymhormia following hypoxic bilateral pallidal lesions. Behav Neurol. 1996;9:17–23.
137. Martinez Bermejo A, Arcas J, Roche MC, et al. [Bilateral hypodensity of the basal ganglia. Clinico-evolutionary correlation in children]. Rev Neurol. 2001;33: 101–11.
138. Hsiao CL, Kuo HC, Huang CC. Delayed encephalopathy after carbon monoxide intoxication – long-term prognosis and correlation of clinical manifestations and neuroimages. Acta Neurol Taiwan. 2004;13:64–70.
139. Kesler SR, Hopkins RO, Weaver LK, et al. Verbal memory deficits associated with fornix atrophy in carbon monoxide poisoning. J Int Neuropsychol Soc. 2001;7:640–6.
140. Pulsipher DT, Hopkins RO, Weaver LK. Basal ganglia volumes following carbon monoxide poisoning: a prospective longitudinal study. Undersea Hyperb Med. 2006;33:245–56.
141. Myers RA, DeFazio A, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol. 1998;54:555–67.
142. Hopkins RO, Woon FL. Neuroimaging, cognitive, and neurobehavioral outcomes following carbon monoxide poisoning. Behav Cogn Neurosci Rev. 2006;5:141–55.
143. Hopkins RO, Weaver LK, Kesner RP. Long term memory impairments and hippocampal magnetic resonance imaging in carbon monoxide poisoned subjects. Undersea Hyperb Med. 1993;20:15.
144. Gale SD, Hopkins RO. Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. J Int Neuropsychol Soc. 2004;10:60–71.
145. Garland H, Pearce J. Neurological complications of carbon monoxide poisoning. Q J Med. 1967;36:445–55.
146. Min SK. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide intoxication. Acta Psychiatr Scand. 1986;73:80–6.
147. Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet. 1989;2:414–9.
148. Thom SR, Taber RL, Mendiguren II, et al. Delayed neuropsychologic sequelae after carbon monoxide poisoning: prevention by treatment with hyperbaric oxygen. Ann Emerg Med. 1995;25:474–80.
149. Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. Anaesth Intensive Care. 1992;20:311–6.
150. Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med. 2007;176:491–7.
151. Jasper BW, Hopkins RO, Duker HV, Weaver LK. Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. Cogn Behav Neurol. 2005;18:127–34.
152. Lee MS, Marsden CD. Neurological sequelae following carbon monoxide poisoning clinical course and outcome according to the clinical types and brain computed tomography scan findings. Mov Disord. 1994;9:550–8.
153. Hopkins RO, Weaver LK, Bigler ED. Psychological/ emotional changes following carbon monoxide poisoning. Undersea Hyperb Med. 1997;24:20.
154. Smith JS, Brandon S. Morbidity from acute carbon monoxide poisoning at three-year follow-up. Br Med J. 1973;1:318–21.
155. Fleminger S, Oliver DL, Williams WH, Evans J. The neuropsychiatry of depression after brain injury. Neuropsychol Rehabil. 2003;13:65–87.

156. Bornson S, Claypoole K, McDonald GJ. Depression and chronic obstructive pulmonary disease: treatment trials. Semin Clin Neuropsychiatry. 1998;3:115–30.
157. Schleifer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. Arch Intern Med. 1989;149:1785–9.
158. Chambers CA, Hopkins RO, Weaver LK, Key C. Cognitive and affective outcomes of more severe compared to less severe carbon monoxide poisoning. Brain Inj. 2008;22:387–95.
159. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomized controlled clinical trial. Med J Aust. 1999;170:203–10.
160. Camporesi EM. Hyperbaric oxygen therapy: a committee report. Bethesda, MD: Undersea and Hyperbaric Medical Society; 1996.
161. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165:1217–39.
162. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162:893–900.
163. Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation: more evidence for routine screening for obstructive sleep apnea before weight loss surgery. Am Surg. 2008;74:834–8.
164. Guilleminault C, Cummiskey J, Motta J, Lynne-Davies P. Respiratory and hemodynamic study during wakefulness and sleep in myotonic dystrophy. Sleep. 1978;1:19–31.
165. Kelly DA, Claypoole KH, Coppel DB. Sleep apnea syndrome: symptomatology, associated features, and neurocognitive correlates. Neuropsychol Rev. 1990;1:323–42.
166. Bliwise DL, King AC, Harris RB. Habitual sleep durations and health in a 50–65 year old population. J Clin Epidemiol. 1994;47:35–41.
167. Young S, Geelhoed GC, Stick SM, et al. The effect of age on oxygen desaturation during histamine inhalation challenge in normal infants. Pediatr Pulmonol. 1993;16:158–62.
168. Agency for Health Care Policy and Research. Systematic review of the literature regarding the diagnosis of sleep apnea. Summary, Evidence Report/Technology Assessment: Number 1. Rockville, MD, 1998
169. Guilleminault C, van den Hoed J, Mitler MM. Clinical overview of the sleep apnea syndromes. In: Guilleminault C, Dement WC, editors. sleep apnea syndromes. New York, NY: Alan R. Liss; 1978. pp. 1–12.
170. Harding SM. Complications and consequences of obstructive sleep apnea. Curr Opin Pulm Med. 2000;6:485–9.
171. Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. 2002;165:677–82.
172. Doran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001;163:685–9.
173. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11:1–16.
174. Findley LJ, Barth JT, Powers DC, et al. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. Chest. 1986;90:686–90.
175. Kales A, Caldwell A, Cadieux R, et al. Severe obstructive sleep apnea-II: associated psychopathology and psychosocial consequences. J Chronic Dis. 1985;38:427–34.
176. Bedard MA, Montplaisir J, Richer F, et al. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol. 1991;13:950–64.
177. Barth JT, Findley LJ, Zillmer EA, et al. Obstructive sleep apnea, hypoxemia, and personality functioning: implications for medical psychotherapy assessment. Adv Med Psychother. 1993;6:29–36.
178. Valencia-Flores M, Bliwise DL, Guilleminault C, et al. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. J Clin Exp Neuropsychol. 1996;18:197–210.
179. Naegele B, Thouvard V, Pepin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep. 1995;18:43–52.
180. Cheshire K, Engleman H, Deary I, et al. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med. 1992;152:538–41.
181. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax. 1997;52:114–9.
182. Barbe F, Mayoralas LR, Duran J, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. Ann Intern Med. 2001;134:1015–23.
183. Neubauer JA. Invited review: physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol. 2001;90:1593–9.
184. Guilleminault C, Eldridge FL, Tilkian A, et al. Sleep apnea syndrome due to upper airway obstruction: a review of 25 cases. Arch Intern Med. 1977;137:296–300.
185. Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of

obstructive sleep apnea: reversal with nasal continuous positive airway pressure. J Clin Psychiatry. 1989;50:348–51.
186. Schwartz DJ, Karatinos G. For individuals with obstructive sleep apnea, institution of CPAP therapy is associated with an amelioration of symptoms of depression which is sustained long term. J Clin Sleep Med. 2007;3:631–5.
187. DeZee KJ, Hatzigeorgiou C, Kristo D, Jackson JL. Prevalence of and screening for mental disorders in a sleep clinic. J Clin Sleep Med. 2005;1:136–42.
188. Li HY, Huang YS, Chen NH, et al. Mood improvement after surgery for obstructive sleep apnea. Laryngoscope. 2004;114:1098–102.
189. McCall WV, Harding D, O'Donovan C. Correlates of depressive symptoms in patients with obstructive sleep apnea. J Clin Sleep Med. 2006;2:424–6.
190. Borak J, Cieslicki JK, Koziej M, et al. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. J Sleep Res. 1996;5:123–7.
191. Ramos Platon MJ, Espinar Sierra J. Changes in psychopathological symptoms in sleep apnea patients after treatment with nasal continuous positive airway pressure. Int J Neurosci. 1992;62:173–95.
192. Bedell SE, Delbanco TL, Cook EF, Epstein FH. Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med. 1983;309:569–76.
193. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. J Am Med Assoc. 1985;253:1420–6.
194. Kaplan CP. Anoxic-hypotensive brain injury: neuropsychological performance at 1 month as an indicator of recovery. Brain Inj. 1999;13:305–10.
195. Groswasser Z, Cohen M, Costeff H. Rehabilitation outcome after anoxic brain damage. Arch Phys Med Rehabil. 1989;70:186–8.
196. Schmidt JG, Drew-Cates J, Dombovy ML. Anoxic encephalopathy: outcome after inpatient rehabilitation. Neurorehabil Neural Repair. 1997;11:189–95.
197. Kozora E, Emery CF, Ellison MC, et al. Improved neurobehavioral functioning in emphysema patients following lung volume reduction surgery compared with medical therapy. Chest. 2005;128:2653–63.
198. Callahan CM, Hendrie HC, Tierney WM. Documentation and evaluation of cognitive impairment in elderly primary care patients. Ann Intern Med. 1995;122:422–9.

Chapter 10

Cognitive Functioning in Asthma: Central Nervous System and Other Influences

Farzin Irani

Introduction

Asthma was officially named by Hippocrates who used the Greek word for "panting." Toward the end of the last century, it was believed to be a psychosomatic illness with emotionally induced wheezing and "smother mother" type derogatory terms used in the literature to suggest that asthma resulted from a coddled but controlled childhood [1]. Now, asthma is clearly recognized as a chronic lung disease characterized by airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. Asthma inflames and narrows the airways in the lungs, which can make breathing difficult and trigger symptoms of coughing, wheezing, shortness of breath, and chest tightness or pain. When symptoms increase or get more intense, an asthma attack, flare, or exacerbation occurs that can be fatal. Asthma is a global health problem that affects 300 million individuals of all ages, ethnic groups, and countries and causes 250,000 premature deaths each year [2]. There is growing recognition of the role of the central nervous system in asthma and its cognitive sequelae in recent years. There are also key sociodemographic variables that are associated with notable health disparities. This chapter will begin by briefly describing asthma and its health burden. This will be followed by a focus on cognitive functioning in asthma, its possible cognitive neuroscience-based underpinnings in the central nervous system, and its interaction with various environmental and clinical variables. Clinical and treatment implications for the cognitive burden associated with asthma will be discussed along with suggestions for future directions.

Asthma as a Public Health Problem

According to 2016 National Health Interview Survey data, current asthma prevalence in the United States is 8.3% in children and adults [3]. During 2008–2013, there was an $80 billion total cost of asthma per year that included $3 billion in losses due to missed work and school days, $29 billion due to asthma-related mortality, and $50.3 billion in medical costs [4]. Asthma has no cure but can be controlled with asthma medications, allergen avoidance, immunotherapy, smoking cessation, oxygen therapy, pulmonary rehabilitation, and physical exercise. It affects all ages; though there may be some differences between asthma beginning in childhood and adult-onset asthma, the general features of asthma are similar in adults and children [5]. There are sex-related differences: boys typically present with more severe asthma and higher hospitalization rates than girls, but this pattern reverses in adults [6, 7].

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Although asthma affects all ethnic groups, its burden is disproportionately shared by certain minority and socioeconomically disadvantaged groups. The prevalence of childhood asthma among Puerto Ricans (19.2%) and Non-Hispanic Blacks (12.7%) is higher than among Non-Hispanic Whites (8%) and Mexican Americans (6.4%). Asthma mortality rates in children and adults are nearly eightfold and threefold higher in Non-Hispanic Blacks than in Non-Hispanic Whites, respectively [8–11]. These groups also experience rates of emergency department visits and hospitalizations that are much higher than differences in asthma prevalence would suggest. These health disparities are especially notable in low socioeconomic or urban settings, likely due to multiple factors operating at the individual and community levels [10, 12]. Known or potential environmental and lifestyle risk factors proposed to account for disparities in asthma or asthma morbidity include cigarette smoking and environmental tobacco smoke, prematurity or low birth weight, allergen exposure, indoor and outdoor air pollution, diet, obesity, vitamin D insufficiency, viral respiratory infections (e.g., due to crowding), poor adherence to prescribed treatment, and stress (acute and chronic) [10]. These environmental and lifestyle risk factors may interact with the multiple genes with various polymorphisms and loci that are linked to the development of asthma related chronic inflammation and its manifestations [13]. Heritability estimates for asthma vary between 35% and 95%, and genome-wide association studies show associations between variation in genes encoding epithelial cell-derived cytokines (interleukin-33 and thymic stromal lymphopoietin) and the *IL1RL1* gene encoding the IL-33 receptor (ST2), which plays a role in innate immune response pathways that promote activation and differentiation of T-helper 2 cells [14]. Variation at the 17q21 asthma locus which encodes the *ORMDL3* and *GSDML* genes have also been proposed; however, given the complexity in the asthma phenotype, ongoing genetics studies continue to try and unravel epigenetic mechanisms.

Cognitive Functioning

Cognition is not typically assessed in primary care or asthma specialty clinics, yet, there is increased risk for cognitive impairment and associated behavioral problems in asthma [12, 15–17].

Children and Adolescents

One of the earliest neuropsychological investigations in asthma was in 1980 and showed that 20 children with severe asthma (ages 9–14) performed significantly worse than children without asthma on the Halstead Neuropsychological Test Battery for Children [18]. This study found that seven of the children in the asthma group were classified as neuropsychologically impaired, while there were none in the non-asthma group. More specifically, the Trail Making, Tactual Performance, and the WISC Mazes tests were found to be most sensitive in discriminating between groups. While this was a small sample, five of those who were classified as neuropsychologically impaired reported experiencing periods of unconsciousness and had "turned blue" during their severe asthma attacks, leading the authors to implicate the role of loss of consciousness and cyanosis that can occur during asthma attacks as adversely influencing neuropsychological performance. Later, in a larger sample (n = 939) of children with mild to moderate asthma (aged 6–12) enrolled in clinical centers of the Childhood Asthma Management Program, different levels of attention were associated with differences in neuropsychological functioning as assessed by the Wechsler Intelligence scales, Wood-Johnson-Revised, Wide Range Assessment of Memory and Learning, and the Gordon Diagnostic Systems Continuous Performance Test [19]. While the focus of this study was to look at developmental trajectories of children's performance on a CPT task and not to compare asthma groups to normative samples, this early study highlighted age-related associations between

attention and other neuropsychological variables in children with asthma.

Since then, several other studies have shown that attention deficit hyperactivity disorder (ADHD) rates are elevated in children with asthma who are in otherwise in good health [20–22]. A large study using the National Survey of Children's Health found that based on interviews conducted with parents/guardians to ascertain physical, emotional, and behavioral health of 102,353 randomly selected children (aged 0–17), asthma groups were twice as likely to have ADHD compared to those without asthma, and rates were threefold greater in those with more severe asthma [22]. Children with asthma were also more likely to have learning disabilities and behavioral disorders, even after controlling for socioeconomic factors. More severe asthma was associated with higher rates of associated problems such as missing school, being bullied and abusing drugs. While this was a survey study that did not measure cognitive functioning, it highlighted comorbidity between asthma, ADHD, academic, and behavioral problems.

Given the increased risk of academic and behavioral problems in poor, often urban, children with asthma, several other researchers have highlighted the additional burden conferred by socioeconomic disadvantage in those with asthma [12, 23, 24]. One survey study showed that inner city preschoolers with asthma had notably lower school readiness scores [25]. In this study of 1058 children from an urban school system, parent-reported school readiness was measured by a survey of readiness skills needed for school entrance (e.g., ability to read simple words, count objects, identify colors). Children with asthma who had limitation of activity (i.e., more severe asthma) were rated as having significantly lower school readiness skills and needed "extra help" compared to children without asthma. This was even after controlling for possible confounds such as the child's sex, Medicaid insurance (as a proxy for poverty), caretaker education, and participation in full-time day care and preschool programs. The authors hypothesized that these children may be less likely to effectively participate in exposure to early educational activities due to medical or behavioral problems, and that developmental problems for urban children with asthma begin before school entry. Another national survey extended these findings to later school years and again found that amongst other poor academic indicators, grade failures were three times higher among lower income children with asthma than children with asthma from higher income families [23].

Using performance-based measures in 31 children (aged 7–11), lower executive functioning scores (as measured by a battery of tests of inhibition, updating, shifting, and planning) were found in children with persistent and poorly controlled asthma [26]. General features of asthma tend to be similar in children and adults, with persistent pulmonary abnormalities noted in both populations [5, 27, 28]. Yet, asthma control tends to be much poorer in younger children, even after adjusting for age-dependent differences in treatment [29]. Goals of asthma treatment are not always attained in younger children, possibly due to undertreatment, insufficient adherence to preventive measures, and lower parental expectations about asthma control [29]. Children and adolescents with severe or poorly controlled asthma who overuse beta-agonist-metered dose inhalers also show lower scores on tests of intelligence and academic achievement [30].

Adults and Older Adults

Beyond childhood, the natural course of asthma over the lifespan tends to be episodic. While some children with asthma may experience remission from their symptoms during the teenage years, longitudinal studies suggest that for many, asthma continues into adult life with possible social (e.g., poor school or work attendance) and economic (e.g., employment) consequences [31]. Much later in adulthood, prevalence of cognitive impairment typically increases with age in part due to chronic illnesses such as hypertension, diabetes mellitus, and chronic obstructive pulmonary disorder (COPD) [32, 33]. Asthma affects 9% of adults over the age of

65, and theoretically may pose additional threats to cognitive functioning in older adults due to the possibility of cumulative effects of chronic inflammation and exposure to periods of hypoxia [33].

Older adults with frequent exacerbations and poor control of asthma show compromised arterial oxygen saturation and selective cognitive impairments [34–37]. Older adults are faced with additional risks such as increased exposure to common airborne allergens and high reservoir dust allergens in their homes, which can influence asthma severity and lower quality of life [34]. Even after controlling for demographic characteristics, self-rated health status, inhaled corticosteroid use, and lung function, one cross-sectional, retrospective analysis of 1380 older adults with asthma (aged 55+) found a 78% increased risk of global cognitive impairment on the Montreal Cognitive Assessment (MoCA) [38]. Environmental influences were not controlled in this study, but better control of asthma itself has been associated with improvements on the Mini-Mental State Exam (MMSE) in older adults with good cognition, mild cognitive impairment and dementia [39, 40]. Poor asthma control and airway obstruction also showed modest, but inconsistent, associations with cognitive function in older adults when compared to normative samples [33]. One prospective, observational cohort included individuals (aged 60 +) with physician-diagnosed asthma who completed measures of processing speed (pattern comparison, Trail Making Test A), executive functioning (Trail Making Test B), attention and working memory (letter number sequencing), immediate and delayed recall (Wechsler Memory Scale), word fluency (animal naming), and global cognition (MMSE). Poor asthma control and forced expiratory lung volumes less than 70% were significantly associated with all cognitive measures in univariate analyses, but not after adjusting for age, sex, race/ethnicity, education, English proficiency, general health status, and comorbidities.

One small study with adults (n = 24) looked at daytime cognitive performance (as measured by the Trail Making Test, Paced Auditory Serial Addition Test, Rey Auditory Verbal Learning Test and subtests of the Wechsler Adult Intelligence Scale) of stable outpatients who took their usual medications and also had nocturnal asthma (i.e., awakened by nocturnal wheeze/cough) [41]. Cognitive deficits were related to short-term sleep deprivation associated with nocturnal awakenings due to asthma symptoms.

Yet, evidence from a few studies has indicated that there may not be cognitive or academic compromise associated with asthma [31, 42, 43]. An older study of 25 children with severe asthma (aged 10–13) found that when compared to 25 matched controls without any chronic health conditions, there was no significant difference in performance on a battery of tests that included the Memory of Semantic Units Test (picture recall, word recognition, and word recall), Bourdon-Vos task (continuous selective attention task), and school performance (mean school grades for arithmetic, linguistic and "all other intellectual topics") [44]. A systematic review of 12 studies also showed no difference between children with asthma and those without asthma in academic achievement as measured by either standardized achievement tests, grade point averages or grade failures in the US, or test scores on school assessments in Europe [31]. One sample of 138 homeless parents and their 4–6-year-old children who resided in emergency shelters showed that while these children had elevated lifetime rates of asthma, they did not show cognitive deficits on measures of intelligence (Wechsler Preschool and Primary Scales of Intelligence and Peabody Picture Vocabulary Test), executive functioning (e.g., Simon Says Task, Dimensional Change Card Sort, Peg-Tapping task, Computerized Pointing Stroop Task, Dinky Toys Task, Gift Delay task), or teacher behavioral rating scales [12, 45]. This study did not control for asthma severity and included a sample with low rates of medication use and high rates of emergency room visits and hospitalizations.

In older adults, a large sample of 203 individuals (aged 64+), mild to moderate chronic airway disease without hypoxemia was not shown to carry excess risk of cognitive dysfunction as measured by the MMSE [39, 46]. A recent meta-analysis of 10 studies indicated

that well-managed asthma during pregnancy was not associated with negative developmental outcomes in children (e.g., increased risk for autism or intellectual disability) [47].

Summary

In order to address these inconsistencies in the literature and empirically review the neuropsychological data associated with asthma, we recently conducted a meta-analysis that inquired whether cognitive deficits are present in individuals with asthma, and if so, which cognitive domains and sociodemographic, illness, and study-related variables moderated effects [48]. In a sample of 2017 individuals with asthma and 2131 matched, healthy comparison participants from 15 studies, whose ages spanned the lifespan, we found that there were cognitive impairments associated with asthma; effect sizes were in the small to medium range (−0.26 to −0.40). Cognitive effects were global, and strongest (medium-sized) effects were found for broader, multifactorial functions involving academic achievement and executive functioning, and additional impact of asthma was found for processing speed, global intellect, attention, visuospatial functioning, language, learning, and memory. Severity of disease was a key moderator, with the greatest cognitive deficits found in those with severe asthma. Consistent with the aforementioned health disparities, those from vulnerable socioeconomic and ethnic minority backgrounds showed the greatest asthma-related cognitive compromise. Effects were independent of the type of population (child vs. adult), type of study (norm-referenced vs. control-referenced), or reported use of oral or inhaled corticosteroid medications.

In addition, cognitive deficits were higher in boys than girls [48]. Asthma prevalence is higher in boys than girls in childhood and then reverses in adolescence when prevalence of asthma in adult women is higher than in men [49]. Boys typically experience more severe asthma and higher hospitalization rates than girls [6, 7]. This could be influenced by differential growth of lung/airway size, and immunologic differences since forced expiratory lung volume rates tend to be higher in girls and young women than in boys and young men [49]. In adulthood, women with asthma have different symptom profiles than men, greater healthcare utilization, more frequent use of short-acting beta-agonists, differences in perception of airflow obstruction, and increased bronchial hyperresponsiveness [50]. Hormonal determinants have been suggested as playing a role in the development and outcomes of the allergic immune response in asthma [49], but much more work is needed in this area to further understand these sex effects.

Overall, despite the presence of methodological concerns surrounding inconsistent control of important sociodemographic and clinical moderators and mediators in this literature, studies that have attempted to examine neuropsychological functioning in asthma suggest the presence of cognitive deficits.

Cognitive Neuroscience Theory

The presence of cognitive deficits in a lung disorder invokes exploration of possible central nervous system (CNS) influences. A couple of mechanisms regarding the role of the CNS are plausible: (1) mechanisms related to blood oxygen saturation as measured by peripheral circulation and (2) mechanisms involving neural and endocrine signaling pathways [1].

Influences from Hypoxia

Without oxygen, cellular function is disrupted and there can be damage to cells; brain function depends on a continuous supply of oxygen [51]. Hypoxia, hypoxemia, or anoxia can cause neuronal injury and impact biochemical and structural changes. Neural changes from hypoxia in vulnerable brain regions with high metabolic demands (e.g., neocortex, hippocampus, basal ganglia, frontal regions, thalamus) can cause cognitive dysfunction. Neuronal injury can be

manifested structurally by lesions and neuronal atrophy, and functionally as neurocognitive and neuropsychiatric impairments.

Baseline arterial hemoglobin oxygen saturation can be compromised in asthma [37, 52, 53]. Oxygen saturation during acute asthma attacks can dip to persistently low levels and influence neural abnormalities [54]. External oxygen is typically given to alleviate hypoxia if saturation falls below 92% [55]. The impact of intermittent hypoxia on cognitive functions has been reliably shown in other lung disorders (e.g., COPD) and other conditions (e.g., sleep-disordered breathing) [56–58]. Adverse impact of chronic or intermittent hypoxia on development, behavior, and academic achievement has also been reported in many well-designed and controlled studies in children, even at mild levels of oxygen desaturation [59]. In asthma, severe asthma attacks can cause some degree of diffuse cerebral hypoxia and lead to loss of consciousness, cyanosis, anoxic brain damage, or even death [60, 61].

Neural substrates. The study of the neural substrates of hypoxia in asthma is in its infancy. Emerging structural and functional neurophenotypes have implicated vulnerability in key brain regions susceptible to hypoxia [62–64]. The cells of the CA1 region of the hippocampus are particularly vulnerable to loss of oxygen. Animal models have been used to examine effects of chronic asthma-induced intermittent brain hypoxia on learning and memory. This work has shown problems in learning and memory that coincide with synaptic structure damage and impaired long-term potentiation in the CA1 region of the hippocampus [65]. This damage has not been attenuated by treatment in these studies. Specifically, intermittent hypoxia during chronic asthma resulted in down-regulation of c-fos, Arc, and neurogenesis, which was responsible for impairment of learning and memory in immature mice on the Morris Water Maze test.

In humans, there are rare neuroimaging studies of asthma, but one recent study of middle-aged men with asthma showed significantly smaller total right and left hippocampal volumes compared to those without asthma, after controlling for demographic characteristics [66]. Interestingly, the association of asthma with smaller hippocampal volumes was significant among males but not females. Another recent structural magnetic resonance imaging and proton magnetic resonance spectroscopy (MRS) study in otherwise healthy adults with and without asthma (n = 40), found associations between hippocampal volume, metabolites, cognitive function and extent of asthma control [67]. Specifically, individuals with asthma showed lower hippocampal *N*-acetylaspartate (NAA) metabolites compared to healthy controls, and poorer cognitive function (measured by the MoCA) that was associated with reduced disease control. NAA is considered the most reliable MRS marker of neural injury in mild cognitive impairment, and lower levels of NAA could predict future cognitive decline [68, 69].

One functional magnetic resonance imaging study examined responses on an asthma-specific Stroop task for asthma-related words (e.g., wheeze, cough, choke) and neutral words in individuals with asthma [70]. Asthma-related words elicited changes in activation in the anterior cingulate cortex and insula, regions which process information related to physiological responses and emotions including threat responses. The authors suggested a neural basis for emotion-induced modulation of airway disease in asthma by indicating that these brain regions may be hyperresponsive to disease-specific emotional and physiological signals and contribute to the dysregulation of peripheral processes in inflammation. Those with asthma who experience greater CNS activation (e.g., due to chronic stress) may have a greater or less well-regulated inflammatory response which can lead to more severe disease and cognitive consequences [71].

Neural-Endocrine Signaling and Stress

The potential role of CNS-mediated activation of neural and endocrine signaling pathways (e.g., the sympathetic nervous system and the hypothalamic–pituitary–adrenal or HPA axis) in response to stress/perceived threat and subsequent alterations of peripheral physiologic processes (including the inflammatory biology of the lung) has received some consideration in the asthma literature [1].

According to this view, the brain can make asthma better through a placebo response or make it worse in stressful situations and environments that lead to asthma exacerbations. Chronic or acute stress can modulate inflammation and influence airflow, symptoms, chronicity, treatment response, and exacerbations [1]. Acute stress can lead to increased cortisol which can suppress airway inflammation, while chronic stress might mediate cortisol resistance and enhance inflammation [71].

Sociodemographic influences. Impoverished environments are particularly at increased risk for stress-based influences, which can initiate immune responses that lead to airway inflammation and worsen asthma [72]. Brain and body systems involved in stress and body management involving the HPA axis impact inflammation and atopic disease [73–75]. Socioeconomically disadvantaged communities often face acute and chronic stressors which can enhance expression of inflammation and airflow obstruction. This has been shown to reduce responsiveness to corticosteroid and bronchodilator medications, based on mechanistic changes in the regulation of beta-adrenergic and glucocorticoid responsiveness [71]. Poor asthma control or more severe disease can then increase the risk for hypoxic events, and interact with mechanisms involving stress, health behaviors, health literacy, illness cognitions, access to care, and disease management variables (e.g., medication adherence, trigger avoidance) [8].

This cascade of events may be particularly impactful for ethnic groups with asthma who tend to carry the greatest health burden, have disproportionately higher prevalence rates, are at greater risk for more severe disease that leads to greater hospitalizations and higher death rates, and also carry the greatest asthma-related cognitive burden as well [12, 48, 76, 77]. Ethnicity is linked to ancestry and may affect asthma independent of socioeconomic status (SES), possibly through genetic variation; however, SES may also impact asthma independently of ethnicity or have synergistic effects due to chronic stress that influences quality of care and exposure to environmental and lifestyle risk factors [10]. Many ethnic groups have experienced systemic injustices that may create mistrust of the healthcare arena due to historic events (e.g., Tuskegee syphilis experiment), and impact healthcare utilization behaviors [78]. Disparities in asthma morbidity and mortality are further influenced by access to quality health care, with a tendency for many minority children to receive fragmented and episodic care from multiple healthcare providers, reduced prescriptions for preventive asthma medications, and fewer prescriptions filled for asthma due to increases in Medicaid copayments [72]. These effects are particularly pronounced for minority children from low income or urban backgrounds who are less likely to afford or receive appropriate preventive medications, and experience behavioral and psychosocial stressors that may impede the family's ability to adhere to treatment recommendations [6, 12, 45]. These variables are likely to have a compounding effect on CNS-mediated mechanisms that impact outcomes.

Clinical Influences

There are a number of other clinical influences on asthma and its management that may interact with the aforementioned CNS-based mechanisms to influence asthma-related cognitive impairment. This includes extent of asthma control, severity of asthma, medication side effects, and comorbid conditions.

Asthma Control

Asthma control is the degree to which the goals of treatment are met (e.g., prevent symptoms/exacerbations, maintain normal lung function and activity levels). Extent of asthma control is measured by symptom control (limitations of daily activity, shortness of breath, sleep disturbance, use of rescue medication), frequency of exacerbations, seriousness of exacerbations (hospitalization, intensive care unit stay, or need for mechanical ventilation), and extent of limitations in lung airflow [79]. Asthma control is

typically measured with the Asthma Control Test or ACT [80], a self-report measure to assess asthma control over the past month. The Asthma Control Questionnaire or ACQ assesses asthma control over the previous week and captures both self-report and lung function by spirometry [81]. Limitations in lung flow are measured using peak expiratory flow rate (PEFR) in an expiration of breath, or forced expiratory volume (FEV), which measures volume rather than the rate of exhaled breath. Methods such as arterial blood gas analysis and oximetry (which measure amount of oxygen found in the hemoglobin of red blood cells) have been used less frequently due to cost and time, while chest radiography is currently used as a last resort to examine the chest with X-ray technology if there are failures to respond to other interventions or mixed results on prior assessments.

Poor control of asthma as measured by these methods has been associated with an increased number of days lost from school, exacerbations, days in hospital, more frequent contacts with the healthcare system, increased risk of obesity, reduced daily physical activity, and poorer cardiovascular fitness [82]. Inadequate asthma control has been further associated with nocturnal awakenings, sleep-disordered breathing and mood disturbance all of which can have an adverse impact on cognition [83, 84]. One review indicated that in children, poor control is associated with greater attentional problems and learning disabilities amongst other disease-related outcomes [82]. Yet, one prospective, observational cohort study indicated that older, inner city adults with poor asthma control and airway obstruction (as measured by the ACQ) did not show poor performance on various measures of cognitive function including the Trail Making Test Part A and B, letter number sequencing, immediate and delayed recall on the Wechsler Memory Scale, animal naming, and the MMSE [33]. Another sample of 359 adults (aged 60+) showed MMSE scores that increased significantly as asthma control increased, even in those with dementia and mild cognitive impairment [39]. Clearly, the literature examining the relationship between asthma control and cognitive functioning is limited, and more work is needed for further lifespan considerations.

Asthma Severity

Asthma severity is the intrinsic intensity of the disease process and dictates steps to initiate treatment. In both pediatric and adult populations, assessment and diagnosis of severe asthma have been difficult. The National Asthma Education and Prevention Program and Global Initiative for Asthma guidelines divided asthma severity based on lung function (FEV), daytime and nocturnal symptoms, and frequency of rescue bronchodilator use; however, researchers have challenged whether this captures asthma's heterogeneous characteristics, and have proposed additional clinical phenotypes [85]. While the debate about various phenotypes continues, it seems that a subset of ~10% of those with asthma have severe disease which remains difficult to treat and accounts for a relatively large proportion of resource expenditure [22, 79, 86]. Severe asthma includes those who are treatment resistant and also includes those with untreated asthma, which can be a problem in communities where current therapies are either not widely available, affordable or accessible [2, 22, 86]. More recent international guidelines have tried to define this severe asthma group as one that "requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy" [79].

Longitudinal epidemiological data has found that severe asthma is associated with increased morbidity, a high degree of comorbid conditions, allergic sensitization, frequent exacerbations, very poor control of asthma, and reduced lung function [87]. These can all increase risk for CNS-mediated cognitive compromise. In addition, this severe group also suffers from significant quality of life impairments such that patients feel broadly limited in life (e.g., daily chores, career, relationships),

burdened by treatment (e.g., concern about side-effects of oral corticosteroids), feel alone due to frightening experiences of breathlessness and exacerbations, and strive to adapt using both positive strategies (acquiring self-management skills) and less positive strategies (avoidance of physical exertion) to adjust to living with the severity of their disease [88]. Yet, there has been very little focus on the impact of severe asthma on cognitive functioning. Our previously described meta-analysis showed that of all the sociodemographic and clinical moderators, the greatest cognitive deficits were associated with more severe asthma ($\delta = -0.58$) [48]. Clearly there is a need to target this population to increase understanding of brain–behavior relationships in this group.

Medication Side-Effects

Asthma is typically treated with short-acting or long-term medications. Bronchodilators open up the bronchial tubes to allow a higher volume of air to be taken in. Quick-relief medications are used to treat acute symptoms and include short-acting beta2-adrenoceptor agonists (SABA) as well as anticholinergic medications for those with moderate or severe symptoms. Long-term control medications are used to prevent further exacerbations and include corticosteroids, typically in inhaled forms, or long-acting beta-adrenoceptor agonists (LABA) or leukotriene receptor antagonists. Inhaled corticosteroids are often recommended if SABAs are being used three times a week, at least, and desired control is still not achieved. Oral corticosteroids are additionally used for acute asthma episodes and when full control has not been achieved despite other interventions.

Acute high-dose use of corticosteroid "bursts" for asthma symptom exacerbations are associated with impairments in memory and reduced hippocampal volumes, as is chronic corticosteroid therapy at more modest doses [54, 89, 90]. Specifically, oral corticosteroid use has established dose-dependent influences on both poorer global cognitive function (measured by the MoCA) and reduced hippocampal volume, with those receiving chronic corticosteroids showing reductions in hippocampal NAA [54, 91, 92]. An exploratory analysis paradoxically found positive effects of inhaled corticosteroids on hippocampal metabolites in those with asthma, leading the authors to suggest that in contrast to use of high systemic doses of corticosteroids, local administration of this medication in small doses may lead to better control of asthma and help avoid some of the adverse CNS asthma sequelae [67]. Further study of medication manipulations may help to understand the relationship between cognition, brain structure and function, and deleterious dose effects of corticosteroid use in those with various asthma phenotypes.

Comorbid Conditions

There are a number of comorbidities in asthma, with prevalence rates that vary among studies, probably because it remains unclear whether the comorbidities are directly or indirectly related to asthma [93]. More commonly discussed co morbidities include atopic dermatitis (commonly known as eczema) and allergic rhinitis (commonly known as hay fever) [94]. These conditions occur more commonly in individuals with asthma and could influence sleep disturbance and use of sedating antihistamines, both of which can adversely impact cognition. Bidirectional relationships between elevated rates of sleep-disordered breathing in individuals with asthma have been noted, which can amplify hypoxia risk and adversely impact school performance, health, and functioning [83, 84]. Specifically, this bidirectionality suggests that those with asthma are more likely to develop sleep disorders and likewise, children with sleep-disordered breathing are more likely to develop asthma [69]. Studies have also demonstrated an association between asthma and obesity, diabetes mellitus, and cardiovascular disease, but the direction and mechanism of causality remain unclear and could be due to systemic inflammation (related to metabolic syndrome) or to epiphenomenon due to lifestyle factors [93].

Elevated levels of depression and anxiety are also found in asthma, especially in early-onset and urban populations [16, 22], [95–98]. One study noted that the rate of depression in patients with asthma was 22/1000 person years (compared to 13/1000 for those without asthma) and these patients had higher mortality rates and health-seeking behaviors that were independent of asthma severity or oral corticosteroid use [99]. A recent meta-analysis of 15 studies (n = 7443) found that youth with asthma display a prevalence rate for anxiety disorders that is more than three times higher than the prevalence in healthy youth [100]. Psychological difficulties may be related to increased stress-induced inflammatory responses and lead to poor adherence to asthma treatment and thus poor outcomes [99]. Asthma may impact mood and other psychological factors that indirectly affect cognitive and brain functioning.

Neuropsychological Treatment Implications

In addition to considering the role of the aforementioned sociodemographic and clinical influences, there are several considerations from a neuropsychological perspective. The effects of preexisting or co-existing asthma is rarely considered in forensic neuropsychology causality determinations, despite the need to evaluate asthma's impact on diagnosis, causality, functional impact determination, prognosis, rehabilitation, and recommendations for both clinical and forensic practice [101]. Neuropsychologists can identify cognitive deficits that could impact perceptual accuracy of asthma symptoms and influence appropriate asthma management. For instance, those who are more capable of attending for longer periods of time and have better executive functioning skills may monitor their asthma with more accurate formulations and execute more effective plans for multi-stepped asthma symptom recognition, response, and monitoring [102]. Consistent with this, as indicated previously, there have been lower executive functioning scores (inhibition, updating, shifting and planning) in school-age children (7–11) with persistent asthma that has been linked to poor controller medication adherence [26]. Given prior work highlighting the role of the hippocampus and learning and memory-based deficits in asthma [65–67], there needs to be greater understanding of whether medication adherence difficulties are due to difficulties in remembering to take the maintenance medications, without which there could be increased risk of exacerbation and compounding of cognitive deficits. Older adults with asthma are particularly vulnerable to increased self-reported memory lapses in medication management of asthma [35, 39, 40]. These cognitive difficulties could then impact asthma control and severity, with adverse impact on cognition. These are areas ripe for neuropsychological intervention.

Yet, cognition is not typically assessed in asthma primary care or specialty clinics and deserves further attention. Further conversation with primary care and pulmonary specialists could help increase efforts toward gathering more cognitive data that considers the various variables that have been discussed here to help improve outcomes in vulnerable groups. Ideally, collaboration with cognitive specialists (e.g., clinical neuropsychologists, school psychologists) can provide information about biopsychosocial contributions, further examine the nature and extent of any cognitive impairments that may be present, and assist with therapeutic plans for asthma management. Cognitive specialists can serve as good liaisons with systems (e.g., school, primary care, specialty care) and provide individualized recommendations focused on providing cognitive and learning-based accommodations/supports, reducing school/work-related absences, preventing cognitive decline, managing comorbid conditions (e.g., mood and anxiety disorders), and providing strategies to improve asthma self-care and management. Given associations between cognition and real-world outcomes such as academic achievement and employability, there is much to be gained by assessing and intervening early for asthma-related cognitive burden.

Conclusions

Overall, asthma is a chronic condition with significant health-related, social and economic consequences to individuals, families, and society. Its burden is disproportionately placed on low-resource socioeconomic, urban, and ethnic minority groups. Cognitive functioning is not typically assessed in primary care or asthma specialty clinics; however, there are global cognitive deficits in this population, with effects in the small to medium range. Possible CNS-based mechanisms may be related to the impact of intermittent or chronic hypoxia on vulnerable brain regions, and CNS-mediated activation of neural-endocrine signaling pathways in response to acute or chronic stress. There are environmental influences along with clinical variables that adversely impact asthma and its management such as poor asthma control, more severe disease, side-effects of corticosteroid use, and presence of comorbid conditions. Neuropsychologists can play a role in considering the influences of these variables as well as key sociodemographic influences (e.g., age, sex, socioeconomic status) that influence the nature and extent of cognitive impairments associated with asthma and its management.

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References

1. Kline JN, Rose RM. Central nervous system influences in asthma. Adv Exp Med Biol. 2014;795:309–19.
2. Bousquet J, Mantzouranis E, Cruz AA, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926–38.
3. Prevention CfDCa, Environmental NCf, Health. Data, statistics, and surveillance: asthma surveillance data. https://www.cdc.gov/asthma/asthmadata.htm. Published 2016. Accessed.
4. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008-2013. Ann Am Thorac Soc. 2018;15(3):348–56.
5. Ségala C, Priol G, Soussan D, et al. Asthma in adults: comparison of adult-onset asthma with childhood-onset asthma relapsing in adulthood. Allergy. 2000;55(7):634–40.
6. Halterman JS, Conn KM, Forbes-Jones E, Fagnano M, Hightower AD, Szilagyi PG. Behavior problems among inner-city children with asthma: Findings from a community-based sample. Pediatrics. 2006;117(2):E192–9.
7. McConnochie KM, Russo MJ, McBride JT, Szilagyi PG, Brooks AM, Roghmann KJ. Socioeconomic variation in asthma hospitalization: excess utilization or greater need? Pediatrics. 1999;103(6):e75.
8. CDC. Asthma Facts – CDC's National Asthma Control Program Grantees. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention; 2013.
9. Barnett Nurmagambetov. Costs of asthma in the United States: 2002–2007. J Allergy Clin Immunol. 2011;127(1):145–52.
10. Forno E, Celedón JC. Health disparities in asthma. Am J Respir Crit Care Med. 2012;185(10):1033–5.
11. Leong AB, Ramsey CD, Celedón JC. The challenge of asthma in minority populations. Clin Rev Allergy Immunol. 2012;43(1–2):156–83.
12. Cutuli J, Herbers J, Rinaldi M, Masten A, Oberg C. Asthma and behavior in homeless 4- to 7-year-olds. Pediatrics. 2010;125(1):145–51.
13. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun. 2006;7(2):95–100.
14. Ober C, Yao T-C. The Genetics of Asthma and Allergic Disease: A 21(st) Century Perspective. Immunol Rev. 2011;242(1):10–30.
15. Austin JK, Huberty TJ, Huster GA, Dunn DW. Academic achievement in children with epilepsy or asthma. Dev Med Child Neurol. 1998;40(4):248–55.
16. Mrazek D, Schuman W, Klinnert M. Early asthma onset: Risk of emotional and behavioral difficulties. J Child Psychol Psychiatry. 1998;39(2):247–54.
17. Dunleavy R, Baade LE. Neuropsychological correlates of severe asthma in children 9–14 years old. J Consult Clin Psychol. 1980;48:214–219.
18. Dunleavy RA, Baade LE. Neuropsychological correlates of severe asthma in children 9-14 years old. J Consult Clin Psychol. 1980;48(2):214–9.
19. Annett RD, Bender BG, Gordon M. Relating children's attentional capabilities to intelligence, memory, and academic achievement: a test of construct specificity in children with asthma. Child Neuropsychol. 2007;64–85.
20. Biederman J, Milberger S, Faraone SV, Guite J, Warburton R. Associations between childhood asthma and ADHD: issues of psychiatric comorbidity and familiality. J Am Acad Child Adolesc Psychiatry. 1994;33(6):842–8.

21. Grizenko N, Osmanlliu E, Fortier M, Joober R. Increased Risk of Asthma in Children with ADHD: Role of Prematurity and Maternal Stress during Pregnancy. J Can Acad Child Adolesc Psychiatry. 2015;24(2):109–15.
22. Blackman JA, Gurka MJ. Developmental and behavioral comorbidities of asthma in children. J Dev Behav Pediatr. 2007;28(2):92–9.
23. Fowler MG, Davenport MG, Garg R. School functioning of United-States children with asthma. Pediatrics. 1992;90(6):939–44.
24. Freudenberg N, Feldman CH, Clark NM, Millman EJ, Valle I, Wasilewski Y. The impact of bronchial asthma on school attendance and performance. J School Health. 1980;50(9):522–6.
25. Halterman JS, Montes G, Aligne CA, Kaczorowski JM, Hightower AD, Szilagyi PG. School readiness among urban children with asthma. Ambul Pediatr. 2001;1(4):201–5.
26. Sonney J, Insel KC. Exploring the intersection of executive function and medication adherence in school-age children with asthma. J Asthma. 2018;1–11.
27. Kelly WJW, Hudson I, Raven J, Phelan PD, Pain MCF, Olinsky A. Childhood Asthma and Adult Lung Function. Am Rev Respir Dis. 1988;138(1):26–30.
28. Blackhall MI. Ventilatory Function in Subjects with Childhood Asthma who have Become Symptom Free. Arch Dis Child. 1970;45(241):363–6.
29. Kuehni CE, Frey U. Age-related differences in perceived asthma control in childhood: guidelines and reality. Eur Respir J. 2002;20(4):880–9.
30. Beausoleil JL, Weldon DP, McGeady SJ. Beta 2-agonist metered dose inhaler overuse: psychological and demographic profiles. Pediatrics. 1997;99 (1):40–3.
31. Milton B, Whitehead M, Holland P, Hamilton V. The social and economic consequences of childhood asthma across the lifecourse: a systematic review. Child Care Health Dev. 2004;30(6):711–28.
32. Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med. 2013;29 (4):753–72.
33. Ray M, Sano M, Wisnivesky JP, Wolf MS, Federman AD. Asthma control and cognitive function in a cohort of elderly adults. J Am Geriatr Soc. 2015;63(4):684–91.
34. Huss K, Naumann PL, Mason PJ, et al. Asthma severity, atopic status, allergen exposure, and quality of life in elderly persons. Ann Allergy Asthma Immunol. 2001;86(5):524–30.
35. Banerjee DK, Lee GS, Malik SK, Daly S. Underdiagnosis of asthma in the elderly. British J Dis Chest. 1987;81(1):23–9.
36. Braman SS. Growing old with asthma: what are the changes and challenges? Expert Rev Respir Med. 2010;4(2):239–48.
37. Moss M, Franks M, Briggs P, Kennedy D, Scholey A. Compromised arterial oxygen saturation in elderly asthma sufferers results in selective cognitive impairment. J Clin Exper Neuropsychol. 2005;139–50.
38. Caldera-Alvarado G, Khan DA, Defina LF, Pieper A, Brown ES. Relationship between asthma and cognition: the cooper center longitudinal study. Allergy. 2013;68(4):545–8.
39. Bozek A, Krajewska J, Jarzab J. The improvement of cognitive function in patients with bronchial asthma after therapy. J Asthma. 2005;47:1148–52.
40. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. J Asthma. 2010;47(2):162–5.
41. Fitzpatrick MF, Engleman H, Whyte KF, Deary IJ, Shapiro CM, Douglas NJ. Morbidity in nocturnal asthma: sleep quality and daytime cognitive performance. Thorax. 1991;46(8):569–73.
42. Annett R, Aylward EH, Lapidus J, Bender BG, DuHamel T. Neurocognitive functioning in children with mild and moderate asthma in the childhood asthma management program. The Childhood Asthma Management Program (CAMP) Research Group. J Allergy Clin Immunol. 2000;105(4):717–24.
43. Taras H, Potts-Datema W. Childhood asthma and student performance at school. J Sch Health. 2005;75(8):296–312.
44. Rietveld S, Colland VT. The impact of severe asthma on schoolchildren. J Asthma. 1999;36 (5):409–17.
45. Cutuli JJ, Herbers JE, Lafavor TL, Ahumada SM, Masten AS, Oberg CN. Asthma and adaptive functioning among homeless kindergarten-aged children in emergency housing. J Health Care Poor Underserved. 2014;25(2):717–30.
46. Incalzil RA, Bellia V, Maggi S, et al. Mild to moderate chronic airways disease does not carry an excess risk of cognitive dysfunction. Aging Clin Exp Res. 2002;14(5):395–401.
47. Whalen OM, Karayanidis F, Murphy VE, Lane AE, Mallise CA, Campbell LE. The effects of maternal asthma during pregnancy on child cognitive and behavioral development: a systematic review. J Asthma. 2018;1–12.
48. Irani F, Barbone JM, Beausoleil J, Gerald L. Is asthma associated with cognitive impairments? A meta-analytic review. J Clin Exp Neuropsychol. 2017;39(10):965–78.
49. Almqvist C, Worm M, Leynaert B, Gender wgoGLW. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. Allergy. 2008;63(1):47–7.
50. McCallister JW, Holbrook JT, Wei CY, et al. Sex differences in asthma symptom profiles and control in the American Lung Association Asthma Clinical Research Centers. Respir Med. 2013;107(10): 1491–500.

51. Hicks SP. Vascular pathophysiology and acute and chronic oxygen deprivation. In: Minckler J, editor. Pathology of the nervous system, vol. 1. New York: McGraw-Hill; 1968. p. 341–50.
52. Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? Thorax. 1995;50(2):186–8.
53. Rudolf M, Riordan JF, Grant BJ, Maberly DJ, Saunders KB. Arterial blood gas tensions in acute severe asthma. Eur J Clin Invest. 1980;10(1):55–62.
54. Brown, Woolston D, Frol A, et al. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol Psychiatry. 2004;55(5):538–45.
55. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. Chest. 2004;125(3):1081–102.
56. Morrell MJ, Twigg G. Neural consequences of sleep disordered breathing: the role of intermittent hypoxia. Adv Exp Med Biol. 2006;588:75–88.
57. Yoon HK, Kang SG, Lee HJ, et al. Apnea-related sleep fragmentation and poor vigilance in children with well-controlled asthma. J Sleep Res. 2013.
58. Borson S, Scanlan J, Friedman S, et al. Modeling the impact of COPD on the brain. Int J Chron Obstruct Pulmon Dis. 2008;3(3):429–34.
59. Bass JL, Corwin M, Gozal D, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. Pediatrics. 2004;114(3):805–16.
60. Newcomb RW, Akhter J. Respiratory failure from asthma. A marker for children with high morbidity and mortality. *Am J Dis Child.* 1988;142(10):1041–1044.
61. Brannan JD, Lougheed MD. Airway hyperresponsiveness in asthma: mechanisms, clinical significance, and treatment. Front Physiol. 2012;3:460.
62. Carlson SM, Kim J, Khan DA, et al. Hippocampal volume in patients with asthma: results from the Dallas heart study. J Asthma. 2016;00–00.
63. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. PLoS ONE. 2012;7(8):e40921.
64. Rosenkranz MA, Esnault S, Christian BT, et al. Mind-body interactions in the regulation of airway inflammation in asthma: a PET study of acute and chronic stress. Brain Behav Immun. 2016.
65. Guo RB, Sun PL, Zhao AP, et al. Chronic asthma results in cognitive dysfunction in immature mice. Exp Neurol. 2013;247:209–17.
66. Carlson SM, Kim J, Khan DA, et al. Hippocampal volume in patients with asthma: results from the Dallas heart study. J Asthma. 2017;54(1):9–16.
67. Kroll JL, Steele AM, Pinkham AE, et al. Hippocampal metabolites in asthma and their implications for cognitive function. Neuroimag Clin. 2018;19:213–21.
68. Modrego PJ, Fayed N, Sarasa M. Magnetic resonance spectroscopy in the prediction of early conversion from amnestic mild cognitive impairment to dementia: a prospective cohort study. BMJ Open. 2011;1(1).
69. Tumati S, Martens S, Aleman A. Magnetic resonance spectroscopy in mild cognitive impairment: Systematic review and meta-analysis. Neurosci Biobehavior Rev. 2013;37(10, Part 2):2571–86.
70. Rosenkranz MA, Busse WW, Johnstone T, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci USA. 2005;102(37):13319–24.
71. Busse WW. The brain and asthma: What are the linkages? Allergy and the Nervous System. 2012;98:14–31.
72. Price JH, Khubchandani J, McKinney M, Braun R. Racial/Ethnic disparities in chronic diseases of youths and access to health care in the United States. BioMed Res Int. 2013;2013.
73. Ritz T, Meuret AE, Trueba AF, Fritzsche A, von Leupoldt A. Psychosocial factors and behavioral medicine interventions in asthma. J Consult Clin Psychol. 2013;81(2):231–50.
74. Cacioppo JT. Social neuroscience: autonomic, neuroendocrine, and immune-responses to stress. Psychophysiology. 1994;31(2):113–28.
75. Annett RD, Stansbury K, Kelly WH, Strunk RC. Association of hypothalamic-pituitary-adrenal axis function with neuropsychological performance in children with mild/moderate asthma. Child Neuropsychol. 2005;333–48.
76. Carr W, Zeitel L, Weiss K. Variations in asthma hospitalizations and deaths in New York City. Am J Public Health. 1992;82(1):59–65.
77. Gottlieb DJ, O'Connor GT, Beiser AS. Poverty, race, and medication use are correlates of asthma hospitalization rates: a small area analysis in Boston. CHEST J. 1995;108(1):28–35.
78. Braganza S, Ozuah PO, Sharif I. The use of complementary therapies in inner-city asthmatic children. J Asthma. 2003;40(7):823–7.
79. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–73.
80. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59–65.
81. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902–7.
82. Pedersen S. Asthma control in children: Is it important and can we measure it? Paediatr Respir Rev. 2016;17:36–8.

83. Sánchez T, Castro-Rodríguez JA, Brockmann PE. Sleep-disordered breathing in children with asthma: a systematic review on the impact of treatment. J Asthma Allergy. 2016;9:83–91.
84. Banasiak NC. Understanding the Relationship Between Asthma and Sleep in the Pediatric Population. *J Pediatr Health Care.* 2016.
85. Moore WC, Meyers DA, Wenzel SE, et al. Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315–23.
86. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. Crit Care. 2002;6 (1):30–44.
87. Chipps BE, Haselkorn T, Paknis B, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. Journal of Allergy and Clinical Immunology. 2018;141(5):1590–1597.e1599.
88. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur Respir J.* 2017;50(3).
89. Brown, Vera, Frol, Woolston., Johnson. Effects of chronic prednisone therapy on mood and memory. In. Vol 99: Journal of Affective Disorders; 2007:279–283.
90. Frol AB, Vasquez A, Getahun Y, Pacheco M, Khan DA, Brown ES. A comparison of clinician-rated neuropsychological and self-rated cognitive assessments in patients with asthma and rheumatologic disorders. Allergy and Asthma Proceedings. 2013;34(2):170–5.
91. Brown ES, Chandler PA. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. Prim Care Companion J Clin Psychiatry. 2001;3 (1):17–21.
92. Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. *Ann N Y Acad Sci.* 2009;1179:41–55.
93. Cazzola M, Segreti A, Calzetta L, Rogliani P. Comorbidities of asthma: current knowledge and future research needs. *Current Opinion in Pulmonary Medicine.* 2013;19(1).
94. Bousquet J, Schünemann HJ, Samolinski B, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs. Journal of Allergy and Clinical Immunology. 2012;130 (5):1049–62.
95. Brumpton BM, Leivseth L, Romundstad PR, et al. The joint association of anxiety, depression and obesity with incident asthma in adults: the HUNT Study. Int J Epidemiol. 2013;42(5):1455–63.
96. McNichol KN, Williams HE, Allan J, McAndrew I. Spectrum of asthma in children. 3. Psychological and social components. *British medical journal.* 1973;4(5883):16–20.
97. Weil CM, Wade SL, Bauman LJ, Lynn H, Mitchell H, Lavigne J. The relationship between psychosocial factors and asthma morbidity in inner-city children with asthma. Pediatrics. 1999;104(6):1274–80.
98. Fritzsche A, Dahme B, Gotlib IH, et al. Specificity of cognitive biases in patients with current depression and remitted depression and in patients with asthma. Psychol Med. 2010;40(5):815–26.
99. Walters P, Schofield P, Howard L, Ashworth M, Tylee A. The Relationship between Asthma and Depression in Primary Care Patients: A Historical Cohort and Nested Case Control Study. PLoS ONE. 2011;6(6):e20750.
100. Dudeney J, Sharpe L, Jaffe A, Jones EB, Hunt C. Anxiety in youth with asthma: A meta-analysis. Pediatr Pulmonol. 2017;52(9):1121–9.
101. Schultz IZ, Sepehry AA, Greer SC. Anoxia-Hypoxia in Forensic Neuropsychological Assessment: Cognitive Impact of Pulmonary Injuries, Respiratory Distress, Cerebral Blood Hypoperfusion, and Major Surgeries. Psychological Injury and Law. 2018;11(2):153–70.
102. Koinis-Mitchell D, McQuaid EL, Seifer R, Kopel SJ, Nassau JH. Symptom perception in children with asthma: Cognitive and psychological factors. In. Vol 2008: Health Psychology; 2009:226–236.

Part III

Developmental, Genetic, and Structural Disorders

Chapter 11

Cerebral Palsy: Effects of Early Brain Injury on Development

Silja Pirilä and Jaap J. van der Meere

Introduction

The term cerebral palsy (CP) was originally coined more than a century ago and loosely translated as brain paralysis. A precise definition has remained elusive because CP is not a single diagnosis but an umbrella term describing non progressive brain lesions involving motor and postural abnormalities that are noted during early development [1] From this perspective, the executive committee for the definition of cerebral palsy has proposed a new definition: CP is a multi-faceted phenomenon wherein motor limitations are often accompanied by disturbances of sensation, cognition, communication, perception, and behaviour, by epilepsy, and by secondary musculoskeletal problems. Other complications include among others feeding difficulties, pain, and functional gastrointestinal abnormalities contributing to bowel obstruction, vomiting and constipation [2].

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According to the new definition, the functional consequences of the disorder have to be emphasized. Indeed, considering the conglomerate of the disorders, it could be the case that the motor disability in a particular child, especially in a mild case, is not necessarily the predominant disability. Research indicated that 88% of the children with CP have three or more disabilities, with cognitive impairments as one of the most frequent ones [3]. A cross-sectional multi-centre survey wherein 8- to 12-year-old children (n = 818) participated, identified from population-based registers of CP in 8 European regions, showed that the most common problems encountered were in the domain of peer problems (32%), followed by hyperactivity (31%) and emotional problems (29%) [4].

Etiology

Pathogenic events affecting the developing brain cause abnormalities or lesions. The patterns of these lesions depend on the stage of brain development: cell proliferation, neuronal migration, and cortical organization [5]. Identifying these patterns may help to understand the pathogenesis of CP which is not yet comprehensively understood. During the early third trimester in utero, especially periventricular white matter is vulnerable to injury. Major neuropathologies arising at this stage are periventricular lesions, for instance, periventricular

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leukomalacia (PVL), and/or complications of intraventricular haemorrhage: periventricular hemorrhagic infarction [6]. These neuropathologies constitute the main lesional patterns in preterm children leading to CP [7]. A meta-analysis yielded a significant decrease in prevalence with increasing gestation age. The decrease in prevalence started at 27 weeks of gestation age [8]. In the same study, no relation was found between the severity of the impairment and gestation age.

Towards the end of the third trimester, cortical or subcortical grey matter appears to be vulnerable to injury and may lead to damage in the parasagittal and central areas, basal ganglia and thalamus with typical involvement of mediolateral thalamus, posterior pallidum, and putamen. This lesional pattern is often seen in term or near to term born infants developing CP. Here, the pathogenesis is thought to be mainly hypoxic-ischemic following severe birth asphyxia. Intrauterine timing—probably late—can be assumed in a minority where the peri- and neonatal history is inconclusive [6]. CP may also be acquired postnatally mainly because of brain damage from bacterial meningitis, viral encephalitis, hyperbilirubinemia, motor vehicle collisions, falls or child abuse.

Neuroimaging

For a long period, investigations of perinatal origins of CP relied on weak proxy evidence of brain injury such as low Apgar scores and other birth and neonatal complications. New possibilities were created after the introduction of the cranial ultrasound (US) in the late 1970s: a non-invasive bedside technique to explore the time of occurrence and evolution of lesions and risk factors involved in the development of high-risk infants [9]. Cranial US abnormalities, especially a white matter echogenicity, predict disability to a certain extent later in life [10]. One way to classify the severity of white matter abnormalities has been developed by de Vries and colleagues [11]. Here, grade I means periventricular areas of increased echogenicity present for 7 days or more, grade II means periventricular areas of increased echogenicity evolving into small localized frontoparietal cysts, and grade III refers to periventricular areas of increased echogenicity evolving into extensive periventricular cystic lesions involving occipital and frontoparietal periventricular white matter. Cranial US gradings have been found to be associated with severity of the motor impairment [12, 13], perceptual-motor disabilities [11, 14, 15], and mental functioning [16–18] Studies are difficult to compare because short term and long term outcome measures are recorded most of the time in broad outcome categories (for instance, a combined score of motor, cognitive, behavioural, visual and auditory skills) that may interfere with precise interpretation [10].

In the early 1990s, magnetic resonance imaging (MRI) was introduced providing detailed images of anatomical structures of the brain, and relations between lesion patterns/morphology with functional outcome were made. In short, a significantly better outcome was seen in the mild pattern group, whereas children with an intermediate or severe pattern had severe delays of motor and cognitive development [19]. The technique was found to be superior for detecting the extent of subtle white matter lesions compared to the cranial US [20–22] and according to the American Association of Neurology, MRI should be part of the evaluation of a child with CP if the etiology has not been established [23].

Some prefer the MRI technique in predicting CP because of its precision [2, 24], others consider the neonatal cranial US as a method of choice because of its simplicity: infants do not need to be transported to the magnet, sedation is not needed, and the investigation is less expensive than MRI. In addition, the specificity of the cranial US is increased if obtained in a systematic way sequentially within regular time intervals by means of a 7.5 MHZ transducer [6, 25]. The predictive power of both instruments was investigated in a prospective 2-year cohort study in prematurely born children when they had reached a median age of 8 years. Overall, the correspondence in findings was low, but in the severe group the correspondence was high. There was only a 1% chance that a child with a normal neonatal cranial US showed a major lesion on MRI at school age. With respect to the predictability of

the IQ, it was of interest that the MRI findings correlated better with mean IQ than the cranial US findings, but these differences were considered not to be of clinical relevance [26].

Due to the limited resolution of the MR images in disorders such as PVL, where white matter injury can be associated with severe volume loss, this technique can provide only macroscopic characterization of white matter anatomy. Therefore, more sophisticated techniques have become available, such as volume measurements, showing significantly reduced total brain, cerebellum and grey matter volumes [27]. Another recent technique, diffusion tensor imaging, showed that not only white matter structures that are the primary target of the anoxic insult (thalamic radiations and periventricular white matter) are concerned, but also other distant tracts and pathways like the corticospinal tract, optic nerves and tracts, and long associative fasciculi including the corpus callosum [28, 29].

Diagnosis

The motor impairments of children eventually diagnosed with CP begin to manifest very early in development, usually before 18 months of age, with delayed of aberrant motor progress; other neurodevelopmental and functional difficulties that often accompany motor signs can appear throughout childhood. There is no explicit upper age limit specified, although the first two or three years of life are most important in the timing of disturbances resulting in CP. In practical terms, disturbances resulting in CP are presumed to occur before the affected function has developed (e.g. walking, manipulation, etc.) [30]. The Cerebral Palsy surveys and registers in Europe [31] suggested dividing CP into three subtypes based on their predominant neuromotor abnormality:

- *Spastic* CP (the most common form) is associated with dysfunctions in corticospinal tracks that result in increased muscle tone, hyperreflexia and the persistence of primitive reflexes [32]. It includes three further subdivisions. In spastic diplegia, lower extremities are bilaterally more affected than upper extremities due to symmetrically afflicted PVL lesions within posterior areas. In spastic quadriplegia all four extremities are affected, and PVL lesions are found in posterior, middle and anterior areas. In spastic hemiplegia, the brain lesion is unilateral and affects one side of the body with upper extremity spasticity more pronounced than lower extremity spasticity.
- *Dyskinetic* CP (differentiated into dystonia and choreoathetosis) results from circumscribed lesions in the basal ganglia and thalamus with dysfunctions in extrapyramidal pathways. It is characterized by a variety of abnormal motor patterns and postures such as involuntary athetoid movements of the limbs or dystonic posturing of the trunk and limbs [33]. All four extremities and also the oral pharyngeal musculature are usually involved. Children with additional central and especially hippocampus involvement are usually also mentally retarded.
- *Ataxic* CP presents loss of orderly muscular coordination so that movements are performed with abnormal force, rhythm and accuracy. It arises from cerebellar dysfunction and includes, among others, wide-based gait, limb dysmetria, tremor (mainly a slow intention tremor) and low tone.

Mixed presentations of CP are classified by the dominant type of tone or movement abnormality, categorized as spasticity, dystonia, choreoathetosis or ataxia, but additional tone or movement abnormality, such as mixture of spastic and dyskinetic components are listed too.

Unfortunately, the classification is not complete. What is notably missing is a description of bulbar and oropharyx involvement. Such difficulties are common and can produce important activity limitations, but there is as yet no scale to assess such functions [2]. In spite of some shortcomings, the classification system shows strong nosological validity. A longitudinal study (n = 93) indicates a permanency in CP as an array of functional impairments, but changes in subtype do occur in an appreciable minority of the children

(28%). This change took place in especially the non-spastic subtype. Children were initially assessed at a mean age of two years and re-assessed at nine years and four months with a mean interval of six years [34]. The follow-up demonstrated that the classification persists over time.

Prevalence

Insight in risk factors such as maternal infections, multiple pregnancies, and too early discharge (with little follow-up) of high-risk infants from the special care units has prevented the expected increase in the prevalence rate and led to a stable number of about 2 per 1000 live births. This rate can hopefully be reduced over the coming decades by preventive measures [24]. Out of all cases with CP, bilateral types (i.e. diplegia and quadriplegia) are most common, accounting for 53.9%. Unilateral type (i.e. hemiplegia) accounts for 31% of all cases. Dyskinetic types account for 6.6% of all cases, followed by ataxia type with 4.1% [31]. CP is more common in males than in females [35], making the influence of biological sex on the prevalence an important area for future research. According to the recent systematic review and meta-analysis [36] the overall prevalence of CP has remained constant in recent years despite increased survival of at-risk preterm infants.

Neuropsychological Functioning

Intelligence

Overall, 30–50% of the children have sub-averaged intelligence demonstrated by an IQ or IQ equivalent of 70 or below (i.e. mental retardation; American usage: learning difficulties). It is well recognized that intelligence is negatively associated with the severity of CP. Nordmark and colleagues [37] found that 50–60% of the children with bilateral CP and severely limited self-mobility had a sub-averaged intelligence level. The percentage of children with a sub-averaged intelligence level ranged between 10 and 30% in those who were able to learn to walk without restrictions or walked with assistive mobility devices [38].

A second observation is that many children show a disharmonic profile: performance IQ is significantly lower than verbal IQ, the latter, at best, within normal limits [39–43, 12, 13, 44] More specifically, basic processing and expression of verbal material as well as vocabulary (at least as measured by the subtests of the Wechsler scales) are performed in the normal range. Tests tapping working memory (Digit Span) and Arithmetic are in many cases performed worse compared to other verbal subtests. Within the performance domain, particular deficits can be noted in visual–perceptual, visual–spatial and visual–constructional skills.

Impairments in Visual Perceptual and Sensorimotor Skills

Reduced non-verbal compared to verbal intelligence is traditionally seen in the developmental neuropsychology as an indication of visual perceptual impairments. This position is challenged by Stiers and Vandenbussche [45]. They reported among others no significant association between visual perceptual impairments and reduced non-verbal to verbal intelligence and concluded that non-verbal intelligence subtests assess a complex of cognitive skills that are distinct from visual perceptual abilities and that the assessment of non-verbal intelligence is not hampered by deficits in perceptual abilities. That CP is associated with a complex of cognitive impairments is also reported by Pirila and colleagues [12]. They used the NEPSY (A Developmental Neuropsychological Assessment [46]) and found that children with spastic diplegia had impaired visuomotor and visual–spatial skills as well as compromised auditory and visual attention abilities. Although these findings are of interest, as has been argued elsewhere [47], IQ tests and

paper and pencil tests such as the NEPSY measure a complex web of cognitive functions. As a consequence, poor scores may be caused by numerous and unknown factors. Scores are unspecific (i.e. many patient groups obtain similar profiles of low scores on such tests) which make test results difficult to interpret. What is needed are tests that unravel visuomotor and spatial skills in its elementary parts. The biological motion processing task might be such a test. It isolates information about motion from feature and semantic information processing, and measures the ability to integrate local motion of dots presented on a screen into a cohesive percept of a point-light walking figure. Using this methodology, poor spatial motion information processing has been reported in adolescents with early bilateral parietooccipital periventricular brain lesions [48]. Based on this and other findings, the dorsal stream of the visual system projecting from the primary visual cortex to the parietal lobe [49] is suggested to be compromised in children with CP [50].

Also, Posner's orienting task [51] has been used to investigate visual perceptual/attention skills in CP. The task measures simple orienting, disengagement, redirection of attention and inhibition of return. The latter refers to the tendency not to shift attention back to a recently attended location. It is thought to have the function of biasing attention away from locations which have been inspected in the recent past to new, as yet uninspected locations. These abilities are thought to be subserved by thalamic and midbrain regions, and demonstrated to be impaired in children with spastic diplegia, especially in those with anterior and diffuse lesions, as compared to children with posterior or no apparent lesions [52, 53]. An adapted version of the Posner task measuring shifts of gaze has been used in babies with transient periventricular echogenicity. The results showed that after disengagement has been developed its fine-tuning occurred more slowly in preterm infants [54].

Grasping and object manipulation tasks demonstrated that spastic CP is characterized by overall slower movements that consist of more sub-movements, a stereotypical shoulder–elbow recruitment order [55], more variable hand trajectories [56], increased trunk movement [57], and an anticipatory movement planning deficit [58, 59]. Especially the latter finding could be of importance concerning the conceptualization of the motor problems in CP. Movement planning involves the ability to predict the future state of the motor system, or the consequences of its action. A growing body of evidence suggests that motor imagery plays a vital role in motor planning. More specifically, imaging a movement (internal movement simulation) involves the same neural mechanisms as those activated when planning and executing overt movements [60]. Mutsaart and colleagues [58, 59] suggest that weak motor planning of adults with spastic CP (exclusively those with left brain damage) is caused at the level of poor motor imaging.

A recent systematic review [61] underlines that visual perceptual impairments are affecting nearly half of the CP population. The severity of the brain damage may influence the extent of the visual perceptual impairments, but factors such as CP subtype, degree of intellectual disability, seizure history or neuro-ophthalmological deficits did not demonstrate a consistent impact on visual perceptual disabilities.

Attention Dysfunctions

All in all, the outcome of in-depth perceptual visual motor experiments suggests that CP is not solely a motor execution problem [62] but also attention dysfunctions are part of the problem. Although some studies failed to report an attention deficit in children with CP [63], others reported attention deficits (distractibility) [64, 65]. A recent Norwegian prevalence study indicated that 3.5% of the children with CP fulfilled the diagnosis of ADHD [66]. Another executive function which is related to attention dysfunction that seems to be compromised is inhibitory control: the ability to inhibit a prepotent response. Christ and colleagues [67] demonstrated that children with bilateral spastic cerebral palsy have impairments in

inhibitory control, beyond that attributable to slow processing speed, on three inhibitory tasks, the Stroop test, a stimulus-response reversal task and an anti-saccade task.

Methylphenidate (MPH), the compound of choice in treating attention deficits, has received so far little attention in the field of CP. To our knowledge, the study by Gross-Tsur and colleagues [68] is the only systematic evaluation available of MPH for children (n = 29) diagnosed with CP and ADHD symptoms. Using a prospective, double-blind, placebo-controlled design, they reported improvement in teacher-reported attending skills. Side effects were minimal. To extend this line of inquiry, a pilot study has been conducted to evaluate the effects of MPH directly in classroom environments [69]. The results showed clinically significant reductions in stereotyped and disruptive behaviours with no change in task-related behaviours. It is obvious that further work using larger randomly selected study samples with complementary measures of behaviour and performance appears warranted.

The Crowding Hypothesis

The disharmonic IQ profile in CP is often explained by the crowding hypothesis, first formulated by Teuber [70]. This developmental principle stipulates that after early insult to the left hemisphere, there will be a sparing of verbal function because it will become subserved by the intact right hemisphere, accompanied by a relative impairment of non-verbal function. Anatomical correlates of the crowding hypothesis are, however, modestly supported by functional magnetic resonance imaging (fMRI) studies in children, adolescents and young adults with early left periventricular brain lesions [71–74]. The idea that the crowding hypothesis could explain the disharmonic profile in CP is not without problems. It is still a matter of debate which factors determine language reorganization and to what extent it takes place in individual cases [75]. Moreover, the notion of a hemisphere being crowded seems to be an oversimplification of the modular approach of brain functioning [76] and is especially hard to reconcile with modern assumptions of the brain as a flexible arrangement of cortical networks [76]. However, the alternative explanation for the crowding hypothesis suggesting direct lesion effects as the sole reason for visuospatial impairments is based on even less evidence [77].

Language and Speech Impairments

In spite of the disharmonic IQ profile, many children obtain low scores on tests tapping expressive and comprehensive language and communication skills [78–80]. Deficits in expressive and comprehensive language functions, defined in terms of vocabulary, grammatical production and verbal comprehension, are suggested to be primarily associated with the left-side lesions due to pre- or perinatal vascular insult [81]. Also an inconsistency between literacy skills and intellectual and verbal abilities has been reported in CP [82–85]. Such an inconsistency is a hallmark of dyslexia which is usually connected with deficits in phonological processing, narrow span of working memory and rapid naming problems. Instead, many children with CP have Verbal IQs that are within the average range. Phonological processing seems also relatively intact in some subtypes of CP, such as spastic diplegia [12, 84]. Questions regarding the role of working memory and rapid naming problems in literacy acquisition remain to be answered.

Part of the language problems may be a consequence of motor impairment per se. It has been reported that, for instance children with dyskinetic (extrapyramidal) CP display a wide range of intellectual abilities, but because of severe dysarthria of the muscles involved in speech, some of these children may have delays in language skills [85]. That the severity of motor impairment plays a role in expressive and comprehension skills is also demonstrated by Pirila and colleagues [13]. In this study, children with a verbal intelligence level at or close to norms showed deficits primarily in the motor speech domain, whereas children with additional cognitive difficulties (IQ level below 70) showed impairments, both in

language (comprehension and expression) and motor speech skills, the latter defined in terms of deficits in phonology/articulation and/or oral motor patterns and structure. Finally, Pirila and colleagues [12] using the NEPSY test, reported that children with spastic diplegia and a verbal IQ in the normal range scored in the normal range concerning phonological processing, comprehension of instructions, comprehension of grammatical sentences, memory for names and narrative memory functions, but deficits were found in speeded naming. That verbal functioning and memory for words are relatively intact in children with hemiplegic CP and a normal intelligence is also suggested in other studies [86].

Arithmetic Difficulties

Evidence is increasing that arithmetic difficulties are somewhat more prevalent than reading difficulties [87, 88] with word decoding and fine motor skills as the strongest predictors [89]. Problems learning to count [90, 91], to add or subtract [92], to subitize (i.e. global perception of small numerosities) [93], and to evaluate quantity [94] are well recognized. One speculation why children with CP are vulnerable to develop arithmetic difficulties is because of their poor eye–hand coordination. When normal children start learning to count, they often use their fingers to point to each element, before they use visual pointing only [95], but children with CP are less able to coordinate pointing with number enumerating [91, 96]. In support of this idea is the finding that the extent of the delay in counting in children with CP is directly related to their eye–hand coordination and visual–spatial deficits [90]. Unfortunately, much of research on learning is based on a limited number of children. Therefore, a longitudinal study concerning the development of mathematical ability in children with CP, where 22 different special schools are participating is very welcomed in the field. The first results suggest that problems in math are mediated by intelligence, working memory, and early numeracy (defined in terms of number concept and simple counting skills seen as precursors to the acquisition of formal mathematical skills). However, problems in math were also associated with time spent on learning mathematics. Given that schools for children with physical disabilities provide physical, speech and other therapies during the school day, it was found that children with CP received an average of only 60% of the amount of arithmetic instruction time that is received by children with mainstream education [97]. The latter finding underlines a good balance between the amount of time spent on therapies and learning activities at school.

Limitations in Theory of Mind

Theory of mind (ToM) refers to our ability to attribute thoughts, beliefs and feelings to ourselves and to other people, and to our understanding that our actions are governed by these thoughts, beliefs and feelings [98]. This ability is central to our social life. It has been well-recognized that individual differences in ToM abilities might be partly explicable in terms of differences in early social experiences. Early conversations about mental causality of behaviour [99] as well as day-to-day interactions experienced within the family, especially parents and siblings, and friends [100] have been put forward as important to later ToM development. Previous research has shown that simple everyday social contact is very seldom the sole purpose of interaction between a speaking partner and a child with severe speech problems and CP [101]. Rather, when a caretaker initiates conversation it is often with a specific purpose in mind, such as feeding, guiding and providing care. Interactions are often slow and cumbersome, and quite often marked by a lack of rhythm and timing. Thus, children with motor speech problems and CP often experience less spontaneous contacts with the environment, and their potential for active manipulation of objects, pretended play and for social interaction is much reduced compared with that of their peers [102]. A limited repertoire in social functioning and lack of adequate caretaker assistance in social functions have even been reported in children with an IQ level in the normal range [103]. It is well-recognized that autism is an important

co-morbidity in CP and more attention should be given to autism spectrum symptoms in the regular follow-up of children with CP in an attempt to enhance social functioning [104].

Longitudinal Follow-Up of the Gross Motor and Cognitive Development

The paucity of longitudinal data represents a gap in our knowledge about the functional plasticity, as the magnitude and nature of deficits may change over time, particularly when a lesion is superimposed on a developing brain [105]. The common practice of assessing cognitive strengths and weaknesses with early brain injuries on the basis of data collected at a single time relying on cross-sectional observations may be considered a snapshot resulting in a source of discrepancies in the literature. Different cognitive levels reported may reflect variations in the lesion characteristics included in each study, but they may also reflect a relationship between the age of children at test and outcome. Put in other words, it is possible that cognitive deficits in children with early lesions vary as a function of age. Consequently, children with CP have to be assessed longitudinally. One example of the necessity to assess them longitudinally is provided by Levine and colleagues [106]. They found that children with early unilateral brain injury, even with relatively small lesions, showed an IQ decline over the course of development. The same holds with respect to reading and spelling abilities. Dahlgren Sandberg [85] reported a decrease in IQ points between the ages of 6 and 12 years. In addition, she found that phonological skills, usually predicting reading and spelling attainment, later on, did not seem to have the same predictive power for literacy development in children with severe speech impairments and CP as in typically developing children. The slower than normal course of cognitive development appears to become visible even in children at about 2 and 4 years of age [85].

That some children's cognitive functioning may drop or fail to keep the normal developmental course has clinical and therapeutic implications. When clinicians use IQ tests they may assume that the outcome reflects learning potential to be stable over time. Clearly, longitudinal assessment is needed with a central consideration in educative and therapeutic assistance. The observation that cognitive functioning may drop or fail to keep the normal developmental course also has theoretical value. Neuropsychological disorders in children are often divided into two groups: developmental and acquired. In the former, disorders become apparent as the child grows and develops, and there is no evidence that a skill was previously mastered and then has been lost. In the latter, children had cognitive systems which were partially established in a normal fashion, and then following the neurological damage they lost some of these skills. CP might have characteristics of both and it has to be seen to what extent arrest or drop in functioning is related to comorbid problems such as epilepsy. In this vein, Chilosi and colleagues [81] reported that epilepsy emerged as a significant predictor on several measures of cognitive and language outcome, not the size and location of brain lesions.

Clearly, more research is needed to explore the developmental trajectories of children with CP, and in particular the trajectories of the subtypes. About ten years ago, studies became available exploring the so-called natural history of gross motor development in children [107]. They highlight a maximum achievement at the age of 9 to 10 years. After this, there is a great variability in the functionality of the motor skills. In sum, on the one hand, the gross motor classification seems rather stable over time; on the other hand, changes in CP type-specific curves concerning functional motor skills are possible [108].

Problems with Cognitive Assessment in the Clinic

A number of obstacles can interfere with obtaining an accurate picture of a child's overall intelligence. Some children are difficult to assess because of their low intellectual potential. Often, these children have only few, if any, possibilities to express their intentions verbally or by means of

assistive communicative means. Some have congenital brain malformations involving large-scale absence of cerebral cortex. Nevertheless, these children may possess clear signs of discriminative awareness: for example, distinguishing familiar from unfamiliar people and environments, social interaction, orienting, musical preferences, appropriate affective responses, and associative learning [109]. It remains an important task of the neuropsychologist to have an estimate of the intelligence level and of the adaptive behaviours and capabilities of these children, because such estimates might have an important function in strengthening the bond between the child and the caretaker, and in enhancing the goals of therapies. Standardized tests are often not possible to use, but it is possible to use behavioural observation methods. One of the most common is Vineland Adaptive Behaviour Scales (2nd edition)in order to gather information about adaptive and functional behaviours.

Although the exact prevalence of communication disorders associated with CP is not known, it has been estimated that approximately 20% of children with a diagnosis of CP have severe communication impairment and are classified as non-verbal [80, 110]. The problem is that traditional standardized neuropsychological tests typically require oral, manual or written answers that may exceed visuomotor, speech and verbal expressive and comprehensive restrictions, seen in many children with CP [13]. A comprehensive study [44] indicated that non-verbal reasoning abilities may go unidentified especially for children with dyskinetic CP or quadriplegia subtypes. When children did not complete the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), they were instead further assessed with various developmental scales (Columbia Mental Maturity Scale, Leiter-R, Test of Nonverbal Intelligence (TONI-2)). As a result, half of the group obtained a DQ or IQ above 70. Clearly, cognitive classification should not solely depend on clinical judgement. Consequently, to measure cognitive capacities in children with multiple severe handicaps neuropsychological methods are needed to tap cognitive abilities to a maximum and motor abilities to a minimum. The availability of such an assessment measure that can estimate verbal and non-verbal capacities independently of motor and expressive communication disabilities would provide invaluable information about the cognitive capacities of children who cannot express themselves orally. Having a truer estimate of their cognitive capacities may also lead to positive consequences concerning their quality of life and to more specific cognitive rehabilitation planning and special training. Within this purpose, modifications to standardized test administration have been recommended using non-traditional responses [110, 111], and presenting test items within multiple-choice or yes–no response paradigms [112]. However, these modifications have questionable validity and lack normative data. Tests that have been designed and normed with the response repertoire of the child with CP in mind are the Leiter International Performance Scale–Revised, the Pictoral Test of Intelligence (2nd edition), and the Columbia Mental Maturity Scale–revised. However, for moderate and severely impaired children, some of the response requirements (pointing or blocking placement) and visual search/scanning skills may remain overly demanding.

The Event-Related Potential methodology has been recommended as an alternative assessment method that should facilitate the measurement of a wide range of cognitive functions over a wide age range with minimal reliance on motor or expressive language functioning [113]. This methodology indeed, has been instrumental for almost 40 years in the investigation of cognitive functioning in normal and pathological central nervous systems from infancy to late-adulthood and awaits in-depth research in the field of CP. In short, the methodology registers event-related brain potentials in subjects carrying out cognitive tests. The latency and amplitude of various so-called components mirror important cognitive steps needed to produce the overt cognitive score, mostly a reaction time.

All in all, the neuromotor disability and communication problems in CP challenge the use of standard neuropsychological tests as used in

the clinic because the handicaps may lead to an over- or under-evaluation of their true abilities because these tests typically require oral, written or pointing answers that may exceed the motor speech and verbal expressive and comprehension restrictions seen in many children. In their systematic review, Yin Foo et al. [114]. aimed to identify and examine intelligence assessments for children with CP. They concluded that assessments used often lack (1) reliability data, (2) consensus regarding the validity data, and (3) population-specific norms. Yin Foo and colleagues point to the need for research to establish psychometrics for children with CP, and for multiple options for appropriate assessment. The availability of alternative assessment measures would provide valuable information about the learning capacity of children with CP and may lead to positive consequences concerning their quality of life, and possibly to more specific cognitive rehabilitation planning and special training. Within this perspective, a series of N-of-1 studies have been carried out, for example by Byrne, Dywan, and Connolly[113] demonstrating that event-related brain potentials can be used to reliably evaluate reading and speech comprehension abilities and executive function capacity independent of behavioural and speech production impediments.

In four successive pioneering laboratory studies, we addressed the possibility that motor speed confounds cognitive skills in assessment of children with mild spastic cerebral palsy. The participants (n = 17: age range 8–17) had a normal IQ and were without vision problems. Using the ERP methodology, we studied the brain activation state before, during and after correct and incorrect responses on tasks tapping orientation and stimulus recognition. The prime event-related potentials were the P300 (reflecting stimulus-related processes before the action takes place), the error-related response-locked negativity (reflecting the awareness of own error making) and the late contingent negative variation (reflecting motor preparation). Findings indicated that reaction time slowness and inaccuracy were primarily related to weak motor preparation and motor execution in our target group. Fundamental cognitive/attention skills were intact in the target group [115–117] The fourth study [118] addressed the issue of error detection and performance adjustment in order to prevent errors in a subsequent trial. The results indicate that, especially in the patient group, error responses were associated with poor motor preparation. However, patients identified their errors, as was reflected by an increase of their error-related negativity potential directly after error making. This error detection was an internal process because external feedback about their performance was not given to the participants. Also, detecting the error led to improvement of future performance in the patient group, as was also the case in the control group. Arriving at this point, it is important to note that in normal adults, feedback activates the performance monitoring system and results in a similar reset of brain activity pattern as detecting errors without external feedback [119]. All in all, findings of our pilot study suggest that a critical key in learning, that is, error monitoring and subsequent performance adjustment, is intact in the group of patients.

Some researchers suggest that the amplitude of the error negativity is related to error significance rather than error detectability [47]. Since the amplitude of the error negativity was most pronounced in the patient group, findings suggest that they were more sensitive about their error making than the control group. Consequently, a second key in learning might also be intact in the patient group, that is, motivation.

So, the overall conclusion of our pilot studies led our laboratory to propose that top-down executive function abilities (error detection and performance adjustment after error making) are intact, together with a compromised motor action system (decreased contingent negative variation before error making) in the patient group. The patients' patterns of brain activity 500 milliseconds before the presentation of the display set, and hence, before preceding action execution, might be causally responsible for error making. Therefore, in-depth investigation of patterns of brain activity preceding errors is needed to understand the source of error making in youth

with mild spastic CP. The key question to answer in the near future is why the motor preparation state in the patient group fluctuates from optimal to less optimal, resulting in respectively correct and error responses.

Moreover, the outcome of the event-related potential studies might challenge the popular poor executive function hypothesis in mild spastic CP. The hypothesis is primarily based on research using manual, oral, and eye movements. Cognitive testing of youth with mild spastic CP without controlling for motor preparation may lead to wrong conclusions about their cognitive abilities. Also, this point has to be taken into account in future research.

Our objectives include planned research to investigate brain–behaviour relations using event-related potentials in tandem with fMRI. The event-related potential methodology is adequate in estimating the duration of cognitive steps: mental chronometry. The fMRI, in turn, is adequate in localizing functions. Studies like these might give a more detailed description of how the intended future motor response is shaped in time on the basis of an ongoing registering and evaluation of stimulus characteristics leading to the overt response. For the time being, the frontier of our knowledge basis suggests that executive function performance on a neuropsychological battery of many children with cerebral palsy is associated with damage to the anterior part of the corpus callosum, detected by MRI methodology [120].

Intervention

Functional Limitations

A key concept in the study of the efficacy of interventions is functionality. Relevant functional domains for children concerning the routines of everyday life include mobility, self-care, toileting, play, learning and social cognition. In addition, many children are dependent on technology, and need the support of medical or assistive devices to compensate for impaired body functions. Standardized instruments that tap functionality in everyday skills and transactions between the child and the environment, put under the umbrella of the activity level components described in the International Classification of Functioning, Disability and Health formulated by the World Health Organization [121, 122] are, for instance, the Pediatric Evaluation of Disability Inventory (PEDI) [123] and the Gross Motor Function Classification System (GMFCS) [108, 124, 125]. Both measures have sound psychometric properties in most areas and are relevant for use in studies exploring the treatment outcome [126].

PEDI is usually given to the primary caregiver who has observed the child cross all or most of the environments in which the child adapts and functions. The instrument measures functional performance in the domains of self-care (eating, grooming, bathing, dressing and toileting), mobility (transfer, indoor locomotion and stairs), and social functions (comprehension, expression, problem resolution, play, self and time information, management of daily routines). In addition, the inventory measures the level of caregiver assistance needed to accomplish functional activities in the domains of self-care, mobility, and social functions. Moreover, the inventory provides information regarding environmental modifications and equipment used by the child as important adjunct information for understanding the child's functional capacity.

The GMFCS was developed to provide a standardized classification of the patterns of motor disability in children with CP aged 1 to 12 years. The focal point is the child's self-initiated movements. The GFMCS is based on a five-level ordinal grading. To differentiate between the levels, functional limitations and the need for assistive technology are examined, including mobility devices and wheeled mobility, rather than quality of movement. Level I means that the child walks without restrictions, but has limitations in more advanced gross motor skills; level II: the child walks without restrictions, but has limitations walking outdoors and in the community; level III: the child walks with assistive mobility devices, with limitations walking outdoors and in the community; level IV:

self-mobility is possible with limitations, and the child is transported or uses power mobility outdoors and in the community; and level V: self-mobility is severely limited, even with the use of assistive technology. The severity of motor function classified with the GMFCS correlates positively with associated impairments (IQ level, epilepsy and visual impairments).

To evaluate the effects of various interventions, such as intensive physiotherapy, botulinum toxin treatment, selective dorsal rhizotomy and orthopaedic surgery, the GMFCS is frequently used in combination with the Gross Motor Function Measure (GMFM) [125, 127]. The GFMF is a test specially designed and validated for measuring gross motor function and the change over time. The test contains 88 items of gross motor function distributed over five dimensions: lying and rolling; sitting; crawling and kneeling; standing; and walking, running and jumping. As well as the GMFCS, the GMFM is constructed to measure quantitative aspects, i.e. how much children can do, not the quality of their performance. Other measures such as the Manual Ability Classification System (MACS) [128, 129], which tests the functionality of manual functions (i.e. how children with CP use their hands when handling objects in daily activities), have been designed following the principles of GMFCS. Scales are best completed within specific specialties: paediatric neurologist, physiotherapist and occupational therapist. Assessments can be completed as soon as the functions mature.

Types and Efficacy of Intervention

The types of treatment chosen depend on the specific symptoms manifested in the functionality of a particular child. Surgical interventions are used to manage orthopaedic problems and/or spasticity. A meta-analysis indicated that selective dorsal rhizotomy (SDR) plus physiotherapy is efficacious in reducing spasticity in children with spastic diplegia and it has a small positive effect on gross motor function [130]. In addition, SDR may be associated with specific changes in cognitive function not solely attributable to generalized effects of elevated mood and reduced physical discomfort but may also be the result of suprasegmental effects on cortical functions [52]. Such effects involve circuits superior to the lumbosacral dorsal roots sectioned during rhizotomy. Positioning aids (used to help the child sit, lie, or stand) such as braces and splints, orthoses (used to prevent deformities and to provide support or protection) and medications (used to help control seizures or to decrease spasticity) are other means to improve functionality. However, the main treatment programs encompass physiotherapy, occupational therapy, and speech therapy, but because CP is a developmental disorder, early intervention is essential in professional management. Early intervention consists of elements derived from above-mentioned therapies plus special education depending on the age of the child. It provides multidisciplinary services to promote a child's health and well-being, enhance emerging competencies, minimize developmental delays and promote adaptive parenting and overall family functioning [131, 132].

That onset, duration and intensity are factors of importance for assessing the efficacy of therapy programs, is shown in a recent evidence-based summary of research on the various intervention options [133]. The basic tenets of neurodevelopmental treatment are to inhibit abnormal tone and primitive reflexes and to facilitate normal movement, primarily through positioning and handling techniques that allow children to experience the sensation of normal movement.

Horseback riding therapy and hippotherapy have become popular to complement traditional physical and occupational therapy. The review of Sterba [134] on the efficacy of these therapies provides valuable information: five of six studies showed improved gross motor function. Improvement in these studies was evaluated by the Gross Motor Function Measure, and studies highlighted the relevance of further investigation into how physiotherapy and other variations of sports therapies should be organized in order to achieve the best outcome.

Direct speech and language therapy (SLT) for children with CP has been systematically reviewed by Pennington and colleagues [80]. They concluded that direct SLT focusing on communication and expressive skills using operant and micro-teaching techniques have been effective for the children who participated. However, for some areas for intervention, no evidence of efficacy was found at all (e.g. dysarthria therapy to aid intelligibility or articulation therapy). Finally, according to the researchers, given the single case methodology used it is difficult to generalize the positive findings to other children.

With respect to early intervention, Hadders-Algra [135] argued that the effects are predominantly studied in infants at high-risk for developmental disorders of which the majority do not develop CP. It implies that our knowledge of early intervention in CP is limited. The handful of studies available show virtually no evidence of effects of early intervention programs. In addition, studies are underpowered. At best, weak evidence suggests that parental coaching on how to challenge infant activities during daily life might be associated with improved functional outcome. For a critical summary concerning early interventions, the reader is referred to a recent evidence-based update of rehabilitation practices [133].

The recommendation for specific early intervention training, in which parents learn to promote infant development [136], means that every successful intervention with a child rests as much on the resources of the family as on those of the interventionist [137]. If needed, social training through means of videotaping, counselling, parent support and discussion groups, etc., might help caretakers to recognize more precisely their child's strengths and deficits which, as a result, widens their range of opportunities for interaction [78, 103]. This is relevant because parental malfunctioning and stress are associated with the severity of the disorder and additional problems [138, 139], including comorbid behavioural problems, such as autism and ADHD. Treating these behavioural disorders in a child could contribute to reducing parental stress [140].

Parents are increasingly considered as experts in the field of care because they have developed a great deal of practical knowledge from their special bond with their child and their long-term experience. According to the review of Jansen and his colleagues[136] of literature on parental participation in physiotherapy for children with physical disabilities, the authors concluded that parents who participate in therapy sessions of their child are likely to develop a more realistic view of their child's potential in terms of daily functioning. Training to give therapy, in turn, can increase parents' confidence in their own competence and reduce parental stress. This idea is in line with the well-recognized shift in services from a professionally dominated medical model towards family-centred practices where main aims of intervention are to promote better functioning in the context of daily life settings [141], and the adaptive family perspective is also visible in the paradigm shift of the concept of disability in the WHO framework from 1980 to 2001 [121, 142].

Please note, the knowledge base about family functioning and caring for a child with congenital physical disabilities such as CP is mainly based on maternal outcomes alone. The importance of distinguishing the experiences of mothers versus fathers is growing given that roles within families are less clearly contained than ever before. Mothers' and fathers' roles continue to shift with increasingly diverse family forms as well as in conjunction with the changing work/family interface. Studies that address the issue suggest that mothers' coping strategies focus more on emotional disclosure and seeking social and informational support. They score lower than fathers in the domains of psychological and physical well-being. Fathers, in turn, demonstrate avoidance and denial to distance themselves emotionally from the situation [143]. One drawback of these gender studies concerns the methodological approach. Mother–father comparisons involve interpersonal relationships and mutual influence. Conventional methods for inferential data analysis, including analysis of variance and general linear regression, assume that observations produced from each individual are independent.

When such analysis is applied to data obtained from interacting dyads, the assumption of independent observations may be violated. To overcome the problem of non-independence in the case of distinguishable dyad members, such as female–male couples, intra-class correlation coefficients are more adequate to ascertain concordance. This type of correlation coefficients correcting for any systematic difference between two observations was used by us in an unpublished pilot study exploring perceived informational, emotional and practical social support. Participants were 38 mothers and fathers of intact families raising children with physical disabilities (primarily cerebral palsy) without behavioural problems. Only intact families caring for children younger than 7 years of age and professionally working outside the home were included in the study. Participants were instructed to complete a questionnaire tapping family needs independently from each other and to express their own opinion as an individual about what they considered to be essential support functions in their family. Findings indicate that especially mothers experienced significantly elevated support needs together with low concordance between mothers and fathers in the emotional and everyday assistance domain. The data of the pilot showed that families and especially mothers caring for children with multiple disabilities are more vulnerable than families caring for children with milder disabilities, and a regression analysis indicated that severity of the physical disability of the child was the most important factor concerning perceived stress in the families, not the gender of the caretaker per se.

Conclusions and Future Directions

Clinicians and researchers are faced with complex issues regarding the disposition of children with CP. Families, policy makers and corporate interests want to know what sort of life to expect for such children. Unfortunately, the majority of cranial US and MRI outcome studies have been correlated only with IQ scores, which are too global and do not provide essential and detailed information on memory, visual–spatial, attention and language functioning that would provide the basis for developing specific remediation or accommodation strategies for a child. Neuropsychological assessment guided by state of the art experimental cognitive models, hand in hand with radiological assessment providing detailed information about side, size and timing of lesions may provide a solid empirical basis for future investigation. Currently it seems that the research is task driven and too much guided by the outdated principle that CP is primarily a neurological motor output problem.

Research has been rather scattered with respect to factors such as age and the subtypes: clearly direct comparisons between, for instance children with diplegia and hemiplegia are needed to see whether the neuropsychological manifestations are different. Insight in these matters is needed to shape intervention techniques. Research on the efficacy of intervention concerning CP is according to many experts surprisingly scarce, with conclusions based on poor research designs (small sample sizes, including many single-subject designs and a lack of control groups) [144]. The ideal method for determining efficacy of a treatment is through randomized clinical trials. Such an approach has much to offer in summarizing the quality of evidence. The future for cerebral palsy is bright with the possibility of breakthroughs in many domains.

References

1. Bax MC. Terminology and classification of CP. Dev Med Child Neurol. 1964;11:295–7.
2. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of CP, April 2005 – Introduction. Dev Med Child Neurol. 2005;47:571–6.
3. Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. Ment Retard Dev D R. 2002;8:234–40.
4. Parkes J, White-Koning M, Dickinson HO, et al. Psychological problems in children with cerebral palsy: a cross-sectional European study. J Child Psychol Psychiat. 2008;49:405–13.
5. Barkovich AJ, Kuzniecky RI, Jackson GD, et al. Classification system for malfunctions of cortical development: Update 2001. Neurology. 2001;57:2168–78.

6. Krägeloh-Mann I. Imaging of early brain injury and cortical plasticity. Exp Neurol. 2004;190:S84–90.
7. Filloux FM. Neuropathophysiology of movement disorders in cerebral palsy. J Child Neurol. 1996;11: S5–12.
8. Himpens E, Van den Broeck C, Oostra A, et al. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Child Neurol 2008;50: Epub ahead of print.
9. Thorburn RJ, Lipscomb AP, Stewart AL, et al. Prediction of death and major handicap in very preterm infants by brain ultrasound. Lancet. 1981;1:119–21.
10. Holling EE, Leviton A. Characteristics of cranial ultrasound white-matter echolucencies that predict disability: a review. Dev Med Child Neurol. 1999;41:136–9.
11. de Vries LS, Eken P, Groenendaal F, et al. Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral palsy. Neuropediatrics. 1993;24:263–8.
12. Pirila S, van der Meere J, Korhonen P, et al. A retrospective neurocognitive study in children with spastic diplegia. Dev Neuropsychol. 2004;26:679–90.
13. Pirila S, van der Meere J, Pentikainen T, et al. Language and motor speech skills in children with cerebral palsy. J Com Dis. 2007;40:116–28.
14. Mercuri E, Guzzetta A, Haataja L, et al. Neonatal neurological examinations in infants with hypoxic-ischaemic encephalopathy: correlation with MRI findings. Neuropediatrics. 1999;30:83–9.
15. van Wezel-Meijler G, van der Knaap MS, Oosting J, et al. Predictive value of neonatal MRI as compared to ultrasound in premature infants with mild periventricular white matter changes. Neuropediatrics. 1999;30:231–8.
16. Biagioni E, Bartalena L, Boldrini A, et al. Electroencephalography in infants with periventricular leukomalacia: prognostic features at preterm and term age. J Child Neurol. 2000;15:1–6.
17. de Vries LS, Rademaker KJ, Groenendaal F, et al. Correlation between neonatal cranial ultrasound, MRI in infancy and neurodevelopmental outcome in infants with a large intraventricular haemorrhage with and without unilateral parenchymal involvement. Neuropediatrics. 1998;29:180–8.
18. Ringelberg J, van der Bor M. Outcome of transient periventricular echodensities in preterm infants. Neuropediatrics. 1993;24:269–73.
19. Krägeloh-Mann I, Helber A, Mader I, et al. Bilateral lesions of thalamus and basal ganglia: origin and outcome. Dev Med Child Neurol. 2002;44:477–84.
20. Maalouf EF, Duggan PJ, Counsell SJ, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics. 2001;107:719–27.
21. Childs AM, Cornette L, Ramenghi LA, et al. Magnetic resonance and cranial ultrasound characteristics of periventricular white matter abnormalities in newborn infants. Clin Radiol. 2001;56:647–55.
22. Inder TE, Anderson NJ, Spencer C, et al. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. Am J Neuroradiol. 2003;24:805–9.
23. Ashwal S, Russman BS, Blasco PA, et al. Practice parameter: Diagnostic assessment of the child with cerebral palsy: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2004;62:851–63.
24. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy. The European Cerebral Palsy Study. JAMA. 2006;296:1602–8.
25. de Vries LS, van Haastert IC, Rademaker KJ, et al. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004; 144:815–20.
26. Rademaker KJ, Uiterwaal CSPM, Beek FJA, et al. Neonatal cranial ultrasound versus MRI and neurodevelopmental outcome at school age in children born preterm. Arc Dis Childhood, Fetal Neonatal Edition. 2005;90:F489–93.
27. Kulak P, Maciorkowska E, Goskic E. Volumetric magnetic resonance imaging study of brain and cerebellum in children with cerebral palsy. BioMed Res Int. 2016;2016:5961928. https://doi.org/10.1155/2016/5961928.
28. Arrigoni F, Peruzzo D, Gagliardi C, et al. Whole-brain DTI assessment of white matter damage in children with bilateral cerebral palsy: evidence of involvement beyond the primary target of the anoxic insult. Am J Neuroradiol. 2016; 37:1347–53.
29. Santhouse AM, Ffytche DH, Howard RJ, et al. The functional significance of perinatal corpus callosum damage: an fMRI study in young adults. Brain. 2002;125:1782–92.
30. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy. April 2006. Dev Med Child Neurol 2006; supplement.
31. Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2000;42:816–24.
32. Tomlin PI. The static encephalopathies. In: Newton RW, editor. Color Atlas of Pediatric Psychiatry. London: Times-Wolfe International; 1995. p. 203–16.
33. Menkes JH, Sarnat HB. Perinatal asphyxia and trauma. In Menkes JH, Sarnat HB, eds. Child Neurology. Philadelphia: Lippincott, Williams & Wilkins, 2000: 401-466.
34. Shevell MI, Majnemer A, Poulin C, et al. Stability of motor impairment in children with cerebral palsy. Dev Med Child Neurol. 2008;50:211–5.

35. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. Dev Med Child Neurol. 2007;49:74–8.
36. Oskoui M, Coutinho F, Dykeman J, et al. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55:509–19.
37. Nordmark E, Hagglund G, Lagergren J. Cerebral palsy in southern Sweden II. Gross motor function and disabilities. Acta Paediatr 2001;90:1277-1282.
38. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. Disabil Rehabil. 2006;28:183–91.
39. Carlsson G, Uvebrandt P, Hugdahl K, et al. Verbal and non-verbal function of children with right versus left-hemispheric cerebral palsy of pre- and perinatal origin. Dev Med Child Neurol. 1994;36:503–12.
40. Fedrizza E, Iverno M, Botteon G, et al. The cognitive development of children born preterm and affected by spastic diplegia. Brain Development. 1993;15:428–32.
41. Fedrizza E, Iverno M, Bruzzone MG, et al. MRI features of cerebral lesions and cognitive functions in preterm spastic diplegia children. Pediatr Neurol. 1996;15:207–12.
42. Goto M, Ota R, Lai M, et al. MRI changes and deficits of higher brain functions in preterm diplegia. Acta Paediatr. 1994;83:506–11.
43. Koeda T, Inoue M, Takeshita K. Constructional dyspraxia in preterm diplegia: isolation from visual and visual perceptual impairments. Acta Paediatr. 1997;86:1068–73.
44. Sigurdardottir S, Eiriksdottir A, Gunnarsdottir E, et al. Cognitive profile in young Icelandic children with cerebral palsy. Dev Med Child Neurol. 2008;50:1–6.
45. Stiers P, Vandenbussche E. The dissociation of perception and cognition in children with early brain damage. Brain Dev. 2004;26:81–92.
46. Korkman M, Kirk U, Kemp SL. NEPSY: Lasten Neuropsykologinen Tutkimus. NEPSY: A Developmental Neuropsychological Assessment. Helsinki, Finland: Psychological Press, 1998.
47. van der Meere JJ. The role of attention. In: Sandberg S, editor. Hyperactivity and attention disorders of childhood. 2nd ed. Cambridge: University Press; 2002. p. 162–213.
48. Pavlova M, Sokolov A, Birbaumer N, et al. Biological motion processing in adolescents with early periventricular brain damage. Neuropsychologia. 2006;4:586–93.
49. Grossman E, Donnelly M, Price R, et al. Brain areas involved in perception of biological motion. J Cognitive Neurosci. 2000;12:711–20.
50. Gunn A, Cory E, Atkinson J, et al. Dorsal and ventral stream sensitivity in normal development and hemiplegia. NeuroReport. 2002;13:843–7.
51. Posner MI, Walker JA, Friedrich FJ, et al. Effects of parietal injury on covert orienting of attention. J Neurol. 1984;4:1863–71.
52. Crafts S, Park TS, White DA, et al. Changes in cognitive performance in children with spastic diplegic cerebral palsy following selective dorsal rhizotomy. Pediatr Neurosurg. 1995;23:68–74.
53. Schatz J, Craft S, White D, et al. Inhibition of return in children with perinatal brain injury. J Int Neuropsychol Soc. 2001;7:275–84.
54. Butcher PR, Kalverboer AF, Geuze RH, et al. A longitudinal study of the development of shifts of gaze to a peripheral stimulus in preterm infants with transient periventricular echogenicity. J Exp Child Psychol. 2002;82:116–40.
55. Steenbergen B, van Thiel E, Hulstijn W, et al. The coordination of reaching and grasping in spastic hemiparesis is characterized by segmentation. Hum Movement Sci. 2000;19:75–105.
56. van Thiel E, Meulenbroek RGJ, Smeets JBJ, et al. Fast adjustments of ongoing movements in hemiparetic cerebral palsy. Neuropsychologia. 2002;40:16–27.
57. van Roon D, Steenbergen B, Meulenbroek RGJ. Trunk recruitment during spoon use in tetraparetic cerebral palsy. Exp Brain Research. 2004;155:186–95.
58. Mutsaarts M, Steenbergen B, Bekkering H. Anticipatory planning deficit and task context effects in hemiparetic cerebral palsy. Exp Brain Research. 2006;172:151–62.
59. Mutsaarts M, Steenbergen B, Bekkering H. Impaired motor imagery in right hemiparetic cerebral palsy. Neuropsychologia. 2007;45:853–9.
60. Johnson SH, Corballis PM, Gazzaniga MS. Within grasp but out of reach: Evidence for a double dissociation between imagined hand and arm movements in the left cerebral hemisphere. Neuropsychologia. 2001;39:36–50.
61. Ego A, Lidzba K, Brovedani P, et al. Visual-perceptual impairment in children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2015;57:46–51.
62. Steenbergen B, Gordon AM. Activity limitations in hemiplegic cerebral palsy: evidence for disorders in motor planning. Dev Med Child Neurol. 2006;48:780–3.
63. Hallahan DP, Stainback S, Ball DW, et al. Selective attention in cerebral palsied and normal children. J Abnorm Child Psychol. 1973;3:280–91.
64. Fassler J. Performance of cerebral palsied children under conditions of reduced auditory input. Exceptional Children. 1970;37:201–9.
65. Cruickshank WM, Bice HV, Wallen NE, et al. Perception and cerebral palsy: studies in figure-background relationship (2nd ed.) Syracuse, N.Y.: Syracuse University Press, 1965.

66. Surén P, Bakken IJ, Aase H. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics. 2012;130:152–8.
67. Christ SE, White DA, Brunstrom JE, et al. Inhibitory control following perinatal brain injury. Neuropsychology. 2003;17:171–8.
68. Gross-Tsur V, Shalev RS, Badini N, et al. Efficacy of methylphenidate in patients with cerebral palsy and attention-deficit hyperactivity disorder (ADHD). J Child Neurol. 2002;17:863–6.
69. Symons FJ, Tervo RC, Kim O, et al. The effects of methylphenidate on the classroom behaviour of elementary school-age children with cerebral palsy: a preliminary observational analysis. J Child Neurol. 2007;22:89–94.
70. Teuber HL. Why two brains? In: Smith FO, Worden FG, editors. The Neurosciences: third study program. Cambridge: MIT Press; 1974. p. 71–4.
71. Lidzba K, Staudt M, Wilke M, et al. Visuospatial deficits in patients with early left-hemispheric lesions and functional reorganization of language: consequence of lesion or reorganization? Neuropsychologia. 2006;44:1088–94.
72. Liégeois F, Connelly A, Helen Cross J, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain. 2004;127:1229–36.
73. Staudt M, Grodd W, Niemann G, et al. Early left periventricular brain lesions induce right hemispheric organization of speech. Neurology. 2001;57:122–5.
74. Staudt M, Lidzba K, Grodd W, et al. Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography. NeuroImage. 2002;16:954–67.
75. Mountcastle VB. The columnar organization of the neocortex. Brain. 1997;120:701–22.
76. Friston KJ. Functional integration in the brain. In: Frackowiak RS, Friston KJ, Frith CD, et al., editors. Human Brain Function. Amsterdam: Elsevier; 2003. p. 971–97.
77. Stephan KE. On the role of general system theory for functional neuroimaging. J Anat. 2004;205:443–70.
78. Pennington L, Goldbart J, Marshall J. Interaction training for conversational partners of children with cerebral palsy: a systematic review. International J Language Com Dis. 2004;39:151–70.
79. Pennington L, Goldbart J, Marshall J. Speech and language therapy to improve the communication skills of children with cerebral palsy (Cochrane review). The Cochrane Library, Issue 4, Chichester, UK: John Wiley & Sons, Ltd, 2004.
80. Pennington L, Goldbart J, Marshall J. Direct speech and language therapy for children with cerebral palsy: findings from a systematic review. Dev Med Child Neurol. 2005;47:57–63.
81. Chilosi AM, Cipriani P, Bertuccelli B, et al. Early cognitive and communication development in children with focal brain lesions. J Child Neurol. 2001;16:309–16.
82. Foley B, Pollatsek A. Phonological processing and reading abilities in adolescents and adults with severe congenital speech impairments. Augmentative Alt Com. 1999;15:156–73.
83. Vandervelden M, Siegel L. Phonological processing and literacy in AAC users and students with motor speech impairments. Augmentative Alt Com. 1999;15:191–209.
84. Dahlgren Sandberg A. Reading and spelling, phonological awareness, and working memory in children with severe speech impairments: a longitudinal study. Augmentative Alt Com. 2001;17:11–26.
85. Dahlgren Sandberg A. Reading and spelling abilities in children with severe speech impairments and cerebral palsy at 6, 9, and 12 years of age in relation to cognitive development: a longitudinal study. Dev Med Child Neurol. 2006;48:629–34.
86. Smith M. Simply a speech impairment? Literacy challenges for individuals with severe congenital speech impairments. Int J Dis Dev Edu. 2001;48:331–53.
87. Fennell EB, Dikel TN. Cognitive and neuropsychological functioning in children with cerebral palsy. J Child Neurol. 2001;16:58–63.
88. Schenker R, Coster WJ, Parush S. Neuroimpairments, activity performance, and participation in children with cerebral palsy mainstreamed in elementary schools. Dev Med Child Neurol. 2005;47:808–14.
89. van Rooijen M, Verhoeven L, Smits DW, et al. Arithemtic performance of children with cerebral palsy: the influence of cognitive and motor factors. Res Dev Disabil. 2012;33:530–7.
90. Arp S, Fagard J. Handicap visuo-manuel et comptage chez l′enfant IMC ancient premature (Visuo-manual handicap and counting in formerly premature children with cerebral palsy). Approche Neuropsychologique des Apprentissages Chez L'enfant. 2001;13:239–48.
91. Camos V. Coordination process in counting. Int J Psychol. 2003;38:24–36.
92. De Barbot F, Meljac C, Truscelli D, et al. Pour une meilleure intégration scolaire des enfants. I .M.C : l'importance des premiers apprentissages en mathématiques (For a better integration of CP children at school : Importance of basic mathematical learning). Vanves, France: C.T.N.E.R.H.I. (Centre Technique National d'Etudes et de Recherches sur les Handicaps et les Inadaptations), PUF, 1989.
93. Arp S, Taranne P, Fagard J. Global perception of small numerosities (subitizing) in cerebral-palsied children. J Clin Exp Neuropsyc. 2006;28:405–19.
94. Camos V, Fayol M, Lacert P, et al. Le denombrement chez des enfants dysphasiques et des enfants dyspraxiques (Counting in dysphasic and dyspraxic children). Approche Neuropsychologique des Apprentissages chez l'enfant. 1998;48:86–91.

95. Alibali MW, DiRusso AA. The function of gesture in learning to count: more than keeping track. Cognitive Dev. 1999;14:37–56.
96. Uvebrandt P. Hemiplegic cerebral palsy aetiology and outcome. Acta Psychol. 1988;345(suppl):1–100.
97. Jenks KM, de Moor J, van Lieshout ECDM, et al. The effect of cerebral palsy on arithmetic accuracy is mediated by working memory, intelligence, early numeracy, and instruction time. Dev Neuropsychol. 2007;3:861–79.
98. Tager-Flusberg H, Baron-Cohen S, Cohen D. An introduction to the debate. In: Baron-Cohen S, Tager-Flusberg H, Cohen D, editors. Understanding other minds: perspectives from autism. Oxford: Oxford University Press; 1993.
99. Dunn J, Brown J, Slomkowski C, et al. Young children's understanding of other people's feelings and beliefs: individual differences and their antecedents. Child Dev. 1991;62:1352–66.
100. Dunn J. The Emanuel Miller memorial lecture 1995. Children's relationships: capital bridging the divide between cognitive and social development. J Child Psychol Psyc 1996;37:507-518.
101. Harris D. Communicative interaction processes involving non-vocal physically handicap children. Topics in Language Dis. 1982;2:21–37.
102. Pirilä S, Nieminen P, Seppänen R-L, et al. The play of disabled children in early development. In: Hujala E, ed. Childhood Education – International Perspectives. Oulu: Education Center, University of Oulu, Finland Association for Childhood Education International, 1996:209-222.
103. Pirila S, van der Meere JJ, Seppanen R-L, et al. A pilot study on children with limitations in self-care, mobility and social functions. Effects on family strengths. Families in Soc 2006;87:285-292.
104. Bjorgaas HM, Elgen I, Ryland HK, Hysing M. Autism spectrum symptoms in children with cerebral palsy: prevalence and co-occurring conditions. Research in Autism Spectrum Disorders. 2014; 8:581–8.
105. Thomas M, Karmiloff-Smith A. Are developmental disorders like cases of adult brain damage? Implications from connectionist modelling. Behav Brain Sci. 2002;25:727–88.
106. Levine SC, Kraus R, Alexander E, et al. IQ decline following early unilateral brain injury: a longitudinal study. Brain Cognition. 2005;59:114–23.
107. Beckung E, Carlsson G, Carlsdotter S, et al. The natural history of gross motor development in children with cerebral palsy aged 1 to 16 years. Dev Med Child Neurol. 2007;49:751–6.
108. Rosenbaum P, Palisano RJ, Bartlett DJ, et al. Development of the Gross Motor Function Classification System for cerebral palsy. Dev Med Child Neurol. 2008;50:249–53.
109. Shewmon DA, Holmes GL, Byrne PA. Consciousness in congenitally decorticate children: developmental vegetative state as self-fulfilling prophecy. Dev Med Child Neurol. 1999;41:364–74.
110. Watson L, Stanley F, Blair E. Report of the Western Australian Cerebral Palsy Register - to the Birth Year 1994. Perth: Western Australian Cerebral Palsy Register; 1999.
111. Sattler JM. Assessment of children. 3rd ed. San Diego: Author; 1988.
112. McCarty SM, St James P, Berninger VW, et al. Assessment of intellectual functioning across the life span in severe cerebral palsy. Dev Med Child Neurol. 1986;28:369–72.
113. Byrne JM, Dywan CA, Connolly JF. An innovative method to assess the receptive vocabulary of children with cerebral palsy using event-related brain potentials. J Clin Exp Neuropsyc. 1995;17:9–19.
114. Yin Foo R, Guppy M, Johnston LM. Intelligence assessment for children with cerebral palsy: a systematic review. Dev Med Child Neurol. 2013;55:911–8.
115. Hakkarainen E, Pirilä S, Kaartinen J, et al. Visual attention study in youth with spastic cerebral palsy using the event-related potential method. J Child Neurol. 2011;26:1525–8.
116. Hakkarainen E, Pirilä S, Kaartinen J, et al. Stimulus evaluation, event preparation, and motor action planning in young patients with mild spastic CP: an event-related brain potential study. J Child Neurol. 2012;27:455–70.
117. Hakkarainen E, Pirilä S, Kaartinen J, et al. Error detection and response adjustment in youth with mild spastic CP: and event-related brain potential study. J Child Neurol. 2013;28:752–7.
118. Hakkarainen E, Pirilä S, Kaartinen J, et al. Brain state before error making in young patients with mild spastic cerebral palsy. J Child Neurol. 2015;30:1–7.
119. Heldmann M, Rüsseler J, Münthe TF. Internal and external information in error processing. BMC Neuroscience. 2008;9:1–8.
120. Di Lieto MC, Brovedani P, Pecini C, et al. Spastic diplegia in preterm-born children: executive function impairment and neuroanatomical correlates. Res Dev Disabil. 2017;61:116–26.
121. World Health Organization. International Classification of Functioning, Disability and Health. Geneva: World Health Organization; 2001.
122. Simeonsson RJ, Leonardi M, Lollar D, et al. Applying the International Classification of Functioning, Disability and Health (ICF) to measure childhood disability. Disabil Rehabil. 2003;25:602–10.
123. Coster WJ, Haley SM. Conceptualization and measurement of disablement in infants and young children. Infants and Young Children. 1992;4:11–22.
124. Palisano R, Rosenbaum P, Walter S, et al. Gross Motor Function Classification System for Cerebral Palsy. Dev Med Child Neurol. 1997;39:214–23.

125. Russell DJ, Rosenbaum PL, Cadman DT, et al. The gross motor function measure: a means to evaluate the effects of physical therapy. Dev Med Child Neurol. 1989;31:341–52.
126. Harvey A, Robin J, Morris ME, et al. A systematic review of measures of activity limitation for children with cerebral palsy. Dev Med Child Neurol. 2008;50:190–8.
127. Russell DJ, Rosenbaum PL, Avery LM, et al. Gross Motor Function Measure (GMFM 88 & GMFM 66). User's Manual. Clinics in Developmental Medicine, No. 159. London: Mac Keith Press, 2002.
128. Eliasson A-C, Krumlinde-Sundholm L, Rösblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. Dev Med Child Neurol. 2006;48:549–54.
129. Morris C, Kurinczuk JJ, Fitzpatrick R, et al. Reliability of the Manual Ability Classification System for children with cerebral palsy. Dev Med Child Neurol. 2006;48:950–3.
130. McLaughlin J, Bjornson K, Temkin N, et al. Selective dorsal rhizotomy: meta-analysis of three randomized controlled trials. Dev Med Child Neurol. 2002;44:17–25.
131. Blauw-Hospers CH, Hadders-Algra M. A systematic review of the effects of early intervention on motor development. Dev Med Child Neurol. 2005;47:421–32.
132. Shonkoff JP, Meisels SJ. Handbook of Early Childhood Intervention. Cambridge: Cambridge University Press; 2000.
133. Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. J Child Neurol. 2014;29:1141–56.
134. Sterba JA. Does horseback riding therapy or therapist-directed hippotherapy rehabilitate children with cerebral palsy? Dev Med Child Neurol. 2007;49:68–73.
135. Hadders-Algra M. Early diagnosis and early intervention in cerebral palsy. Front Neurol. 2014;5:1–13.
136. Jansen LMC, Ketelaar M, Vermeer A. Parental experience of participation in physical therapy for children with physical disabilities. Dev Med Child Neurol. 2003;45:58–69.
137. Dunst CJ. Family-centered practices: birth through high-school. J Spec Edu. 2002;36:139–47.
138. Brehaut JC, Kohen DE, Raina P, et al. The health of primary caregivers of children with cerebral palsy: How does it compare with that of other Canadian caregivers? Pediatrics. 2004;114:182–91.
139. Pirila S, van der Meere JJ, Seppanen R-L, et al. Children with functional motor limitations: the effects on family strengths. Child Psych Hum Dev. 2005;35:281–95.
140. Guyard A, Michelsen SI, Arnaud S, et al. Family adaptation to cerebral palsy in adolescents: an european multicenter study. Res Dev Disabil. 2017;61:138–50.
141. Ekström Ahl L, Johansson E, Granat T, et al. Functional therapy for children with cerebral palsy: an ecological approach. Dev Med Child Neurol. 2005;47:613–9.
142. World Health Organization. International Classification of Impairments, Disabilities and Handicaps. Geneva: World Health Organization; 1980.
143. Bemister TB, Brooks BL, Dyck RH, et al. Parent and family impact of raising a child with perinatal stroke. BMC Pediatr. 2014;14:1–11.
144. Cicerone KD, Langenbahn DM, Braden C, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Arch Phys Med Rehab. 2011;92:519–30.

Chapter 12

Autism Spectrum Disorder: A Cognitive Neuroscience Perspective

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History and Background

Leo Kanner, an Austrian-born American psychiatrist, first described autism in 1943 [1]. His observations of a small group of children with behavioral symptoms of social withdrawal, impaired language/communication and obsession with sameness led to recognition of autism as a specific pervasive developmental disorder. At about the same time Austrian psychiatrist Hans Asperger independently described similar symptoms in a small group of children except that the "Asperger" children were high functioning with better language and cognitive skills than those described by Kanner [2]. Both Kanner and Asperger used the word autistic to describe the pathology in the children they observed—a term rooted in the Greek "autos" (self) and coined by Swiss psychiatrist Eugen Bleuler to describe symptoms in his schizophrenic patients. Before Kanner and Asperger defined autism as a specific disorder, children with autistic symptoms were most likely classed and treated as mentally retarded or, if they were high functioning, perhaps as schizophrenic.

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The core symptoms described by Kanner and Asperger remain the same, but the diagnosis of autism has evolved and new criteria specified in the DSM-5 [3] (in use as of May 2013) define a continuum of impairments in social communication and restricted and repetitive patterns of behavior that define Autism Spectrum Disorders (ASD). Formerly distinct classifications such as Asperger's disorder are now considered to be a part of the spectrum.

Diagnosis

Screening Guidelines

Increased awareness of autism in the general public has resulted in increased recognition of symptoms in infants and toddlers. The majority (80%) of parents of children with ASD recognize symptoms in the first two years of life and approximately 30% recognize symptoms before their child is 12 months old [4]. Early parent concerns that predict a subsequent diagnosis of ASD include abnormal sensory behavior and motor development at 6 months of age and social communication deficits and repetitive behaviors at 12 months of age [5]. In 25–30% of children, ASD manifests as a regression of communication and social skills after 15–24 months of apparently normal development [6–9]. There is reasonable evidence that ASD can be reliably

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diagnosed in the second year of life [10, 11] and some possibility that there are much earlier behavioral markers associated with ASD. Reviews of data from early screening suggest that screening of infants 18–24 months of age is effective in early detection and that the stability of diagnosis in this age range is as high as 82–93% [12, 13]. Prospective studies of infants who are at high risk for ASD because of affected siblings have found reliable markers in infants less than 12 months who were later diagnosed with ASD [14–16]. These behaviors include abnormalities in eye contact, visual attention (slow disengagement and orienting), visual tracking, imitation, social smiling, orienting to name, temperament, and unusual sensory behaviors. A comprehensive review of studies reporting on early development in ASD suggests that these behaviors do provide stable markers for diagnosis of ASD under the age of two [17]. A review of findings from studies of high-risk infants has provided some surprising information about early signs and symptoms of autism [18]. These studies suggest that many critical diagnostic symptoms are not present in early infancy but develop gradually over the first 2–3 years of life. For example, at six months of age, ASD infants showed abnormal motor development and unusual visual interests, but typical social behavior.

A family physician or pediatrician is frequently the first to be consulted when parents are concerned about symptoms of autism. If neurological signs, such as seizures, are among the symptoms of concern, the child may be referred to a pediatric neurologist. The American Academy of Pediatrics has provided guidelines for the diagnosis and ongoing care management for children with Autism Spectrum Disorders [19–21]. The Council on Children with Disabilities has provided a screening tool for identification of children at risk for ASD [22]. Routine screenings to identify at-risk children are recommended at 9-, 18-, 24- and 30-month visits. The screening instrument and updated recommendations are available online from the American Academy of Pediatrics (http://www.pediatrics.org/cgi/content/full/118/1/405). These policy guidelines were reaffirmed in 2014. The Center for Disease Control (CDC) supports this policy and has developed guidelines (A.L.A.R.M) for early screening and care based on American Academy of Pediatrics and the American Academy of Neurology/Child Neurology Society policy (https://www.cdc.gov/ncbddd/autism/hcp-recommendations.html).

Clinical and Research Criteria

Clinical criteria for the diagnosis of autism are based on the DSM-5 and ICD10 specifications [3, 23]. The DSM-5 represents a substantial change in autism diagnosis. The DSM-IV identified four separate disorders (autistic disorder, Asperger's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified). DSM-5 considers these categories to be on a continuum–Autism Spectrum Disorders (ASD). Criteria for a diagnosis of autism require impaired behavior in each of two domains (social communication and social interaction; and restricted, repetitive patterns of behavior, interests, or activities). Symptoms must be persistent, present early in development, cause significant impairment in function and must not be better explained by intellectual disability. While the clinical diagnosis is most commonly based on DSM criteria and expert judgment, there are many assessment instruments used to enhance the specification of clinical features in research and treatment settings. The current gold standards for diagnostic instruments are the Autism Diagnostic Interview, Revised (ADI-R), and the Autism Diagnostic Observation Schedule, second edition (ADOS-2) [24–26]. These instruments score impairment in several domains and have excellent reliability and validity. Both instruments are, however, relatively expensive, require extensive training for the test administrator and a lengthy administration time. Many additional assessments are used to evaluate clinical features of autism. For example, the *Scales of Independent Behavior-Revised (SIB-R)* [27] assess adaptive functioning. The *Social Responsiveness Scales, second edition (SRS-2)*

[28] provide measures of social function and social communication including social awareness, social information processing, and capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupation/traits. The Childhood Autism Rating Scale (CARS) is broadly used as a measure of symptom severity [29].

Autism is associated with other psychiatric and medical conditions including in a small percentage, Fragile X (1%) and tuberous sclerosis (0.4–2.8%) [30]. The most common medical condition associated with autism is epilepsy, and even in the absence of epilepsy there may be an elevated incidence of epileptiform abnormalities in the EEG. Studies with larger sample sizes (more than 100 subjects) have reported epilepsy rates that range from 0 to 39% [9, 31–37]. The wide range of rates is probably attributable to widely varying population samples, and in some cases, varying definitions of epilepsy. While there is a peak onset of epilepsy in early childhood, and a possible second peak of onset in adolescence [38], epilepsy can develop in autism anytime during childhood and adolescence (with some less common instances of onset in adulthood as well). Commonly diagnosed psychiatric conditions comorbid with ASD include ADHD in as many as 30–50% [39] and clinically significant anxiety symptoms in 40–80% [40, 41].

Increased Prevalence of Autism: It's not the Vaccine

Is the prevalence of autism increasing? Considerable media attention has been devoted to a potential increase in the prevalence of autism spectrum disorders over the past couple of decades. Speculation about reasons for such an increase in the rate of autism has included most prominently a concern over the role of environmental factors, particularly childhood vaccination. A comprehensive review by Canadian psychiatrist and epidemiologist Eric Fombonne compiled survey data from 14 different countries over the last several decades to track changing rates of autism [37]. Fombonne reported that early surveys using Kanner's strict diagnostic criteria estimated rates of autism at 3.8 per 10,000 while later surveys using DSM-IV [42] and ICD-10 [23] diagnostic criteria estimated autism rates at 20 per 10,000. A Finnish study reviewed by Fombonne illustrates the result of using less strict diagnostic criteria. Using Kanner's criteria, this survey estimated autism prevalence at 2.3 per 10,000 while the prevalence in the exact same large sample using DSM-IV and ICD-10 criteria was estimated to be nearly 3 times larger–7.6 per 10,000 [43].

Despite growing evidence that increased rates of autism most likely reflect changes in diagnostic criteria and an increased awareness of the symptoms of pervasive developmental disorders and not an epidemic rise in autism, concerns have persisted that environmental factors are responsible for the purported rate increase. The major focus of these hypotheses has been the measles–mumps–rubella (MMR) vaccine and a mercury-based preservative (thimerosal) used in many other childhood vaccines [44, 45]. The paper authored by British physician Wakefield and colleagues that first raised this concern was based on fraudulent data [46]. After investigation, the paper was retracted from the journal Lancet and Wakefield subsequently lost his medical license. This fraudulent claim has, however, persisted despite lack of any scientific support. Numerous studies have found no evidence for the association of these vaccines and the increased rate of autism in this country or worldwide (review: [47]). Some of the strongest evidence that there is no such association comes from large ecological studies showing the rise in incidence of autism has occurred in countries where the vaccines in question were not used, or that there is no difference in the incidence of autism in vaccinated and unvaccinated children, or that the rate has continued to increase after discontinuation of the vaccine (e.g., [48–50]). There is also no biological evidence to support these allegations (for reviews see: [51, 52]). An unfortunate result of these unsupported speculations can be seen in recent outbreaks of measles in unvaccinated children in Europe, Japan, and the US [53]. Morton Gernsbacher and her

colleagues have provided a thoughtful analysis of some of the reasons for this "disconnection" between scientific evidence and popular perception [54].

While the MMR vaccine is not a factor in the increase in ASD prevalence, there is evidence that environmental factors in combination with genetic and immunological factors may underlie the rise in prevalence. A small body of evidence suggests association of ASD rates and environmental toxins commonly found in cosmetics, fragrances, pesticides, detergents, food flavorings, and traffic-related air pollution (reviews: [55–57]). One study that demonstrated the effect of antibiotics on prenatal brain development suggests a potential environmental factor that may also explain the larger proportion of males in ASD [58]. An antibiotic-induced absence of maternal microbiome in germ-free mice perturbed microglia that affect fetal brain development both pre- and post-natally—this perturbation was more severe in male embryos and in adult females.

Is there a true increase in the prevalence of autism? It is difficult to say. The diagnosis has become increasingly inclusive, and the signs and symptoms are more commonly recognized by parents and physicians. In any case it is clear that autism spectrum disorders pose an important public health problem. As many as 1 in 68 children will meet the diagnosis for ASD–a pervasive developmental disorder that affects their ability to learn and to function in a social environment (https://www.cdc.gov/ncbddd/autism/data.html). Early diagnosis and treatment are crucial.

Biological Underpinnings

Heritability of ASD, Genetics, and Epigenetics

Heritability of ASD

Autism spectrum disorders have been described as one of the most heritable of mental health disorders and are assessed through the study of a large population-based sample of monozygotic and dizygotic twins with at least one twin with an ASD diagnosis [59]. A study of approximately 5000 siblings revealed that recurrence rates were approximately twice as high in full-siblings as half-siblings [60]. Although researchers acknowledge that these studies often are confounded by shared environment (and gene–environment interactions have been acknowledged in autism), there appears to be a contribution of genetic factors to the neurological origin of ASD.

Genetic Studies—Estimating and Understanding Risk

The hunt for genetic links can help us understand autism, a behaviorally defined disorder, as a product of cellular and molecular differences that contribute to atypical neurodevelopment. Studies have identified single genes and collections of genes that appear to co-vary with different subtypes of autism. One hope for the future of genetic analysis is that these analyses will ultimately help identify likely subtypes in young children and help tailor better behavioral treatments. Of course, identification of genes can also lead to identifying neural pathways that may be feasible drug targets for pharmacological treatments.

The key to understanding genetics in mental health disorders centers around the concept of risk. For our purposes, genetic risk is the likelihood of developing an ASD due to the contribution made by genes, as opposed to environmental factors or a combination of gene and environmental factors. A recent paper maps genetic risk for ASD onto neuropsychiatric variation in the population overall, specifically focusing on adaptability and social communication [61]. This paper and others like it take a "common variation" approach to autism genetics. The common variant approach holds that a potentially large number of genes, many with weak individual contributions to overall risk, can explain a large proportion of autism cases. Work from Gaugler and colleagues [62] reveals that the combined weak effects of many genes—the individuals' genetic background in a sense—

accounted for approximately 49% of ASD risk. One hope is that this approach can identify networks of involved genes, but the statistical power needed to identify replicable common variant networks demands sample sizes even larger than the thousands currently participating (see [63] for a review). An alternative perspective, often referred to as the "rare variant" approach holds that some rare gene variants can have large effect sizes. Each of this type of gene variant confers a substantial increase in risk (see, for example, [64]). These are more difficult to identify in the population and over evolutionary time are culled from the gene pool due to the relatively lower reproductive fitness of carriers. These gene variants can be inherited. The third type of risk comes from de novo mutations. These are not inherited but instead arise through mutations around the time of fertilization.

The common and rare variant perspectives have guided the push to understand the heritable nature of autism and more generally the behaviors and symptoms related to autism. Perhaps not surprisingly, the two perspectives also enrich understanding of different parts of the autism spectrum. The common variant risk for ASD is associated with high cognitive ability in the general population [65]. Hagenaars and colleagues [66] examined the shared genetic underpinnings for cognitive functions, mental, and physical health in a large (>100,000) population sample. They found intriguing relationships in the genetic correlations between cognitive phenotypes and health-related variables. For example, the study revealed strong genetic correlations with both educational attainment (positive) and coronary artery health (negative) suggesting an interesting shared genetic load between two cognitive and physical health variables that warrants further attention. In contrast, rare variants tend to be related to more severe intellectual impairment and in some cases seizure disorders [67].

A recent analysis suggests that these two approaches contribute additively to ASD risk [68]. These different approaches may help the reader understand why one collection of genetic associations seems to associate ASDs with high cognitive ability while the other collection of genetic associations associates ASDs with low cognitive ability. Much as we have learned a great deal about the range of symptom presentation and comorbidities in ASD from related mental health disorders, so too is the genetics community finding shared genetic risk for autism and other mental health disorders [69]. Perhaps similar to a spectrum of symptoms in autism, the genetic risk should be considered in terms of a spectrum of associated disorders.

Epigenetics

The word epigenetics literally means "above" the genome. Epigenetic effects include changes in gene expression without changing the underlying gene sequence. For example, adding certain tags, such as methyl groups to regions of DNA, can result in particular genes being more or less expressed. Similarly, epigenetic changes can affect the way that DNA strands are wrapped, making the underlying sequence either more or less available for reading. One other way in which epigenetic effects manifest is through noncoding DNA. What used to be thought of as "junk" DNA was found to be important during the developmental regulation of gene expression. Parental imprinting is another epigenetic effect in which small subsets of genes are silenced depending upon parent of origin. For example, in maternal imprinting, the alleles of a particular gene inherited from the mother are silent, while the alleles inherited from the father are active.

There are many examples of epigenetic regulation relevant to autism spectrum disorders (for a review, see [70]). A region of chromosome 15 (15q11–13) has been a focus for studies of epigenetic regulation and is also the most frequent chromosomal rearrangement in ASD (for review see [71]). This region overlaps what is deleted in Angelman's and Prader–Willi Syndrome (maternally imprinted for Prader–Willi and paternally imprinted for Angelman). This region of chromosome 15 is frequently duplicated (Dup15q) and depending on the parent of origin, duplications in this region carry a high risk for

ASD [72]. Interestingly, several genes that code for the receptor subunits of the brain's primary inhibitory neurotransmitter, GABA, are found in this region, tying together evidence from epigenetics, autism brain tissue studies [73] and physiological studies of animal models of autism showing an imbalance of excitation and inhibition [74].

Epigenetics also suggest a mechanism for environmental effects on early neurodevelopment. Epidemiological evidence has demonstrated that overwhelmingly stressful events such as natural disasters that occur during gestation result in a higher number of infants born with neurodevelopmental disorders [75]. Early prenatal administration of vitamins, especially those high in the B-vitamin folate, has been associated with a reduction in ASD risk [76]. Folate is a significant contributor to the one-carbon metabolism cycle that is an essential part of the intense methylation that occurs during typical neurodevelopment. A better understanding of the ways in which epigenetic regulation is atypical in neurodevelopmental disorders can help us identify and support ways to normalize epigenetic processes.

Brain Structure

Studies of neuroanatomic abnormality in autism are often inconsistent and controversial. This is not surprising given the heterogeneity of the diagnosis and behavioral symptoms. There has been a veritable explosion of the number of MRI anatomic studies in the last two decades. Imaging and analytic methods in these studies are generally variable and samples are frequently small. However, a few recent imaging studies report data from large to very large samples and provide the important opportunity to examine variability and to map brain structure to behavior.

A few things are clear. There is widespread but heterogeneous brain structural abnormality in autism that can be seen on postmortem exam and MRI. Abnormalities are developmental in nature and most likely begin during prenatal or early post-natal brain development. The most common findings are summarized below, but an exhaustive review is beyond the scope of this chapter. The most commonly reported and replicated findings include abnormalities in the brainstem, cerebellum, limbic system, and overall brain size.

Postmortem Studies

Reviews of the postmortem literature summarize neuropathology in ASD with the most consistent findings in pathology of the cerebellum and brainstem (summaries of neuropathology in a total of 58 postmortem cases in [77–83]). Neuropathology in these studies involves reduced numbers of Purkinje neurons in the cerebellar vermis and hemispheres [84–92].

A consensus paper provides a review of cerebellar pathology (anatomic, genetic, and neurochemical) in autism and the association of this pathology with motor and cognitive symptoms [93]. Points of consensus include agreement that the anatomy of the cerebellum is abnormal in ASD, that the pathology onset is prenatal but progresses post-natally and that the motor and cognitive symptoms of ASD are consistent with cerebellar pathology.

In addition to cerebellar and brainstem pathology, abnormality in limbic structures (hippocampus, amygdala, subiculum, entorhinal cortex, anterior cingulate gyrus, mammillary body, septum) has also been found in a majority of autism cases examined [84, 85, 90, 94, 95]. When present, limbic system abnormality involved increased packing density of neurons and reduction in neuron sizes or a reduced number of neurons [96].

Few abnormalities have been reported in the cerebral cortex on postmortem exam, however, a number of irregularities in cell migration and white matter have been identified including neuronal disorganization, thickened cortices, high neuronal density, neurons in the molecular layer, irregular laminar patterns (poor gray-white matter boundaries), ectopias and smaller and less compact minicolumns [84, 97–100].

Adult brain weight has been found to be normal or lighter than normal in autism but brain

weight from children has been found to be statistically heavier than controls [101]. A review of 55 postmortem autism cases [102] shows highly variable brain weight results. On average, the autism cases were 6% heavier than age-matched controls (a large averaged database). The brains of young children (3–5) were statistically larger than controls but those of older children and adults were not. In the cerebellar nuclei and the inferior olive, Bauman found large neurons in children and small pale neurons in adults [103].

MRI Studies

The first quantitative MRI studies in autism identified abnormally reduced size of the cerebellar hemispheres [104, 105] and subregions within the vermis in children and adults [106, 107]. From that time until 2003, twelve additional studies with a total of several hundred subjects from seven independent labs reported significantly reduced size in one or another subregion of the vermis [108–119] or hemispheres [113], or in overall cerebellar gray matter [120]. In some few cases, cerebellar size reduction was so substantial that it could be detected by visual inspection [121]. Similar hypoplasia in the brainstem has also been reported [114]. A recent study found reduced volume in cerebellar vermis gray matter (lobule VII) in children with ASD was significantly correlated with severity of clinical symptoms of social communication and repetitive behaviors [122]. There is considerable evidence to support the association of the cerebellum in both motor and non-motor function in ASD (reviews: [78, 93]).

While postmortem findings are highly consistent regarding cerebellar and brainstem abnormality, a number of older MRI studies failed to find cerebellar hypoplasia in autism [e.g., 123–125]. Some reported larger than normal overall cerebellar volume in autism [126, 127], but these effects were related to overall larger brain size and not to specific cerebellar overgrowth. Unlike postmortem studies, MRI studies usually employ group analysis rather than a case by case comparison. So, the critical issues are statistical power, sample heterogeneity and the nature of the control sample. For example, while Purkinje cell loss manifests as a dramatic effect on postmortem exam, it is reflected only in small volume changes on MRI (around 10% in the posterior vermis—much less in the whole cerebellum). Most study samples are small (under 20), and variability in measures is nearly always quite large. Additionally, if the brain is large as is commonly reported in autism (see below), the cerebellum will be proportionally large and hypoplastic regions of the cerebellum will not be reflected in absolute numbers. There is also some evidence of an association of verbal IQ and cerebellar measures (e.g., some have reported that the size of the cerebellar vermis is normal or larger than normal in those with high verbal IQ [127, 128]). It is also the case that studies finding no difference in cerebellar vermal measures have studied autism samples with normal or above normal verbal IQ.

Cortical abnormalities found in ASD include reduced parietal gray matter volume [129]. Consistent with reduced parietal volume are reports of reduced thickness of the posterior corpus callosum [117, 130–132]. There is also evidence of abnormal frontal gyrification patterns [133] and sulcal shifting in frontal and temporal cortex [134]. Additional findings include reduced amygdala or hippocampal volume [115, 135–137]; enlarged amygdala or hippocampal volume [138, 139]; and reduced cross-sectional area of the dentate gyrus [140]. Some of the variability in these findings may be age-related with young children showing enlarged limbic regions [126, 139] but adolescents and adults showing no difference [117, 141, 142] or smaller limbic regions [135, 136]. Comprehensive analysis of a very large structural MRI dataset from the Autism Brain Imaging Data Initiative (ABIDE) found reduced gray matter volume in ASD relative to age- and IQ-matched typical controls in the thalamus, cerebellum, regions of the orbital and inferior frontal gyrus, the amygdala, and the parahippocampal gyrus [143]. This study also found age-related gray matter reduction in regions of the medial and inferior frontal gyrus, the inferior parietal lobes, and the superior temporal gyrus.

Increased total brain area or volume has also been reported in autism—these findings are generally consistent in young children but more varied in older children and adults. For example, total brain volume was found to be enlarged in autism in young children (age 4) [126] and in children younger than 12 [144]. Cortical volume was enlarged in autism in young (age 2–3) but not in older children [113, 145]. Enlarged or normal head circumference has been reported in both children and adults [reviews: 81, 102, 144, 146, 147]). For an excellent review of brain size studies see [148]. Enlarged brain volume in children but not adults on MR studies would be consistent with postmortem findings of increased brain weight in children with autism but normal or lighter brain weight in adults (see postmortem section above).

Some of the most interesting and promising neuroanatomic findings are those that suggest a developmental progression of ASD. The general finding is that of early brain overgrowth followed by slowed or no growth [review: 102, 108, 113, 117, 126, 135, 139, 141, 142, 145, 149, 150]. Strong evidence for this model comes from large sample longitudinal studies that report increased whole-brain volumes, regional volumes, and cortical thickness in young children, but decreased volumes in older children and adults [151–153].

White Matter Connectivity

Important for understanding disrupted behavioral function in autism is that abnormal growth patterns suggest associated abnormal connectivity during critical periods of development [154–156]. There is neuroanatomic evidence from white matter studies to support this model. Diffusion tensor imaging (DTI) studies have found increased white matter connectivity in frontal regions in toddlers and reduced connectivity in older children, adolescents, and adults [157–161].

Some studies have linked abnormal connectivity to regions supporting behavioral function. For example, Barnea-Goraly [162] reported reduced fractional anisotropy (FA) seen on diffusion tensor imaging (DTI) in regions associated with social cognition including fusiform gyrus and the superior temporal sulcus (face processing); anterior cingulate, amygdala, ventromedial prefrontal cortex (awareness of mental states and emotion); callosal fibers that connect prefrontal with motor, sensory, and auditory cortices (connectivity that supports development of social skills). Similarly, Lee and colleagues found evidence on diffusion tensor imaging of white matter abnormality in temporal lobe regions that might be expected to affect language and social communication [163].

Nordahl and colleagues reported abnormal cortical folding in children and adolescents with autism that is consistent with abnormal patterns of brain development and subsequent abnormalities of connectivity in frontal and parietal cortex [83]. Recent work by Lewis and colleagues provided evidence for the relationship between early brain overgrowth in autism and reduced long-distance white matter connectivity. Based on Ramón y Cajal's hypothesis that neural circuit design is under pressure to minimize cellular costs and conduction delays, and evidence that larger brain size is associated with reduced long-range connectivity across species [164–166], Lewis and colleagues hypothesized that the early brain overgrowth in autism would result in reduced long-range connectivity [167–169]. Lewis and Elman used neural network modeling to examine this hypothesis and demonstrated that increased conduction delays presumably associated with early brain overgrowth lead to reduced long-range structural and functional connectivity, and also poorer performance [169]. Their results provide theoretical support for a tie between the early brain overgrowth and reduced connectivity in autism. Using diffusion tensor imaging (DTI) with tractography, Lewis demonstrated that in healthy young adults, a larger brain is associated with reduced long-range connectivity and have thus provided direct evidence of structural reduction in long-range connectivity in adults with autism [170, 171].

In summary, developmental growth patterns reported from imaging [113, 145, 172] and

postmortem studies [101] are consistent with an ongoing pathologic process [79] that involves early overgrowth followed by slowed growth during maturation. These abnormal developmental patterns may result in abnormal white matter connectivity [154–156, 161, 170, 171] and an accelerated loss of brain tissue with aging [79].

Brain Function

Functional Connectivity

Structural connectivity is a direct measure of white matter fibers that connect brain regions providing pathways for communication between cell assemblies. Functional "connectivity" is, however, inferred from correlations between regions of brain activity observed on MRI, EEG (electroencephalography), or MEG (magnetoencephalography). These imaging methods provide an indirect measure of the neurochemistry that drives brain communication (functional connectivity). While a correspondence of functional and structural connectivity is to be expected, structural pathways provide only a partial explanation for functional connections. Multimodal approaches that integrate information across levels of analysis will ultimately guide understanding of the complexity of brain function (for a review of these issues and methods see: [173]).

The pattern of early brain overgrowth followed by slowed or no subsequent growth in ASD predicts a disruption of structural and functional connections that drive the clinical and behavioral symptoms in the disorder. Studies examining the expected reduced long-range and increased local or short-range connectivity have, however, been largely inconclusive. The functional connectivity findings from various imaging methods are both inconsistent and controversial—a result that is in large part due to differences in methods, error inherent in each imaging approach and sample heterogeneity (review: [41]).

In spite of general inconsistency in this literature, there is some reasonable consensus from both fMRI and EEG/MEG default mode or resting state studies that long-range connectivity is reduced, but there is little agreement on the localization of these abnormalities (reviews: [174–176]). For short-range or local over-connectivity there is little or no consensus. EEG/MEG connectivity is generally analyzed as a function of frequency but that is rarely the case for fMRI although there is evidence that results may differ in high- and low-frequency bands [177]. Some studies have noted that functional connectivity is not static and that variance over time reflecting reduced consistency of the connection in ASD is an important factor contributing to overall strength of connectivity [178, 179].

Both reduced and increased connectivity have been linked to behavioral and neuropsychological deficits in ASD. For example, abnormalities of functional connectivity have been associated with behaviors including severity of clinical symptoms, attention, language, social communication, sensory response, and repetitive behaviors [176, 177, 180–190]. The majority of the functional connectivity literature in ASD comes from default mode or resting state studies. A number of researchers have suggested that examination of task-related functional connectivity may provide different and important insight into the dynamics of brain function and that it may be more important to examine task-related modulations of connectivity than to examine static differences [191]. While dozens of studies have found reduced functional connectivity during tasks that represent deficits for ASD (reviewed in: [192]), Keehn and colleagues found increased long-range and local connectivity during a visual search task at which ASD participants excelled. An exciting possibility regarding the malleability of functional connectivity comes from a small intervention that used training in the magnet to increase weak functional connectivity in target regions [193]. Training in four sessions over eight days produced increased connectivity in the targeted regions and significantly improved social and behavioral scores on parent report questionnaires [28].

From Neurons to Behavior

Neurocognitive Models of ASD

Early cognitive models hypothesized a framework for neuropsychological function in autism (for reviews see: Baron-Cohen et al. [194–196]; Russell [197]; Hill and Frith [198]; Levy [199]). The *Theory of Mind* (TOM) deficits model, proposes that the origin of social communication in autism is an impaired ability to attribute feelings and thoughts to others—that is to understand one's own or another's state of mind. The *Executive Function Deficits* model is based on patterns of impairment in ASD that are typically associated with frontal lobe function. These deficits include planning, set shifting, perseveration, working memory, and control of action and inhibition [198, 200, 201]. The *Weak Central Coherence* model is based on the bias to process details that results in enhancement of segments of information at the expense of context. This model suggests a weakened ability to integrate or bind details into a coherent whole that affects many domains of behavior in autism [202–204]. Although all of these cognitive models have been associated with underlying neural systems, they are largely descriptive, and each explains only a portion of the clinical and behavioral symptoms of ASD. All are important, however, as frameworks within which to advance research and develop treatment interventions.

Prospective studies of infants at risk for ASD have provided critical developmental data resulting in more comprehensive and sophisticated models that incorporate cognitive and brain development and underlying neural mechanisms. The most common and promising of these is a model of abnormal functional connectivity that provides a framework which accommodates explanations of abnormal development across levels of function from cells to behavior, reviews: [175, 188, 205–207].

The first study to suggest a model of disrupted connectivity was conducted by Horwitz and colleagues more than three decades ago [208]. This early positron-emission tomography (PET) study demonstrated that in adults with autism there was reduced correlation in resting cerebral metabolism in brain regions that serve directed attention including frontal and parietal cortex and the thalamus. These authors were the first to suggest the failure of integrated long-distance communication in the autistic brain. Subsequent models proposed that early brain overgrowth could result in abnormal white matter and functional over- and under-connectivity that could predict the clinical and behavioral and cognitive features common to ASD [154–156, 169].

Piven provides a comprehensive framework that expands the earlier models to incorporate mechanisms that may underlie early brain overgrowth and that manifest ultimately in the clinical and behavioral symptoms of ASD [206]. Piven reviews evidence for a framework that proposes an increase in early neural progenitor cells that results in early brain overgrowth leading to disruption of the formation of neural connections. The early abnormalities in structural and functional connectivity disrupt sensorimotor function and attention and this disruption of early experience leads to the emergence of the clinical, behavioral, and cognitive symptoms that define ASD (see Fig. 12.1). This framework can incorporate genetic precursors as well as a model that proposes an excitatory–inhibitory imbalance in brain neurotransmission as an underlying mechanism that contributes to the cognitive and behavioral deficits of ASD [209–211].

Neuropsychological Profiles

Attention

Attentional dysfunction is a prominent feature of autism, first noted by Kanner in his early descriptions of the disorder [1]. While attentional dysfunction is not a criterion for clinical diagnosis of autism, visual attention dysfunction and slow attention orienting have been identified as markers in early diagnosis [14, 17, 18, 212]. This early disruption of attention orienting is proposed to underlie the emergence of social and behavioral deficits that define ASD including

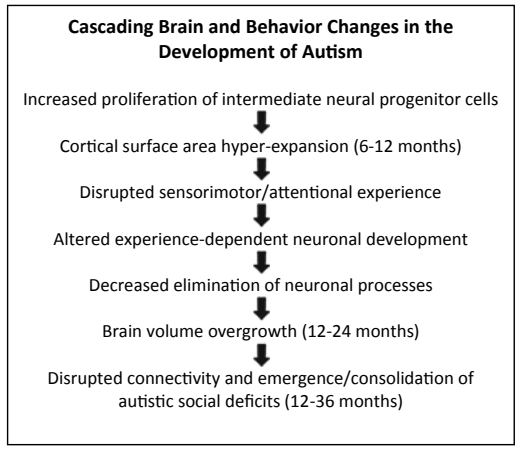

Fig. 12.1 Adapted from Fig. 2 [206]

social-emotional regulation, social communication, joint attention, and eye contact [213–216], (reviews: [206, 217]).

Many studies of infants at risk for ASD use observational methods to identify diagnostic markers. Attention orienting (overt and covert) can, however, be measured objectively. For example, infants later diagnosed with ASD showed slow visual orienting measured by saccadic reaction time at 7 months of age [214]. These authors, as others, propose that disrupted attention affects development of social function in these infants. Bryson and colleagues also used eye-tracking to demonstrate an asymmetric (left-sided) slow attention disengagement in infants 6–12 months who were later diagnosed with ASD [213]. At 12 months these infants showed atypical emotional distress (irritability). Bryson suggests that this asymmetric impairment of attention disengagement represents slow orienting and notes that attention training might be an important component for early intervention.

Slow attention orienting and slow disengagement can be measured independently, but are clearly related. An early study that used electrophysiological markers of visual attention distribution suggests a mechanism for this association [218]. This study found that adults with autism who had abnormal widening of parietal sulci showed abnormally focused (spotlight) attention. This highly focused attention was associated with faster behavioral response and earlier and larger event-related potential (ERP) responses to visual stimuli at their attended focus. This spotlight attention effect is consistent with a current study that demonstrated a narrowed functional field of view in ASD children [219] and also consistent with early clinical observations of stimulus over-selectivity and overfocused attention [220, 221]. While this narrowed focus may produce superior performance within the attentional spotlight, there is a cost. The spotlight focus is associated with gating of surrounding visual information which slows attention disengagement and prohibits rapid response to information outside the attentional spotlight (i.e., slow reorienting of attention). These results are also interesting in the context of a study that found an association between behavioral measures of sensory over-reactivity and overfocused attention in young children with autism [222].

Impaired attention orienting and disengagement are present in ASD in the first year of life, and there is substantial evidence that these deficits are lifelong (review: [217, 223]). Adults and children with autism have been reported to have: difficulty disengaging attention from a spatial focus and shifting to a new location [224–226]; slowed shifting of spatial attention [227–229]; difficulty adjusting an attentional lens [230–232];

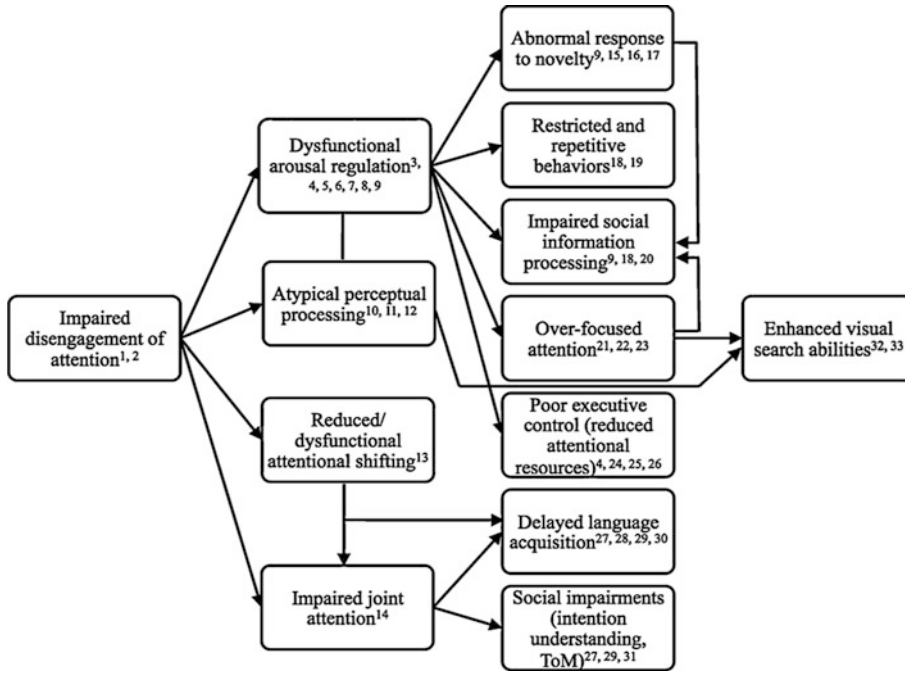

Fig. 12.2 From Keehn et al. [238] Fig. 3. **Outline of developmental framework**. *Longitudinal or correlational findings supporting link or association of abnormal attention with ASD symptomatology* [2, 4, 7, 8, 14–16, 18, 21, 27–29, 31–33], *previous theories that hypothesized link of impaired attention to autism behaviors* [9, 12, 13, 17, 19, 21], *findings from literature on typically developing subjects, and supporting link of attention with autism* [5–8, 10–12, 22, 23], (1) Elsabbagh et al. (2009); (2) Zwaigenbaum et al. (2005), (3) Anderson and Colombo (2009), (4) Keehn et al. (2010), (5) Field (1981), (6) Harman et al. (1997), (7) Johnson et al. (1991), (8) McConnell and Bryson (2005), (9) Dawson and Lewy (1989a), (10) Colombo et al. (1995), (11) Gardner et al. (1992), (12) Colombo (1995), (13) Courchesne et al. (1994), (14) Schietecatte et al. (2011), (15) Gomot et al. (2008), (16) Keehn and Joseph (2008), (17) Gold and Gold (1975), (18) Garon et al. (2009), (19) Hutt et al. (1964), (20) Pierce et al. (1997), (21) Liss et al. (2006), (22) Britton and Delay (1989), (23) Tracy et al. (2000), (24) Ciesielski et al. (1995), (25) Geurts et al. (2009a, b), (26) Raymaekers et al. (2004), (27) Charman (2003), (28) Dawson et al. (2004), (29) Presmanes et al. (2007), (30) Thurm et al. (2007), (31) Schietecatte et al. (2011), (32) Joseph et al. (2009) and (33) Keehn et al. (2012)

and abnormal distributions of visual attention spatial focus [218, 219]. Landry and Bryson found severe impairment in disengagement of attention from a spatial focus in the majority of children with autism spectrum disorder tested [233]. This study employed a comparison group of children with Down syndrome in whom attentional disengagement was normal.

There is growing evidence to support the model that disruption of basic attentional mechanisms may underlie clinical symptoms of autism such as language acquisition and social communication. For example, a study done by Keehn and Joseph [234] found that children with ASD were not responsive to the onset of targets during visual search. This inattention to novel information was significantly related to greater socio-communicative impairment in children with ASD. Keehn and colleagues [235] also found impaired efficiency of the attention orienting network in children and adolescents with ASD on the Attention Network Test [236, 237]. This impairment was associated with deficits in social function. Keehn has proposed a model to explain the developmental influence of impaired attention orienting/disengaging on the development of social communication [238]. See Fig. 12.2. Slowed manipulation of attentional resources would particularly interfere with dynamic social interactions. Interestingly, there

is evidence that slowing facial movement and vocalizations significantly improve emotional expression recognition and imitation in autistic children [239]. An inability to follow the rapid ebb and flow of normal social interaction would also interfere with the expression of joint or shared attention—a skill that is a prerequisite for language acquisition and a skill that is impaired in autism [240–242]. There is evidence that children with autism have difficulty orienting to social stimulation and that this deficit is correlated with deficits in shared attention [243].

In addition to deficits in orienting and disengaging attention, experimental tasks requiring dynamic manipulation of attention have typically found attentional dysfunction manifested in numerous ways [review: 223, 244]. Focused or sustained attention has generally been found to be intact in autism (except that it may be "overfocused" and slow to disengage), but more complex attentional operations including divided and shared or joint attention, susceptibility to distraction and attentional zoom have been found to be impaired [217, 222, 232, 244–251].

Courchesne and colleagues found that adolescents with autism were slow to shift (reorient) attention between auditory and visual information [249]. Using the same task, Akshoomoff found similarly slow attention shifting in children with acquired cerebellar damage [250]. While typically developing children were able to shift attention between auditory and visual information almost instantaneously, children with autism (and those with cerebellar lesions) required more than two seconds to reorient attention. Similarly, a recent study found significantly worse than typical performance in ASD children on cross-modal shifting tasks [252].

Electrophysiological (ERP) responses during spatial attention processing in autism and in patients with acquired cerebellar lesions demonstrated deficits in attention orienting that may represent dysfunction in long-range cerebello-frontal attention pathways [253]. In a task that required attention orienting to peripheral space, an electrophysiological marker thought to index attention orienting was significantly delayed and reduced over frontal cortex in adults with autism, and the latency delay was significantly associated with the size of the posterior cerebellar vermis. An fMRI study of visual-spatial processing in autism also found evidence for dysfunction in frontoparietal networks [254]. Neuroanatomic studies have identified developmental structural abnormalities in both the cerebellum, frontal, and parietal cortex [103, 108, 112, 255]. An fMRI study of spatial attention in autism has implicated both parietal and cerebellar dysfunction [186]. Haist et al. found abnormal activation in both superior and inferior parietal regions during spatial attention shifts in adults with autism. In addition, reduced activation in dorsolateral prefrontal cortex and the posterior cerebellar vermis in the autism subjects suggested a dysfunctional cerebello-frontal attention system. These studies suggest that both a frontal-cerebellar network that supports spatial attention orienting and a posterior network that supports disengaging of spatial attention may be impaired in autism. Disruption of these long-range attention networks would also be consistent with a model of abnormal structural and functional connectivity.

Sensation, Perception, and Motor Function

Abnormal sensorimotor function is one of the earliest observable signs of ASD and this early disruption of sensorimotor experience subsequently results in the higher level cognitive, social, and behavioral features that define ASD. In a recent perspective piece [256], a good case was made for considering the early neural events and associated early atypical sensorimotor behaviors as setting up a very different set of future interactions with the world, the end result being the collection of features we define as ASD. In this section, we will review some of these features and separate them loosely into sections covering Sensation, Perception, and Movement. Although no clear line denotes the boundaries among these broad categories, this review of sensorimotor behavior moves from the sensory periphery through higher level perceptual phenomena, including multisensory perception, and finally to motor output.

Sensation

Abnormal responses to sensory stimuli are a commonly reported feature of autism, and as such they form a component of the diagnosis on several standardized assessments. For example, the evaluation of sensory responses comprises 3 out of 15 items on the Childhood Autism Rating Scale [29]. Abnormalities in sensory responses are evaluated in some detail by the Diagnostic Interview of Communication and Social Behavior (DISCO) [257, 258] and the Sensory Profile (SP) [259]. The DISCO is based on clinical observation and evaluates the proximal sensory abnormalities (e.g., smell, taste, touch) most commonly reported as clinical symptoms in autism [260]. The SP assessment represents a more even distribution across all sensory systems.

Secondhand or observational reports of sensory sensitivities are plentiful, with parents and/or other observers documenting greater proportions of sensory-seeking or sensory-defensiveness behaviors in ASD children and adults than in either normal or other clinical controls [261–266]. Behaviors exhibited by individuals with autism can include an unusual interest in bright lights or shiny objects, twisting or flicking hands or objects near the eyes, negative reactions (including covering the ears) to loud sounds, an unusual tendency to explore objects or people by smelling them, discomfort during grooming or dental work, frequent twirling or spinning, and indifference to heat, pain, or cold. The less-frequent self-reports corroborate the observational findings, with autistic individuals reporting more sensory distortions than typically developing controls [264, 267]. There is some indication that sensory abnormalities abate with age [261, 268], although Minshew and colleagues found increased numbers of sensory abnormalities in autistic individuals compared to normal controls at all ages in a sample ranging from 8 to 54 years [264]. Robertson and Baron-Cohen have provided a comprehensive review of sensory-perceptual processing in autism that includes evidence for abnormalities in brain structure, function, neurochemistry, and genetics that may underlie sensory dysfunction [269].

Despite the seemingly indisputable association of sensory processing abnormalities with autism, the basic mechanisms underlying these sensory sensitivities are not at all clear. There is some evidence for dysfunction at the level of sensory input. For example, a review of evidence for fundamental problems in vision finds typical visual acuity, but numerous deficits including problems with eye movement, visuomotor integration, and strabismus [270]. In audition, there is evidence for delayed neural timing and poor tracking of pitch changes [271]. Reviews report evidence for disruption of sensory neural oscillations [272] and a number of neurophysiological markers of abnormal sensory processing [273]. Rogers and Ozonoff [14] point out that "[t]here is a widely held assumption that sensory and repetitive behaviors are closely related… [and] that either repetitive behaviors have sensory origins or that both types of symptoms are driven by chronic hypo- or hyper-arousal." Rogers and Ozonoff compiled a comprehensive review of studies through 2003 in order to evaluate evidence for abnormalities in general arousal levels, in arousal to specific stimuli, or in habituation to stimuli as an explanation for the unusual response to sensory stimuli found in autism. They concluded that there was no reliable support for a general heightened level of arousal in autism, although there was *some* consistent support for under-arousal to stimuli. Either way, the idea of motor stereotypies functioning to regulate levels of stimulation and/or arousal levels appeared to be unsupported.

While most sensory studies have investigated auditory and visual processing, some research on the tactile modality suggests that there are multiple mechanisms to consider regarding somatosensory response in autism. Both O'Riordan et al. [274] and Cascio et al. [275] found that high-functioning individuals with autism were not different from normal controls in their ability to detect light pressure against the skin. However, additional findings from the

Cascio study were that autistic adults had lower detection thresholds for vibrotactile stimuli on their forearms (but not the palm), and that they had lower hot and cold pain thresholds overall. Guclu et al.'s [276] finding that high-functioning autistic children and typically developing children had similar detection thresholds for vibrotactile stimuli on the fingers is consistent with the Cascio results. Tommerdahl et al. [277] recently reported that the improved tactile spatial localization that accompanies adaptation to a long-duration (5 s) vibrotactile stimulus in normal adults is absent in high-functioning autistic adults. The authors suggest that the lack of improvement in autistic subjects implies abnormal corticocortical connectivity.

Perception

Studies of visual perception in autism have found evidence for superior performance in some tasks and impaired performance in others. A review by Dakin and Frith compiles evidence that in ASD simple lower order visual perceptual processing is enhanced while more complex higher order processing is impaired [278]. See Fig. 12.3. ASD subjects have demonstrated superior processing of detail: on block design subtests from the WISC [279]; on detection of embedded figures [280, 281]; visual search for simple or conjoined features [282–284]; and on reproduction of impossible figures [285, 286]. In processing higher order (or integrated) information, ASD subjects have demonstrated impaired use of context in orientation discrimination [287] and in visual illusion [204] (although note that a subsequent study [288] using different illusions and methods did not replicate this finding).

Studies that have attempted to gather objective measures of auditory perception have found superior pitch discrimination and categorization abilities in high-functioning individuals with autism compared to normal control subjects [274, 289], though it is not yet known whether this "enhanced" processing is a characteristic of lower functioning autism as well. Researchers have also attempted to trace early auditory transmission along the brainstem by measuring the brainstem auditory evoked potential (BAEP) [290–296], examine subcortical sensory gating by measuring pre-pulse inhibition as indexed by the P50 wave [297–299], and assess processing

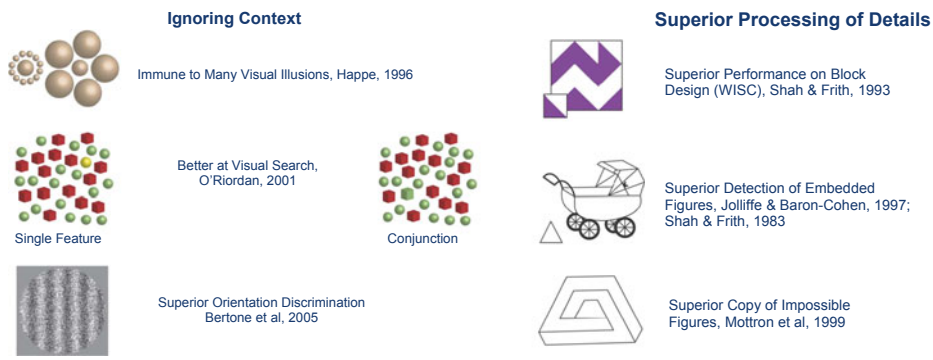

Fig. 12.3 From: Fig. 2, Dakin and Frith [278]. Figures show examples of tasks in which ASD subjects showed superior processing of detail (local processing bias) and superior performance as a result of suppressing or ignoring context

in auditory cortical areas by measuring early electroencephalographic or magnetoencephalographic potentials [300–302]. Results in each of these areas have been contradictory, with inconsistent findings possibly stemming from differences between the presence or absence of mental retardation in the various samples, other issues relating to study controls, or methodological differences between studies.

The majority of attempts to reconcile the variety of findings in autism studies of sensory perception have generally agreed that auditory and visual perception of simple or low-level information is superior, while perception of more complex or higher level information is impaired in autism. The Dakin and Frith review of visual perception studies concludes that there is robust evidence for superior local processing in autism [278]. They caution however that the evidence for reduced global processing is less convincing. One possible reason for this inconsistency comes from studies of attentional zoom lens. Ronconi and colleagues found that ASD children were able to narrow attentional focus (zoom in) as well as typical children, but were less able than typical children when broadening attentional scope (zoom out) [232]. This suggests that the quality of global processing would depend on the scope of initial attentional focus (broad or narrow). Kaldy reviews evidence that also supports an attentional rather than a perceptual explanation for superior local processing [303]. The intense attentional engagement that accompanies slowed disengagement is an alternate explanation for superior sensory perception. This hypothesis receives some support from an ERP study that found visual search efficiency was associated with attention-related but not perception-related ERP components [304].

A review of auditory perceptual studies concluded that the variability in results could be explained by the complexity of the material and the tasks [305]. Samson and colleagues found that studies using low-level auditory stimulation (e.g., pure tones) and simple tasks (e.g., detection, identification, chord disembedding) reported superior behavioral results and shorter latency brain responses in ASD subjects while studies using more complex material and tasks reported poor behavioral performance and abnormal brain responses in ASD subjects. The authors suggest that the "neural complexity" required to perform the higher level tasks may be deficient in autism. Mottron and colleagues have proposed an "Enhanced Perceptual Functioning" processing model in which the general profile of visual and auditory perceptual processing (enhanced low-level processing and impaired complex processing) can be explained by overdependence on low-level sensory-perceptual processing. There is some support for this model from recent functional MR studies. Two separate studies used embedded figure tasks to examine task-associated brain activation in autism and control subjects [190, 306]. Both reported that in autism subjects there was increased activation in early visual brain regions and reduced activation in the frontal and parietal regions that were robustly activated in control subjects. While there is as yet little consensus regarding the specific underlying explanatory model for the sensory-perceptual profile in autism, findings reviewed here seem at least generally compatible with local (sensory) functional over-connectivity and long-range (association) under-connectivity [e.g., 196]. A review of enhanced perceptual abilities in ASD and an updated version of the enhanced perceptual functioning model proposes that the abnormalities of network connectivity in ASD underlie a predisposition to veridical mapping (coupling of perceptual information and homological data) and the high rate of superior perception and savant abilities [307].

Movement

Differences in movement were part of the earliest descriptions of autism [1, 2]. Clinical neurological assessments frequently identify motor skill deficits in individuals with ASD [308, 309]. When comprehensive, normalized tests of motor impairment are used for studying motor skill in autism, deficits are identified that range from gross to fine and simple to complex. In a study of concordant and discordant sibling pairs, Hilton and colleagues [309] found that the affected

siblings were far more likely to score at least 1 standard deviation below the mean for the general population, and a low motor score correlated with ASD severity. A study comparing children with an ASD diagnosis with an ASD + ADHD diagnosis revealed significantly more instances of motor impairment in the ASD + ADHD group [310]. Tasks involving motor sequencing, as well as motor learning are also a common challenge for individuals with ASD [311]. Finally, individuals with ASD are frequently labeled "clumsy" and may even have a comorbid diagnosis of Developmental Coordination Disorder [312]. Dyspraxia refers to a difficulty in organizing, planning or executing skilled movement in a manner that impairs movement fluidity and speed, and is out of proportion to any underlying motor deficits. Deficits in dyspraxia are observed in ASD as well, but interestingly do not appear to indicate or relate to a larger pattern of gross or fine, simple or complex motor impairment (see Fig. 12.4; [313]). These findings suggest that in future revisions of our evolving concept of ASD, motor impairment might be considered a core characteristic of ASD. That said, lower intellectual ability generally speaking appears to be correlated with weaker motor skill [314, 315].

Many of the earliest observable signs of ASD are motor. Early differences in orienting behavior and atypical body movements and motor development are common early signs [12, 14]. The aspect of motor, and especially orienting behavior that interests us, is that these early differences persist, creating delays and inaccuracies in gaze shifts as well as consistent sensory feedback resulting from overly variable movements. This early atypical orienting and exploratory motor development can set a child on a path toward atypical social behavior.

One of the most foundational motor skills for functional engagement with the environment is balance. Balance deficits are observed across a

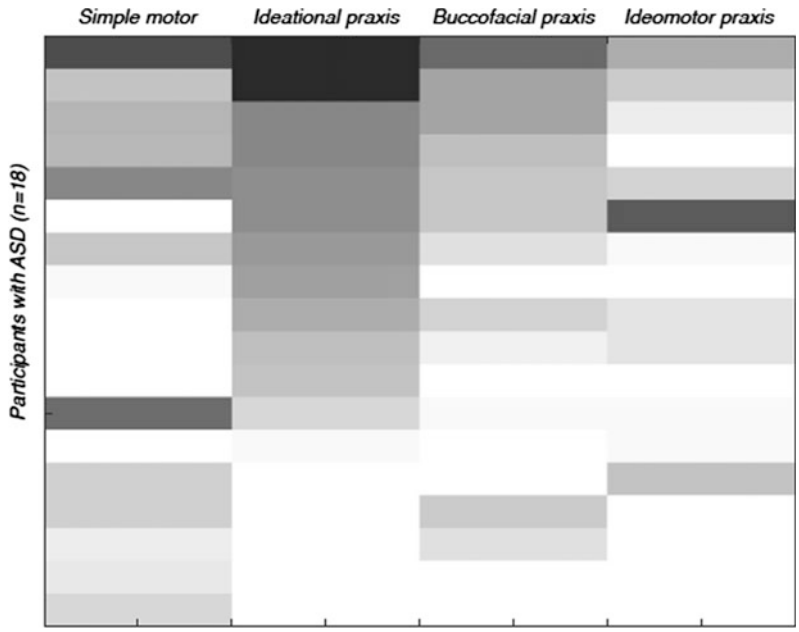

Fig. 12.4 (From: Miller et al. [313]) Variability within and across ASD participants for simple motor and praxis indices. Color represents the number of subtests affected (typical/atypical) on each praxis category and simple motor index. Scores on each dyspraxia battery subtest were summed by first normalizing the scores for each test and then averaging the tests for each subscale. For the numerical tasks like finger tapping and finger sequencing, participants scored a "1" for normal if their score was with one standard deviation of the mean of the typical participants and "0" or atypical if it was outside that range. Lightest color represents least impaired performance (lowest number of atypical subtests)—darkest represents most impaired (highest number of atypical subtests)

wide age range of individuals with ASD and normal intelligence [316–321]. In an early study from Minshew and colleagues [319], the impairments were most pronounced in conditions that perturbed either visual (eyes-closed or sway-referenced surroundings) or somatosensory stimulation (sway-referenced platform). Other studies confirm that while balance skill can appear typical in easy conditions, increased challenges due to closing eyes, standing on one foot, or decreasing the stability of the balance surface [322] substantial deficits in ASD balance performance are revealed.

Static and dynamic balance skills are essential for functional gait behavior. Several studies have reported atypical gait in individuals with ASD. Qualitative evaluations have revealed a lack of smoothness or overall coordination, atypical trunk and arm postures, or asymmetrical gait [323–327]. Quantitative evaluations have confirmed the lack of smoothness and irregular trunk movements, and in addition have shown significant differences in other spatial and temporal gait parameters [328–331]. While the specific gait parameters identified as abnormal vary from study to study, shorter step/stride length in ASD is a common finding.

Reaching and grasping behaviors are also extremely important for functional interaction with the environment. Children with ASD appear to be slower in performing anticipatory postural adjustments, such as one would make to grab or let go of a heavy object [332]. Children with ASD also failed to anticipate making a hand movement that was very predictable—a departure from what is observed in typical children [333]. A quantitative analysis of reaching behavior shows multiple specific deficits. Several studies demanding multistep reaching movements suggest deficits in sequential reach planning for individuals with ASD [334, 335]. These studies illustrate a lack of integration of movements that compose a sequence, and importantly most movements are not singular but executed as part of a sequence. In addition to problems with motor sequencing, both anecdotal reports and studies of arm movement trajectory reveal variability in the movement itself [336–339]. This is interesting because reaching movements are typically very repeatable both within and across subjects. One suggestion for the degree of variability has been the injection of noisy or biased sensory feedback into the movement. Mari and colleagues [338] showed differences in timing of a reach-to-grasp movement that varied with intellectual ability in a sample of 20 children with ASD, with children who had the lowest IQ ranges also having the slowest, almost Parkinsonian movements. The control children were matched for age, intellectual ability, and handedness, yet did not share the variance in movement quality and timing observed in the ASD group.

Fine motor skills have been studied most often as part of larger motor skill batteries and have recently been the focus of a number of investigations. A large study of 10–14-year-old children with ASD reported that 79% of the children showed fine motor skill deficits as part of the Movement Assessment Battery for Children (M-ABC; [340, 341]). One report found that gross and fine motor skill deficits were roughly equivalent in children with ASD [342]. Grasping is an important early motor skill for an infant exploring his or her world. At school age, items to manipulate become smaller and handwriting becomes increasingly necessary, demanding improved fine motor control. Precision grip is important for holding a writing implement. Researchers examined temporal execution of grip onset with respect to load onset and peak grip force. Both ASD and developmentally delayed groups had developmental trajectories between ages 2 and 6 that differed in comparison with typical children on two measures of grip timing, but not force [343]. These results suggest that problems with timing patterns of action affect fine motor control in addition to other timing problems in gross motor patterns, such as gait.

Illegible handwriting was specifically noted by Hans Asperger in his initial description of this disorder [2, 344]. Fuentes and colleagues led a study of handwriting in individuals with ASD quantifying this observation, especially noting deficits in letter form quality, and reporting the correlation to overall motor performance [345]. Handwriting is interesting in that it requires not

only fine motor skill, but also visual perceptual and visuomotor-integration skill together with proprioception [346]. Since various researchers have reported consistently poor visual-motor integration [347, 348] it is not surprising that handwriting skill is particularly weak in individuals with ASD.

Studies of eye movement behavior are somewhat more developed than other studies of motor behavior in autism, with many studies of eye movements and attention potentially indicating failures of motor planning. Most studies have focused on the social aspect of looking behavior (see, for example, [349, 350]) but have neglected details regarding saccade metrics and timing. A few studies that explicitly examined eye movement metrics during standard visually guided target tasks have found increased variability in trial-to-trial amplitude in the saccades of individuals with ASD [351–353]. Miller and colleagues [313] also tied an examination of basic saccade metrics and timing to other aspects of motor behavior and found that those participants who were irregular in the finger-tapping task, also had greater metrical and timing irregularities in their saccadic eye movements. Other studies examined disengagement of attention in addition to eye movement metrics [14, 216, 226, 233]. Although this literature is mixed, many studies find a hypometria in the primary saccade that is often compensated by secondary or "corrective" saccades [351, 353]. Since the refractory period is at least 100 ms, this inaccuracy is problematic in terms of gathering information from dynamic scenes. An eye-tracking study of a magician's performance suggests that these differences may hamper an ASD individual's ability to successfully collect information from a dynamic environment [354]. Over the course of development, the accumulation of missed information can lead to deficits in social and communicative behaviors.

The motor system is itself foundational as it allows the developing child to interact with the environment. Not surprisingly, deficits in movement have recently been linked to socio-communicative deficits. Warlaumont and colleagues [355] documented and analyzed the microstructure of daily adult–child interactions during everyday activities for young children both with and without autism. They found that adults (unknowingly) rewarded a child's vocalizations with a response when it was more speech-related than not. Furthermore, a child's own vocalization is more likely to be speech-related if a previous speech-related vocalization had been rewarded by an adult's response. This feedback loop had the effect of fewer rewards for vocalization attempts for children on the spectrum as their vocalizations were perceived as less speech-related. This is one way in which motor skill deficits can have cascading effects.

Another recent study [356] reported associations between fine motor skills and both expressive and receptive language skills. A group with gross motor (but not fine motor) skill deficits showed no relationship with expressive language and a surprisingly significant negative association with receptive language. The authors also found associations between deficits in fine and gross motor skill deficits and social interactions. Other studies [357] have also found evidence supporting the link between gross motor skill and socialization skill.

Language

Although no longer a diagnostic criterion per se, language impairment is a major feature of autism. Delays in expressive and receptive language and phonology are prevalent and a subset of children with ASD never acquire language [358–361] (review: [362]. Language profiles are considered increasingly relevant for differentiation of subphenotypes and understanding the neurobiological bases of this disorder. The level of language impairment correlates with severity of autistic symptoms, especially when combined with higher level, nonverbal abilities [363, 364]. Currently, some experts in the field believe that children with autism are language impaired as well as autistic. At the same time, there is a considerable variability both with respect to the level of language impairment and the impairment profile. A review of language studies in autism [365] suggests that, while language deficits in

autism range from no functional language to normal standardized scores on language measures, all affected children can be assigned into three main language impairment subtypes: those scoring within the normal range of standardized tests of language (about 25%), those scoring more than one or two standard deviations below the mean across most of language tests (about 50%), and those with borderline language abilities with an inconsistent pattern across the tests (about 25%). Universal and specific language deficits in autism reside in higher order syntactic and pragmatic domains. However, a majority of the children in the language impaired group also show phonological short-term memory problems as well as morphological deficits. During preschool age, children with autism generally fall into two broad subtypes: those with prevailing phonology (perception and production of speech sounds) and grammar deficits; and those with prevailing pragmatic and semantic deficits In the latter group, the major weaknesses include word retrieval and sentence comprehension [366].

Several behavioral studies have found relatively normal single-word semantic processing in children and adolescents in autism, when stimuli were presented in the visual modality [367–369]. However, higher level semantic processing may not be intact. Behavioral and ERP studies have shown that children with autism have difficulty integrating semantic information, for example, using semantic context in stimulus pairs and sentences [370–375]. In an ERP study, Dunn et al. [373, 374] tested the hypothesis that in contrast to language processing in typically developing children, language processing in high-functioning verbal children with autism is little influenced by semantic context. In autistic children an electrophysiological index of semantic processing (the N400) was not modulated by word category, providing support for diminished context effect. Siegal and Blades [376] have suggested that auditory processing might be a key factor in these deficits. The few studies that used event-related potentials to examine auditory phoneme discrimination in autism [377–379] reported that automatic within-modality auditory phoneme discrimination is not impaired in high-functioning children with this disorder. However, a study on low-functioning adults with autism found that an ERP index of this process, the mismatch negativity (MMN), is impaired even for simple tone contrast [380].

A landmark FMRI study done by Just et al. [188] found that, during sentence comprehension, individuals with autism showed more net activation in Wernicke's area, but less net activation in Broca's area, than their controls. This finding was interpreted as an overreliance on "local," word-level, processing during language comprehension (hyperactivation in Wernicke's area) with diminished semantic and syntactic integration abilities (hypoactivation in Broca's area). Further, this study found decreased functional connectivity among all brain region pairs that yielded significant connectivity measures, including midrange (inferior temporal–inferior extrastriate; inferior parietal lobe–inferior extrastriate) and long-distance (e.g., calcarine-inferior frontal gyrus; dorsolateral prefrontal cortex–inferior extrastriate) connections. Interestingly, the ordering of the pairs of brain regions by the amount of power in their connection was the same in autistic and control groups. The authors concluded that this suggests a quantitative rather than qualitative impairment in cross-region functional connectivity in autism, reflecting a more general problem with long-distance under-connectivity that affects the widespread networks of language processing.

An earlier positron-emission tomography (PET) study on neural organization of language in autism [381] found: reversed hemispheric dominance during verbal auditory stimulation; a trend toward reduced activation of auditory cortex during nonverbal acoustic stimulation; and reduced cerebellar activation during nonverbal auditory perception and expressive language. These results are compatible with the downstream effects of cerebellar abnormality on perceptual and language processing in autism and with a model of reduced long-range cortical-subcortical connectivity. The cerebellum has been associated with verbal IQ and a variety of language functions including lexical retrieval, verb and antonym generation, grammatical

morphology, syntactic comprehension, and discrimination [review: 382–389].

Converging lines of evidence indicate that normal development entails not only emerging specialization of but also integration among the neural processors, from the lower to the highest information processing levels [390–392]. The more specialized systems become during maturation, the more critical integration among them becomes. Balance between these two types of fundamental processes is essential for engendering functionally efficient and adaptive behavior. In particular, normal acquisition and use of language are contingent on multilevel integrative mechanisms. These include audiovisual and motor integration at the sensory and phonetic levels of processing during formation of native language-specific phonetic representations [393], something that normally developing infants learn through the exposure to audiovisual speech. Vocabulary acquisition, in addition, involves integration across somatosensory and motor modalities, through which environmental experience about objects and actions is received. In order to form lexical representations of objects/events, stable integrative links among the constituent sensory-motor parts must be built. Non-lexical mental representations of objects, events, and relations among them can only be represented by flexible, dynamic, temporary integration of lower level sensory, and category information [394]. During language processing, an online integration of semantic word or intuitive representations of meaning must be accomplished [395]. In autism, these many processes might be perturbed by insufficient integration among the neural processors that serve different functions. A current study provides evidence for this model, demonstrating that ASD children are not sensitive to audiovisual synchrony (a failure of audiovisual integration) and that this deficit is associated with language ability [396].

Social Networks and Emotion

Social dysfunction in autism is a critical diagnostic criterion. Difficulties with social function are among the most troublesome of behavioral symptoms and are the problem behaviors most frequently targeted by clinical interventions. Most current studies have focused on eye gaze and face processing to evaluate social function. However, there is little consistency in results from these studies, and little or no consensus regarding the mechanisms that may underlie clinical social dysfunction in autism.

Individuals with autism have been found to exhibit atypical gaze patterns when looking at human faces. While typically developing children and adults spend more total time fixated on eyes than on other features like noses and mouths, autistic children and adults do not appear to afford special status to the eyes. Study results differ, however, depending on whether static or dynamic images are used and as a function of task requirements (review: [397]). Some studies that track eye movements over photographs of faces report that people with autism spend less time on the eyes than typically developing control subjects [398–400]. However, other studies have found no difference in viewing patterns [401–403]. One study with ASD children found that neither ASD children nor typically developing children spent more time fixating on the eyes than the nose or mouth [404]. These researchers subsequently grouped the eyes, nose, and mouth into an "internal" face zone and an "external" zone (the rest of the head). Fixation times to these zones were not different for any of their participant groups, although all groups spent more time on the "internal" zone compared to the "external" zone.

Conclusions from studies finding a gaze preference biased away from the eyes often infer that this pattern of processing represents "avoidance" of the eyes. There is, however, no direct evidence that this is the case. There is rather an indication from these studies that people with autism merely attend to other core features of the face, not necessarily that they "avoid" looking at the eyes. For example, a study by Spezio and colleagues found that high-functioning subjects with autism performed as well as control subjects on an emotion identification task, although their judgments were

determined using a very different processing strategy [405]. As in previous studies, the autism subjects spent approximately equal time looking at each of the three major facial features (left eye, right eye, mouth) while control subjects spent significantly more time looking at the two eyes. The processing bias in autism observed in these studies is consistent with the more general visual perceptual bias for detailed processing described in the earlier section on perception. A recent review of the face processing literature suggests that these perceptual processing abnormalities in ASD may be quite general and independent of social function [406]. A comprehensive review of face processing studies by Jemel et al. concludes that overall the findings support a "locally oriented perception of faces" with generally no deficit in perception of global features or face identity and emotion recognition [407].

Additional evidence that abnormal face processing patterns in autism may not reflect gaze avoidance comes from a recent study by Rutherford and Towns [403] which demonstrates that task requirements can influence gaze patterns. This study used a more difficult task than the studies cited above, in which people with autism were asked to view photographs of faces and choose a label that described the emotion (simple or complex) expressed in the picture (the previous studies asked participants to either identify pictures as familiar or unfamiliar, or whether a face showed emotion or was neutral). Rutherford and Towns demonstrated that under these more demanding conditions, people with autism did look more at eyes than at the mouth, and that the ratio of attention to these features did not differ from that of controls. Another study that used an explicit attention-directing task instruction ("look at the eyes" or "look at the mouth") found normal performance of autism subjects on a face processing task [408].

The gaze patterns of people with autism appear to change when dynamic images are used. Klin and colleagues [349, 409] have shown that when video clips of faces are used, people with autism fixate on the mouths one and a half times as much than they do eyes. In contrast, typically developing controls fixate on the eyes three times more than they do mouths. The authors hypothesize that their autistic participants are attempting to integrate sound with vision and focus on the mouth in order to integrate speech sounds. However, the authors acknowledge that motion alone may account for their results. Additionally, these studies used no control for attention, and as the studies described above suggest, manipulating attentional bias may drastically alter results. Two recent reviews and meta-analyses of eye-tracking studies that examine social orienting and attention in ASD report largely inconsistent results with diverse methods. Findings from Tegmark's review of 38 studies were that social attention is reduced when measured by looking time but that the size of this effect is related to scene complexity [410]. Additionally, nonsocial stimuli vary considerably by study and are not always matched to social stimuli for complexity and salience. Findings from the Guillon et al. review were that social orienting was not qualitatively abnormal and that attention to faces varied with context [411]. This review additionally found little support for diminished looking to eyes and increased looking to mouths.

The other major thrust of social research in autism is functional imaging studies that examine activation in brain systems associated with face processing. In typical function these networks include the fusiform gyrus, the superior temporal sulcus, the amygdala and prefrontal cortex [407, 412]. The first study to report abnormal BOLD activation during face processing in autism concluded that the patterns seen in the autism subjects were more typical of object than face perception [413]. A flood of subsequent fMRI studies reported various abnormalities but particularly reduced activation of the fusiform face area and the amygdala [196, 406, 407, 412, 414]. A study by Dalton and colleagues combined functional MR with eye-tracking and found that in autism activation in the amygdala and fusiform was significantly correlated with the amount of time gaze was fixated on the eyes of the stimulus [398]. Dalton et al. hypothesized that their results suggested an increased emotional response associated with eye fixation. However, many other studies reported

contradictory findings demonstrating normal fusiform activation in a variety of tasks, and normal amygdala activation when familiar faces were viewed [415]. Normal activation of the amygdala under some task conditions demonstrates that while individuals with autism may commonly use alternative face processing strategies and atypical brain systems, typical social networks including the fusiform and the amygdala can be employed by individuals with autism and are recruited during some social processing tasks.

Similar to a number of findings in face processing studies, an fMRI study of voice processing in autism showed activation in the superior temporal sulcus in control subjects during voice processing compared to nonvocal sounds, but no preferential activation of this region in the majority of autism subjects [416]. The authors conclude that this may reflect an attentional bias toward nonvocal sounds and that these findings, like those from face processing studies, may reflect abnormal functioning of a social brain network. There is some support for this model from structural data reviewed previously suggesting white matter abnormalities in temporal lobe regions that could affect language and social communication [163], and in reduced functional connectivity among temporal and other cortical and subcortical regions [188, 417].

Interestingly, functional abnormalities observed in both face and voice processing can be normalized by attentional manipulation as can be seen in an FMRI study done by Wang and colleagues [418]. In this study, children with autism and typically developing controls viewed cartoon scenes accompanied by spoken remarks. The vignette ending was either sincere or ironic. The child's task was to determine whether the speaker meant what he said. Children with autism performed the task as well as controls, and BOLD activation patterns during face and voice processing were similar in the two groups except that control children showed robust activation of medial prefrontal cortex while children with autism showed none. However, when task instructions were changed to call explicit attention to the face or the voice, both groups showed activation in medial prefrontal regions. These findings suggest that abnormalities observed in social brain networks may reflect a processing bias that favors nonsocial information, but this bias can be altered by simple attention-directing instructions.

Treatment

Autism is a lifelong disorder. There is no "cure" and no treatment for autism per se, but there are many effective educational, behavioral and pharmacological treatments for specific symptoms that may not only reduce symptoms but also improve overall function. Several reviews summarize the most common behavioral and pharmacologic treatments [419–422]. The American Academy of Pediatrics provides comprehensive guidelines for both medical and nonmedical management of children with ASD [21].

Behavioral

While there is general agreement that early, intensive intervention is crucial, individual variability in symptom patterns and in response means that there is no one-size-fits-all approach. Behavioral interventions can be roughly grouped into three categories: (1) interventions targeting communication and language development, (2) interventions targeting social competence, and (3) interventions targeting unwanted behaviors [421]. Most of the treatment methods described below can be effectively applied to targeted behavior in any or all of these categories. A review of randomized controlled trials for early interventions found that it was difficult to assess efficacy as most of the trials were at high risk for bias, samples were small, and there was little attempt to identify active treatment components [423].

Several of the most commonly used intervention programs are modifications of Applied Behavior Analysis (ABA). ABA follows principles developed by B.F. Skinner, in which all skills are broken down into smaller, individually

teachable components; techniques such as shaping, prompting, and chaining are used to train those new behaviors. Discrete Trial Training (DTT), developed by Lovaas [424–426], was the first application of ABA methods for children with ASD. DTT is a formal, structured therapy, in which an adult trainer decides upon a skill to teach, gives an instruction, and either provides a prompt as to what the appropriate response should be, or provides an external positive reinforce for an appropriate response. The entire "trial" is repeated until the child has mastered the targeted skill.

Other interventions such as pivotal response training (PRT) [427, 428] and incidental teaching [429–431] rely on behavioral techniques and discrete teaching episodes, but attempt to use a more naturalistic approach. In these interventions, the adult waits for the child to initiate communication rather than directing it; also, intrinsic rather than extrinsic reinforcement is used. PRT focuses on "pivotal" behaviors, those that have a widespread effect on a range of behaviors, rather than on specific verbal responses. Incidental teaching relies on setting up the teaching environment so that the child is motivated to communicate (for example, many toys and activities are available, but out of reach of the child). The Picture Exchange Communication System (PECS) [432, 433] attempts to teach functional communication to children with ASD who have delayed verbal abilities. The child is initially taught to exchange a picture for a desired item, then expands his or her picture vocabulary, then ultimately learns to arrange multiple pictures in a sentence to communicate a request or comment. PECS is meant to augment communication rather than replace speech training. See Lei and Ventola for a review of PRT interventions [434].

The Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) [435, 436] is a comprehensive program of services that relies on developing a highly structured physical environment. A primary emphasis in this method is on delivery of information through the visual modality to take advantage of perceived visual processing strengths in children with ASD, and in consideration of potential auditory processing deficits. Visual supports (i.e., printed schedules using words or pictures) are used to make tasks or the sequence of daily events predictable and understandable. A less-structured approach to teaching communication skills is based on the Developmental, Individual-Difference, Relationship-Based model (DIR) [437]. This approach emphasizes play and child-centered interactions expecting that fostering positive affect during interactions will teach the child that communication with others is satisfying and enjoyable. Floortime [438] is a popular offshoot of this technique.

Many interventions target social competence specifically. For example, in peer-mediated techniques, siblings or classmates are taught skills to facilitate social interactions with children with ASD [439]. In training with social stories, short, sometimes illustrated stories are written in the first person and teach a child what to expect and how to behave in a specific situation [440, 441]. Other methods include social games, social skills groups, and video modeling, which involve showing videotapes of an adult, other child, or even the child with ASD him or herself [442]. A recent review of social skills group interventions finds these treatments to be only moderately effective [443].

A new approach to treatment in ASD follows from the developmental evidence that foundational skills (attention and sensorimotor) are disrupted in the first year of life and result in a cascade of maldevelopment of higher level cognitive and social skills [444]. Interventions that target these foundational skills may affect many cognitive and social behaviors. For example, a recent study that aimed at improving attention, successfully improved academic performance after eight weeks of in-school training [445]. A promising new method for behavioral treatment is via video games. Games are inherently engaging and can be played at home to increase training time. "Brain Training" games are becoming increasingly popular and a number of companies are marketing games for cognitive enhancement. There is some evidence that attention can be improved by commercially available nonspecific active video games [446–

448]. Evidence-based games in ASD can, however, be designed to target specific attentional functions. A recent small sample trial used gaze-driven video games played at home for 8 weeks by ASD teens and found significant improvement in attention orienting, disengagement, and eye movement fixation stability [449].

Pharmacologic

To date, no medical intervention has been found to be effective for treating the core symptoms of autism. However, a number of pharmacological treatments are used to reduce secondary dysfunctional behaviors or symptoms in patients with ASD. A recent analysis of survey data from the National Ambulatory Medical Care Survey (NAMCS) and the outpatient portion of the National Hospital Ambulatory Medical Care Survey (NHAMCS) found that psychotropic medications were prescribed in 79% of children and adolescents with ASD [450]. General categories of symptoms and their associated pharmacological interventions are as follows: ADHD-like symptoms such as hyperactivity, inattention, or impulsivity are treated with psychostimulants, atomoxetine (a selective norepinephrine reuptake inhibitor, SNRI), antidepressants, alpha-2 adrenergic agonists, or Alzheimer's disease therapeutics [451]; aggression, irritability, and self-injurious behaviors are treated with typical and atypical antipsychotics, antiepileptics, or beta-blockers (see: [452, 453]); stereotypies or repetitive behaviors are treated with selective serotonin reuptake inhibitors (SSRIs) or clomipramine (for reviews see: [454, 455]).

There is, however, some excitement about treatments that are early in the developmental pipeline. There are drugs, such as oxytocin, that have been studied for many years in animal models and human experiments that target one specific symptom of autism—in this case social cognition. However, the results of clinical trials with oxytocin have been mixed [456]. It is possible that alternate treatment regimens, perhaps conducted in combination with some sort of retraining would have greater effect. There are also drugs that seek to remediate the neural underpinnings of autism at a foundational level. For example, Insulin-like growth factor 1 (IGF-1) is currently being tested in early clinical trials. The interest in IGF-1 emerged from this growth factor's importance in brain growth and development in general, and from the relation of a specific pathway involving IGF that is dysregulated in tuberous sclerosis, Phelan-McDermid syndrome, Rett Syndrome, and perhaps also idiopathic ASD [457]. Recently, Marchetto and colleagues [458] demonstrated that fibroblasts from eight individuals with autism and five age/gender-matched healthy controls were molecularly programmed to induce pluripotent stem cells (iPSC), neural progenitor cells (NPC), and neurons. The iPSC-induced NPC were compared in autism individuals with early brain overgrowth and non-autism controls with normal brain size. The autism individuals with the early brain enlargement phenotype had neural progenitor cell clones that proliferated faster than the controls, had increased percentage of Ki67, decreased NPC doubling times, and fewer excitatory synapses. The authors suggested that rapid proliferation of neural stem cells in autism may contribute to early large brain growth. The authors used this personalized cell culture to test the effect of IGF-1. The IGF-1 treatment applied during early development increased the number of GABAergic neurons in the ASD-derived cell cultures. When applied at a later stage, to mature fully differentiated ASD-derived cell cultures, IGF-1 improved neuronal activity in most cases. Although more work remains to be done, the iPSC method provides a potential path for testing out future drugs before they are administered to children. These two studies on IGF-1 introduce phase 1 studies of a potential treatment for a causative mechanism of autism.

Finally, it is important to note that one of the reasons for the lack of successful treatments for the core symptoms of ASD is that the lack of robust and objective methods for quantifying behavioral change in individuals with ASD before and after treatment. In fact, poor outcome assessment has been identified as the most likely reason for the Seaside Therapeutics failed trial of

arbaclofen [459]. Our field needs to establish more quantitative and objective outcome assessments that will permit the sensitivity we need to measure change for multiple specific cognitive, social, and behavioral endpoints.

Summary and Conclusions

Seventy-five years after Kanner's initial description of autism, we have failed to find biological markers and so the diagnosis of autism remains behavioral and must rely on subjective observations. The cause of autism remains unknown. There is limited consensus about neuroanatomic abnormality and limited agreement about specific cognitive impairment and effective treatments.

While we may not yet understand the underlying mechanisms in autism, the underlying cause for inconsistent findings in autism research is quite clear. Given a subjective behavioral diagnosis and particularly the change to broader diagnostic criteria, the samples drawn for study are extremely heterogeneous. There is as yet no reliable method for creating subgroups. Other than for large-scale collaborative efforts in genetics and imaging, in the studies considered here (and many more that we were unable to include) the sample sizes remain unfortunately small given the heterogeneity observed in the autism spectrum. One direction that shows promise is an effort to select individuals that share a particular feature or phenotype for study samples. This attempt at managing heterogeneity has face-validity and is also consistent with the National Institute of Mental Health's focus on Research Domain Criteria. This effort seeks to understand the neural mechanisms that underlie a particular cognitive or behavioral feature, such as attention orienting or attention focus.

A few findings have been replicated often enough to be considered robust. Among those are neuroanatomic abnormalities in the cerebellum and brainstem and overall enlargement of the brain in young children. Evidence for a bias toward local (detailed) processing, particularly in the visual modality appears to be robust, and this processing bias has been noted in many domains including face processing and language. While the exact nature and underlying neural basis for attentional problems remains somewhat controversial, the finding of difficulty in orienting and disengagement of visual attention ("sticky" attention) that is present early in development and persists throughout the lifespan has been replicated in a number of different ways by several independent groups and has reasonable consensus. Newer studies reviewed above have demonstrated that sometimes simple directions that alter attentional bias can normalize both behavior and the underlying neural response.

A promising model that has the potential to explain a profile that includes both strengths and weaknesses in cognition and behavior is based on work identifying unique patterns of brain development in autism. Abnormal early brain overgrowth may result in reduced long-distance white matter connectivity that disrupts integrated processing across brain systems. This early brain overgrowth affects attention and sensorimotor experience, which then disrupts cognitive and social development resulting in the features that define ASD. This model can provide a framework for studies with translational implications to guide development of specifically targeted interventions. One of the major advances in autism research and treatment is that diagnosis can now be made in children as young as two years of age and so treatment intervention can begin very early when it has the potential to provide maximal amelioration of clinical symptoms.

References

1. Kanner L. Autistic disturbances of affective contact. Nervous Child. 1943;2:217–50.
2. Asperger H. Die "Autistischen Psychopathen" im Kindesalter. Archiv fu¨r Psychiatrie und Nervenkrankheiten. 1944;117:76–136.
3. American Psychiatric Association, Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.). 2013, Arlington, VA: American Psychiatric Association.

4. Chawarska K, et al. Parental recognition of developmental problems in toddlers with autism spectrum disorders. J Autism Dev Disord. 2007;37 (1):62–72.
5. Sacrey LA, et al. Can parents' concerns predict autism spectrum disorder? A prospective study of high-risk siblings from 6 to 36 months of age. J Am Acad Child Adolesc Psychiatr. 2015;54(6):470–8.
6. Lord C, Shulman C, DiLavore P. Regression and word loss in autistic spectrum disorders. J Child Psychol Psychiatry. 2004;45(5):936–55.
7. Turner LM, et al. Follow-up of children with autism spectrum disorders from age 2 to age 9. Autism. 2006;10(3):243–65.
8. Werner E, Dawson G. Validation of the phenomenon of autistic regression using home videotapes. Arch Gen Psychiatry. 2005;62(8):889–95.
9. Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. Pediatrics. 1997;99(4):560–6.
10. Chawarska K, et al. Autism spectrum disorder in the second year: stability and change in syndrome expression. J Child Psychol Psychiatry. 2007;48 (2):128–38.
11. Charman T, Baird G. Practitioner review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children. J Child Psychol Psychiatry. 2002;43 (3):289–305.
12. Zwaigenbaum L, et al. Early Screening of Autism Spectrum Disorder: Recommendations for Practice and Research. Pediatrics. 2015;136(Suppl 1):S41–59.
13. Ozonoff S, et al. Diagnostic stability in young children at risk for autism spectrum disorder: a baby siblings research consortium study. J Child Psychol Psychiatry. 2015;56(9):988–98.
14. Zwaigenbaum L, et al. Behavioral manifestations of autism in the first year of life. Int J Dev Neurosci. 2005;23(2–3):143–52.
15. Bedford R, et al. Neurocognitive and observational markers: prediction of autism spectrum disorder from infancy to mid-childhood. Mol Autism. 2017;8:49.
16. Gammer I, et al. Behavioural markers for autism in infancy: scores on the Autism Observational Scale for Infants in a prospective study of at-risk siblings. Infant Behav Dev. 2015;38:107–15.
17. Zwaigenbaum L, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. Pediatrics. 2009;123(5):1383–91.
18. Rogers SJ. What are infant siblings teaching us about autism in infancy? Autism Research. 2009;2 (3):125–37.
19. Myers SM, Johnson CP. Management of children with autism spectrum disorders. Pediatrics. 2007;120(5):1162–82.
20. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007;120(5):1183–215.
21. Gupta VB, et al. Identifying children with autism early? Pediatrics. 2007;119(1):152–3.
22. Council on Children With Disabilities. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics. 2006;118(1):405–20.
23. World Health Organization, *International Classification of Diseases: Tenth Revision*. 1992, Geneva, Switzerland: World Health Organization.
24. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 1994;24(5):659–85.
25. Lord C, et al. Autism Diagnostic Observation Schedule. 2nd ed. Torrance, CA: Western Psychological Services; 2012.
26. Rutter M, LeCouteur A, Lord C. The Autism Diagnostic Interview-Revised. Los Angeles: Western Psychological Services; 2003.
27. Bruininks RH, et al. Scales of Independent Behavior-Revised Comprehensive Manual. Itasca, IL: Riverside Publishing; 1996.
28. Constantino JN, Gruber CP. The Social Responsiveness Scale Manual, Second Edition (SRS-2). Los Angeles: Western Psychological Services; 2012.
29. Schopler E, Reichler R, Renner B Rochen. Childhood autism rating scale. Los Angeles: Western Psychological Services; 1993.
30. Fombonne E. Epidemiological studies of pervasive developmental disorders. In: Volkmar F, Kiln A, Paul R, Cohen DJ, editors. Handbook of autism and pervasive developmental disorders. 3rd ed. Hoboken, NJ: Wiley; 2005. p. 42–69.
31. Voigt RG, et al. Laboratory evaluation of children with autistic spectrum disorders: a guide for primary care pediatricians. Clin Pediatr (Phila). 2000;39 (11):669–71.
32. Rossi PG, et al. EEG features and epilepsy in patients with autism. Brain Dev. 1995;17(3):169–74.
33. Kawasaki Y, et al. Brief report: electroencephalographic paroxysmal activities in the frontal area emerged in middle childhood and during adolescence in a follow-up study of autism. J Autism Dev Disord. 1997;27(5):605–20.
34. Kielinen M, et al. Associated medical disorders and disabilities in children with autistic disorder: a population-based study. Autism. 2004;8(1):49–60.
35. Hara H. Autism and epilepsy: a retrospective follow-up study. Brain Dev. 2007;29(8):486–90.
36. Danielsson S, et al. Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. Epilepsia. 2005;46(6):918–23.
37. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. J Clin Psychiatry. 2005;66(Suppl 10):3–8.

38. Volkmar FR, Nelson DS. Seizure disorders in autism. J Am Acad Child Adolesc Psychiatry. 1990;29(1):127–9.
39. Leitner Y. The co-occurrence of autism and attention deficit hyperactivity disorder in children - what do we know? Front Hum Neurosci. 2014;8:268.
40. Nadeau J, et al. Treatment of comorbid anxiety and autism spectrum disorders. Neuropsychiatry (London). 2011;1(6):567–78.
41. Vasa RA, et al. A systematic review of treatments for anxiety in youth with autism spectrum disorders. J Autism Dev Disord. 2014;44(12):3215–29.
42. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. 2000, Washington, DC: American Psychiatric Association.
43. Kielinen M, Linna SL, Moilanen I. Autism in Northern Finland. Eur Child Adolesc Psychiatry. 2000;9(3):162–7.
44. Blaxill MF, Redwood L, Bernard S. Thimerosal and autism? A plausible hypothesis that should not be dismissed. Med Hypotheses. 2004;62(5):788–94.
45. Bernard S, et al. Autism: a novel form of mercury poisoning. Med Hypotheses. 2001;56(4):462–71.
46. Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. BMJ. 2011;342:c7452.
47. Fombonne E. Thimerosal disappears but autism remains. Arch Gen Psychiatry. 2008;65(1):15–6.
48. Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. Arch Gen Psychiatry. 2008;65(1):19–24.
49. Andreae MC, Freed GL, Katz SL. Safety concerns regarding combination vaccines. Perspective of select European countries. Hum Vaccin. 2005;1 (1):1–5.
50. Institute of Medicine. Immunization Safety Review: Vaccines and Autism. Washington, DC: National Academies Press; 2004.
51. Barbaresi WJ, Katusic SK, Voigt RG. Autism: a review of the state of the science for pediatric primary health care clinicians. Arch Pediatr Adolesc Med. 2006;160(11):1167–75.
52. Baird G, et al, Measles vaccination and antibody response in autism spectrum disorders. Arch Dis Child, 2008.
53. Parker AA, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. N Engl J Med. 2006;355(5):447–55.
54. Gernsbacher M, Dawson M, Goldsmith HH. Three reasons not to believe in an autism epidemic. Curr Dir Psychol Sci. 2005;14(2):55–8.
55. Sealey LA, et al. Environmental factors in the development of autism spectrum disorders. Environ Int. 2016;88:288–98.
56. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Curr Probl Pediatr Adolesc Health Care. 2014;44 (10):277–318.
57. Matelski L, Van de Water J. Risk factors in autism: Thinking outside the brain. J Autoimmun. 2016;67:1–7.
58. Thion MS, et al. Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell;2017.
59. Hallmayer J, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011;68(11):1095–102.
60. Constantino JN, et al. Autism recurrence in half siblings: strong support for genetic mechanisms of transmission in ASD. Mol Psychiatry. 2013;18 (2):137–8.
61. Robinson EB, et al. Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. Nat Genet. 2016;48 (5):552–5.
62. Gaugler T, et al. Most genetic risk for autism resides with common variation. Nat Genet. 2014;46 (8):881–5.
63. de la Torre-Ubieta L, et al. Advancing the understanding of autism disease mechanisms through genetics. Nat Med. 2016;22(4):345–61.
64. Pinto D, et al. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. Am J Hum Genet. 2014;94(5):677–94.
65. Clarke TK, et al. Common polygenic risk for autism spectrum disorder (ASD) is associated with cognitive ability in the general population. Mol Psychiatry. 2016;21(3):419–25.
66. Hagenaars SP, et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112 151) and 24 GWAS consortia. Mol Psychiatry. 2016;21 (11):1624–32.
67. Merikangas AK, et al. The phenotypic manifestations of rare genic CNVs in autism spectrum disorder. Mol Psychiatry. 2015;20(11):1366–72.
68. Weiner DJ, et al. Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. Nat Genet. 2017;49(7):978–85.
69. Consortium C.-D.G.o.t.P.G. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013;45:984–94.
70. Ciernia A Vogel, LaSalle J. The landscape of DNA methylation amid a perfect storm of autism aetiologies. Nat Rev Neurosci. 2016;17(7):411–23.
71. Schanen NC, Epigenetics of autism spectrum disorders. Hum Mol Genet. 2006; 15 Spec No (2): R138–50.

72. Cook EH Jr, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. Am J Hum Genet. 1997;60(4):928–34.
73. Blatt GJ. GABAergic cerebellar system in autism: a neuropathological and developmental perspective. Int Rev Neurobiol. 2005;71:167–78.
74. Levitt P. Disruption of interneuron development. Epilepsia. 2005;46(Suppl 7):22–8.
75. Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. Environ Health Perspect. 2012;120(7):a258–60.
76. Schmidt RJ, et al. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology. 2011;22(4):476–85.
77. Donovan AP, Basson MA. The neuroanatomy of autism – a developmental perspective. J Anat. 2017;230(1):4–15.
78. Becker EB, Stoodley CJ. Autism spectrum disorder and the cerebellum. Int Rev Neurobiol. 2013;113:1–34.
79. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. Int J Dev Neurosci. 2005;23(2–3):183–7.
80. Palmen SJ, et al. Neuropathological findings in autism. Brain. 2004;127(Pt 12):2572–83.
81. Courchesne E, Redcay E, Kennedy DP. The autistic brain: birth through adulthood. Curr Opin Neurol. 2004;17(4):489–96.
82. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci. 2008;31(3):137–45.
83. Nordahl CW, et al. Cortical folding abnormalities in autism revealed by surface-based morphometry. J Neurosci. 2007;27(43):11725–35.
84. Bailey A, et al. A clinicopathological study of autism. Brain. 1998;121(5):889–905.
85. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism. In: Bauman ML, Kemper TL, editors. The Neurobiology of Autism. 3rd ed. Baltimore: John Hopkins University Press; 1994. p. 119–45.
86. Fehlow PK, Bernstein EA Early infantile autism and excessive aerophagy with symptomatic megacolon and ileus in a case of Ehlers-Danlos syndrome. Padiatrie und Grenzgebiete 1993;31(4): 259–67.
87. Kemper TL, Bauman M. Neuropathology of infantile autism. J Neuropathol Experiment Neurol. 1998;57(7):645–52.
88. Ritvo ER, Freeman BR Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC Autopsy Research Report. Am J Psychiatry. 1986;143(7):862–66.
89. Williams RS, Hauser SL. Autism and mental retardation: neuropathologic studies performed in four retarded persons with autistic behavior. Arch Neurol. 1980;37(12):749–53.
90. Wegiel J, et al. Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. Acta Neuropathol Commun. 2014;2:141.
91. Skefos J, et al. Regional alterations in purkinje cell density in patients with autism. PLoS ONE. 2014;9(2):e81255.
92. Fatemi SH, et al. Purkinje cell size is reduced in cerebellum of patients with autism. Cell Mol Neurobiol. 2002;22(2):171–5.
93. Fatemi SH, et al. Consensus paper: pathological role of the cerebellum in autism. Cerebellum. 2012;11(3):777–807.
94. Guerin P, et al. Neuropathological study of a case of autistic syndrome with severe mental retardation. Develop Med Child Neurol. 1996;38(3):203–11.
95. Raymond GV, Bauman ML, Kemper TL. Hippocampus in autism: a Golgi analysis. Acta Neuropathol. 1996;91(1):117–9.
96. Schumann CM, Amaral DG. Stereological analysis of amygdala neuron number in autism. J Neurosci. 2006;26(29):7674–9.
97. Casanova MF, et al. Minicolumnar pathology in autism. Neurology. 2002;58(3):428–32.
98. Casanova MF, et al. Minicolumnar abnormalities in autism. Acta Neuropathol. 2006;112(3):287–303.
99. McKavanagh R, Buckley E, Chance SA. Wider minicolumns in autism: a neural basis for altered processing? Brain. 2015;138(Pt 7):2034–45.
100. Stoner R, et al. Patches of disorganization in the neocortex of children with autism. N Engl J Med. 2014;370(13):1209–19.
101. Bauman ML, Kemper TL. Is autism a progressive process? Neurology. 1997;48(Suppl):285.
102. Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. Biol Psychiatry. 2005;58(1):1–9.
103. Bauman ML. Microscopic neuroanatomic abnormalities in autism. Pediatrics. 1991;87(5 Pt 2):791–6.
104. Gaffney GR, Tsai LY, et al. Cerebellar structure in autism. Am J Dis Child. 1987;141(12):1330–2.
105. Murakami JW, et al. Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. Arch Neurol. 1989;46(6):689–94.
106. Courchesne E, et al. Abnormal neuroanatomy in a nonretarded person with autism. Unusual findings with magnetic resonance imaging. Arch Neurol. 1987;44(3):335–41.
107. Courchesne E, et al. Hypoplasia of cerebellar vermal lobules VI and VII in autism. New England J Med. 1988;318(21):1349–54.
108. Carper RA, Courchesne E. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain. 2000;123:836–44.

109. Ciesielski KT, et al. Hypoplasia of cerebellar vermis in autism and childhood leukemia in 5th International Child Neurology Congress. Tokyo, Japan: Karger; 1990.
110. Ciesielski KT, Knight JE. Cerebellar abnormality in autism: a nonspecific effect of early brain damage? Acta Neurobiol Exp. 1994;54(2):151–4.
111. Ciesielski KT, et al. Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. Neuropsychologia. 1997;35(5):643–55.
112. Courchesne E, et al. Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging. Am J Roentgenol. 1994;162(1):123–30.
113. Courchesne E, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology. 2001;57(2):245–54.
114. Hashimoto T, et al. Development of the brainstem and cerebellum in autistic patients. J Autism Develop Disord. 1995;25:1–18.
115. Kates WR, et al. Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. Annal Neurol. 1998;43(6):782–91.
116. Levitt JG, et al. Cerebellar vermis lobules VIII-X in autism. Prog Neuro-Psychopharmacol Biol Psychiatry. 1999;23(4):625–33.
117. Saitoh O, et al. Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. Neurology. 1995;45 (2):317–24.
118. Zilbovicius M, et al. Hypoplasia of vermal lobules I-V, but not of lobules VI-VII, in childhood autism. Neurology. 1995;45(Suppl. 4):A162.
119. Kaufmann WE, et al. Specificity of cerebellar vermian abnormalities in autism: a quantitative magnetic resonance imaging study. J Child Neurol. 2003;18(7):463–70.
120. McAlonan GM, et al. Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain. 2002;125(Pt 7):1594–606.
121. Miles JH, Hillman RE. Value of a clinical morphology examination in autism [see comments]. Am J Med Genet. 2000;91(4):245–53.
122. D'Mello AM, et al. Cerebellar gray matter and lobular volumes correlate with core autism symptoms. Neuroimage Clin. 2015;7:631–9.
123. Holttum JR, et al. Magnetic resonance imaging of the posterior fossa in autism. Biol Psychiatry. 1992;32(12):1091–101.
124. Piven J, et al. An MRI study of autism: the cerebellum revisited [see comments]. Neurology. 1997;49(2):546–51.
125. Filipek PA. Quantitative magnetic resonance imaging in autism: the cerebellar vermis. Curr Opinion Neurol. 1995;8(2):134–8.
126. Sparks BF, et al. Brain structural abnormalities in young children with autism spectrum disorder. Neurology. 2002;59(2):184–92.
127. Hardan AY, et al. Posterior fossa magnetic resonance imaging in autism. J Am Acad Child Adolesc Psychiatry. 2001;40(6):666–72.
128. Courchesne E, Townsend J, Saitoh O. The brain in infantile autism: posterior fossa structures are abnormal [see comments]. Neurology. 1994;44 (2):214–23.
129. Courchesne E, Press GA, Yeung-Courchesne R. Parietal lobe abnormalities detected with MR in patients with infantile autism [see comments]. Am J Roentgenol. 1993;160(2):387–93.
130. Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. Arch Neurol. 1995;52 (8):794–801.
131. Manes F, et al. An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. J Neuropsychiatry Clin Neurosci. 1999;11(4):470–4.
132. Piven J, et al. An MRI study of the corpus callosum in autism. Am J Psychiatry. 1997;154(8):1051–6.
133. Hardan AY, et al. Increased frontal cortical folding in autism: a preliminary MRI study. Psychiatry Res. 2004;131(3):263–8.
134. Levitt JG, et al. Cortical sulcal maps in autism. Cereb Cortex. 2003;13(7):728–35.
135. Aylward EH, et al. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology. 1999;53(9):2145–50.
136. Pierce K, et al. Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. Brain. 2001;124(Pt 10):2059–73.
137. Herbert MR, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain. 2003;126(Pt 5):1182–92.
138. Howard MA, et al. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. NeuroReport. 2000;11(13):2931–5.
139. Schumann CM, et al. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci. 2004;24(28):6392–401.
140. Saitoh O, Karns C, Courchesne E. Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism. Brain. 2001;124(7):1317–24.
141. Haznedar MM, et al. Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am J Psychiatry. 2000;157 (12):1994–2001.
142. Piven J, et al. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Dev Disord. 1998;28(2): 105–10.

143. Osipowicz K, Bosenbark DD, Patrick KE. Cortical changes across the autism lifespan. Autism Res. 2015;8(4):379–85.
144. Aylward EH, et al. Effects of age on brain volume and head circumference in autism. Neurology. 2002;59(2):175–83.
145. Carper RA, et al. Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage. 2002;16(4):1038–51.
146. Davidovitch M, Patterson B, Gartside P. Head circumference measurements in children with autism. J Child Neurol. 1996;11(5):389–93.
147. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. JAMA. 2003;290(3):337–44.
148. Herbert MR. Large brains in autism: the challenge of pervasive abnormality. Neuroscientist. 2005;11 (5):417–40.
149. Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. Biol Psychiatry. 2005;57(2):126–33.
150. Courchesne E, Campbell K, Solso S. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res. 2011; 1380:138–45.
151. Lange N, et al. Longitudinal volumetric brain changes in autism spectrum disorder ages 6-35 years. Autism Res. 2015;8(1):82–93.
152. Zielinski BA, et al. Longitudinal changes in cortical thickness in autism and typical development. Brain. 2014;137(Pt 6):1799–812.
153. Schumann CM, et al. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. J Neurosci. 2010;30(12):4419–27.
154. Akshoomoff N, Pierce K, Courchesne E. The neurobiological basis of autism from a developmental perspective. Dev Psychopathol. 2002;14 (3):613–34.
155. Belmonte MK, et al. Autism and abnormal development of brain connectivity. J Neurosci. 2004;24 (42):9228–31.
156. McAlonan GM, et al. Mapping the brain in autism: a voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain. 2005;128(Pt 2):268–76.
157. Cheng Y, et al. Atypical development of white matter microstructure in adolescents with autism spectrum disorders. Neuroimage. 2010;50(3):873–82.
158. Ke X, et al. White matter impairments in autism, evidence from voxel-based morphometry and diffusion tensor imaging. Brain Res. 2009;1265:171–7.
159. Shukla DK, et al. White matter compromise of callosal and subcortical fiber tracts in children with autism spectrum disorder: a diffusion tensor imaging study. J Am Acad Child Adolesc Psychiatry. 2010;49(12):1269–78, 1278 e1–2.
160. Shukla DK, Keehn B, Muller RA. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. J Child Psychol Psychiatry. 2011;52 (3):286–95.
161. Solso S, et al. Diffusion tensor imaging provides evidence of possible axonal overconnectivity in frontal lobes in autism spectrum disorder toddlers. Biol Psychiatry. 2016;79(8):676–84.
162. Barnea-Goraly N, et al. White matter structure in autism: preliminary evidence from diffusion tensor imaging. Biol Psychiatry. 2004;55(3):323–6.
163. Lee JE, et al. Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. Neurosci Lett. 2007;424(2):127–32.
164. Rilling JK, Insel TR. Differential expansion of neural projection systems in primate brain evolution. NeuroReport. 1999;10(7):1453–9.
165. Zhang K, Sejnowski TJ A universal scaling law between gray matter and white matter of cerebral cortex. Proc Natl Acad Sci USA. 2000;97 (10):5621–6.
166. Jancke L, et al. The relationship between corpus callosum size and forebrain volume. Cereb Cortex. 1997;7(1):48–56.
167. Lewis J, Courchesne E, Elman J. Growth trajectories and cortico-cortical connections. The 37th Annual Gatlinburg Conference: On Research & Theory in Intellectual & Developmental Disabilities. 2004; San Diego, CA.
168. Lewis J, Elman J, Courchesne E. Brain overgrowth and reduced long-distance connectivity in autism. The 11th Annual Meeting of the Organization for Human Brain Mapping. 2005; Toronto.
169. Lewis JD, Elman JL. Growth-related neural reorganization and the autism phenotype: a test of the hypothesis that altered brain growth leads to altered connectivity. Dev Sci. 2008;11(1):135–55.
170. Lewis JD, et al. Network efficiency in autism spectrum disorder and its relation to brain overgrowth. Front Hum Neurosci. 2013;7:845.
171. Lewis JD, et al. Callosal fiber length and interhemispheric connectivity in adults with autism: brain overgrowth and underconnectivity. Hum Brain Mapp. 2013;34(7):1685–95.
172. Bernhardt BC, et al. Neuroimaging-based phenotyping of the autism spectrum. Curr Top Behav Neurosci. 2017;30:341–55.
173. Mash LE, et al. Multimodal approaches to functional connectivity in autism spectrum disorders: an integrative perspective. Dev Neurobiol; 2017.
174. Li D, Karnath HO, Xu X. Candidate biomarkers in children with autism spectrum disorder: a review of MRI studies. Neurosci Bull. 2017;33(2):219–37.
175. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. PLoS ONE. 2017;12(5):e0175870.

176. Rane P, et al. Connectivity in autism: a review of MRI connectivity studies. Harv Rev Psychiatry. 2015;23(4):223–44.
177. Duan X, et al. Resting-state functional under-connectivity within and between large-scale cortical networks across three low-frequency bands in adolescents with autism. Prog Neuropsychopharmacol Biol Psychiatry. 2017;79(Pt B):434–41.
178. Chen H, et al. Intrinsic functional connectivity variance and state-specific under-connectivity in autism. Hum Brain Mapp. 2017;38(11):5740–55.
179. Falahpour M, et al. Underconnected, but not broken? Dynamic functional connectivity MRI shows underconnectivity in autism is linked to increased intra-individual variability across time. Brain Connect. 2016;6(5):403–14.
180. Abbott AE, et al. Repetitive behaviors in autism are linked to imbalance of corticostriatal connectivity: a functional connectivity MRI study. Soc Cogn Affect Neurosci. 2018;13(1):32–42.
181. Abbott AE, et al. Patterns of atypical functional connectivity and behavioral links in autism differ between default, salience, and executive networks. Cereb Cortex. 2016;26(10):4034–45.
182. Keown CL, et al. Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. Cell Rep. 2013;5(3):567–72.
183. Nair A, et al. Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. Brain. 2013;136(Pt 6):1942–55.
184. Tomasi D, Volkow ND Reduced local and increased long-range functional connectivity of the thalamus in autism spectrum disorder. Cereb Cortex; 2017.
185. Belmonte MK, Yurgelun-Todd DA. Functional anatomy of impaired selective attention and compensatory processing in autism. Brain Res Cogn Brain Res. 2003;17(3):651–64.
186. Haist F, et al. The functional neuroanatomy of spatial attention in autism spectrum disorder. Development Neuropsychol. 2005;27(3):425–58.
187. Just MA, et al. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 2007;17(4):951–61.
188. Just MA, et al. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain. 2004;127:1811–21.
189. Koshino H, et al. Functional connectivity in an fMRI working memory task in high-functioning autism. Neuroimage. 2005;24(3):810–21.
190. Ring HA, et al. Cerebral correlates of preserved cognitive skills in autism: a functional MRI study of embedded figures task performance. Brain. 1999;122(Pt 7):1305–15.
191. Pillai AS, et al, Altered task-related modulation of long-range connectivity in children with autism. Autism Res 2017.
192. Keehn B, et al. Functional connectivity for an "Island of sparing" in autism spectrum disorder: An fMRI study of visual search. Hum Brain Mapp. 2012.
193. Ramot M, et al, Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback. Elife 2017;6.
194. Baron-Cohen SH, Tager-Flusberg, Cohen D, Understanding other minds: perspectives from autism, ed. S. Baron-Cohen H, Tager-Flusberg, Cohen D 1993;Oxford: Oxford University Press.
195. Baron-Cohen S. Mindblindness: An Essay on Autism and Theory of Mind. Cambridge, MA: MIT Press; 1995.
196. Baron-Cohen S, Belmonte MK. Autism: a window onto the development of the social and the analytic brain. Annual Rev Neurosci. 2005;28:109–26.
197. Russell J, Cognitive Theories of Autism, in Cognitive Deficits in Brain Disorders, Harrison JE, Owen AM (eds.) 2002, Martin Dunitz: London. p. 295–323.
198. Hill EL, Frith U. Understanding autism: insights from mind and brain. Philos Trans R Soc Lond B Biol Sci. 2003;358(1430):281–9.
199. Levy F. Theories of autism. Aust N Z J Psychiatry. 2007;41(11):859–68.
200. Russell J. Autism as an executive disorder. Oxford: Oxford University Press; 1997.
201. Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning autistic individuals: relationship to theory of mind. J Child Psychol Psychiatry. 1991;32(7):1081–105.
202. Frith U, Happe F. Autism: beyond "theory of mind". Cognition. 1994;50(1–3):115–32.
203. Frith U. Autism: explaining the enigma. Oxford: Blackwell; 1989.
204. Happe FG. Studying weak central coherence at low levels: children with autism do not succumb to visual illusions. A research note. J Child Psychol Psychiatry. 1996;37(7):873–7.
205. Kana RK, Libero LE, Moore MS. Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. Phys Life Rev. 2011;8(4):410–37.
206. Piven J, Elison JT, Zylka MJ. Toward a conceptual framework for early brain and behavior development in autism. Mol Psychiatry. 2017;22(10):1385–94.
207. Vasa RA, Mostofsky SH, Ewen JB. The Disrupted Connectivity Hypothesis of Autism Spectrum Disorders: Time for the Next Phase in Research. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1(3):245–52.
208. Horwitz B, et al. The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization. Arch Neurol. 1988;45(7):749–55.

209. van Bon BW, et al. Disruptive de novo mutations of DYRK1A lead to a syndromic form of autism and ID. Mol Psychiatry. 2016;21(1):126–32.
210. Wolff JJ, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. Am J Psychiatry. 2012;169(6):589–600.
211. Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav. 2003;2:255–67.
212. Sacrey LA, Bryson SE, Zwaigenbaum L. Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: a longitudinal study from 6 to 36 months of age. Behav Brain Res. 2013;256:441–50.
213. Bryson S, et al, Impaired disengagement of attention and its relationship to emotional distress in infants at high-risk for autism spectrum disorder. J Clin Exp Neuropsychol, 2017;1–15.
214. Elison JT, et al. Frontolimbic neural circuitry at 6 months predicts individual differences in joint attention at 9 months. Dev Sci. 2013;16(2):186–97.
215. Elsabbagh M, et al. Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. Biol Psychiatry. 2013;74 (3):189–94.
216. Elsabbagh M, et al. Visual orienting in the early broader autism phenotype: disengagement and facilitation. J Child Psychol Psychiatry. 2009;50 (5):637–42.
217. Sacrey LA, et al. Impairments to visual disengagement in autism spectrum disorder: a review of experimental studies from infancy to adulthood. Neurosci Biobehav Rev. 2014;47:559–77.
218. Townsend J, Courchesne E. Parietal damage and narrow "spotlight" spatial attention. J Cogn Neurosci. 1994;6(3):220–32.
219. Song Y, et al. Can They See It? The Functional Field of View Is Narrower in Individuals with Autism Spectrum Disorder. PLoS ONE. 2015;10 (7):e0133237.
220. Lovaas OI, Koegel RL, Schreibman L. Stimulus overselectivity in autism: a review of research. Psychol Bull. 1979;86(6):1236–54.
221. Lovaas OI, et al. Selective responding by autistic children to multiple sensory input. J Abnorm Psychol. 1971;77(3):211–22.
222. Liss M, et al. Sensory and attention abnormalities in autistic spectrum disorders. Autism. 2006;10 (2):155–72.
223. Townsend, J., B. Keehn, and M. Westerfield, *Abstraction of Mind: Attention in autism*, in *Cognitive Neuroscience of Attention*, M. Posner, Editor. 2012, Guilford Press: New York. p. 357–373.
224. Wainwright JA, Bryson SE. Visual-spatial orienting in autism. J Autism Dev Disord. 1996;26(4): 423–38.
225. Wainwright-Sharp JA, Bryson SE. Visual orienting deficits in high-functioning people with autism. J Autism Dev Disord. 1993;23(1):1–13.
226. Kawakubo Y, et al. Electrophysiological abnormalities of spatial attention in adults with autism during the gap overlap task. Clin Neurophysiol. 2007;118 (7):1464–71.
227. Harris N, et al. Neuroanatomic contributions to slowed orienting of attention in children with autism. Cogn Brain Res. 1999;8:61–71.
228. Townsend J, et al. Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci. 1999;19(13):5632–43.
229. Townsend J, Courchesne E, Egaas B. Slowed orienting of covert visual-spatial attention in autism: Specific deficits associated with cerebellar and parietal abnormality. Dev Psychopathol. 1996;8 (3):503–84.
230. Mann TA, Walker P. Autism and a deficit in broadening the spread of visual attention. J Child Psychol Psychiatry. 2003;44(2):274–84.
231. Burack JA. Selective attention deficits in persons with autism: preliminary evidence of an inefficient attentional lens. J Abnorm Psychol. 1994;103 (3):535–43.
232. Ronconi L, et al. Zoom-out attentional impairment in children with autism spectrum disorder. Cortex. 2013;49(4):1025–33.
233. Landry R, Bryson SE. Impaired disengagement of attention in young children with autism. J Child Psychol Psychiatry. 2004;45(6):1115–22.
234. Keehn B, Joseph RM. Impaired prioritization of novel onset stimuli in autism spectrum disorder. Journal of Child Psychololgy and Psychiatry, and Allied Disciplines. 2008;49(12):1296–303.
235. Keehn B, et al. Attentional networks in children and adolescents with autism spectrum disorder. Journal of Child Psychololgy and Psychiatry, and Allied Disciplines. 2010;51(11):1251–9.
236. Fan J, et al. Testing the behavioral interaction and integration of attentional networks. Brain Cogn. 2009;70(2):209–20.
237. Fan J, et al. Testing the efficiency and independence of attentional networks. Journal of Cognitve Neuroscience. 2002;14(3):340–7.
238. Keehn B, Muller RA, Townsend J. Atypical attentional networks and the emergence of autism. Neurosci Biobehav Rev. 2013;37(2):164–83.
239. Tardif C, et al. Slowing down presentation of facial movements and vocal sounds enhances facial expression recognition and induces facial-vocal imitation in children with autism. J Autism Dev Disord. 2007;37(8):1469–84.
240. Loveland KA, Landry SH. Joint attention and language in autism and developmental language delay. J Autism Dev Disord. 1986;16(3):335–49.
241. Roeyers H, Van Oost P, Bothuyne S. Immediate imitation and joint attention in young children with autism. Developmental Psychopathology. 1998;10 (3):441–50.
242. Tronick, E., *Affectivity and sharing*, in *Social interchange in infancy: Affect cognition and*

communication, E.Z. Tronick, Editor. 1982, University Park Press: Baltimore, MD.
243. Dawson G, et al. Children with autism fail to orient to naturally occurring social stimuli. J Autism Dev Disord. 1998;28(6):479–85.
244. Allen G, Courchesne E. Attention function and dysfunction in autism. Frontiers in Bioscience. 2001;6:D105–19.
245. Murphy JW, et al. Susceptibility to distraction in autism spectrum disorder: probing the integrity of oscillatory alpha-band suppression mechanisms. Autism Res. 2014;7(4):442–58.
246. Soriano MF, et al, Autism: hard to switch from details to the whole. J Abnorm Child Psychol. 2017.
247. Courchesne E, Akshoomoff N, Townsend J. Recent advances in autism. Curr Opin Pediatr. 1990;2: 685–93.
248. Bast N, Poustka L, Freitag CM. The locus coeruleus-norepinephrine system as pacemaker of attention - a developmental mechanism of derailed attentional function in autism spectrum disorder. Eur J Neurosci. 2018;47(2):115–25.
249. Courchesne E, et al. Impairment in shifting attention in autistic and cerebellar patients. Behav Neurosci. 1994;108(5):848–65.
250. Akshoomoff NA, Courchesne E. Intramodality shifting attention in children with damage to the cerebellum. J Cogn Neurosci. 1994;6:388–99.
251. Sokhadze EM, et al, Atypical processing of novel distracters in a visual oddball task in autism spectrum disorder. Behav Sci (Basel), 2017. 7(4).
252. Reed P, McCarthy J. Cross-modal attention-switching is impaired in autism spectrum disorders. J Autism Dev Disord. 2012;42(6):947–53.
253. Townsend J, et al. Event-related brain response abnormalities in autism: Evidence for impaired cerebello-frontal spatial attention networks. Cogn Brain Res. 2001;11(1):127–45.
254. Silk TJ, et al. Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: a functional MRI study. Am J Psychiatry. 2006;163(8):1440–3.
255. Courchesne E. Abnormal early brain development in autism. Mol Psychiatry. 2002;7(Suppl 2):S21–3.
256. Johnson MH. Autism as an adaptive common variant pathway for human brain development. Dev Cogn Neurosci. 2017;25:5–11.
257. Leekam SR, et al. The Diagnostic Interview for Social and Communication Disorders: algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder. J Child Psychol Psychiatry. 2002;43(3):327–42.
258. Wing L, et al. The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use. J Child Psychol Psychiatry. 2002;43(3):307–25.
259. Dunn W. Sensory profile. San Antonio, TX: The Psychological Corporation; 1999.
260. Wing L. The handicaps of autistic children–a comparative study. J Child Psychol Psychiatry. 1969;10(1):1–40.
261. Kern JK, et al. The pattern of sensory processing abnormalities in autism. Autism. 2006;10(5):480–94.
262. Leekam SR, et al. Describing the sensory abnormalities of children and adults with autism. J Autism Dev Disord. 2007;37(5):894–910.
263. Rogers SJ, Hepburn S, Wehner E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. J Autism Dev Disord. 2003;33(6):631–42.
264. Minshew NJ, Hobson JA. Sensory sensitivities and performance on sensory perceptual tasks in high-functioning individuals with autism. J Autism Dev Disord, 2008.
265. Little LM, Dean E, Tomchek S, Dunn W. Sensory processing patterns in autism, attention deficit hyperactivity disorder, and typical development. Phys Occup Ther Pediatr, 2017: p. 1–12.
266. Perez Repetto L, Jasmin E, Fombonne E, Gisel E, Couture M. Longitudinal study of sensory features in children with autism spectrum disorder. Autism Res Treat. 2017. 2017:1–8.
267. Davis RA, et al. Subjective perceptual distortions and visual dysfunction in children with autism. J Autism Dev Disord. 2006;36(2):199–210.
268. Kern JK, et al. Sensory correlations in autism. Autism. 2007;11(2):123–34.
269. Robertson CE, Baron-Cohen S. Sensory perception in autism. Nat Rev Neurosci. 2017;18(11):671–84.
270. Little, J.A., *Vision in children with autism spectrum disorder: a critical review*. Clin Exp Optom, 2018.
271. Otto-Meyer, S., et al., *Children with autism spectrum disorder have unstable neural responses to sound.* Exp Brain Res, 2018.
272. Simon DM, Wallace MT. Dysfunction of sensory oscillations in Autism Spectrum Disorder. Neurosci Biobehav Rev. 2016;68:848–61.
273. Marco EJ, et al. Sensory processing in autism: a review of neurophysiologic findings. Pediatr Res. 2011;69(5 Pt 2):48R–54R.
274. O'Riordan M, Passetti F. Discrimination in autism within different sensory modalities. J Autism Dev Disord. 2006;36(5):665–75.
275. Cascio C, et al. Tactile perception in adults with autism: a multidimensional psychophysical study. J Autism Dev Disord. 2008;38(1):127–37.
276. Guclu B, et al. Tactile sensitivity of normal and autistic children. Somatosens Mot Res. 2007;24(1–2):21–33.
277. Tommerdahl M, et al. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. Brain Res. 2007;1154:116–23.

278. Dakin S, Frith U. Vagaries of visual perception in autism. Neuron. 2005;48(3):497–507.
279. Shah A, Frith U. Why do autistic individuals show superior performance on the block design task? J Child Psychol Psychiatry. 1993;34(8):1351–64.
280. Jarrold C, Gilchrist ID, Bender A. Embedded figures detection in autism and typical development: preliminary evidence of a double dissociation in relationships with visual search. Developmental Science. 2005;8(4):344–51.
281. Jolliffe T, Baron-Cohen S. Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? J Child Psychol Psychiatry. 1997;38(5):527–34.
282. Plaisted K, O'Riordan M, Baron-Cohen S. Enhanced visual search for a conjunctive target in autism: a research note. J Child Psychol Psychiatry. 1998;39(5):777–83.
283. O'Riordan MA, et al. Superior visual search in autism. J Exp Psychol Hum Percept Perform. 2001;27(3):719–30.
284. O'Riordan MA. Superior visual search in adults with autism. Autism. 2004;8(3):229–48.
285. Brosnan MJ, et al. Gestalt processing in autism: failure to process perceptual relationships and the implications for contextual understanding. J Child Psychol Psychiatry. 2004;45(3):459–69.
286. Mottron L, Belleville S, Menard E. Local bias in autistic subjects as evidenced by graphic tasks: perceptual hierarchization or working memory deficit? J Child Psychol Psychiatry. 1999;40 (5):743–55.
287. Bertone, A., et al., *Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity.* Brain, 2005.
288. Ropar D, Mitchell P. Are individuals with autism and Asperger's syndrome susceptible to visual illusions? J Child Psychol Psychiatry. 1999;40 (8):1283–93.
289. Bonnel A, et al. Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. J Cogn Neurosci. 2003;15(2):226–35.
290. Skoff BF, Mirsky AF, Turner D. Prolonged brainstem transmission time in autism. Psychiatry Res. 1980;2(2):157–66.
291. Tanguay PE, et al. Auditory brainstem evoked responses in autistic children. Arch Gen Psychiatry. 1982;39(2):174–80.
292. Maziade M, et al. Prolongation of brainstem auditory-evoked responses in autistic probands and their unaffected relatives. Arch Gen Psychiatry. 2000;57(11):1077–83.
293. Wong V, Wong SN. Brainstem auditory evoked potential study in children with autistic disorder. J Autism Dev Disord. 1991;21(3):329–40.
294. Grillon C, Courchesne E, Akshoomoff N. Brainstem and middle latency auditory evoked potentials in autism and developmental language disorder. J Autism Dev Disord. 1989;19(2):255–69.
295. Courchesne E, et al. Functioning of the brain-stem auditory pathway in non-retarded autistic individuals. Electroencephalogr Clin Neurophysiol. 1985;61 (6):491–501.
296. Kwon S, et al. Electrophysiologic assessment of central auditory processing by auditory brainstem responses in children with autism spectrum disorders. J Korean Med Sci. 2007;22(4):656–9.
297. Orekhova EV, et al. Sensory gating in young children with autism: Relation to age, IQ, and EEG gamma oscillations. Neurosci Lett. 2008;434 (2):218–23.
298. Kemner C, et al. Normal P50 gating in children with autism. J Clin Psychiatry. 2002;63(3):214–7.
299. Perry W, et al. Sensorimotor gating deficits in adults with autism. Biol Psychiatry. 2007;61(4):482–6.
300. Kemner C, et al. Auditory event-related brain potentials in autistic children and three different control groups. Biol Psychiatry. 1995;38(3):150–65.
301. Ceponiene R, et al. Speech-sound-selective auditory impairment in children with infantile autism: they can perceive but do not attend. Proc Natl Acad Sci. 2003;100:5567–72.
302. Tecchio F, et al. Auditory sensory processing in autism: a magnetoencephalographic study. Biol Psychiatry. 2003;54(6):647–54.
303. Kaldy Z, et al. The Mechanisms Underlying the ASD Advantage in Visual Search. J Autism Dev Disord. 2016;46(5):1513–27.
304. Milne E, et al. Visual search performance is predicted by the degree to which selective attention to features modulates the ERP between 350 and 600ms. Neuropsychologia. 2013;51(6):1109–18.
305. Samson F, et al. Can spectro-temporal complexity explain the autistic pattern of performance on auditory tasks? J Autism Dev Disord. 2006;36 (1):65–76.
306. Manjaly ZM, et al. Neurophysiological correlates of relatively enhanced local visual search in autistic adolescents. Neuroimage. 2007;35(1):283–91.
307. Mottron L, et al. Veridical mapping in the development of exceptional autistic abilities. Neurosci Biobehav Rev. 2013;37(2):209–28.
308. Haas RH, et al. Neurologic abnormalities in infantile autism. J Child Neurol. 1996;11(2):84–92.
309. Hilton CL, et al. Motor impairment in sibling pairs concordant and discordant for autism spectrum disorders. Autism. 2012;16(4):430–41.
310. Mattard-Labrecque C, Amor L Ben, Couture MM. Children with Autism and Attention Difficulties: A Pilot Study of the Association between Sensory, Motor, and Adaptive Behaviors. J Can Acad Child Adolesc Psychiatry. 2013;22(2):139–46.
311. Mostofsky SH, et al. Evidence for a deficit in procedural learning in children and adolescents with

autism: implications for cerebellar contribution. J Int Neuropsychol Soc. 2000;6(7):752–9.
312. Sumner E, Leonard HC, Hill EL. Overlapping Phenotypes in Autism Spectrum Disorder and Developmental Coordination Disorder: A Cross-Syndrome Comparison of Motor and Social Skills. J Autism Dev Disord. 2016;46(8):2609–20.
313. Miller M, et al. Dyspraxia, motor function and visual-motor integration in autism. Behav Brain Res. 2014;269:95–102.
314. Chukoskie L, Townsend J, Westerfield M. Motor skill in autism spectrum disorders: a subcortical view. Int Rev Neurobiol. 2013;113:207–49.
315. Mostofsky SH, et al. Developmental dyspraxia is not limited to imitation in children with autism spectrum disorders. J Int Neuropsychol Soc. 2006;12(3):314–26.
316. Chang CH, et al. Visual tasks and postural sway in children with and without autism spectrum disorders. Res Dev Disabil. 2010;31(6):1536–42.
317. Fournier KA, et al. Decreased static and dynamic postural control in children with autism spectrum disorders. Gait Posture. 2010;32(1):6–9.
318. Kohen-Raz R, Volkmar FR, Cohen DJ. Postural control in children with autism. J Autism Dev Disord. 1992;22(3):419–32.
319. Minshew NJ, et al. Underdevelopment of the postural control system in autism. Neurology. 2004;63(11):2056–61.
320. Molloy CA, Dietrich KN, Bhattacharya A. Postural stability in children with autism spectrum disorder. J Autism Dev Disord. 2003;33(6):643–52.
321. Travers BG, et al. Motor difficulties in autism spectrum disorder: linking symptom severity and postural stability. J Autism Dev Disord. 2013;43 (7):1568–83.
322. Graham SA, et al. The Influence of Task Difficulty and Participant Age on Balance Control in ASD. J Autism Dev Disord. 2015;45(5):1419–27.
323. Hallett M, et al. Locomotion of autistic adults. Arch Neurol. 1993;50(12):1304–8.
324. Esposito G, et al. Analysis of unsupported gait in toddlers with autism. Brain Dev. 2011;33(5):367–73.
325. Rinehart NJ, et al. Gait function in newly diagnosed children with autism: Cerebellar and basal ganglia related motor disorder. Dev Med Child Neurol. 2006;48(10):819–24.
326. Rinehart NJ, et al. Gait function in high-functioning autism and Asperger's disorder: evidence for basal-ganglia and cerebellar involvement? Eur Child Adolesc Psychiatry. 2006;15(5):256–64.
327. Shetreat-Klein M, Shinnar S, Rapin I. Abnormalities of joint mobility and gait in children with autism spectrum disorders. Brain Dev. 2014;36(2):91–6.
328. Nobile M, et al. Further evidence of complex motor dysfunction in drug naive children with autism using automatic motion analysis of gait. Autism. 2011;15(3):263–83.
329. Vernazza-Martin S, et al. Goal directed locomotion and balance control in autistic children. J Autism Dev Disord. 2005;35(1):91–102.
330. Vilensky JA, Damasio AR, Maurer RG. Gait disturbances in patients with autistic behavior: a preliminary study. Arch Neurol. 1981;38(10):646–9.
331. Weiss MJ, et al. Gait analysis of teenagers and young adults diagnosed with autism and severe verbal communication disorders. Front Integr Neurosci. 2013;7:33.
332. Schmitz C, et al. Motor control and children with autism: deficit of anticipatory function? Neurosci Lett. 2003;348(1):17–20.
333. Rinehart NJ, et al. An examination of movement kinematics in young people with high-functioning autism and Asperger's disorder: further evidence for a motor planning deficit. J Autism Dev Disord. 2006;36(6):757–67.
334. Cattaneo, L., et al., *Impairment of actions chains in autism and its possible role in intention understanding*. Proc Natl Acad Sci U S A, 2007. 104(45): p. 17825–30.
335. Fabbri-Destro M, et al. Planning actions in autism. Exp Brain Res. 2009;192(3):521–5.
336. Glazebrook C, et al. The role of vision for online control of manual aiming movements in persons with autism spectrum disorders. Autism. 2009;13 (4):411–33.
337. Glazebrook CM, Elliott D, Lyons J. A kinematic analysis of how young adults with and without autism plan and control goal-directed movements. Mot Control. 2006;10(3):244–64.
338. Mari M, et al. The reach-to-grasp movement in children with autism spectrum disorder. Philos Trans R Soc Lond B Biol Sci. 2003;358 (1430):393–403.
339. Campione GC, et al. Three-Dimensional Kinematic Analysis of Prehension Movements in Young Children with Autism Spectrum Disorder: New Insights on Motor Impairment. J Autism Dev Disord. 2016;46(6):1985–99.
340. Goldman S, et al. Motor stereotypies in children with autism and other developmental disorders. Dev Med Child Neurol. 2009;51(1):30–8.
341. Green, D., et al., *Impairment in movement skills of children with autistic spectrum disorders.* Developmental Medicine and Child Neurolology, 2009.
342. Provost B, Heimerl S, Lopez BR. Levels of gross and fine motor development in young children with autism spectrum disorder. Phys Occup Ther Pediatr. 2007;27(3):21–36.
343. David FJ, et al. Coordination of precision grip in 2-6 years-old children with autism spectrum disorders compared to children developing typically and

children with developmental disabilities. Front Integr Neurosci. 2012;6:122.
344. Lai MC, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PLoS ONE. 2011;6(6):e20835.
345. Fuentes CT, Mostofsky SH, Bastian AJ. Children with autism show specific handwriting impairments. Neurology. 2009;73(19):1532–7.
346. Kushki A, Chau T, Anagnostou E. Handwriting difficulties in children with autism spectrum disorders: a scoping review. J Autism Dev Disord. 2011;41(12):1706–16.
347. Fulkerson SC, Freeman WM. Perceptual-motor deficiency in autistic children. Percept Mot Skills. 1980;50(1):331–6.
348. Mayes SD, Calhoun SL. Ability profiles in children with autism: influence of age and IQ. Autism. 2003;7(1):65–80.
349. Klin A, et al. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry. 2002;59(9):809–16.
350. McPartland JC, et al. Patterns of visual attention to faces and objects in autism spectrum disorder. J Autism Dev Disord. 2011;41(2):148–57.
351. Johnson BP, et al. A closer look at visually guided saccades in autism and Asperger's disorder. Front Integr Neurosci. 2012;6:99.
352. Luna B, et al. Maturation of executive function in autism. Biol Psychiatry. 2007;61(4):474–81.
353. Takarae Y, et al. Oculomotor abnormalities parallel cerebellar histopathology in autism. J Neurol Neurosurg Psychiatry. 2004;75(9):1359–61.
354. Kuhn G, Kourkoulou A, Leekam SR. How magic changes our expectations about autism. Psychol Sci. 2010;21(10):1487–93.
355. Warlaumont AS, et al. A social feedback loop for speech development and its reduction in autism. Psychol Sci. 2014;25(7):1314–24.
356. Mody M, et al. Communication Deficits and the Motor System: Exploring Patterns of Associations in Autism Spectrum Disorder (ASD). J Autism Dev Disord. 2017;47(1):155–62.
357. Pusponegoro HD, et al. Gross Motor Profile and Its Association with Socialization Skills in Children with Autism Spectrum Disorders. Pediatr Neonatol. 2016;57(6):501–7.
358. Hudry K, et al. Early language profiles in infants at high-risk for autism spectrum disorders. J Autism Dev Disord. 2014;44(1):154–67.
359. Hudry K, et al. Preschoolers with autism show greater impairment in receptive compared with expressive language abilities. Int J Lang Commun Disord. 2010;45(6):681–90.
360. Kamio Y, et al. Atypical lexical/semantic processing in high-functioning autism spectrum disorders without early language delay. J Autism Dev Disord. 2007;37(6):1116–22.
361. Rapin I, et al. Subtypes of language disorders in school-age children with autism. Dev Neuropsychol. 2009;34(1):66–84.
362. Eigsti IM, et al. Language acquisition in autism spectrum disorders: A developmental review. Research in Autism Spectrum Disorders. 2011;5(2):681–91.
363. Tager-Flusberg H, Joseph RM. Identifying neurocognitive phenotypes in autism. Philos Trans R Soc Lond B Biol Sci. 2003;358(1430):303–14.
364. Bailey A, Phillips W, Rutter M. Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. J Child Psychol Psychiatry. 1996;37:89–126.
365. Tager-Flusberg H. Strategies for conducting research on language in autism. J Autism Dev Disord. 2004;34:75–80.
366. Allen, D.A. and I. Rapin, *Autistic children are also dysphasic*, in *Neurobiology of infantile autism*, H. Naruse and E. Ornitz, Editors. 1992, Excerpta Medica: Amsterdam. p. 73–80.
367. Toichi M, Kamio Y. Verbal association for simple common words in high-functioning autism. J Autism Dev Disord. 2001;31:483–90.
368. Kamio Y, Toichi M. Dual access to semantics in autism: is pictorial access superior to verbal access? J Child Psychol Psychiatry. 2000;41:859–67.
369. Eskes GA, Bryson SE, McCormick TA. Comprehension of concrete and abstract words in autistic children. J Autism Dev Disord. 1990;20:61–73.
370. Frith U, Snowling M. Reading for meaning and reading for sound in autistic and dyslexic children. J Dev Psychol. 1983;1:329–42.
371. Snowling M, Frith U. Comprehension in "hyperlexic" readers. J Exp Child Psychol. 1986;42:392–415.
372. Jolliffe T, Baron-Cohen S. Linguistic processing in high-functioning adults with autism or Asperger's syndrome. Is global coherence impaired? Psychol Med. 2000;30:1169–87.
373. Dunn M, et al. Electrophysiologic correlates of semantic classification in autistic and normal children. Developmental Neuropsychology. 1999;16:79–99.
374. Dunn MA, Bates JC. Developmental change in neutral processing of words by children with autism. J Autism Dev Disord. 2005;35(3):361–76.
375. Valdizan JR, et al. Cognitive evoked potentials in autistic children][Article in Spanish. Rev Neurol. 2003;36:425–8.
376. Siegal M, Blades M. Language and auditory processing in autism. Trends Cogn Sci. 2003;7:378–80.
377. Ceponiene, R., et al., *Speech-sound-selective auditory impairment in children with autism: they can*

perceive but do not attend. Proc Natl Acad Sci U S A, 2003. 100(9): p. 5567–72.
378. Gomot M, et al. Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning. Psychophysiology. 2002;39:577–84.
379. Lepisto T, et al. The discrimination of and orienting to speech and non-speech sounds in children with autism. Brain Res. 2005;1066(1–2):147–57.
380. Ferri R, et al. The mismatch negativity and the P3a components of the auditory event-related potentials in autistic low-functioning subjects. Clin Neurophysiol. 2003;114:1671–80.
381. Müller RA, et al. Brain mapping of language and auditory perception in high-functioning autistic adults: a PET study. J Autism Dev Disord. 1999;29:19–31.
382. Marien P, et al. The lateralized linguistic cerebellum: a review and a new hypothesis. Brain Lang. 2001;79(3):580–600.
383. Fiez JA, et al. PET activation of posterior temporal regions during auditory word presentation and verb generation. Cereb Cortex. 1996;6(1):1–10.
384. Fiez JA, et al. A positron emission tomography study of the short-term maintenance of verbal information. J Neurosci. 1996;16(2):808–22.
385. Justus T. The cerebellum and English grammatical morphology: evidence from production, comprehension, and grammaticality judgments. J Cogn Neurosci. 2004;16(7):1115–30.
386. Marvel CL, Schwartz BL, Isaacs KL. Word production deficits in schizophrenia. Brain Lang. 2004;89(1):182–91.
387. Fabbro F, et al. Long-term neuropsychological deficits after cerebellar infarctions in two young adult twins. Neuropsychologia. 2004;42(4):536–45.
388. Xiang H, et al. Involvement of the cerebellum in semantic discrimination: an fMRI study. Hum Brain Mapp. 2003;18(3):208–14.
389. Gebhart AL, Petersen SE, Thach WT. Role of the posterolateral cerebellum in language. Ann N Y Acad Sci. 2002;978:318–33.
390. Bates, E., *On the nature and nurture of language*, in *Frontiere della biologia [Frontiers of biology]. The brain of homo sapiens.*, R. Levi-Montalcini, et al., Editors. 2000, Giovanni Trecanni: Rome.
391. Brock J, et al. The temporal binding deficit hypothesis of autism. Dev Psychopathol. 2002;14:209–24.
392. Elman J, et al. Rethinking innateness: A connectionist perspective on development. Cambridge: MIT Press; 1996.
393. Cheour M, et al. Development of language-specific phoneme representations in the infant brain. Nat Neurosci. 1998;1(5):351–3.
394. Barsalou LW, et al. Grounding conceptual knowledge in modality-specific systems. Trends Cogn Sci. 2003;7:84–91.
395. Kutas M, Federmeier KD. Electrophysiology reveals semantic memory use in language comprehension. Trends in Cognitive Sciences. 2000;4:463–70.
396. Righi, G., et al., *Sensitivity to audio-visual synchrony and its relation to language abilities in children with and without ASD.* Autism Res, 2018.
397. Boraston Z, Blakemore SJ. The application of eye-tracking technology in the study of autism. J Physiol. 2007;581(Pt 3):893–8.
398. Dalton KM, et al. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 2005;8(4):519–26.
399. Pelphrey KA, et al. Visual scanning of faces in autism. J Autism Dev Disord. 2002;32(4):249–61.
400. Sterling, L., et al., *The Role of Face Familiarity in Eye Tracking of Faces by Individuals with Autism Spectrum Disorders.* J Autism Dev Disord, 2008.
401. van der Geest JN, et al. Looking at images with human figures: comparison between autistic and normal children. J Autism Dev Disord. 2002;32(2):69–75.
402. van der Geest JN, et al. Gaze behavior of children with pervasive developmental disorder toward human faces: a fixation time study. J Child Psychol Psychiatry. 2002;43(5):669–78.
403. Rutherford, M.D. and A.M. Towns, *Scan Path Differences and Similarities During Emotion Perception in those With and Without Autism Spectrum Disorders.* J Autism Dev Disord, 2008.
404. Anderson C, Colomboa J, DJ S. Visual Scanning and Pupillary Responses in Young Children with Autism Spectrum Disorder. J Clin Exp Neuropsychol. 2006;28:1238–56.
405. Spezio ML, et al. Abnormal use of facial information in high-functioning autism. J Autism Dev Disord. 2007;37(5):929–39.
406. Behrmann M, Thomas C, Humphreys K. Seeing it differently: visual processing in autism. Trends Cogn Sci. 2006;10(6):258–64.
407. Jemel B, Mottron L, Dawson M. Impaired face processing in autism: fact or artifact? J Autism Dev Disord. 2006;36(1):91–106.
408. Lopez B, Donnelly N, Hadwin JA, Leekam SR. Face processing in high-functioning adolescents with autism: Evidence for weak central coherence. Visual Cognition. 2004;11(6):673–88.
409. Klin A, Jones W. Altered face scanning and impaired recognition of biological motion in a 15-month-old infant with autism. Dev Sci. 2008;11(1):40–6.
410. Tegmark M. Social attention in ASD: A review and meta-analysis of eye-tracking studies. Res Dev Disabil. 2016;48:79–93.
411. Guillon Q, et al. Visual social attention in autism spectrum disorder: insights from eye tracking studies. Neurosci Biobehav Rev. 2014;42:279–97.

412. Golarai G, Grill-Spector K, Reiss AL. Autism and the development of face processing. Clin Neurosci Res. 2006;6(3):145–60.
413. Schultz RT, et al. Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry. 2000;57(4):331–40.
414. Herbert MR. Neuroimaging in disorders of social and emotional functioning: what is the question? J Child Neurol. 2004;19(10):772–84.
415. Pierce K, et al. The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain. 2004;127(Pt 12):2703–16.
416. Gervais H, et al. Abnormal cortical voice processing in autism. Nat Neurosci. 2004;7(8):801–2.
417. Murias M, et al. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. Biol Psychiatry. 2007;62(3):270–3.
418. Wang AT, et al. Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. Arch Gen Psychiatry. 2007;64(6):698–708.
419. Ospina MB, et al. Behavioural and Developmental Interventions for Autism Spectrum Disorder: A Clinical Systematic Review. PLoS ONE. 2008;3(11):e3755.
420. Seida JK, et al. Systematic reviews of psychosocial interventions for autism: an umbrella review. Dev Med Child Neurol. 2009;51(2):95–104.
421. Mastergeorge, A.M., et al., *Nonmedical interventions for autism spectrum disorders.*, in *Autism Spectrum Disorders: A research review for practitioners*, S.J.R. S. Ozonoff, & R.L. Hendren, Editor. 2003, American Psychiatric Publishing, Inc.: Arlington. p. 133–160.
422. Deokar, A.M., M.B. Huff, and H.A. Omar, *Clinical management of adolescents with autism.* Pediatr Clin North Am, 2008. 55(5): p. 1147–57, viii.
423. French, L. and E.M.M. Kennedy, *Research Review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: a systematic review.* J Child Psychol Psychiatry, 2017.
424. Lovaas OI, Smith T. A comprehensive behavioral theory of autistic children: paradigm for research and treatment. J Behav Ther Exp Psychiatry. 1989;20(1):17–29.
425. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. J Consult Clin Psychol. 1987;55(1):3–9.
426. Lovaas OI, Schreibman L, Koegel RL. A behavior modification approach to the treatment of autistic children. J Autism Child Schizophr. 1974;4(2):111–29.
427. Pierce K, Schreibman L. Increasing complex social behaviors in children with autism: effects of peer-implemented pivotal response training. J Appl Behav Anal. 1995;28(3):285–95.
428. Pierce K, Schreibman L. Multiple peer use of pivotal response training to increase social behaviors of classmates with autism: results from trained and untrained peers. J Appl Behav Anal. 1997;30(1):157–60.
429. McGee GG, et al. Promoting reciprocal interactions via peer incidental teaching. J Appl Behav Anal. 1992;25(1):117–26.
430. McGee GG, et al. A modified incidental-teaching procedure for autistic youth: acquisition and generalization of receptive object labels. J Appl Behav Anal. 1983;16(3):329–38.
431. McGee GG, Krantz PJ, McClannahan LE. The facilitative effects of incidental teaching on preposition use by autistic children. J Appl Behav Anal. 1985;18(1):17–31.
432. Bondy A, Frost L. The Picture Exchange Communication System. Behav Modif. 2001;25(5):725–44.
433. Bondy, A.S. and L.A. Frost, *The picture exchange communication system.* Semin Speech Lang, 1998. 19(4): p. 373–88; quiz 389; 424.
434. Lei J, Ventola P. Pivotal response treatment for autism spectrum disorder: current perspectives. Neuropsychiatr Dis Treat. 2017;13:1613–26.
435. Schopler, E., G.B. Mesibov, and K. Hearsey, *Structured teaching in the TEACCH system.*, in *Learning and Cognition in Autism*, E.S.G.B. Mesibov, Editor. 1995, Plenum: New York. p. 243–268.
436. Mesibov GB, Schopler E. The development of community-based programs for autistic adolescents. Child Health Care. 1983;12(1):20–4.
437. Greenspan S, Weider S. Developmental patterns and outcomes in infants and children with disorders in relating and communicating: a chart review of 200 cases of children with autistic spectrum diagnoses. Journal of Developmental and Learning Disprders. 1997;1:87–141.
438. Wieder S, Greenspan SI. Climbing the symbolic ladder in the DIR model through floor time/interactive play. Autism. 2003;7(4):425–35.
439. Bass JD, Mulick JA. Social play skill enhancement of children with autism using peers and siblings as therapists. Psychology in the Schools. 2007;44(7):727–35.
440. Gray CA, Garand JD. Social stories: Improving responses of students with autism with accurate social information. Focus on Autistic Behavior. 1993;8:1–10.
441. Quirmback LM, et al. Social stories: Mechanisms of effectiveness in increasing game play skills in children diagnosed with Autism Spectrum Disorder using a pretest posttest repeated measures randomized control group design. J Autism Dev Disord. 2009;39:299–321.
442. Delano ME. Video modeling interventions for individuals with autism. Remedial and Special Education. 2007;28(1):33–42.

443. Gates JA, Kang E, Lerner MD. Efficacy of group social skills interventions for youth with autism spectrum disorder: A systematic review and meta-analysis. Clin Psychol Rev. 2017;52:164–81.
444. Piven J, Elison JT, Zylka MJ. Toward a conceptual framework for early brain and behavior development in autism. Mol Psychiatry. 2018;23(1):165.
445. Spaniol, M.M., et al., *Attention Training in Autism as a Potential Approach to Improving Academic Performance: A School-Based Pilot Study.* J Autism Dev Disord, 2017.
446. Achtman RL, Green CS, Bavelier D. Video games as a tool to train visual skills. Restor Neurol Neurosci. 2008;26(4–5):435–46.
447. Granek JA, Gorbet DJ, Sergio LE. Extensive video-game experience alters cortical networks for complex visuomotor transformations. Cortex. 2010;46(9):1165–77.
448. Mishra J, et al. Neural basis of superior performance of action videogame players in an attention-demanding task. J Neurosci. 2011;31(3):992–8.
449. Chukoskie, L., M. Westerfield, and J. Townsend, *A novel approach to training attention and gaze in ASD: A feasibility and efficacy pilot study.* Dev Neurobiol, 2017.
450. Gerhard T, et al. National patterns in the outpatient pharmacological management of children and adolescents with autism spectrum disorder. J Clin Psychopharmacol. 2009;29(3):307–10.
451. Aman, M.G., et al., *Treatment of inattention, overactivity, and impulsiveness in autism spectrum disorders.* Child Adolesc Psychiatr Clin N Am, 2008. 17(4): p. 713–38, vii.
452. Stigler, K.A. and C.J. McDougle, *Pharmacotherapy of irritability in pervasive developmental disorders.* Child Adolesc Psychiatr Clin N Am, 2008. 17(4): p. 739–52, vii–viii.
453. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. J Child Adolesc Psychopharmacol. 2008;18(2):157–78.
454. Filipek PA, Steinberg-Epstein R, Book TM. Intervention for autistic spectrum disorders. NeuroRx. 2006;3(2):207–16.
455. Leskovec TJ, Rowles BM, Findling RL. Pharmacological treatment options for autism spectrum disorders in children and adolescents. Harv Rev Psychiatry. 2008;16(2):97–112.
456. Young LJ, Barrett CE. Neuroscience. Can oxytocin treat autism? Science. 2015;347(6224):825–6.
457. Ebrahimi-Fakhari D, Sahin M. Autism and the synapse: emerging mechanisms and mechanism-based therapies. Curr Opin Neurol. 2015;28(2):91–102.
458. Marchetto MC, et al. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. Mol Psychiatry. 2017;22 (6):820–35.
459. Budimirovic DB, et al. Updated report on tools to measure outcomes of clinical trials in fragile X syndrome. J Neurodev Disord. 2017;9:14.

Chapter 13

Genetic Syndromes Associated with Intellectual Disabilities

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Intellectual disability, formerly referred to as mental retardation, is defined by significant limitations in cognitive functioning and the ability to adapt to the demands of daily life with an onset before the age of 18 years [1]. The most recent estimate from the Centers for Disease Control (CDC) is that nearly 7 of every 1,000 children in the United States have an intellectual disability [2]. The CDC also estimates that nearly one-half of these children also have another diagnosed developmental disability (https://www.cdc.gov/ncbddd/developmentaldisabilities/documents/intellectualdisabilities.pdf). In the not too distant past, the causes of most cases of intellectual disability were unknown, especially for cases of more mild impairment [3]. Recent advances in genetics, especially molecular genetics, however, have led to the identification of more than 1,000 conditions associated with intellectual disability [4]. Many of these conditions are quite rare, such as 5p-syndrome, or cri-du-chat, which occurs only once per 50,000 births [5]. Nevertheless, genetic abnormalities are thought to collectively account for 15–50% of these cases of intellectual disability [6–8]. Even mild intellectual disability can often be traced to a genetic abnormality, with estimates as high as 50% [5]. Most importantly for present purposes, the profile of impairments at all levels, from the behavioral to the neural, varies with etiology, sometimes in quite dramatic ways [5]. These etiology-related differences in the degree or the nature of the impairments across domains of neuropsychological functioning have important implications for clinical assessment.

It would obviously be impossible to review all of the genetic conditions associated with intellectual disability in a single chapter. Moreover, there is little empirically validated information about the prototypical neuropsychological profile for many conditions. Consequently, we have focused here on three genetic syndromes: Down syndrome (DS), fragile X syndrome (FXS), and Williams syndrome (WS). We have chosen these syndromes because they occur relatively frequently, have been well-studied from a neuropsychological perspective, and contrast in interesting ways with regard to their neuropsychological profiles. These syndromes also illustrate nicely the challenges that arise in the neuropsychological assessment of individuals with intellectual disabilities more generally.

This chapter is organized into three major sections. The first section is devoted to a review of what is known about these syndromes in terms of prevalence, genetic bases, phenotypic manifestations, and underlying brain pathology. In describing each syndrome, we consider the cognitive, language, and social–affective dimensions

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of the phenotype, all of which have relevance to the neuropsychological assessment of affected individuals. In describing these dimensions of the phenotypes, we pay considerably more attention to the linguistic dimension not only because this reflects our particular research interest, but also because language is an important dimension of difference among these and other genetic syndromes associated with intellectual disabilities. In the second section, we focus on issues in assessment that are common to these syndromes and other syndromes associated with intellectual disabilities. In the third section of this chapter, we briefly discuss the family context of individuals affected by these syndromes, especially as the family context relates to assessment.

Down Syndrome

Genetics, Prevalence, and Overview

First described by Langdon Down in the mid-nineteenth century, DS is the leading genetic cause of intellectual disability and has a prevalence rate of 1 in approximately 700 live births [9]. In 1959, Jerome Lejeune found that DS is caused by an extra copy of all or a segment of chromosome 21 [10], giving rise to the syndrome name trisomy 21. Most individuals with DS have a full trisomy; that is, three copies of the 225 genes [11] encoded on the long arm (designated q) of chromosome 21. However, 1–2% of affected individuals have a partial trisomy, with only a subset of chromosome 21 genes triplicated. Understanding the mechanisms leading to the DS phenotype has proven to be challenging. In contrast to FXS, which involves only one gene, and WS, which involves relatively few genes, understanding the DS phenotype requires unraveling the specific contributions of each of the 225 implicated genes and understanding how the products of these genes interact over the course of development [12, 13].

Approximately 95% of cases of DS are caused by nondisjunction, an error in meiotic cell division prior to fertilization. As the embryo with trisomy 21 develops, the extra chromosome 21 is replicated in virtually every cell [14]. Errors in meiotic cell division leading to DS are overwhelmingly of maternal origin [15] and advanced maternal age is the most important risk factor for the nondisjunction form of DS [16]. Maternal age-related nondisjunction is thought to occur because of the accumulation of toxic environmental effects, degradation of meiotic machinery over time, and/or suboptimal hormonal signaling [17]. An additional 2% of cases of DS are caused when nondisjunction of chromosome 21 takes place during one of the cell divisions post-fertilization. In this condition, termed mosaicism, there is a mixture of cells, some containing 46 and some containing 47 chromosomes. On average, individuals with mosaic DS are less impaired cognitively, depending upon the proportion of affected cells [18]. The remaining 2% of cases are caused by translocation, in which part of chromosome 21 breaks off during division and attaches to another chromosome. Although the total number of chromosomes in the cells of an individual with a translocation is 46, extra genetic material is present.

As is the case for all genetic syndromes, DS produces both structural and functional abnormalities in multiple organ systems, with a characteristic phenotype [15]. The phenotype of DS includes cognitive impairment, a distinctive facial appearance, and muscle hypotonia [17]. Other characteristics that are observed with considerable frequency in DS are short stature, congenital heart disease, childhood onset leukemia, gastrointestinal abnormalities, neuropathology associated with dementia, hearing loss, and vision problems. In all, 45 birth defects have been identified as being more common in DS than in the general population, although there is wide variability in the number and severity of symptoms displayed across individuals [19]. Most individuals with DS display IQs between 35 and 70 [20]. The intellectual disability in DS is thought to be associated with specific brain regions and impaired performance on specific cognitive tasks [12, 21]. In the following paragraphs, we briefly review three models that have been proposed to account for the relationship between genes, brain, and behavior in DS.

In rare cases, the etiology of DS results from a partial trisomy, with only some of the genes on chromosome 21 being triplicated. DNA analyses of the smallest regions of overlap across individuals with partial trisomies and consideration of genotype–phenotype associations for these individuals initially suggested that a relatively small region on the distal end of the long arm of chromosome 21 is associated with the expression of some of the specific features of DS [22, 23]. This region, which comprises between 5 and 10% of the length of 21q, has been labeled as the Down syndrome critical region (DSCR). The *critical region model* proposes that most of the features of the DS phenotype are the product of one or more genes located within this small region [24].

Mouse models have provided an important tool for evaluating the DSCR model [25, 26]. These models can be utilized because of the well-conserved content and order of genes on the long arm of human chromosome 21 relative to the distal segment of mouse chromosome 16 [27–29]. For example, the Ts65Dn mouse contains a trisomic segment for about half the genes on human chromosome 21 and displays the facial, cranial, and mandibular characteristics of DS. With such a model, however, it is difficult to analyze the effects of single genes because three copies of many genes are present. In contrast, transgenic mice overexpress only one or a few candidate genes, allowing a direct genotype–phenotype analysis, although not consideration of interactions between larger groups of genes [29].

In a recent consideration of the validity of the DSCR hypothesis, Olson and colleagues manipulated several different mouse models. They first examined characteristics of the Ts1Rhr mouse, which is trisomic for only the mouse orthologs of 33 genes from the human DSCR [24]. These mice did not display the expected craniofacial anomalies of DS. Second, Olson et al. selectively reduced the trisomy of the DS critical region in Ts65Dn mice by crossbreeding with Ms1Rhr mice in which the 33 DSCR genes are missing. This manipulation did not eliminate the DS craniofacial phenotype in Ts65Dn/Ms1Rhr offspring. These results have led some researchers to conclude that the presence of the genes in the DSCR is neither sufficient nor necessary to generate the characteristic facial appearance of DS [30] and that alternative genetic models for the DS phenotype must be considered.

The *amplified developmental instability model* is one such alternative. This model suggests that the presence of a threshold number of genes—regardless of which genes—leads to the DS phenotype by causing a nonspecific disruption of gene regulation and expression. This disruption is thought to alter the usual balance of development and determines most of the characteristics of DS [31, 32]. This model is supported by the finding of individual variation in the population of individuals with DS and the observation of characteristics of DS in other syndromes and in the population at large.

The *gene dosage effects model*, perhaps the most straightforward alternative to the DSCR model, suggests that three copies of a particular gene or series of genes cause a 1.5-fold increase in the expression of gene products, thus leading to the DS phenotype [33, 34]. The secondary effects of this gene dosage imbalance are thought to cause the subsequent over- or underexpression of other genes, which will have different effects in different cell types, at different developmental stages [35, 36], and in different individuals [37]. Recent studies have suggested that only a subset of genes show a significant difference in expression levels between trisomic and typical individuals, which may provide one source of individual variability in the DS phenotype [36].

Behavioral Phenotype

The cognitive profile of individuals with DS emerges during childhood and includes, as a primary component, a weakness in auditory short-term memory relative to both visual-spatial short-term memory and nonverbal mental age (MA) [38–40]. Auditory short-term memory is typically measured on tasks requiring repetition of digits or nonsense words (i.e., memory for speech sounds). Backward memory for verbal and visual information, which indexes more effortful and strategic central processes in memory, is also impaired [41]. By adolescence, however, the ability to remember and

reproduce sequences of visual information, as measured with the Bead Memory subtest of the Stanford-Binet Intelligence Test [42], lags behind the ability to analyze and reproduce spatial models, as measured with the Pattern Analysis subtest of the Stanford-Binet [43]. Thus, working memory for both auditory and visual information appears to be selectively impaired in DS, although with different developmental trajectories.

Another feature of the DS phenotype is that the vast majority of children with DS experience some degree of hearing loss, which may be conductive or sensorineural, unilateral, or bilateral [44]. A recent study found that 81% of preschool-aged children with DS had abnormal hearing [45]. Conductive hearing loss in DS may be caused by otitis media—fluid in the middle ear—resulting from dysmorphology affecting the Eustachian tube and/or immune deficiencies leading to increased respiratory illnesses [44]. Children with DS may be especially vulnerable to negative influences on the language learning process resulting from hearing loss [46].

Linguistic Dimensions of the Phenotype

Language may be the developmental domain that is most affected in individuals with DS [43, 47, 48]. In general, receptive language is less problematic than expressive, with most young children with DS displaying levels of receptive language that are commensurate with their nonverbal cognitive level [49]. By adolescence, however, even syntax comprehension lags behind nonverbal MA. In contrast, vocabulary comprehension keeps pace with, or exceeds, nonverbal MA [50, 51]. Because of the asynchronous development of comprehension and production, we focus on each in turn.

The uneven relationship among vocabulary comprehension, syntax comprehension, and nonverbal cognition depends on the measures used to assess these domains. When tested with a measure assessing relatively concrete words based on frequency of occurrence, vocabulary comprehension appears in advance of MA for adolescents with DS. When tested with a measure based on conceptual difficulty with an emphasis on relational words, vocabulary comprehension is commensurate with nonverbal MA estimates [52]. As adolescents with DS mature and accumulate additional real-life experiences, they continue to accumulate vocabulary knowledge provided that the underlying concepts are fairly concrete.

In contrast to vocabulary comprehension, syntax comprehension is a domain of great challenge for individuals with DS. Chapman et al. sought to understand the nature and sources of variation in syntax comprehension [53]. They used hierarchical linear modeling to examine longitudinal predictors of syntax comprehension across a 6-year period in 31 participants with DS who were enrolled between 5 and 20 years of age. Syntax comprehension, as measured by the Test for Auditory Comprehension of Language-Revised (TACL-R) [54], was predicted best by three variables measured at the start of study: auditory verbal short-term memory, visual short-term memory, and CA. Age at study start also predicted the change in slope for growth in comprehension. For a child of 7.5 years at study start, comprehension growth rate was positive; for a child of 12.5 years, the slope was positive but shallower, whereas the predicted growth rate was negative for participants who entered the study at age 17.5 years, suggesting a regression in early adulthood.

In another study examining the sources of syntax comprehension skill, Miolo et al. examined predictors of performance on a sentence comprehension task requiring participants to act out intended sentence meanings by manipulating objects [55]. The two syntax comprehension subtests of the TACL-3 [56] were also administered. The group with DS showed a larger discrepancy (relative to syntax comprehension-matched typically developing [TD] participants) between visual short-term memory and auditory short-term memory (as measured by digit recall and nonword

repetition, respectively), as well as between syntax comprehension and production. For the DS group, auditory short-term memory accounted for a significant portion of the variance in performance on both the TACL-3 and the act-out comprehension task. Hearing status accounted for 23% of the variance in performance on the Grammatical Morphemes subtest of the TACL-3. Visual short-term memory did not contribute significant variance to any of the outcome measures. Results of Miolo et al. demonstrate the importance of auditory short-term memory to syntax comprehension in DS and provide additional evidence for the interdependence of language and other areas of cognitive development in affected individuals [57].

Abbeduto and colleagues [58] examined correlations between syntax comprehension, vocabulary comprehension, and nonverbal MA in 25 adolescents and young adults with DS, matched for nonverbal MA with 19 adolescents and young adults with FXS, and 24 TD 3- to 6-year-olds. Participants with DS and FXS were also matched on IQ and CA. Syntax and vocabulary comprehension were measured using the TACL-R. Age-equivalent scores for overall comprehension were significantly lower for participants with DS than for the participants with FXS. In addition, participants with DS demonstrated an uneven profile of subtest scores, with a significantly higher score for vocabulary relative to grammatical morphology and syntax comprehension. In comparison, MA-matched FXS and TD groups demonstrated a flat performance profile for the TACL-R subtests. All three participant groups demonstrated significant associations between nonverbal MA and each of the TACL-R subtests, suggesting that cognitive ability imposes strong constraints on language comprehension.

Moving from comprehension to production, children with DS are less likely to accompany prelinguistic communicative gestures with vocalizations than are TD children [59, 60]. Additionally, young children with DS appear to show a preference for the use of gestures rather than spoken words [61]. Delays are also observed in nonverbal requesting behaviors in DS [62, 63]. Nonverbal requesting also is related to problem-solving in toddlers with DS, relative to MA-matched TD children and CA- and MA-matched children with other developmental delays [64]. For toddlers with DS, Fidler and colleagues suggest that weaknesses in both requesting and problem-solving, accompanied by concurrent strengths in the initiation of social routines and requests for dyadic interaction, may reflect decreased persistence and motivation to engage in challenging tasks [65].

The types of vocalization produced during early development by children with DS are similar to those of TD infants [66], but the transition from babbling to the appearance of first words is substantially delayed, varying from 8 to 45 months [67–70]. Both first words and first multiword combinations emerge at roughly the same MAs as reported for TD children [70, 71], but with early spoken vocabulary displaying a slower than typical rate of development [72]. A longitudinal study by Zampini and D'Odorico [73] showed that vocabulary size began increasing for children with DS at 36 months of age; however, their overall vocabulary size remained less than that of TD children of the same developmental age.

By adolescence, expressive language in individuals with DS is characterized by especially serious deficits in vocabulary, syntax, and speech intelligibility. Chapman et al. examined language production in 47 children and adolescents with DS, ranging in age from 5 to 20 years [74]. Participants were matched groupwise for nonverbal MA with 47 TD children, 2–6 years of age. Measures of production, including mean length of utterance (MLU), total words, and number of different words, were significantly lower in the group with DS relative to the MA-matched comparison group, whereas rate of speaking (i.e., utterances per minute) was higher. Participants with DS also had poorer intelligibility.

Chapman et al. [75] examined predictors of language production for the same cohort. Measures of production included number of different

word roots and MLU in morphemes (both derived from a narrative sample), as well as intelligibility. Hearing, chronological age (CA), and nonverbal cognition were significant predictors of the number of different words, accounting for 8, 35, and 13% of the variance, respectively, for DS. Hearing status, CA, and nonverbal cognition were also significant predictors of MLU, accounting for 7, 35, and 24% of the variance, respectively, for DS. Finally, hearing and CA accounted for 8 and 24% of the variance in speech intelligibility, with comprehension failing to account for significant additional variance to the regression model. Although these results emphasize the importance of language comprehension for the prediction of expressive vocabulary and syntax, they also suggest a contribution of hearing to the ability of individuals with DS to produce utterances that are intelligible and syntactically complete.

An important developmental issue is whether language production plateaus in late childhood or early adolescence for individuals with DS, especially as regards the acquisition of syntax. Chapman and colleagues [53] investigated this issue in a longitudinal examination of 31 individuals with DS, ages 5–20. Hierarchical linear modeling was used to predict change in MLU for spontaneous utterances over the course of 6 years. It was found that individuals with DS continued to make progress in expressive language, with average MLU increasing from 3.48 words (SD 1.76) to 4.93 words (SD 2.14) across the 6-year observation period. Thus, there was no evidence of a plateau, contrary to previous claims [76].

Examination of narrative language samples may be especially informative of the ways in which nonverbal cognition and expressive language jointly contribute to the ability of individuals with DS to produce a spoken description in a more structured context than conversation. When recounting the wordless film, *The Pear Story*, Boudreau and Chapman found that participants with DS produced longer narratives, recalled more events overall, and expressed more inferential relationships than did MLU-matched TD participants [77]. Thus, despite deficits in expressive syntax, individuals with DS mentioned more of the content of the story than did TD children with the same MLU. As expected, MA-matched comparison children produced a greater number of different words, and both MA- and syntax comprehension-matched comparison groups had, on average, longer utterances than the group with DS. Presumably, participants with DS compensated for challenges in the area of syntax by using additional, but shorter, utterances to express the content of the story.

Miles and Chapman [78] report findings similar to those of Boudreau and Chapman [77]. In response to the wordless picture book, *Frog, Where Are You?*, Miles and Chapman found that participants with DS recounted significantly more components of the story's plot, more incidents of the boy's search for the frog, and more of the dog's misadventures than did TD children matched for MLU. Together, these studies suggest that individuals with DS demonstrate a deeper conceptual understanding of a story (one more in line with their comprehension skills) despite a relative impairment in expressive syntax.

A more recent study by Channell, McDuffie, Bullard, and Abbeduto examined the macrostructural (i.e., episodic structures of the story) and microstructural (i.e., use of specific word categories) components of narrative storytelling [73]. The participants were 10- to 15-year-olds with DS who told a story from one of two wordless picture books: *Frog Goes to Dinner* or *Frog on His Own*. Participants with DS expressed fewer macrostructural components of the story than their cognitively matched TD peers. Importantly, however, this finding was no longer significant when MLU was controlled for, which is consistent with findings from previous studies [77, 78]. With regard to microstructural components, adolescents with DS produced fewer verbs and adverbs than their cognitively matched TD peers

and the difference in verb use remained even after controlling for MLU. It would appear, then, that syntactic and lexical impairments constrain narrative production in individuals with DS, but that they appear able to somewhat "rise above" these impairments to produce narratives of reasonable quality, although still not at age-appropriate levels.

Neural Bases of the Phenotype

At birth, the brains of infants with DS appear structurally indistinguishable from those of typical individuals; however, abnormal expression of proteins from chromosome 21 genes has recently been detected in cortical tissues of fetuses with DS. These gene products include those implicated in oxidative stress, folate metabolism, and synaptic transmission [79].

Differences in brain function have been documented in infants with DS. Karrer and colleagues, for example, used event-related potentials to study visual attention in a group of infants with DS [80]. Although there were no behavioral differences in measures of visual fixation and attention, event-related responses to an oddball paradigm did distinguish the DS group from TD infants in terms of the area of the Nc component as measured at the frontal midline recording site (Fz). The Nc component is interpreted as an index of infant cognitive processing and may reflect the updating of a visual memory trace that should decrease in amplitude with repeated exposure to a stimulus. In contrast to the TD infants, those with DS demonstrated little decrement in the Nc over trials. Karrer et al. interpreted these findings as indicating that infants with DS may have less efficient memory processes than TD infants, even in the absence of differences that can be detected with traditional behavioral tests of cognitive development.

Learning impairments in DS are thought to be related to cognitive processes that rely on the hippocampus, prefrontal cortex, and cerebellum [21]. Uecker et al. [81] report a study in which 10 infants and children with DS, under the age of 30 months who performed within normal limits on the Bayley Scales of Infant Development (BSID) [82], were trained with three different tasks: a response task requiring the children to turn in a consistent direction; a cue task requiring children to make an association between a visual cue and a goal; and a place task in which the goal remained constant and the start position varied. Children with DS, who required more trials to learn all three tasks, performed similarly to TD comparison children in the response and cue tasks, but more poorly in the place task, presumably reflecting a deficit in hippocampal function.

Pennington and colleagues examined whether task performance in older children and adolescents with DS was more consistent with hippocampus-mediated long-term memory deficits, prefrontal cortex-mediated working memory deficits, or generalized cognitive deficits [12]. Twenty-five adolescents with DS, between 11 and 19 years of age, were compared with TD children matched pairwise based on nonverbal MA, with a mean of 4.5 years. Four neuropsychological tests tapping hippocampal function and six tests tapping prefrontal function were administered, as well as a series of benchmark tasks assessing areas of cognitive and language functioning known to be affected in DS (i.e., verbal short-term memory, receptive and expressive vocabulary, and syntax). Although performances on the prefrontal and hippocampal tasks were intercorrelated, participants with DS performed less well than the comparison children on the measures designed to assess memory functions mediated by the hippocampus. No significant between-group differences were observed for the tasks of prefrontal functioning. In addition, regression analysis revealed that both the hippocampal and the prefrontal tasks made significant contributions to the prediction of nonverbal MA, after controlling for CA. Finally, CA and prefrontal task performance, but not hippocampal task performance, accounted for significant variance in syntax development.

Individuals with DS also experience an acceleration of age-related cognitive decline in the form of neuropathological changes consistent with Alzheimer's disease (AD)—including senile plaques and neurofibrillary tangles that are observed in virtually all adults with DS by 35–40 years of age [83, 84]. Plaques consist of a protein, beta-amyloid, which derives from the overexpression of the *APP* (amyloid precursor protein) gene on chromosome 21. However, the physiological signs of Alzheimer's and clinical signs of dementia dissociate to some degree in DS, with clinical signs of dementia present in only 50% of individuals with DS over the age of 50 [85, 86]. Age-related atrophy and loss of brainstem cholinergic neurons projecting to the hippocampus is common in both DS and AD [26] and is thought to be related to overexpression of the *APP* gene.

Summary

The behavioral phenotype of DS begins to emerge early in development and is characterized by both a delay and uneven profile of cognitive and language skills. IQ levels range from 30 to 70, with delays in verbal short-term and visual sequential memory relative to visual–spatial cognition. Language represents the behavioral domain that is most affected for individuals with DS. Although the development of language skills continues into adolescence and adulthood, expressive language becomes increasingly impaired relative to comprehension. Within both comprehension and production, vocabulary knowledge is stronger than knowledge of syntax and grammatical morphology. Speech intelligibility is a major concern for individuals with DS and may be related to hearing status, as well as to difficulties with orofacial structures and oral-motor function. Current research is focusing on identifying those genes and gene interactions that affect brain development and organization in DS, ultimately leading to the emergence of the DS behavioral phenotype.

Fragile X Syndrome and Related Conditions

Genetics, Prevalence, and Overview

FXS is the leading inherited cause of intellectual disability. The prevalence of affected individuals is 1 in 4,000 males and 1 in 6,000–8,000 females [87]. The syndrome results from a mutation in the *FMR1* gene on the X chromosome [88]. In the healthy allele, there are approximately 55 or fewer repetitions of the CGG sequence of nucleotides comprising the gene [89]. In FXS, there is an expansion to more than 200 repetitions [90]. This *full mutation* typically leads to hypermethylation and transcriptional silencing so that the gene does not produce its normal protein (FMRP), which is involved in important ways in experience-dependent neural development [91, 92]. Less extreme expansions of the *FMR1* gene are also associated with adverse phenotypic consequences, although the biological mechanisms are different than in the full mutation case [93]. In particular, individuals with the *FMR1 premutation* (i.e., 55–200 CGG repeats) display some of the same behavioral features as do individuals with FXS, albeit typically in a less severe form [94]. Premutation carriers are also at risk for conditions not seen in FXS [93], which we describe in the following sections. In this section, we consider both the full mutation and the premutation phenotypes.

Full Mutation

Behavioral phenotype. The FXS phenotype is characterized by a profile of relative weaknesses and strengths across various neurocognitive domains [95]. Domains that are characterized by especially serious delays or impairments include the ability to process sequential information [96–98], auditory short-term memory [99], and attention, particularly problems in inhibitory

control and sustained attention [95, 98, 100–102]. Neurocognitive domains that are relatively strong in FXS, although still generally delayed relative to CA expectations, include the processing of simultaneous information [103], long-term memory [99], and social cognition—at least as indexed by the ability to distinguish one's own from another's representation of the world [104, 105].

Individuals with FXS also evidence relatively high rates of psychopathology and challenging behaviors [106, 107]. Hyperarousal [108], hyperactivity [98, 103, 109–115], repetitive behaviors [116], and anxiety, particularly social anxiety [112, 115, 117–119], are frequent in individuals with FXS. Aggression can also be a problem for those with FXS [120].

There is also a relatively high comorbidity between FXS and autism spectrum disorder (ASD) [121, 122]. ASD-like behaviors (e.g., eye gaze aversion, ritualistic behaviors, and hand-flapping and other self-stimulating behaviors) are frequent in individuals with FXS [123–126]. Indeed, some researchers suggest that more than 90% of this population displays ASD-like behaviors [127]. Moreover, these behaviors are often sufficiently frequent and severe to warrant a comorbid diagnosis of ASD [121, 128]. Although large-scale population-based studies have not been conducted, a rate of ASD in FXS as high as 60% has been reported, although there is considerable variability across studies [121, 122, 129–134]. There is controversy, however, as to whether the categorical diagnosis of ASD masks some clinically important differences between the symptom profiles and underlying problems in FXS relative to nonsyndromic ASD [135].

Although there is a characteristic phenotype associated with the *FMR1* full mutation, there is also considerable within-syndrome variability. Much of this variability is related to the sex of the individual with the full mutation, reflecting the moderating effects of the second X chromosome carried by females and the process of X inactivation [127]. On average, IQ is much lower for affected males than females, with more than 90% of males and 25–50% of females with the syndrome having IQs below 70 [136]. Nevertheless, males and females with the full mutation of the *FMR1* gene appear to display very similar profiles of neurocognitive deficits, psychopathology, and comorbid conditions [137, 138], although this conclusion largely reflects a synthesis of studies measuring similar constructs in either males or females; direct comparisons of the two sexes under similar task and measurement conditions have been relatively rare [135].

There is, however, also considerable phenotypic variation within each sex. Such variation is partly due, in one way or another, to differences in the *FMR1* gene among individuals [88]. Among males with the full mutation, there is variation in terms of the size of the CGG expansion, the extent to which there is methylation across cells, and whether some cells contain the premutation rather than the full mutation [139]. Among females, there is not only similar variation, but also variation in the relative proportion of cells in which the affected X chromosome, rather than the healthy allele, is active, or functioning [140]. Such variations among males and females with the full mutation are important because they are associated with variations in FMRP levels and thereby with variations in the phenotype [141–146]. No doubt, other genes are also involved in moderating the effects of the *FMR1* mutation [147]; however, little is known about these background gene effects. It also is likely that environmental variation moderates the manifestation of the phenotype in both males and females.

Linguistic dimensions of the phenotype. Language problems are common in FXS [148]. Children with FXS make the transition from communicating nonverbally into producing their first words many months later than do their typical peers, and some individuals with FXS never make the transition [149, 150]. Those who do make the transition, continue to lag behind their TD CA-matched peers in all domains of language, although some domains are more problematic than others [151, 152]. Additionally, lower IQ, increased attentional problems, poorer

auditory short-term memory, and increased ASD severity in FXS are negatively related to some aspects of language skill [153–156].

Studies of vocabulary development in FXS have yielded inconsistent findings [157]. Some studies have found vocabulary to be a relative strength for many individuals with FXS. For example, in a study of expressive vocabulary, Roberts et al. examined the early communication profiles of 21- to 77-month-old boys with FXS using the Communication and Symbolic Behavior Scales (CSBS) [158], a structured assessment of early social communication development [159]. Mean scores for the boys with FXS were higher for *use of different words* than for most other CSBS domains. In a study of receptive vocabulary in adolescents and young adults with FXS, Abbeduto et al. [58] found that scores on the Word Classes and Relations subtest of the TACL-R [54], a standardized test of spoken language comprehension employing a forced-choice response format, were well below CA expectations, but similar to expectations based on nonverbal cognition. However, Price et al. [160] found that the receptive vocabulary scores of boys with FXS, as measured by the Vocabulary subtest of the TACL-3 [50], were lower than those of their younger TD peers, even after controlling for nonverbal IQ. Moreover, Martin et al. found that the development of expressive vocabulary across three years on the Antonyms subtest of the Comprehensive Assessment of Spoken Language [161] was more impaired than would be expected based upon nonverbal MA expectations [162].

Children who have ASD in addition to FXS are likely to show poorer vocabulary comprehension skills than children with only FXS [154, 163–166], although not all studies find such a relationship [160] and this may be due in part to differences in IQ that are confounded with ASD status [135]. At the same time, there is evidence that vocabulary, measured both receptively and expressively, is a strength in children with FXS relative to those with nonsyndromic ASD, even when differences in CA, nonverbal cognitive ability, and ASD symptom severity are controlled [157]. The extent to which vocabulary development is delayed also varies with sex and CA, as well as with task, modality, contextual factors, such as maternal education [148], and cognitive factors, such as auditory short-term memory [155].

Syntax is an area of relative weakness, although there is variability related to age, ASD status, gender, and modality [167]. Receptive syntax, for example, has been found to be below nonverbal MA expectations for young boys with FXS [165, 168, 169], but at MA-consistent levels for older adolescents and young adults with FXS [58, 170, 171]. Syntactic impairments are also greater for individuals with FXS and comorbid ASD than for those with FXS only, even after controlling for differences in cognitive ability [154, 172]. Males are more impaired than females in the syntactic domain, although this appears to be due largely to differences in their levels of cognitive functioning [148]. In contrast to receptive syntax, which appears to catch up to cognitive development by adolescence, expressive syntax is below MA expectations for both children and adults with FXS [157, 162, 164, 173–177]. It is likely that this asynchrony reflects the fact that speaking and listening require at least partly different levels or types of syntactic knowledge as well as the use of different psychological processes to access and use that knowledge.

There is also evidence that there is variability in the degree of impairment across different syntactic features. Levy et al. [149] analyzed the syntactic characteristics of language samples collected in conversation and narration from boys with FXS, with comparisons made to samples produced by TD children who were matched to the FXS sample on gross measures of language ability. Boys with FXS were found to be more delayed than the TD matches on several measures of expressive syntactic skill (e.g., the relative use of sentences with dependent clauses). The boys with FXS, however, also scored at more advanced levels than the TD children on

many other measures; for example, the former made fewer errors in number agreement (e.g., "the boys is"). In a similar vein, Finestack and Abbeduto [175] found that although adolescents and young adults produce utterances that are syntactically simple, they are most often grammatical, which contrasts with similarly aged individuals with DS. This variable syntactic profile, with pockets of strength and weakness, raises the possibility that syntactic development is not simply delayed, but also different in FXS.

Pragmatics, or the ability to use language for social ends (e.g., expressing one's needs, interests, and intentions or signaling misunderstanding to a conversational partner), is an area of relative weakness for individuals with FXS. In fact, pragmatic ability is more impaired on average than is the ability to master syntax (i.e., grammar) or vocabulary [144]. Broad-based measures of adaptive behavior that include an assessment of pragmatic skills (e.g., the Vineland Adaptive Behavior Scales [178]), for example, indicate that scores in the pragmatic domain lag behind scores in other adaptive skill domains [179–181]. Studies in which more narrowly defined aspects of pragmatics have been assessed, usually through experimental or laboratory-based measures, have also uncovered substantial impairments. These methods have documented below MA performance in providing informative descriptions of intended referents in non-face-to-face interactions [182], recognizing and taking steps to correct problems in comprehending other people's messages [183–185], and producing utterances that are on topic rather than semantically unrelated or tangential [186, 187], especially for those individuals who are affected by both FXS and ASD [184, 188].

Verbal perseveration (i.e., the excessive repetition of a sound, word, phrase, or topic) is an especially serious problem for individuals with FXS [86, 186–190]. Perseveration is a pragmatic problem at least in the sense that it results in a failure to adhere to conversational expectations regarding informativeness. Perseveration also interferes with normal linguistic interaction [189]. Males with FXS produce more perseverative language than do linguistic level-matched TD children [149] or developmental level-matched males with ASD, DS, or other forms of intellectual disability [187, 190, 191], suggesting that it may be syndrome-specific, at least for males with FXS [192]. The causes of perseveration, however, are not well understood and different types of perseveration (e.g., word repetition vs. topic repetition) may reflect different underlying problems, such as problems with arousal regulation and autonomic dysfunction [193].

Neural bases of the phenotype. The brain bases of the FXS behavioral phenotype are beginning to be understood through studies employing structural and functional neuroimaging and studies of the biochemical pathways altered by the *FMR1* mutation. In terms of brain structure, Kates et al. suggest that FXS is characterized by numerous, nonspecific abnormalities of structure [194]. In fact, individuals with FXS are characterized by an increased volume (relative to TD individuals) of many structures, including the fourth and lateral ventricles, hippocampus, caudate nucleus, amygdala, and (at least in females) the thalamus [126]. There is also a relative decrease in the volume of the cerebellar vermis and temporal lobe [194, 195]. Note that, for the most part, these findings reflect differences among groups of participants, with the small sample sizes of most studies making it difficult to reliably estimate the proportion of affected individuals showing the structural anomalies described.

Many of these structural differences map onto aspects of the behavioral phenotype. The caudate nucleus has connections to the prefrontal cortex and thus is thought to play a critical role in the executive function impairments of individuals with FXS [195]. In fact, Reiss et al. found the volume of the caudate to be larger in individuals with FXS relative to controls and observed a negative correlation between caudate size and IQ in this population, suggesting that an unusually large caudate may also be less efficient functionally [196]. The volume of the cerebellar vermis has been found to be negatively correlated with severity of ASD symptoms, communication problems, and repetitive behavior in

affected females such that more severe ASD symptoms were associated with a greater decrease in the volume of the cerebellar lobes [197]. The cerebellar vermis may also contribute to problems in attention, language, tactile defensiveness, and repetitive movements as well as to hyperactivity through its connections with the frontal lobes [194, 195]. Decreased volume of the temporal lobe and amygdala is thought to contribute to problems in auditory processing and social anxiety, respectively [195]. The amygdala is also involved in the regulation of hypothalamic–pituitary–adrenal (HPA) system, which is known to be dysregulated in FXS [108, 198, 199].

Functional patterns of brain activity are also atypical in FXS. Several fMRI studies have demonstrated that activation patterns in FXS are relatively insensitive to task demands in a variety of higher order cognitive tasks (e.g., working memory) compared to TD individuals [142, 200]. Such findings suggest that individuals with FXS are not recruiting strategies and resources that reflect an appreciation of the more nuanced features of the cognitive task at hand. Moreover, FMRP levels are correlated with activation patterns in several brain regions, at least for females with FXS [146].

Some brain abnormalities in FXS are shared with other neurodevelopmental disorders, whereas other abnormalities may be syndrome-specific. fMRI studies have been able to map some aspects of the social impairments observed in individuals with nonsyndromic ASD to atypical functioning of select neural systems, especially those involving the amygdala [201]. In processing visual depictions of emotional facial expressions, for example, individuals with nonsyndromic ASD display hypoactivation of the fusiform gyrus and hyperactivation of the amygdala [202]. Individuals with FXS also show a pattern of hypoactivation in the right fusiform gyrus [203]. At the same time, however, individuals with FXS also show greater activation during emotional face processing relative to typical controls and individuals with nonsyndromic ASD in several other brain regions, including the left hippocampus [203]. Similarly, structural MRI studies have uncovered similarities and differences between FXS and nonsyndromic ASD [204, 205], including smaller amygdala volume in individuals with FXS than in those with nonsyndromic ASD [206].

Although FXS is a genetic disorder with distinctive brain pathology, it is important to recognize that there are also environmental contributions to the phenotype [207]. Thus, IQ is predicted by measures of the home environment (e.g., enrichment opportunities as measured by the Home Observation for Measurement of the Environment [HOME] Inventory) for boys and girls with FXS [208, 209]. There is also evidence of lower levels of psychological well-being (e.g., more depressive symptoms) among some mothers of individuals with FXS compared to mothers parenting sons or daughters with other conditions, such as DS [210–216]. The lower well-being of these mothers may result from the challenging behaviors of the child with FXS or from their own biological vulnerabilities as a result of carrying the *FMR1* premutation [217]. Whatever the source, however, lower levels of maternal well-being may translate into less than optimal interactions with the child with FXS, further hindering the child's development [207]. Importantly, several observational studies by Brady, Warren, and colleagues have demonstrated that maternal interactions with their children influence the subsequent language and behavioral development of children with FXS [218–221]. These observational studies have led to interventions designed to change maternal behavioral and with positive results on language and communication in children and adolescents with FXS, providing an experimental demonstration of the importance of the learning environment for children with FXS [222–226].

Premutation

Until relatively recently, it was assumed that carriers of the *FMR1* premutation were unaffected; however, this assumption is now known to be false. In fact, the premutation is associated

with a complex pattern of alterations in several biochemical processes important for neural development. Although most individuals who have the premutation have typical levels of FMRP, there appears to be a decrease in FMRP levels for many who carry premutations with more than 100 CGG repeats [227]. In addition, Tassone and colleagues have found levels of *FMR1* messenger RNA (mRNA) in carriers of the premutation that are 2–8 times greater than the levels characteristic of individuals with the healthy *FMR1* allele [227]. Larger premutations are especially subject to this increase in mRNA levels [228]. Excess mRNA provides a toxic context for neural development, with adverse phenotypic consequences, such as the formation of inclusions in astrocytes and neurons [229]. In light of recent prevalence estimates that suggest that 1 in 151 women, and perhaps half as many men, in the United States are affected by the *FMR1* premutation [230], these issues raise serious public health concerns.

As regards the phenotype, it has become clear from recent studies that the premutation is associated with a distinct behavioral profile [231, 232]. Although males with the premutation generally have IQs in the range of typical individuals, many display problems (relative to TD age-matched peers) in several cognitive domains, including executive function, attention, and long-term memory [94, 233, 234]. They are also at elevated risk for various forms of psychopathology, such as ADHD, anxiety, obsessive–compulsive disorders, and even ASD [94, 233–236], as well as physical problems such as headaches and seizures [237, 238]. All of these problems, however, occur less often and in a less severe form, on average, in males with the premutation than in males with the full mutation. Nevertheless, it is important to note that in some cases of the premutation, developmental delays serious enough to warrant a diagnosis of intellectual disability do occur [94].

Females with the premutation, especially those with larger expansions, are at elevated risk (relative to age-matched TD females) for depression, obsessive–compulsive disorder, anxiety, and ASD [235, 236, 239]. Although several studies have not found support for a cognitive phenotype for premutation females [228, 234, 240], a large-scale national survey of parents reporting on their children found that attention problems and even developmental delays are more common in females with the *FMR1* premutation than in matched comparison children with healthy *FMR1* alleles [94]. Recently, data have emerged suggesting that females with the premutation have subtle but clinically meaningful challenges in language, including high rates of dysfluency, topic perseveration, inclusion of unnecessary details, poor organization, and failure to provide important background information [241–244].

The *FMR1* premutation is also associated with two conditions, not found in the full mutation case. Males and, to a lesser extent, females with the premutation are at elevated risk during late adulthood for fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is a neurodegenerative disorder [164, 245]. FXTAS is characterized by intention tremor and ataxia, problems in memory and executive function, and increased anxiety and disinhibition [246, 247]. The condition worsens with age, and many individuals with FXTAS transition into dementia and have a shortened life expectancy [245]. Women who carry the premutation are also at elevated risk for primary ovarian insufficiency (POI), a condition associated with premature menopause (i.e., before age 40), decreased fertility, increased levels of several hormones, and endocrine problems [248, 249].

Summary

Expansions in the *FMR1* gene are associated with a range of developmental problems. Individuals who have the full mutation have especially severe problems in the inhibitory and sustained aspects of attention, auditory memory, and sequential processing. All aspects of language are impaired relative to chronical age expectation in FXS, although the social aspects of language and verbal perseveration are areas of particular challenge. Comorbid conditions, most notably ASD, are common as well. The

syndrome is characterized by considerable variation in the phenotype, however, with more severe symptoms in males than in females. In part, these behavioral variations are related to variations in the *FMR1*-related protein. Anomalies in brain structure and function are extensive. The *FMR1* premutation is also associated with a phenotype, including milder symptoms of FXS as well as FXTAS and POI.

Williams Syndrome

Genetics, Prevalence, and Overview

Early characterizations of individuals with WS, also called Williams–Beuren syndrome, described participants as being able to comprehend and produce complex linguistic constructions despite demonstrating severe intellectual disability [250]. This characterization quickly advanced arguments that the WS phenotype was the prototypical example of modularity in the organization of the brain, as demonstrated by "intact" language in the presence of severely impaired cognitive skills [251]. More recent empirical findings, however, have revealed that overall IQ scores mask a striking pattern of strengths and weaknesses in the nonverbal cognitive domain. For example, data reported by Mervis and John [252] demonstrated that in children with WS between 4 and 17 years of age, the mean Spatial standard score was 24 points lower than the mean Nonverbal Reasoning standard score when using the Differential Ability Scales-II [253].

Moreover, although language is a relative strength for individuals with WS, language ability does not exceed nonverbal cognitive levels [252] and strong associations between language and cognition in individuals with WS, in direct opposition to modularity proposals. Just as specific associations between cognition and language have been identified for FXS and DS, are also there associations in WS, although the profile of associations is unique to this syndrome. In addition, significant impairments have been noted within the language domain, particularly in the areas of pragmatic skills [254] and relational/conceptual vocabulary [255]. Overall, current research supports, not the notion of modularity of brain organization, but the interdependence of language with patterns of strengths and weaknesses in other cognitive domains.

With an estimated prevalence of 1 in 7500 live births [256], WS is less prevalent than either DS or FXS. WS is a complex neurodevelopmental disorder caused by a microdeletion of approximately 26 genes on chromosome 7q11.23 [257], with both sexes equally likely to be affected [258]. Approximately 95% of individuals with WS have the same deletion breakpoints, referred to as the *classic deletion,* which can be confirmed using fluorescent in situ hybridization (FISH). WS is associated with a recognizable pattern of physical characteristics, which includes a distinctive pattern of dysmorphic facial features, cardiovascular disease (especially supravalvar aortic stenosis), growth deficiency, connective tissue abnormalities, excessive blood calcium levels (i.e., hypercalcemia), and intellectual disability [259].

Behavioral Phenotype

Although there is a wide range of cognitive functioning spanning from intellectual functioning in the average range to severe intellectual disability, most children with WS present with developmental delays in early childhood and mild to moderate intellectual disability during the school-age years [252]. Importantly, WS is associated with a distinct pattern of strengths and weaknesses within the cognitive domain, that can influence the interpretation and validity of overall IQ scores. More specifically, relative strengths are observed in verbal short-term memory, nonverbal reasoning, and the structural and concrete aspects of language (e.g., vocabulary for nouns); furthermore, in general, performance across these different domains is relatively comparable [252].

In contrast, individuals with WS demonstrate a significant weakness in spatial ability. This is particularly apparent in the area of visuospatial construction, in which performance is approximately 20 points lower than performance in nonverbal reasoning or verbal ability (e.g., [252, 260, 261]. Because of this weakness in spatial ability, overall assessments of cognitive functioning that include items assessing spatial skills can misrepresent the overall functioning levels of the individual. This is a contributing factor to the characterization of WS as the prototypical example of modularity in the organization of the brain, as demonstrated by "intact" language in the presence of severely impaired cognitive skills [262]. It is important to note the considerable heterogeneity observed across individuals with WS; although as a group this pattern of performance is well documented, not every individual with WS will demonstrate this specific profile.

Another characteristic of the WS behavioral phenotype is hypersociability, with most individuals with WS demonstrating a strong interest in interacting with other people [263, 264]. Early in life, infants and toddlers with WS demonstrate a strong preference for social over nonsocial stimuli [265]. This strong preference for social stimuli has been speculated to interfere with the ability of young children with WS to engage in prelinguistic joint attention behaviors, which require that children learn to switch or coordinate their attentional focus between objects and people.

Fidler et al. [266] examined the emotional responsivity and perspective-taking ability of preschool-aged children with WS using a task in which the examiner uses nonverbal affective cues to indicate a strong preference for or dislike of a snack item. The child is then provided an opportunity to give one of the snack items to the examiner. The authors found that children with WS were more likely to mimic and/or intentionally imitate the examiner's facial affect and vocalizations than MA-matched children with developmental disabilities of nonspecific etiologies. This interest in the adult, however, did not improve children's decision-making performance; children with WS were just as likely to give the experimenter the liked food as the disliked food (39 vs. 36%).

Thurman and Mervis [267], when conducting a series of studies focused exploring the regulatory function of social referencing in children with WS or DS between 42 and 71 months, observed a similar pattern of findings. More specifically, Thurman and Mervis used a social referencing task to assess each child's ability to regulate his/her own behavior toward an ambiguous stimulus (remote-controlled robot covered by a cloth) in response to an adult's behavioral reaction (Joy or Fear). Each child was administered two trials (one Joyful trial and one Fearful trial) that were conducted on different days and differed in terms of the ambiguous stimulus, examiner, and playroom. During each trial, the child and the examiner played together; after some time playing a second examiner activated the stimulus robot (hidden under a cloth on a low table in the playroom). The examiner demonstrated either a Joyful or Fearful behavioral reaction in response to the ambiguous stimulus. Results indicated that children with WS shifted attention between the adult and the stimulus less often than the children with DS. In addition, children with WS demonstrated longer "looks" to the examiner on average and were more likely to imitate superficially the experimenter's fearful reaction than were the children with DS. However, as seen by Fidler et al. [266], this did not translate into an improved ability to regulate his/her own behavior toward the fearful stimulus.

These studies highlight an important caveat to the WS social phenotype. That is, despite their sociable nature, children with WS demonstrate a number of difficulties with regard to navigating reciprocal social interactions and communicating socially (i.e., pragmatic language). These difficulties are significant enough that many children exceed thresholds for a classification of ASD. A number of researchers have considered the performance of young children with WS limited

to no spoken language ability on the Autism Diagnostic Observation Schedule (ADOS) [268], a direct observation measure for ASD symptomatology. A significant proportion of the children in the samples reported by Klein-Tasman and colleagues [269], Klein-Tasman and colleagues [270], and Lincoln and colleagues [271] demonstrated difficulties integrating eye contact with nonverbal and verbal communicative acts, using prelinguistic gestures of initiating joint attention (e.g., pointing, giving, showing), and nearly all children demonstrated difficulties in play. In fact, the number of socio-communicative difficulties was frequent and severe enough for some children to earn scores within the ASD range (48% [270] and 10% [271]). Moreover, several similarities in terms of socio-cognitive deficits have been noted between children with WS and children with nonsyndromic ASD, including difficulties in understanding why actions are being done [272], difficulties in social attention—although the types of difficulties differ across groups [273], and difficulties in regulating interpersonal distance [274].

Finally, individuals with WS are also anxious, distractible, hyperactive, and more likely to experience difficulties with peer relationships than either CA- or MA-matched peers [254]. In fact, Leyfer et al. [275] found that over 80% of children and adolescents with WS, aged 4–16 years, met the criterion for at least one DSM-IV diagnosis, the most prevalent diagnoses being ADHD (65%) and specific phobias (54%). In addition, using both teacher and caregiver ratings, Klein-Tasman et al. [276] found that high rates of attentional problems and symptoms of anxiety were endorsed in both home and school settings in children with WS ages 6–17 years. Interestingly, in the same study, teachers were more likely to endorse aggressive and oppositional behaviors than were parents. The literature on WS has primarily focused on the hypersociability and friendliness associated with the WS phenotype. However, Klein-Tasman et al. [276] noted that almost a third of children with WS are demonstrating substantial challenging behaviors in the classroom.

Linguistic Dimensions of the Phenotype

For most individuals with WS, language is an area of relative strength. Despite the perception of largely intact expressive language abilities in WS, language performance is rarely commensurate with CA expectations. In general, verbal performance is consistent with nonverbal reasoning expectations, but significantly higher than spatial performance [252]. That said, the development of language for children with WS differs from that of TD children and other children with ID, and weakness within the language domain have been documented.

Administration of the Mullen Scales of Early Learning (MSEL) [277] has confirmed that the WS cognitive profile is apparent in toddlers and preschoolers with WS, with performance weakest in the fine motor domain and considerably stronger in receptive and expressive language [278]. In addition, 2-year-olds with WS, although scoring below the 10th percentile in vocabulary on the Words and Sentences version of the MacArthur-Bates Communicative Development Inventories (CDI) [279], have been found to display larger overall expressive vocabularies when compared to 2-year-old children with DS [280]. Interestingly, Mervis and colleagues [281] followed the language development of 10 children with WS (CA range: 4–26 months) over the span of several years and found that 9/10 children produced their first words several months before they first understood or produced a referential pointing gesture. Both TD children and children with DS demonstrate the opposite pattern in which referential pointing precedes the onset of first words. This delay in the emergence of referential pointing may be the result of a deficit in fine motor skills and/or pragmatic development

and suggests an atypical pattern of early language development in children with WS.

In general, vocabulary is a relative strength for individuals with WS, although there are areas of weakness within this domain [278]. Receptive concrete vocabulary (e.g., labels for objects, actions, and observable attributes) are consistently identified as an area of strength. For example, Mervis and John [255] found that 83% of their sample of 129 children and adolescents with WS earned a standard score on the Peabody Picture Vocabulary Test-4 (PPVT-4; 282) of at least 70. Expressive concrete vocabulary, as measured by the Expressive Vocabulary Test-2 [282], was found to be comparable, with mean EVT-2 standard score for the sample 2 points lower than mean PPVT-4 standard score. In contrast to the relative strength in concrete vocabulary, individuals with WS demonstrate difficulty with relational/conceptual vocabulary (e.g., terms for spatial, temporal, and quantitative concepts). In a group of 5- to 8-year-old children with WS, mean concrete vocabulary standard scores for the participants with WS were more than 30 points higher than mean relational vocabulary standard scores. The weaknesses in relational vocabulary were not restricted to spatial vocabulary options. The authors posited that difficulties processing spatial, temporal, and quantitative information may underlie the weakness in both abstract vocabulary knowledge and visual-spatial processing that are hallmark of the WS phenotype.

As mentioned previously, initial claims were made that grammatical abilities of individuals with WS were intact, thereby providing evidence for a modular organization of the brain in which cognitive skills were affected but the language was spared [250, 262, 283]. It has consistently been demonstrated that the spontaneous language of individuals with WS is more syntactically complex than that of CA- and IQ-matched individuals with DS [284–286]. Children with WS are also more proficient at producing tense marking than younger children with SLI who are matched for MLU [287, 288]. However, it is important to recognize that individuals with DS or SLI have deficits in morphosyntax relative to their levels of nonverbal cognition, which leads to an "exaggeration" of the syntactic capabilities of individuals with WS [289]. When matched with TD children based on CA or MA, the findings suggest that, on average, the grammatical abilities of children with WS are commensurate with, rather than in advance of, their level of cognitive development (290–293).

Mervis and colleagues conducted an extensive examination of the correlations among MLU, cognitive ability, and grammatical complexity in children with WS [294]. These investigators collected expressive language samples during play from 39 participants with WS, ranging in age from 2 to 12 years. Two measures of grammatical complexity—mean length of utterance in morphemes and the index of productive syntax (IPSyn) [295]—were lower than scores reported for TD children at ages 3–6 years. Thus, rather than being advanced in syntactic development, children with WS were substantially delayed relative to CA expectations. Moreover, for children with WS, MLU and IPSyn scores were consistent with cognitive ability, but lower than expected for auditory short-term memory and vocabulary comprehension.

Morris and Mervis [296] compared the morphological abilities of children with WS to a group of younger TD 3-year-olds matched for MLU. Use of plurals, determiners, and verb tense was similar for the two groups, indicating that the morphological abilities of the children with WS were at the level expected given the length of their utterances. However, the children with WS had larger receptive vocabularies than the MLU-matched, TD children, suggesting that utterance length and grammatical complexity are less than expected relative to vocabulary well developed for WS. This discrepancy between vocabulary and morphology was observed even though English is a relatively uninflected language. Children with WS learning languages that

are morphologically more complex than English (e.g., French, Italian, and Hebrew). Do more poorly than younger, MA-matched, TD children [291, 297, 298]. Thus, these studies suggest that grammatical morphology, like other aspects of syntax, is not advanced in individuals with WS relative to their levels of cognitive ability or vocabulary comprehension.

In contrast to DS, auditory short-term or working memory is a relative strength for individuals with WS and may provide support for language learning in this population [294]. Robinson et al. explored the consequences of this strength in memory by examining the association between verbal short-term memory and language in 39 children with WS, ages 4–16 years [299]. Participants with WS were matched to a comparison group of younger TD children based on performance on the Test for Reception of Grammar (TROG) [300], a test which examines grammar comprehension. After controlling for CA, measures of forward digit span, backward digit span, and nonword repetition predicted TROG scores for the children with WS. After controlling for CA and forward digit span, nonword repetition and backward digit span both accounted for unique variance in TROG scores. Robinson et al. proposed that auditory working memory, represented by nonword repetition performance, and verbal working memory, represented by backward digit span, contributed to the ability of individuals with WS to comprehend and produce vocabulary and grammar [299]. In fact, the group with WS showed a significantly stronger relationship between backward digit span and TROG scores than did children with typical development. These findings suggest that individuals with WS may use a basic cognitive strength, in the form of verbal working memory, to overcome their challenges in language learning that result from their relative weaknesses in nonverbal cognitive ability [265].

Studies of syntax comprehension also support the facilitative role of strong auditory memory skills in WS. Grant and colleagues found that performance on the TROG was significantly and positively correlated with nonword repetition performance for a group of participants with WS ranging in age from 8 to 35 years [293]. These findings support the view that auditory working memory is a characteristic strength for individuals with WS and contributes to relatively strong levels of performance in the domains of vocabulary and syntax.

Neural Bases of the Phenotype

A number of structural brain abnormalities have been observed in individuals with WS relative to TD controls. For example, individuals with WS have been shown to demonstrate a reduction in total brain volume that appears to result from a paucity of cerebral white matter [301, 302]). In addition, alterations in gyrification [303–305], the basal ganglia and brainstem (e.g., [302, 305, 306], and corpus callosum [304, 307, 308] have been reported.

Evidence is beginning to emerge for the neural underpinnings of the behavioral profile of WS. For example, behavioral research findings suggest that although the WS phenotype is associated with a relative strength in face recognition abilities, the way in which these individuals process faces may differ from TD peers or peers with other neurodevelopmental disorders [309–313]. In line with these behavioral findings, alterations in both structure and function within the brain regions important for face processing (e.g., fusiform gyrus) have been observed (e.g., 302, 309, 314). Neurobiological investigations have also linked abnormal dorsal stream neural processing to the hallmark visuospatial construction deficits associated with WS (e.g., [315–317] and a significant reduction in resting blood flow and absent differential response to visual stimuli and reduced synaptic activity [316]. In addition, hippocampal dysfunction may contribute to the neurocognitive

difficulties, such as spatial navigation, associated with WS [318–320].

Summary

The behavioral phenotype of WS is characterized by mild to moderate cognitive delay, a relative strength in verbal working memory and language, and severe challenges in the area of visual–spatial construction ability. This unique pattern of cognitive skills provides a double dissociation relative to the cognitive profile of individuals with DS. In addition, individuals with WS typically display personality traits of overfriendliness, anxiety, and empathy. Although WS was considered previously to demonstrate the independence of language from cognition, it is now known that language skills in WS are commensurate with general levels of cognitive ability. In addition, individuals with WS may rely to a greater extent on verbal working memory to support the process of language acquisition than do TD language learners. Currently, studies have not identified a causal association between the visual-spatial abilities and the social approach behaviors of individuals with WS.

Issues in the Neuropsychological Assessment of Individuals with Intellectual Disabilities of Genetic Origin

The research on the behavioral phenotypes of DS, FXS, and WS described in the foregoing sections, although based largely on studies of groups and central tendencies, has important implications for practitioners interested in the neuropsychological assessment of individuals for the purpose of treatment. There are also limitations of the research conducted on these syndromes to date that leave gaps in our knowledge of how best to assess individuals with genetic syndromes in clinical practice.

Implications

The research on behavioral phenotypes described in this chapter can serve as a guide for practitioners as regards the domains of psychological and behavioral functioning that deserve special scrutiny when designing an assessment plan for an individual with one of the syndromes considered. In the case of DS, for example, problems in expressive syntax and auditory memory are likely to be especially severe and thus should be the focus of special attention in any assessment and eventually intervention effort. In contrast, the social dimensions of language in FXS and WS and spatial cognition in WS are likely to warrant special consideration in an assessment as they are quite likely to be areas of substantial impairment. This is not to say that all individuals with a particular syndrome will "fit" the characteristic phenotype because, as already discussed, research suggests that there is considerable within-syndrome variability. In fact, there may well be more variability within a syndrome than between the syndromes that we have considered. Nevertheless, the phenotypes we have described for each syndrome represent a profile that has a high probability of adequately characterizing a reasonably large proportion of affected individuals [321]. Thus, the skillful clinician, who is likely to have only a limited amount of time and resources for assessing any individual client, can use the phenotypes described in this chapter as a basis for planning the assessment, while recognizing that the plan must be flexible and adapted as it unfolds to adequately capture the unique characteristics of the individual client.

It is apparent from the review of the behavioral phenotypes of the three syndromes on which we have focused that the differences between them are seldom adequately captured by

the types of gross summary measures generated by many standardized tests available today. Certainly, a full-scale IQ is not adequate for distinguishing the syndromes. Even a distinction between a performance IQ and a verbal IQ will fail to provide a clinically adequate characterization of these syndromes. Although a verbal IQ or a language age might favor individuals with WS over those with FXS, and the latter over those with DS, much of clinical importance is hidden by such a broad-based composite score, including the fact that it is the syntactic and pragmatic dimensions of language rather than the lexical dimension that will be the most likely to distinguish the syndromes. Similarly, a performance or nonverbal IQ will fail to capture the very substantial spatial deficits of individuals with WS or the seriousness of the sequential processing deficits of those with FXS, each of which is low relative to even other nonverbal skills. Similarly, the relatively strong (at least early in development) visual memory skills of individuals with DS and their exceptionally poor auditory memory skills, will be hidden by an IQ, and the specificity of these problems will not be captured by either a nonverbal or verbal composite. Moreover, even a conceptually coherent domain, such as syntax, is comprised of sub-domains that can pose variable degrees of challenges, as evidenced by the especially serious problems that individuals with FXS have producing sentences with dependent clauses and individuals with DS have with the use of verbs and inflectional morphology. In short, gross composite measures that collapse a wide swath of psychological and behavioral functioning are likely to obscure the profile of relative strengths and weaknesses that distinguish one syndrome from others. Perhaps most importantly, such measures also are unlikely to be sensitive to clinically meaningful change in a treatment study, especially those of relatively short duration [322, 323].

In our own research on language, we have moved away from gross summary measures derived from standardized tests and have created our own measures to probe more narrowly defined areas of language that are of interest because of their value in everyday social interaction and/or because they are hypothesized to be especially challenging to the population of interest. In some cases, we also have begun to document the psychometric properties of those measures, especially from the perspective of their potential utility in treatment studies. Here we provide two examples of such measures.

The first measure is a non-face-to-face laboratory-based task to examine the ability of older school-age children, adolescents and young adults with intellectual disability to formulate utterances in which the intended referent would be clear to other people [182]. In this task, the participant is the speaker and a researcher serves as listener. The speaker's job is to describe a novel target shape so that the listener can select the corresponding shape from a set of potential referents. There are multiple shapes constituting the set of potential referents, and each recurs on multiple trials so as to resemble natural conversation, which entails both introducing new topics and returning to previously discussed topics. During the interaction, the speaker and listener are separated by an opaque partition, and thus only the verbal channel of communication can be used to provide information.

In one study, we found that this task successfully discriminated adolescents and young adults with FXS or DS from younger TD children matched on nonverbal cognition and distinguished the two syndrome groups from each other [182]. In particular, the participants with FXS or DS were less likely than nonverbal MA-matched TD children to create unique (i.e., one-to-one) mappings between their descriptions and the target shapes; instead, they often extended the same description to multiple shapes (e.g., using "the muffin" to refer to two or more different shapes). The latter descriptions are technically ambiguous and thus, not informative to the listener. The participants with FXS were also less likely than either the NVMA-matched TD children or the age and nonverbal IQ- and MA-matched participants with DS to continue to use their previously successful descriptions on

subsequent trials; for example, the participants with FXS might use "house" to refer to a shape on one trial, but "muffin" to refer to the same shape on subsequent trials despite the fact that the former was successfully understood by the listener. Although technically informative, such inconsistency increases the processing demands on the listener. In contrast, the participants with DS were less likely than those with FXS or the TD children to scaffold their listener's understanding linguistically (e.g., by saying "It looks kind of like a house" rather than simply "It's a house"). These findings indicate that FXS and DS are each characterized by an asynchronous profile of pragmatic strengths and weaknesses and that the profiles are overlapping but not identical. Such findings also reinforce the need for the development of measures that provide insight into narrowly defined domains of psychological and behavioral functioning because of their potential importance to adaptive functioning, their internal coherence according to developmental theory, or their bases in brain mechanisms thought to be affected in the syndrome of interest.

The second measure is a set of standardized procedures for collecting expressive language samples. In expressive language sampling, the goal is to collect and analyze a relatively brief sample of an individual's speech under conditions that yield a representative picture of his or her language abilities. The representativeness of the sample is achieved by collecting the samples in social interactions that are familiar and meaningful to the individual. Expressive sampling procedures have been used clinically and for research purposes for decades; however, neither their psychometric properties nor the influence of variations in the interactions in which the samples are collected have been well understood for populations of individuals with intellectual disabilities. This led us to develop standardized, yet naturalistic, interactions for collecting these samples and for ensuring consistency of administration across participants, examiners, and occasions of assessment [324]. These samples have been analyzed in ways that allow derivations of variables reflecting skill in vocabulary, syntax, articulation, and utterance planning. Preliminary data on psychometric properties, such as test-retest reliability, suggest that these procedures are very promising for characterizing an individual's linguistic strengths and weaknesses and for measuring change within the context of a treatment [325].

The procedures we developed involve collecting expressive language samples in *conversation* with an examiner, with the topics of conversation specified and with scripted procedures for their introduction and follow up, and in *narration*, with the focus on telling the story in a wordless picture book with minimal scaffolding provided by the examiner. In a sample of children, adolescents, and adults with FXS, we found minimal practice effects in repeated administrations of these procedures as well as excellent test-retest reliability over a 4-week interval and with evidence of construct validity in the form of correlations with scores on a parent-report measure of communicative ability for both conversation and narration [325]. These procedures also have been found to discriminate, at a group level, between individuals with intellectual disabilities and children with typical development, between individuals with FXS and those with DS in ways consistent with previous research on the linguistic phenotypes of these disorders, and between subgroups of individuals with FXS [175–177, 324, 326].

Any good researcher or clinician appreciates the fact that no test, whether standardized or experimental and laboratory-based, provides a "pure" measure of any psychological construct; instead, there is always an impact on the performance of capabilities and characteristics that fall "outside" of the construct of interest. For example, a test of memory that requires recalling the spatial position of differently colored beads but also requires placing beads on a stick or string requires motor skill as well as spatial memory. If the individual being tested has a movement disorder, the motor component of the

task may "swamp" the contribution of his or her spatial memory skills to test performance, changing the very meaning or function of the test. As another example, most standardized tests, regardless of their content, depend on interacting and being at ease with the examiner and on attending to his or her instructions and prompts. If the individual being tested is plagued by social anxiety, as is true for many with FXS, the task may be more a reflection of this challenge than of the construct the test is actually intended to measure. In the case of individuals with intellectual disabilities, such "extraneous" factors complicate interpretation of scores on any measure because these individuals have impairments in virtually all domains of psychological and behavioral functioning. Moreover, the variable profiles that constitute the behavioral phenotypes of the syndromes described in this chapter complicate test interpretation even further because different extraneous factors will be important for individuals with different syndromes. It may be possible to minimize the influence of some of these factors (e.g., allow warm-up time or always rely on a familiar examiner to reduce social anxiety); however, it is virtually impossible to minimize all such factors through such testing accommodations.

In the context of research, we often try to clarify the performance of individuals with a disability on the measure of interest by examining correlations with measures of skills in other domains. For example, John, Rowe, and Mervis [327] conducted a study to examine the extent to which individuals with WS could monitor their comprehension of spoken messages and verbally signal noncomprehension by asking clarifying questions (e.g., "Which one do you mean?") or stating the nature of the problem (e.g., "I don't have any like that."). John et al. found that their young participants with WS signaled noncomprehension in this way in less than half of the instances in which it was necessary to do so. Moreover, the extent to which they successfully signaled noncomprehension was significantly correlated with their scores on both a measure of receptive vocabulary and a measure of theory of mind (i.e., the ability to recognize other people's knowledge, especially when it is different from self-knowledge). In a similar study of youth with FXS or DS, Abbeduto et al. found that the rate of successful noncomprehension signaling was correlated with a measure of receptive vocabulary and syntax [183]. Together, these findings raise the possibility that signaling noncomprehension reflects not just skill in comprehension monitoring and knowing when and how to signal noncomprehension, but also skill in understanding vocabulary and syntax and the ability to process other people's mental states. The implication of these findings for clinical practice is that the assessment of individuals with these and other forms of intellectual disability can benefit by a comprehensive approach in which multiple domains of functioning are assessed and potential relationships among the different domains are carefully considered.

A different approach to dealing with the multifactorial nature of any measure of a psychological or behavioral construct is to employ multiple measures of the construct of interest, each with somewhat different performance demands. The value of this approach is demonstrated by several studies in which expressive language samples have been obtained from the same participants in conversation and narration of fictional events. Narrative tasks, for example, appear to elicit more complex syntactic forms from participants with intellectual disabilities as well as from young TD children, whereas conversational contexts tend to elicit more varied vocabulary forms [324, 328]. Consequently, differences in ability among diagnostic groups are more likely to be detected in conversation than narration for some dimensions of language skill (e.g., vocabulary), whereas the reverse is true for other dimensions of language (e.g., syntax). The implication for clinicians is to rely on "triangulation" from multiple assessment devices designed to "measure the same thing" to hone in on the true level of ability for the construct of interest when assessing an

individual with an intellectual disability, whatever its origin.

Limitations

Virtually all of the measures available for assessing the psychological and behavioral functioning of individuals with intellectual disabilities, whether standardized tests or laboratory-based experimental measures, are "static" in the sense that they indicate what the client knows or does not know and can or cannot do at the time of the assessment. These measures reflect the accumulated effects of the interactions of genes and environment over the course of development, indicating in large measure how much of the typical developmental path has been traversed to that point. What these measures do not provide, however, are insights into the ways in which the individual learns and acquires new skills or attempts to solve problems at the current point in time. However, it is precisely the processes underlying learning and problem-solving about which we want to know, because it is these processes we hope to change through treatment. In targeting vocabulary, for example, it would be better to improve the way in which an individual approaches learning when he or she encounters a new word rather than simply teaching a predetermined (and limited) set of new words within the context of an intervention. Careful analysis of the profile of errors that a client makes in response to items on a standardized tests can occasionally provide some insights into the more dynamic processes of interest; however, these tests are not designed with such dynamic processes in mind, and thus the analysis of error profiles is often compatible with multiple interpretations of underlying processes and thus, ultimately, of limited clinical utility.

Unfortunately, much of the research on the phenotypes associated with the genetic syndromes described in this chapter has largely ignored the dynamic processes underlying learning and problem-solving. A notable exception is in the area of vocabulary learning in which there have been numerous studies involving a variant of the "fast mapping" paradigm employed in studies of typical language development. The premise underlying this paradigm is that young children encountering a novel word do not wait to be explicitly taught or somehow learn its full meaning; instead, they appear to create at least a tentative mapping of the word and its intended referent. These initial mappings are not random or idiosyncratic, but highly constrained by general principles and strategies that ensure a reasonable first approximation to the adult meanings of words. Carey, for example, demonstrated that when TD preschoolers heard the novel word "chromium" uttered along with a vague gesture toward two objects, one an odd greenish color and the other a more standard color (e.g., red), the children assumed that the word "chromium" referred to the color for which they had no label [329].

Although there is controversy about the nature of the constraints on children's initial mappings, there is consensus that considerable insight into how children learn new words can be gained by studying these "fast mappings" as they occur and the types of information on which these mappings are based. Moreover, the usefulness of this paradigm for understanding word learning in atypical populations has also been demonstrated. For example, Baron-Cohen et al. [330] demonstrated that, in contrast to young TD children who attend to a speaker's direction of gaze as a cue to identifying the referent of a novel word, children with ASD often assume that the novel word refers to the object that is the child's own focus of attention. In several recent studies, we have used the fast mapping paradigm to illuminate the effectiveness of word learning processes and the types of cues used to form initial mappings in children with a variety of learning challenges [331–334]. These studies have yielded patterns of performance that distinguish children with FXS from TD children as well as

from children with ASD. Knowledge of these fast mapping processes could be the basis of interventions designed to encourage the use of more adaptive learning strategies; however, standardized measures (along with appropriate normative data) are not yet available for use by clinicians.

Families and the Neuropsychological Assessment of Individuals with Intellectual Disabilities of Genetic Origin

Parents and other family members play an important role in the assessment process [335]. In the assessment of individuals with DS, FXS, or WS, parents are often a critical source of information during the assessment. Information about the mental health of individuals with these genetic conditions can often be gleaned only through the reports of parents because they have the opportunity to observe their sons and daughters on a daily basis and in a variety of contexts. Moreover, many individuals with these disorders are unable to verbalize their issues because of linguistic or cognitive limitations, an inability to engage in accurate self-reflection, or because of the various mental health comorbidities that might even be the basis of the referral for assessment in the first place. Parental report also often provides useful insights into various aspects of cognitive and linguistic functioning, supplementing more direct assessment methods.

Once an assessment is completed, clinicians share their recommendations for further testing and intervention with parents on the assumption that parents will implement those recommendations. If parents are unreliable in their input or fail to follow through on recommendations, the assessment process fails. Unfortunately, parents often may be grappling with many issues that function as barriers to their successful participation in the assessment process, and this may be especially true for the parents of individuals with DS, FXS, or WS.

Parents who are dealing with stress or their own mental health challenges may be unable to provide objective input to the evaluation process, fully understand information emerging from the assessment, seek out resources, participate in their child's course of treatment, and support the child's development. In the case of individuals with developmental disabilities, many parents report experiencing higher levels of stress and also perform poorly on measures of individual emotional well-being and family functioning compared to parents raising a TD child [336–338], although some adapt to, and even thrive in the face of, their caregiving responsibilities [339, 340].

At the same time, there are etiology-related differences among parents in terms of their experience of stress and psychological well-being [341–343]. Parents of children with DS have typically been characterized by lower reported stress and higher levels of adaptive parental and familial functioning compared to other disability groups (especially early in development), a finding that has often been referred to as the "Down syndrome advantage" [344–346]. In contrast, mothers of individuals with FXS appear to be at risk for poor psychological outcomes. These mothers report higher levels of parenting stress and lower levels of psychological well-being than do mothers of typical children [347–351] and mothers of youth with other disabilities [349, 350, 352]. Moreover, mood disorders, especially depression and anxiety, are quite frequent among these mothers [352–354]. These etiology-related differences among mothers may arise from reactions to the different phenotypes of their children, other contextual factors (e.g., the number of children with disabilities in the family), or genetic differences among the mothers themselves (e.g., biological mothers of individuals with FXS virtually always carry either the *FMR1* full mutation or the premutation). Etiology-related differences among fathers and siblings have also been documented [335].

Thus, there may well be etiology-related differences in the ability of family members to participate successfully in the assessment process. For this reason, Head and Abbeduto [355] have argued for a systems approach to assessment. Minimally, this approach requires contextualizing the assessment of the individual in terms of a broader assessment of the family's needs. The latter may include a comprehensive assessment of all family members, including a psychological assessment of parents, or be less extensive and formal. Whatever form the family assessment takes, it will require that the clinician conducting the neuropsychological assessment be part of a multidisciplinary team that can share observations and diagnostic information. Without such a systems approach, there is the risk that the neuropsychological assessment may be based in part on faulty data or, worse yet, never be implemented.

References

1. Schalock RL. et al. AAIDD. Intellectual Disability: Definition, Classification, and Systems of Supports (11th Edition). Washington, DC: American Association on Intellectual and Developmental Disability; 2010.
2. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Visser S, Kogan MD. Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics. 2011 Jun;127(6):1034-42.
3. Hodapp RM. Development and disabilities: intellectual, sensory, and motor impairments. New York, NY: Cambridge University Press; 1998.
4. Batshaw ML, Leon E, Kisling MS. The genetics underlying developmental disabilities. In: Bushaw ML, Rozien NS, editors. Children with disabilities, 8th ed. Baltimore: Brookes; 2019
5. Dykens EM, Hodapp RM, Finucane BM. Genetics and mental retardation syndromes: a new look at behavior and interventions. Baltimore, MD: Paul H Brookes Publishing; 2000.
6. Hunter AG. Outcome of the routine assessment of patients with mental retardation in a genetics clinic. Am J Med Genet. 2000;90(1):60–8.
7. Moeschler JB, Shevell M. American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. Pediatrics. 2006;117 (6):2304–16.
8. Shashi V, McConkie-Rosell A, Rosell B, Schoch K, Vellore K, McDonald M, Jiang YH, Xie P, Need A, Goldstein DB. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2014;16(2):176–82.
9. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A. National Birth Defects Prevention Network. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Res A Clin Mol Teratol. 2010;88(12):1008–16.
10. Lejeune J, Gautier M, Turpin R. Etudes des chromosomes somatique de neuf enfants mongoliens. Comptes Rendus de l'Academic les Sciences. 1959;48:1721–2.
11. Hattori M, Fujiyama A, Taylor TD. The DNA sequence of human chromosome 21. Nature. 2000;405:311–9.
12. Pennington BF, Moon J, Edgin J, et al. The neuropsychology of Down syndrome: evidence for hippocampal dysfunction. Child Dev. 2003; 74:75–93.
13. Roper RJ, Reeves RH. Understanding the basis for Down syndrome phenotypes. PLoS Genet. 2006;2: e50.
14. Epstein CJ. Epilogue: toward the twenty-first century with Down syndrome – a personal view of how far we have come and of how far we can reasonably expect to go. Prog Clin Biol Res. 1995;393:241–6.
15. Antonarakis SE, Epstein CJ. The challenge of Down syndrome. Trends Mol Med. 2006;12:473–9.
16. Sherman SL, Freeman SB, Allen EG, Lamb NE. Risk factors for nondisjunction of trisomy 21. Cytogenet Genome Res. 2005;111:273–80.
17. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. Ment Retard Dev Disabil Res Rev. 2007;13:221–7.
18. Fishler K, Koch R. Mental development in Down syndrome mosaicism. Am J Ment Retard. 1991;96:345–51.
19. Torfs CP, Christianson RE. Maternal risk factors and major associated defects in infants with Down syndrome. Epidemiology. 1999;10:264–70.
20. Chapman RS, Hesketh LJ. Behavioral phenotype of individuals with Down syndrome. Ment Retard Dev Disabil Res Rev. 2000;6:84–95.
21. Nadel L. Down's syndrome: a genetic disorder in biobehavioral perspective. Genes Brain Behav. 2003;2:156–66.
22. Delabar JM, Theophile D, Rahmani Z, et al. Molecular mapping of twenty-four features of Down syndrome on chromosome 21. Eur J Hum Genet. 1993;1:114–24.
23. Sinet PM, Theophile D, Rahmani Z, et al. Molecular mapping of the Down syndrome phenotype on chromosome 21. Prog Clin Biol Res. 1993;384: 63–86.

24. Olson LE, Richtsmeier JT, Leszl J, Reeves RH. A chromosome 21 critical region does not cause specific Down syndrome phenotypes. Science. 2004;306:687–90.
25. Moore CS, Roper RJ. The power of comparative and developmental studies for mouse models of Down syndrome. Mamm Genome. 2007;18:431–43.
26. Reeves RH, Garner CC. A year of unprecedented progress in Down syndrome basic research. Ment Retard Dev Disabil Res Rev. 2007;13:215–20.
27. Galdzicki Z, Siarey RJ. Understanding mental retardation in Down's syndrome using trisomy 16 mouse models. Genes Brain Behav. 2003;2:167–78.
28. Olson LE, Roper RJ, Sengstaken CL, et al. Trisomy for the Down syndrome 'critical region' is necessary but not sufficient for brain phenotypes of trisomic mice. Hum Mol Genet. 2007;16:774–82.
29. Rachidi M, Lopes C. Mental retardation in Down syndrome: from gene dosage imbalance to molecular and cellular mechanisms. Neurosci Res. 2007;59:349–69.
30. Nelson DL, Gibbs RA. Genetics. The critical region in trisomy 21. Science. 2004;306:619–21.
31. Pritchard MA, Kola I. The, "gene dosage effect" hypothesis versus the "amplified developmental instability" hypothesis in Down syndrome. J Neural Transm Suppl. 1999;57:293–303.
32. Shapiro BL. Down syndrome – a disruption of homeostasis. Am J Med Genet. 1983;14:241–69.
33. Epstein CJ. Developmental genetics. Experientia. 1986;42:1117–28.
34. Mao R, Zielke CL, Zielke HR, Pevsner J. Global up-regulation of chromosome 21 gene expression in the developing Down syndrome brain. Genomics. 2003;81:457–67.
35. Dauphinot L, Lyle R, Rivals I, et al. The cerebellar transcriptome during postnatal development of the Ts1Cje mouse, a segmental trisomy model for Down syndrome. Hum Mol Genet. 2005;14:373–84.
36. Sultan M, Piccini I, Balzereit D, et al. Gene expression variation in Down's syndrome mice allows prioritization of candidate genes. Genome Biol. 2007;8:R91.
37. Monks SA, Leonardson A, Zhu H, et al. Genetic inheritance of gene expression in human cell lines. Am J Hum Genet. 2004;75:1094–105.
38. Chapman R. Language and communication in individuals with Down Syndrome. In: Abbeduto L, editor. International review of research in mental retardation: language and communication, vol. 27. New York, NY: Academic Press; 2003. p. 1–34.
39. Jarrold C, Baddeley AD, Phillips CE. Verbal short-term memory in Down syndrome: a problem of memory, audition, or speech? J Speech Lang Hear Res. 2002;45:531–44.
40. Merrill EC, Lookadoo R, Rilea S. Memory, language comprehension, and mental retardation. New York, NY: Academic Press; 2003. p. 151.
41. Vicari S, Carlesimo A, Caltagirone C. Short-term memory in persons with intellectual disabilities and Down's syndrome. J Intellect Disabil Res. 1995;39 (Pt 6):532–7.
42. Thorndike R, Hagen E, Sattler J. Stanford-Binet Intelligence Scale. 4th ed. Chicago, IL: The Riverside Publishing Company; 1986.
43. Chapman RS, Hesketh LJ. 'Language, cognition, and short-term memory in individuals with Down syndrome': erratum. Down Syndr Res Pract. 2002;8:37.
44. Roizen NJ, Batshaw ML, Pellegrino L, Roizen NJ. Down syndrome. Children with disabilities. 6th ed. Baltimore, MD: Paul H Brookes Publishing; 2007. p. 263–73.
45. Shott SR, Joseph A, Heithaus D. Hearing loss in children with Down syndrome. Int J Pediatr Otorhinolaryngol. 2001;61:199–205.
46. Roberts J, Hunter L, Gravel J, et al. Otitis media, hearing loss, and language learning: controversies and current research. J Dev Behav Pediatr. 2004;25:110–22.
47. Roberts JE, Price J, Malkin C. Language and communication development in Down Syndrome. Ment Retard Dev Disabil Res Rev. 2007;13:26–35.
48. Abbeduto L, Warren SF, Conners FA. Language development in Down syndrome: From the prelinguistic period to the acquisition of literacy. Developmental Disabilities Research Reviews. 2007;13 (3):247–61.
49. Miller LJ, McIntosh DN, McGrath J, et al. Electrodermal responses to sensory stimuli in individuals with fragile X syndrome: a preliminary report. Am J Med Genet. 1999;83:268–79.
50. Chapman RS, Schwartz SE, Kay-Raining Bird E. Language skills of children and adolescents with Down syndrome: I. Comprehension. J Speech Hear Res. 1991;34:1106–20.
51. Rosin M, Swift E, Bless D, Vetter D. Communication profiles of adolescents with Down Syndrome. J Child Commun Disord. 1988;12:49–64.
52. Miolo GG. Sentence comprehension in adolescents with down Syndrome and typically developing children: role of sentence voice, visual context, and auditory-verbal short-term memory. J Speech Lang Hear Res. 2005;48:172–88.
53. Chapman RS, Hesketh LJ, Kistler DJ. Predicting longitudinal change in language production and comprehension in individuals with Down syndrome: hierarchical linear modeling. J Speech Lang Hear Res. 2002;45:902–15.
54. Carrow-Woolfolk E. Test for auditory comprehension of language – revised. Austin, TX: Pro-Ed; 1985.
55. Miolo G, Chapman RS, Sindberg HA. Sentence comprehension in adolescents with Down Syndrome and typically developing children: role of sentence voice, visual context, and auditory-verbal

short-term memory. J Speech Lang Hear Res. 2005;48:172–88.
56. Carrow-Woolfolk E. Test for auditory comprehension of language. 3rd ed. Circle Pines, MN: American Guidance Services; 1999.
57. Miolo GG, Chapman RS, Sindberg HA. Sentence comprehension in adolescents with Down syndrome and typically developing children: role of sentence voice, visual context, and auditory-verbal short-term memory. J Speech Lang Hear Res. 2005; 48:172–88.
58. Abbeduto L, Murphy MM, Cawthon SW, et al. Receptive language skills of adolescents and young adults with Down syndrome or fragile X syndrome. Am J Ment Retard. 2003;108:149–60.
59. Greenwald C, Leonard L. Communicative and sensorimotor development of Down's Syndrome children. Am J Ment Defic. 1979;84:296–303.
60. te Kaat-van den Os DJ, Jongmans MJ, Volman MCJ, Lauteslager PE. Do gestures pave the way?: A systematic review of the transitional role of gesture during the acquisition of early lexical and syntactic milestones in young children with Down syndrome. Child Language Teaching and Therapy. 2015;31(1):71–84.
61. Stefanini S, Caselli M, Volterra V. The link between gesture and speech in children with Down syndrome. Down Syndrome Research and Practice. 2009;12(3):173–4.
62. Mundy P, Kasari C, Sigman M, Ruskin E. Nonverbal-communication and early language-acquisition in children with Down-Syndrome and in normally developing-children. J Speech Hear Res. 1995;38:157–67.
63. Sigman M, Ruskin E, Arbelle S, Corona R, Dissanayake C, Espinosa M, Kim N, López A, Zierhut C, Mervis CB, Robinson BF. Continuity and change in the social competence of children with autism, Down syndrome, and developmental delays. Monogr Soc Res Child Developm. 1999; i-139.
64. Fidler DJ, Philofsky A, Hepburn S, Rogers S. Nonverbal requesting and problem-solving by toddlers with Down Syndrome. Am J Ment Retard. 2005;110:312–22.
65. Fidler D, Hepburn S, Rogers S. Early learning and adaptive behaviour in toddlers with Down syndrome: evidence for an emerging behavioural phenotype? Down Syndr Res Pract. 2006;9:37–44.
66. Smith IM, Bryson SE. Imitation and action in autism – a critical-review. Psychol Bull. 1994;116: 259–73.
67. Berglund E, Eriksson M, Johansson I. Parental reports of spoken language skills in children with Down syndrome. J Speech Lang Hear Res. 2001;44:179–91.
68. Berry P, Gunn P, Andrews R, Price C. Characteristics of Down syndrome infants and their families. Aus Paediatrics J. 1981;17:40–3.
69. Miller J. Profiles of language development in children with Down syndrome. In: Miller J, Leddy M, Leavitt L, editors. Improving the communication of people with Down syndrome. Baltimore, MD: Paul H. Brookes; 1999. p. 11–40.
70. Miller J, Leddy M, Miolo G, Sedey A. The development of early language skills in children with Down syndrome. In: Nadel L, Rosenthal D, editors. Down syndrome: living and learning in the community. New York, NY: Wiley; 11995. p. 115–20.
71. Cardoso-Martins C, Mervis CB, Mervis CA. Early vocabulary acquisition by children with Down syndrome. Am J Ment Defic. 1985;90:177–84.
72. Beeghly M, Cicchetti D. An organizational approach to symbolic development in children with Down syndrome. New Dir Child Dev. 1987;36:5–29.
73. Zampini L, D'Odorico L. Vocabulary development in children with Down syndrome: longitudinal and cross-sectional data. Journal of Intellectual and Developmental Disability. 2013;38(4):310–7.
74. Chapman RS, Seung H-K, Schwartz SE, Bird EK-R. Language skills of children and adolescents with Down syndrome: II. Production deficits. J Speech Lang Hear Res. 1998;41:861–73.
75. Chapman RS, Seung H-K, Schwartz SE, Kay-Raining Bird E. Predicting language production in children and adolescents with Down syndrome: the role of comprehension. J Speech Lang Hear Res. 2000;43:340–50.
76. Fowler AE. The course of language learning in children with Down syndrome Constraints on language acquisition: studies of atypical children. Hillsdale, NJ: Erlbaum; 1994.
77. Boudreau DM, Chapman RS. The relationship between event representation and linguistic skill in narratives of children and adolescents with Down syndrome. J Speech Lang Hear Res. 2000;43: 1146–59.
78. Miles S, Chapman RS. Narrative content as described by individuals with Down syndrome and typically developing children. J Speech Lang Hear Res. 2002;45:175–89.
79. Ferrando-Miguel R, Cheon MS, Lubec G. Protein levels of genes encoded on chromosome 21 in fetal Down Syndrome brain (Part V): overexpression of phosphatidyl-inositol-glycan class P protein (DSCR5). Amino Acids. 2004;26:255–61.
80. Karrer JH, Karrer R, Bloom D, et al. Event-related brain potentials during an extended visual recognition memory task depict delayed development of cerebral inhibitory processes among 6-month-old infants with Down syndrome. Int J Psychophysiol. 1998;29:167–200.
81. Uecker A, Mangan PA, Obrzut JE, Nadel L. Down syndrome in neurobiological perspective: an emphasis on spatial cognition. J Clin Child Psychol. 1993;22:266–76.
82. Bayley N. Bayley scales of infant development. San Antonio, TX: The Psychological Corporation; 1993.

83. Mann DM, Esiri MM. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. J Neurol Sci. 1989;89:169–79.
84. Zigman WB, Lott IT. Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev. 2007;13:237–46.
85. Menendez M. Down syndrome, Alzheimer's disease and seizures. Brain Dev. 2005;27:246–52.
86. Wisniewski KE, Rabe A, Wisniewski HM. Pathological similarities between Alzheimer's disease and Down's syndrome: is there a genetic link?': commentary. Integr Psychiatry. 1987;5:165–6.
87. Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. Genet Med. 2001;3:359–71.
88. Brown WT. The molecular biology of the fragile X mutation. In: Hagerman R, Hagerman PJ, editors. Fragile X syndrome: diagnosis, treatment and research. 3rd ed. Baltimore, MD: Johns Hopkins University Press; 2002. p. 110–35.
89. Nolin SL, Brown WT, Glicksman A, et al. Expansion of the fragile X CGG repeat in females with premutation or intermediate alleles. Am J Hum Genet. 2003;72:454–64.
90. Oostra BA, Willemsen R. A fragile balance: FMR1 expression levels. Hum Mol Genet. 2003;12 (Spec No 2):R249–R57.
91. Klintsova AY, Greenough WT. Synaptic plasticity in cortical systems. Curr Opin Neurobiol. 1999;9:203–8.
92. Bhakar AL, Dölen G, Bear MF. The pathophysiology of fragile X (and what it teaches us about synapses). Annu Rev Neurosci. 2012;35:417–43.
93. Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. Am J Hum Genet. 2004;74:805–16.
94. Bailey DB Jr, Raspa M, Olmstead M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. Am J Med Genet. 2008;146A(16):2060–9.
95. Cornish K, Turk J, Hagerman R. Annotation: the fragile X continuum: new advances and perspectives. J Intellect Disabil Res. 2008;52:469–82.
96. Burack JA, Shulman C, Katzir E, et al. Cognitive and behavioural development of Israeli males with fragile X and Down syndrome. Int J Behav Dev. 1999;23:519–31.
97. Dykens E, Volkmar F. Medical conditions associated with autism. In: Cohen D, Volkmar F, editors. Handbook of autism and pervasive developmental disorders. 2nd ed. New York, NY: Wiley; 1987. p. 388–407.
98. Dykens EM, Hodapp RM, Leckman JF. Strengths and weaknesses in the intellectual functioning of males with fragile X syndrome. Am J Ment Defic. 1987;92:234–6.
99. Freund LS, Reiss AL. Cognitive profiles associated with the fra(X) syndrome in males and females. Am J Med Genet. 1991;38:542–7.
100. Bregman JD, Dykens E, Watson M, Ort SI. Fragile-X syndrome: variability of phenotypic expression. J Am Acad Child Adolesc Psychiatry. 1987;26:463–71.
101. Flanagan T, Enns JT, Murphy MM, et al. Differences in visual orienting between persons with Down or fragile X syndrome. Brain Cogn. 2007;65:128–34.
102. Tonnsen BL, Grefer ML, Hatton DD, Roberts JE. Developmental trajectories of attentional control in preschool males with fragile X syndrome. Res Dev Disabil. 2015;36:62–71.
103. Dykens EM, Hodapp RM, Ort S, Finucane B. The trajectory of cognitive development in males with fragile X syndrome. J Am Acad Child Adolesc Psychiatry. 1989;28:422–6.
104. Grant CM, Apperly I, Oliver C. Is theory of mind under-standing impaired in males with fragile X syndrome? J Abnorm Child Psychol. 2007;35: 18–28.
105. Cornish K, Burack JA, Rahman A, et al. Theory of mind deficits in children with fragile X syndrome. J Intellect Disabil Res. 2005;49:372–8.
106. Abbeduto L, Chapman R. Language and communication skills in children with Down syndrome and Fragile X. In: Fletcher P, Miller J (eds.) Trends in language acquisition research, vol. 4: Developmental theory and language disorders. Amsterdam, The Netherlands: John Benjamins; 2005. p. 53–72.
107. Machalicek W, McDuffie A, Oakes A, Ma M, John Thurman A, Rispoli MJ, Abbeduto L. Examining the operant function of challenging behavior in young males with Fragile X Syndrome: A summary of 12 cases. Res Dev Disabil. 2014;35:1694–704.
108. Wisbeck JM, Huffman LC, Freund L, et al. Cortisol and social stressors in children with fragile X: a pilot study. J Dev Behav Pediatr. 2000;21:278–82.
109. Mazzocco MM, Pennington BF, Hagerman RJ. The neurocognitive phenotype of female carriers of fragile X: additional evidence for specificity. J Dev Behav Pediatr. 1993;14:328–35.
110. Baumgardner TL, Reiss AL, Freund LS, Abrams MT. Specification of the neurobehavioral phenotype in males with fragile X syndrome. Pediatrics. 1995;95:744–52.
111. Bailey DB Jr, Roberts JE, Hooper SR, et al. Research on fragile X syndrome and autism: implications for the study of genes, environments, and developmental language disorders. Mahwah, NJ: Lawrence Erlbaum; 2004.
112. Bregman JD, Leckman JF, Ort SI. Fragile X syndrome: genetic predisposition to psychopathology. J Autism Dev Disord. 1988;18:343–54.
113. Freund LS, Reiss AL, Abrams MT. Psychiatric disorders associated with fragile X in the young female. Pediatrics. 1993;91:321–9.
114. Cornish K, Cole V, Longhi E, Karmiloff-Smith A, Scerif G. Mapping developmental trajectories of attention and working memory in fragile X

syndrome: Developmental freeze or developmental change? Dev Psychopathol. 2013;25(2):365–76.
115. Thurman AJ, McDuffie A, Hagerman R, Abbeduto L. Psychiatric symptoms in boys with Fragile X Syndrome: A comparison with nonsyndromic autism spectrum disorder. Res Dev Disabil. 2014;35(5):1072–86.
116. Oakes A, Thurman AJ, McDuffie A, Bullard LM, Hagerman RJ, Abbeduto L. Characterising repetitive behaviours in young boys with fragile X syndrome. J Intellect Disabil Res. 2016;60(1):54–67.
117. Mazzocco MlM M, Baumgardner T, Freund LS, Reiss AL. Social functioning among girls with fragile X or Turner syndrome and their sisters. J Autism Dev Disord. 1998;28:509–17.
118. Cordeiro L, Ballinger E, Hagerman R, Hessl D. Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: prevalence and characterization. Journal of neurodevelopmental disorders. 2010;3(1):57.
119. Chromik LC, Quintin EM, Lepage JF, Hustyi KM, Lightbody AA, Reiss AL. The influence of hyperactivity, impulsivity, and attention problems on social functioning in adolescents and young adults with fragile X syndrome. J Attent Disord. 2019;23 (2):181–8.
120. Hessl D, Tassone F, Cordeiro L, Koldewyn K, McCormick C, Green C, Wegelin J, Yuhas J, Hagerman RJ. Brief report: Aggression and stereotypic behavior in males with fragile X syndrome—Moderating secondary genes in a "single gene" disorder. J Autism Developm Disord. 2008 Jan 1;38 (1):184–9.
121. Harris SW, Hessl D, Goodlin-Jones B, Ferranti J, Bacalman S, Barbato I, Tassone F, Hagerman PJ, Herman K, Hagerman RJ. Autism profiles of males with fragile X syndrome. Am J Mental Retard. 2008;113(6):427-38.
122. Kaufmann WE, Kidd SA, Andrews HF, Budimirovic DB, Esler A, Haas-Givler B, Stackhouse T, Riley C, Peacock G, Sherman SL, Brown WT, Berry-Kravis E. Autism spectrum disorder in fragile X syndrome: Cooccurring conditions and current treatment. Pediatrics. 2017;139 (Suppl 3):S194–206.
123. Bailey DB Jr, Mesibov GB, Hatton DD, et al. Autistic behavior in young boys with fragile X syndrome. J Autism Dev Disord. 1998;28:499–508.
124. Bailey DB Jr, Hatton DD, Mesibov G, et al. Early development, temperament, and functional impairment in autism and fragile X syndrome. J Autism Dev Disord. 2000;30:49–59.
125. Bailey DB Jr, Hatton DD, Skinner M, Mesibov G. Autistic behavior, FMR1 protein, and developmental trajectories in young males with Fragile X syndrome. J Autism Dev Disord. 2001;31:165–74.
126. Feinstein C, Reiss AL. Autism: the point of view from fragile X studies. J Autism Dev Disord. 2001;28:393–405.
127. Hagerman RJ, Berry-Kravis E, Hazlett HC, Bailey DB Jr, Moine H, Kooy RF, Tassone F, Gantois I, Sonenberg N, Mandel JL, Hagerman PJ. Fragile X syndrome. Nat Rev Dis Primers. 2017;29(3):17065.
128. McDuffie A, Thurman AJ, Hagerman RJ, Abbeduto L. Symptoms of autism in males with fragile X syndrome: A comparison to nonsyndromic ASD using current ADI-R scores. J Autism Dev Disord. 2015;45:1925–37.
129. Brown WT. Autism is associated with the Fragile-X syndrome. J Autism Dev Disord. 1982;12:303–8.
130. Demark JL, Feldman MA, Holden JJ. Behavioral relationship between autism and fragile X syndrome. Am J Ment Retard. 2003;108:314–26.
131. Hatton DD, Sideris J, Skinner M, et al. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. Am J Med Genet A. 2006;140:1804–13.
132. Kaufmann WE, Cortell R, Kau AS, et al. Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. Am J Med Genet A. 2004;129:225–34.
133. Rogers SJ, Wehner EA, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. J Dev Behav Pediatr. 2001;22:409–17.
134. Sabaratnam M, Murthy NV, Wijerante A, et al. Autistic-like behaviour profile and psychiatric morbidity in fragile X Syndrome. Eur Child Adolesc Psychiatry. 2003;12:172–7.
135. Abbeduto, L., McDuffie, A., & Thurman, A. J. (2014). The fragile X syndrome-autism comorbidity: what do we really know? *Frontiers in Genetics,* October 16;5:355.
136. Keysor CS, Mazzocco MM. A developmental approach to understanding fragile X syndrome in females. Microsc Res Tech. 2002;57:179–86.
137. Keysor CS, Mazzocco MlM M, McLeod DR, Hoehn- Saric R. Physiological arousal in females with fragile X or Turner syndrome. Dev Psychobiol. 2002;41:133–46.
138. Kau AS, Meyer WA, Kaufmann WE. Early development in males with fragile X syndrome: a review of the literature. Microsc Res Tech. 2002;57:174–8.
139. Nolin SL, Glicksman A, Houck GE Jr, et al. Mosaicism in fragile X affected males. Am J Med Genet. 1994;51:509–12.
140. Tassone F, Hagerman RJ, Chamberlain WD, Hagerman PJ. Transcription of the FMR1 gene in individuals with fragile X syndrome. Am J Med Genet. 2000;97:195–203.
141. Cohen IL, Nolin SL, Sudhalter V, et al. Mosaicism for the FMR1 gene influences adaptive skills development in fragile X-affected males. Am J Med Genet. 1996;64:365–9.
142. Kwon H, Menon V, Eliez S, et al. Functional neuroanatomy of visuospatial working memory in fragile X syndrome: relation to behavioral and

molecular measures. Am J Psychiatry. 2001;158: 1040–51.
143. Loesch DZ, Huggins RM, Bui QM, et al. Effect of the deficits of fragile X mental retardation protein on cognitive status of fragile x males and females assessed by robust pedigree analysis. J Dev Behav Pediatr. 2002;23:416–23.
144. Bailey DB Jr, Hatton DD, Tassone F, et al. Variability in FMRP and early development in males with fragile X syndrome. Am J Ment Retard. 2001;106:16–27.
145. Loesch DZ, Huggins RM, Hagerman RJ. Phenotypic variation and FMRP levels in fragile X. Ment Retard Dev Disabil Res Rev. 2004;10:31–41.
146. Menon V, Kwon H, Eliez S, et al. Functional brain activation during cognition is related to FMR1 gene expression. Brain Res. 2000;877:367–70.
147. Belmonte MK, Bourgeron T. Fragile X syndrome and autism at the intersection of genetic and neural networks. Nat Neurosci. 2006;9:1221–5.
148. Abbeduto L, Brady N, Kover ST. Language development and fragile X syndrome: profiles, syndrome-specificity, and within-syndrome differences. Ment Retard Dev Disabil Res Rev. 2007;13:36–46.
149. Levy Y, Gottesman R, Borochowitz Z, et al. Language in boys with fragile X syndrome. J Child Lang. 2006;33:125–44.
150. Brady N, Skinner M, Roberts J, Hennon E. Communication in young children with fragile X syndrome: a qualitative study of mothers' perspectives. Am J Speech Lang Pathol. 2006;15:353–64.
151. Abbeduto L, Hagerman RJ. Language and communication in fragile X syndrome. Ment Retard Dev Disabil Res Rev. 1997;3:313–22.
152. Finestack LH, Richmond EK, Abbeduto L. Language development in individuals with fragile X syndrome. Top Lang Disord. 2009;29(2):133–48.
153. Cornish et al. 2013.
154. Lewis P, Abbeduto L, Murphy M, et al. Cognitive, language and social-cognitive skills of individuals with fragile X syndrome with and without autism. J Intellect Disabil Res. 2006;50:532–45.
155. Pierpont EI, Richmond EK, Abbeduto L, Kover ST, Brown WT. Contributions of phonological and verbal working memory to language development in adolescents with fragile X syndrome. Journal of Neurodevelopmental Disorders. 2011;3(4):335.
156. McDuffie A, Kover S, Abbeduto L, Lewis P. Profiles of Receptive and Expressive Language Abilities in Boys With Comorbid Fragile X Syndrome and Autism. American Journal on Intellectual and Developmental Disabilities. 2012;117(1):18–32.
157. Thurman AJ, McDuffie A, Hagerman RJ, Josol CK, Abbeduto L. Language skills of males with fragile X syndrome or nonsyndromic autism spectrum disorder. J Autism Dev Disord. 2017;47(3):728–43.
158. Wetherby A, Prizant B. CSBS manual: communication and symbolic behavior scales manual. Normed ed. Baltimore, MD: Paul H Brookes Publishing; 2003.
159. Roberts JE, Mirrett P, Anderson K, et al. Early communication, symbolic behavior, and social profiles of young males with fragile X syndrome. Am J Speech Lang Pathol. 2002;11:295–304.
160. Price J, Roberts J, Vandergrift N, Martin G. Language comprehension in boys with fragile X syndrome and boys with Down syndrome. J Intellect Disabil Res. 2007;51(4):318–26.
161. CASL Carrow-woolfolk.
162. Martin GE, Losh M, Estigarribia B, Sideris J, Roberts J. Longitudinal profiles of expressive vocabulary, syntax and pragmatic language in boys with fragile X syndrome or Down syndrome. International Journal of Language & Communication Disorders. 2013;48(4):432–43.
163. Philofsky A, Hepburn SL, Hayes A, et al. Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. Am J Ment Retard. 2004;109:208–18.
164. Roberts J, Price J, Barnes E, et al. Receptive vocabulary, expressive vocabulary, and speech production of boys with fragile X syndrome in comparison to boys with Down Syndrome. Am J Ment Retard. 2007;112:177–93.
165. Roberts JE, Hatton DD, Bailey DB Jr. Development and behavior of male toddlers with fragile X syndrome. J Early Interven. 2001;24:207–23.
166. Roberts JE, Mirrett P, Burchinal M. Receptive and expressive communication development of young males with fragile X syndrome. Am J Ment Retard. 2001;106:216–30.
167. Abbeduto L, McDuffie A, Brady N, Kover S. Language development in fragile X syndrome: syndrome-specific features, within-syndrome variation, and contributing factors. In: Burack J, Hodapp R, Zigler E, editors. Handbook of mental retardation and development. Oxford: Oxford University Press; in press.
168. Price J, Roberts J, Vandergrift N, Martin G. Language comprehension in boys with fragile X syndrome and boys with Down syndrome. J Intellect Disabil Res. 2007;51:318–26.
169. Oakes A, Kover ST, Abbeduto L. Language comprehension profiles of young adolescents with fragile X syndrome. American Journal of Speech-Language Pathology. 2013;22:615–26.
170. Paul R, Cohen DJ, Breg WR, et al. Fragile X syndrome: its relations to speech and language disorders. J Speech Hear Disord. 1984;49:328–32.
171. Paul R, Dykens E, Leckman JF, et al. A comparison of language characteristics of mentally retarded adults with fragile X syndrome and those with nonspecific mental retardation and autism. J Autism Dev Disord. 1987;17:457–68.
172. Komesidou R, Brady NC, Fleming K, Esplund A, Warren SF. Growth of Expressive Syntax in Children With Fragile X Syndrome. Journal of

Speech, Language, and Hearing Research. 2017;60 (2):422–34.
173. Price JR, Roberts JE, Hennon EA, Berni MC, Anderson KL, Sideris J. Syntactic complexity during conversation of boys with fragile X syndrome and Down syndrome. Journal of Speech, Language, and Hearing Research. 2008;51:3–15.
174. Estigarribia B, Roberts JE, Sideris J, Price J. Expressive morphosyntax in boys with fragile X syndrome with and without autism spectrum disorder. International Journal of Language and Communication Disorders. 2011;46:216–30.
175. Finestack LH, Abbeduto L. Expressive language profiles of verbally expressive adolescents and young adults with Down syndrome or fragile X syndrome. Journal of Speech, Language, and Hearing Research. 2010;53:1334–48.
176. Finestack LH, Sterling AM, Abbeduto L. Discriminating Down syndrome and fragile X syndrome based on language ability. Journal of Child Language. 2013;40:244–65.
177. Kover ST, McDuffie A, Abbeduto L, Brown WT. Effects of sampling context on spontaneous expressive language in males with fragile X syndrome or Down syndrome. Journal of Speech, Language, and Hearing Research. 2012;55:1022–38.
178. Sparrow S, Balla D, Cicchetti D. Vineland adaptive behavior scales. Circle Pines, MN: American Guidance Co; 1984.
179. Bailey DB Jr, Hatton DD, Skinner M. Early developmental trajectories of males with fragile X syndrome. Am J Ment Retard. 1998;103:29–39.
180. Fisch GS, Holden JJ, Carpenter NJ, et al. Age-related language characteristics of children and adolescents with fragile X syndrome. Am J Med Genet. 1999;83:253–6.
181. Dykens EM, Burack JA, Hodapp RM, Zigler E. Maladaptive behavior and dual diagnosis in persons with genetic syndromes. Handbook of mental retardation and development. New York, NY: Cambridge University Press; 1998. p. 542–62.
182. Abbeduto L, Murphy MM, Richmond EK, et al. Collaboration in referential communication: comparison of youth with down syndrome or fragile x syndrome. Am J Ment Retard. 2006;111:170–83.
183. Abbeduto L, Murphy MM, Kover ST, et al. Signaling noncomprehension of language: a comparison of fragile X syndrome and Down syndrome. Am J Ment Retard. 2008;113:214–30.
184. Martin GE, Barstein J, Hornickel J, Matherly S, Durante G, Losh M. Signaling of noncomprehension in communication breakdowns in fragile X syndrome, Down syndrome, and autism spectrum disorder. J Commun Disord. 2017;65:22–34.
185. Thurman AJ, Kover ST, Ted Brown W, Harvey DJ, Abbeduto L. Noncomprehension signaling in males and females with fragile X syndrome. J Speech Lang Hear Res. 2017;1–16.
186. Belser RG, Sudhalter R. Conversational characteristics of children with fragile X syndrome: repetitive speech. Am J Ment Retard. 2001;106:28–38.
187. Sudhalter V, Cohen IL, Silverman W, Wolf-Schein EG. Conversational analyses of males with fragile X, Down syndrome, and autism: comparison of the emergence of deviant language. Am J Ment Retard. 1990;94:431–41.
188. Klusek J, Martin GE, Losh M. A comparison of pragmatic language in boys with autism and fragile X syndrome. J Speech Lang Hear Res. 2014;57 (5):1692–707.
189. Murphy MM, Abbeduto L. Gender differences in repetitive language in fragile X syndrome. J Intellect Disabil Res. 2007;51:387–90.
190. Ferrier LJ, Bashir AS, Meryash DL, Johnston J. Conversational skills of individuals with fragile-X syndrome: a comparison with autism and Down syndrome. Dev Med Child Neurol. 1991;33: 776–88.
191. Sudhalter VV, Maranion MM, Brooks PP. Expressive semantic deficit in the productive language of males with fragile X syndrome. Am J Med Genet. 992;43:65–71.
192. Bennetto L, Pennington BF. The neuropsychology of fragile X syndrome: a preliminary report. In: Hagerman RJ, Cronister AC, editors. Fragile X syndrome: diagnosis, treatment, and research. 2nd ed. Baltimore, MD: Johns Hopkins University Press; 1996. p. 210–48.
193. Klusek J, Martin GE, Losh M. Physiological arousal in autism and fragile X syndrome: group comparisons and links with pragmatic language. Am J Intellect Developm Disabil. 2013;118(6):475–95.
194. Kates WR, Folley BS, Lanham DC, et al. Cerebral growth in fragile X syndrome: review and comparison with Down syndrome. Microsc Res Tech. 2002;57:159–67.
195. Hessl D, Rivera SM, Reiss AL. The neuroanatomy and neuroendocrinology of fragile X syndrome. Ment Retard Dev Disabil Res Rev. 2004;10:17–24.
196. Reiss AL, Freund LS, Baumgardner TL, et al. Contribution of the FMR1 gene mutation to human intellectual dysfunction. Nat Genet. 1995;11:331–4.
197. Mazzocco MlM M, Kates WR, Baumgardner TL, et al. Autistic behaviors among girls with fragile X syndrome. J Autism Dev Disord. 1997;27:415–35.
198. Hessl D. Is it all genes? The impact of environmental and neurohormonal variables on outcome in children with fragile X. 8th International Fragile X Conference. Chicago, IL; 2002.
199. Hessl D, Glaser B, Dyer-Friedman J, Reiss AL. Social behavior and cortisol reactivity in children with fragile X syndrome. J Child Psychol Psychiatry. 2006;47:602–10.
200. Rivera SM, Menon V, White CD, et al. Functional brain activation during arithmetic processing in females with fragile X Syndrome is related to

FMR1 protein expression. Hum Brain Mapp. 2002; 16:206–18.
201. Dalton KM, Nacewicz BM, Johnstone T, et al. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 2005;8(4):519–26.
202. Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. Biol Psychiatry. 2002;51:68–80.
203. Dalton KM, Holsen L, Abbeduto L, Davidson RJ. Brain function and gaze-fixation during facial emotion processing in fragile-X and autism. Autism Res. 2008;1:231–9.
204. Hoeft F, Walter E, Lightbody AA, Hazlett HC, Chang C, Piven J, Reiss A. Neuroanatomical differences in toddler boys with fragile X syndrome and idiopathic autism. Arch Gen Psychiatry. 2011;68:295–305.
205. Meguid N, Fahim C, Yoon U, Nashaat NH, Ibrahim AS, Mancini-Marie A. Brain morphology in autism and fragile X syndrome correlates with social IQ: first report from the Canadian-Swiss-Egyptian neurodevelopmental study. J Child Neurol. 2010;25:599–608.
206. Hazlett HC, Poe MD, Lightbody AA, Gerig G, Macfall JR, Ross AK. Teasing apart the heterogeneity of autism: same behavior, different brains in toddlers with fragile X syndrome and autism. J Neurodev Disord. 2009;1:81–90.
207. Murphy MM, Abbeduto LP. Indirect genetic effects and the early language development of children with genetic mental retardation syndromes: the role of joint attention. Infants Young Child. 2005;18: 47–59.
208. Dyer-Friedman J, Glaser B, Hessel D, et al. Genetic and environmental influences on the cognitive outcomes of children with fragile X syndrome. J Am Acad Child Adolesc Psychiatry. 2002;41: 237–44.
209. Glaser B, Hessl D, Dyer-Friedman J, et al. Biological and environmental contributions to adaptive behavior in fragile X syndrome. Am J Med Genet A. 2003;117:21–9.
210. Abbeduto L, Murphy MM. Language, social cognition, maladaptive behavior, and communication in Down syndrome and fragile X syndrome. In: Rice ML, Warren SF, editors. Developmental language disorders: from phenotypes to etiologies. Mahwah, NJ: Lawrence Erlbaum Associates, Publishers; 2004. p. 77–97.
211. Bailey DB Jr, Skinner D, Hatton D, Roberts J. Family experiences and factors associated with the diagnosis of fragile X syndrome. J Dev Behav Pediatr. 2000;21:315–21.
212. Johnston C, Hessl D, Blasey C, et al. Factors associated with parenting stress in mothers of children with fragile X syndrome. J Dev Behav Pediatr. 2003;24:267–75.
213. Poehlmann J, Clements M, Abbeduto L, Farsad V. Family experiences associated with a child's diagnosis of fragile X or Down syndrome: evidence for disruption and resilience. Ment Retard. 2005; 43:255–67.
214. Lewis P, Abbeduto L, Murphy M, et al. Psychological well-being of mothers of youth with fragile X syndrome: syndrome specificity and within-syndrome variability. J Intellect Disabil Res. 2006;50:894–904.
215. Roy JC, Johnsen J, Breese K, Hagerman R. Fragile X syndrome: what is the impact of diagnosis on families? Dev Brain Dysfunc. 1995;8:327–35.
216. York A, von Fraunhofer NTJ, Sedgwick P. Fragle-X syndrome, Down's syndrome and autism: awareness and knowledge amongst special educators. J Intellect Disabil Res. 1999;43:314–24.
217. Esbensen AJ, Seltzer MM, Abbeduto L, et al. Family well-being in Down syndrome and fragile X syndrome. Speech and language development and intervention in Down syndrome and fragile X syndrome. Baltimore, MD: Paul H Brookes Publishing; 2008. p. 275–92.
218. Brady N, Warren SF, Fleming K, Keller J, Sterling A. Effect of sustained maternal responsivity on later vocabulary development in children with fragile X syndrome. Journal of Speech, Language, and Hearing Research. 2014;57(1):212–26.
219. Sterling AM, Warren SF, Brady N, Fleming K. Influences on maternal responsivity in mothers of children with fragile X syndrome. American journal on intellectual and developmental disabilities. 2013;118(4):310–26.
220. Warren SF, Brady NC. The role of maternal responsivity in the development of children with intellectual disabilities. Mental retardation and developmental disabilities research reviews. 2007; 13(4):330–8.
221. Warren SF, Brady N, Sterling A, Fleming K, Marquis J. Maternal responsivity predicts language development in young children with fragile X syndrome. American Journal on Intellectual and Developmental Disabilities. 2010;115(1):54–75.
222. McDuffie A, Oakes A, Machalicek W, Ma M, Bullard L, Nelson S, Abbeduto L. Early language intervention using distance video-teleconferencing: a pilot study of young boys with Fragile X syndrome and their mothers. American Journal of Speech-Language Pathology. 2016;25(1):46–66.
223. McDuffie, A., Machalicek, W., Bullard, L., Nelson, S., Mello, M., Tempero-Feigles, R.,… & Abbeduto, L. (2016). A Spoken-Language Intervention for School-Aged Boys With Fragile X Syndrome. American journal on intellectual and developmental disabilities, 121(3), 236–265.
224. McDuffie, A., Banasik, A., Bullard, L., Nelson, S., Feigles, R. T., Hagerman, R., & Abbeduto, L. (2017). Distance delivery of a spoken language intervention for school-aged and adolescent boys with fragile X syndrome. Developmental Neurorehabilitation, 1–16.

225. Bullard L, McDuffie A, Abbeduto L. Distance delivery of a parent-implemented language intervention for young boys with fragile X syndrome. Autism & Developmental Language Impairments. 2017;2:2396941517728690.
226. Oakes A, Ma M, McDuffie A, Machalicek W, Abbeduto L. Providing a parent-implemented language intervention to a young male with fragile X syndrome: Brief report. Developmental neurorehabilitation. 2015;18(1):65–8.
227. Tassone F, Hagerman RJ, Taylor AK, et al. Clinical involvement and protein expression in individuals with the FMR1 premutation. Am J Med Genet. 2000;91:144–52.
228. Allen EG, Sherman S, Abramowitz A, et al. Examination of the Effect of the Polymorphic CGG Repeat in the FMR1 Gene on Cognitive Performance. Behav Genet. 2005;35:435–45.
229. Greco CM, Berman RF, Martin RM, et al. Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). Brain. 2006;129:243–55.
230. Seltzer MM, Baker MW, Hong J, Maenner M, Greenberg J, Mandel D. Prevalence of CGG expansions of the FMR1 gene in a US population-based sample. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(5):589–97.
231. Renda MM, Voigt RG, Babovic-Vuksanovic D, et al. Neurodevelopmental disabilities in children with intermediate and premutation range fragile X cytosine-guanine-guanine expansions. J Child Neurol. 2014;29(3):326–30.
232. Grigsby J, Cornish K, Hocking D, et al. The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. J Neurodev Disord. 2014;6(1):28.
233. Aziz M, Stathopolu E, Callias M, et al. Clinical features of boys with fragile X premutations and intermediate alleles. Am J Med Genet B. 2003;121B:119–27.
234. Moore CJ, Daly EM, Schmitz N, et al. A neuropsychological investigation of male premutation carriers of fragile X syndrome. Neuropsychologia. 2004;42:1934–47.
235. Goodlin-Jones BL, Tassone F, Gane LW, Hagerman RJ. Autistic spectrum disorder and the fragile X premutation. J Dev Behav Pediatr. 2004;25: 392–8.
236. Hessl D, Tassone F, Loesch DZ, et al. Abnormal elevation of FMR1 mRNA is associated with psychological symptoms in individuals with the fragile X premutation. Am J Med Genet B. 2005;139B:115–21.
237. Au J, Akins RS, Berkowitz-Sutherland L, et al. Prevalence and risk of migraine headaches in adult fragile X premutation carriers. Clin Genet. 2013;84 (6):546–51.
238. Chonchaiya W, Au J, Schneider A, et al. Increased prevalence of seizures in boys who were probands with the FMR1 premutation and co-morbid autism spectrum disorder. Hum Genet. 2012;131(4):581–9.
239. Goodrich-Hunsaker NJ, Wong LM, McLennan Y, et al. Adult female fragile X premutation carriers exhibit age-and CGG repeat length-related impairments on an attentionally based enumeration task. Front Hum Neurosci. 2011;5:63.
240. Steyaert J, Legius E, Borghgraef M, Fryns JP. A distinct neurocognitive phenotype in female fragile-X premutation carriers assessed with visual attention tasks. Am J Med Genet A. 2003;116:44–51.
241. Klusek J, McGrath SE, Abbeduto L, Roberts JE. Pragmatic Language Features of Mothers With the FMR1 Premutation Are Associated With the Language Outcomes of Adolescents and Young Adults With Fragile X Syndrome. J Speech Lang Hear Res. 2016;59(1):49–61.
242. Sterling AM, Mailick M, Greenberg J, Warren SF, Brady N. Language dysfluencies in females with the FMR1 premutation. Brain Cogn. 2013;82(1):84–9.
243. Losh M, Klusek J, Martin GE, Sideris J, Parlier M, Piven J. Defining genetically meaningful language and personality traits in relatives of individuals with fragile X syndrome and relatives of individuals with autism. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(6):660–8.
244. Movaghar A, Mailick M, Sterling A, Greenberg J, Saha K. Automated screening for Fragile X premutation carriers based on linguistic and cognitive computational phenotypes. Sci Rep. 2017;7 (1):2674.
245. Hagerman RJ, Ono MY, Hagerman PJ. Recent advances in fragile X: a model for autism and neurodegeneration. Curr Opin Psychiatry. 2005;18: 490–6.
246. Berry-Kravis E, Goetz CG, Leehey MA, et al. Neuropathic features in fragile X premutation carriers. Am J Med Genet A. 2007;143:19–26.
247. Grigsby J, Leehey MA, Jacquemont S, et al. Cognitive impairment in a 65-year-old male with the fragile X-associated tremor-ataxia syndrome (FXTAS). Cogn Behav Neurol. 2006;19:165–71.
248. Cronister A, Hagerman RJ, Wittenberger M, Amiri K. Mental impairment in cytogenetically positive fragile Xfemales. Am J Med Genet. 1991;38:503–4.
249. Welt CK, Smith PC, Taylor AE. Evidence of early ovarian aging in fragile X premutation carriers. J Clin Endocrinol Metab. 2004;89:4569–74.
250. Bellugi U, Marks S, Bihrle A, Sabo H. Dissociation between language and cognitive functions in Williams syndrome. In: Bishop D, Mogford K, editors. Language development in exceptional circumstances. London: Churchill Livingstone; 1988. p. 177–89.
251. Piattelli-Palmarini M. Speaking of learning: How do we acquire our marvelous facility for expressing ourselves in words? Nature. 2001;411:887–8.

252. Mervis CB, John AE. Cognitive and behavioral characteristics of children with Williams syndrome: Implications for intervention approaches. American Journal of Medical Genetics Part C Seminars in Medical Genetics. 2010;154C:229–48.
253. Elliott CD. Differential ability scales. San Antonio, TX: Harcourt Assessment; 2007.
254. Thurman AJ, Fisher MH. The Williams syndrome social phenotype: Disentangling the contributions of social interest and social difficulties. In Hodapp RM, Fidler DJ (Eds.). International Review of Research in Developmental Disabilities 2015 Jan 1 (Vol. 49, pp. 191–227). Academic Press.
255. Mervis CB, John AE. Vocabulary abilities of children with Williams syndrome: Strengths, weaknesses, and relation to visuospatial construction ability. Journal of Speech, Language, and Hearing Research. 2008;51:967–82.
256. Strømme P, Bjørnstad PG, Ramstad K. Prevalence estimation of Williams syndrome. J Child Neurol. 2002;17:269–71.
257. Hillier LW, Fulton RS, Fulton LA, et al. The DNA sequence of human chromosome 7. Nature. 2003;424:157–64.
258. Cunniff C, Frias JL, Kaye CI, Moeschler J, Panny SR, Trotter TL. Health care supervision for children with Williams syndrome. Pediatrics. 2001;107:1192–204.
259. Mervis CB, Morris CA. Williams syndrome. In: Mazzocco MM, Ross JL, editors. Neurogenetic developmental disorders: Variation of manifestation in childhood. Cambridge, MA: MIT Press; 2007. p. 199–262.
260. Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC. The Williams Syndrome Cognitive Profile. Brain Cogn. 2000; 44:604–28.
261. Udwin O, Yule W, Martin N. Cognitive abilities and behavioural characteristics of children with idiopathic infantile hypercalcaemia. J Child Psychol Psychiatry. 1987;28:297–309.
262. Bellugi U, Bihrle A, Jernigan T, et al. Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. Am J Med Genet Suppl. 1990;6:115–25.
263. Klein-Tasman BP, Li-Barber KT, Magargee ET. Honing in on the social phenotype in Williams syndrome using multiple measures and multiple raters. J Autism Dev Disord. 2011;41:341–51.
264. Klein-Tasman BP, Mervis CB. Distinctive personality characteristics of 8-, 9-, and 10-year-old children with Williams syndrome. Developmental Neuropsychology. 2003;23:271–92.
265. Mervis CB, Robinson BF, Rowe ML, et al. Language abilities of individuals with Williams syndrome. International review of research in mental retardation: language and communication in mental retardation, vol. 27. Orlando, FL: Academic Press; 2003. p. 35–81.
266. Fidler DJ, Hepburn SL, Most DE, et al. Emotional responsivity in young children with Williams syndrome. Am J Ment Retard. 2007;112: 194–206.
267. Thurman AJ, Mervis CB. The regulatory function of social referencing in preschoolers with Down syndrome or Williams syndrome. Journal of Neurodevelopmental Disorders. 2013;5:2.
268. Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule – generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000;30(205–23):272.
269. Klein-Tasman BP, Mervis CB, Lord C, Phillips KD. Socio-communicative deficits in young children with Williams syndrome: performance on the Autism Diagnostic Observation Schedule. Child Neuropsychol. 2007;13:444–67.
270. Klein-Tasman BP, Phillips KD, Lord CE, Mervis CB, Gallo F. Overlap with the autism spectrum in young children with Williams syndrome. J Dev Behav Pediatr. 2009;30:289–99.
271. Lincoln AJ, Searcy YM, Jones W, Lord C. Social interaction behaviors discriminate young children with autism and Williams syndrome. J Am Acad Child Adolesc Psychiatry. 2007;46:323–31.
272. Sparaci L, Stefanini S, D'Elia L, Vicari S, Rizzolatti G. What and why understanding in autism spectrum disorders and Williams syndrome: similarities and differences. Autism Research. 2014;7:421–32.
273. Riby DM, Hancock PJ, Jones N, Hanley M. Spontaneous and cued gaze-following in autism and Williams syndrome. Journal of Neurodevelopmental Disorders. 2013;5:13.
274. Lough E, Hanley M, Rodgers J, South M, Kirk H, Kennedy DP, Riby DM. Violations of personal space in young people with autism spectrum disorders and Williams syndrome: insights from the social responsiveness scale. J Autism Dev Disord. 2015;45:4101–8.
275. Leyfer OT, Woodruff-Borden J, Klein-Tasman BP, et al. Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. Am J Med Genet B Neuropsychiatr Genet. 2006;141B:615–22.
276. klein tasmin 2015.
277. Mullen E. The mullen scales of early learning. Circle Pines, MN: American Guidance Services; 1995.
278. Mervis CB, Becerra AM. Language and communicative development in Williams syndrome. Ment Retard Dev Disabil Res Rev. 2007;13:3–15.
279. Fenson L, Dale PS, Reznick JS. The MacArthur communicative development inventories: users guide and technical manual, 1993.
280. Mervis CB, Robinson BF. Early expressive vocabularies of children with Williams syndrome or Down syndrome: a comparison. Dev Neuropsychol. 2000;17:111–26.

281. Mervis CB, Bertrand J. Developmental relations between cognition and language: evidence from Williams syndrome. In: Adamson LB, Romsky MA, editors. Communication and language acquisition: discoveries from a typical development. Baltimore, MD: Paul Brookes Publishing; 1997. p. 75–106.
282. Dunn LE, Dunn DM. Peabody Picture Vocabulary Test. 4th ed. Minneapolis, MN: Pearson Assessments; 2007.
283. Bellugi U, Lichtenberger L, Mills D, et al. Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome. Trends Neurosci. 1999;22:197–207.
284. Klein BP, Mervis CB. Contrasting patterns of cognitive abilties of 9-and 10-year-olds with Williams syndrome or Down syndrome. Dev Neuropsychol. 1999;16:177–96.
285. Mervis CB, Morris CA, Klein-Tasman BP, et al. Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions. Dev Neuropsychol. 2003;23:243–68.
286. Joffe V, Varlokosta S. Patterns of syntactic development in children with Williams syndrome and Down's syndrome: evidence from passives and wh-questions. Clin Linguist Phon. 2007;21 (9):705–27.
287. Mervis CB, Klein-Tasman BP. Williams syndrome: cognition, personality, and adaptive behavior. Ment Retard Dev Disabil Res Rev. 2000;6:148–58.
288. Rice ML, Mervis CB, Klein BP. Morphological abilities of children with specific language impairment or Williams syndrome. Cambridge, MA: MIT Press; 1999.
289. Mervis CB, Robinson BF, Pani JR. Visuospatial construction. Am J Hum Genet. 1999 Nov; 65 (5):1222–9.
290. Mervis CB. Williams syndrome: 15 years of psychological research. Dev Neuropsychol. 2003; 23:1–12.
291. Volterra V, Capirci O, Pezzini G, Sabbadini L. Linguistic abilities in Italian children with Williams syndrome. Cortex. 1996;32:663–77.
292. Zukowski A. Uncovering grammatical competence in children with Williams syndrome. Unpublished dissertation, Buston University; 2001.
293. Grant J, Karmiloff-Smith A, Gathercole S, et al. Phonological short-term memory and its relationship to language in Williams syndrome. Cogn Neuropsychiatry. 1997;2:81–99.
294. Mervis CB, Morris CA, Bertrand J. Neurodevelopmental disorders. In: Tager-Flusberg H, editor. Williams syndrome: findings from an integrated program of research. Cambridge, MA: MIT Press; 1999. p. 65–110.
295. Scarborough HS. Index of productive syntax. Appl Psycholinguistics. 1990;11:1.
296. Morris CA, Mervis CB. Williams syndrome and related disorders. Ann Rev Genomics Hum Genet. 2000;1:461–84.
297. Karmiloff-Smith A, Grant J, Berthoud I, et al. Language and Williams syndrome: how intact is "intact"? Child Dev. 1997;68:246–62.
298. Levy Y, Hermon S. Morphological abilities of Hebrew-speaking adolescents with Williams syndrome. Dev Neuropsychol. 2003;23:59–83.
299. Robinson BF, Mervis CB, Robinson BW. The roles of verbal short-term memory and working memory in the acquisition of grammar by children with Williams syndrome. Dev Neuropsychol. 2003;23:13–31.
300. Bishop DV. Test for reception of grammar (TROG). Manchester: Chapel Press; 1983.
301. Reiss AL, Eliez S, Schmitt JE, et al. Neuroanatomy of Williams syndrome: a high-resolution MRI study. J Cogn Neurosci. 2000;12(Suppl. 1):65–73.
302. Thompson PM, Lee AD, Dutton RA, et al. Abnormal cortical complexity and thickness profiles mapped in Williams syndrome. J Neurosci. 2005;25(16):4146–58.
303. Jernigan TL, Bellugi U. Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. Arch Neurol. 1990;47(5):529–33.
304. Schmitt JE, Eliez S, Bellugi U, Reiss AL. Analysis of cerebral shape in Williams syndrome. Arch Neurol. 2001;58(2):283–7.
305. Reiss AL, Eckert MA, Rose FE, et al. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. Journal of Neuroscience 2004 May 26; 24(21):5009–15.310.
306. Jernigan TL, Bellugi U, Sowell E, Doherty S, Hesselink JR. Cerebral morphologic distinctions between Williams and Down syndromes. Arch Neurol. 1993;50(2):186–91.
307. Wang PP, Doherty S, Hesselink JR, Bellugi U. Callosal morphology concurs with neurobehavioral and neuropathological findings in two neurodevelopmental disorders. Arch Neurol. 1992;49(4): 407–11.
308. Tomaioulo F, Di Paola M, Caravale B, et al. Morphology and morphometry of the corpus callosum in Williams syndrome: a T1-weighted MRI study. NeuroReport. 2002;13:2281–4.
309. Mills DL, Alvarez TD, St George M, et al. Electrophysiological studies of face processing in Williams syndrome. J Cogn Neurosci. 2000;12:47–64.
310. Annaz D, Karmiloff-Smith A, Johnson MH, Thomas MS. A cross-syndrome study of the development of holistic face recognition in children with autism, Down syndrome, and Williams syndrome. J Exp Child Psychol. 2009;102:456–86.
311. Leonard HC, Annaz D, Karmiloff-Smith A, Johnson MH. Brief report: Developing spatial frequency biases for face recognition in autism and Williams syndrome. J Autism Dev Disord. 2011;41:968–73.
312. Riby DM, Hancock PJ. Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. J Autism Dev Disord. 2009;39:421–31.

313. Riby DM, Jones N, Brown PH, Robinson LJ, Langton SR, Bruce V, Riby LM. Attention to faces in Williams syndrome. J Autism Dev Disord. 2011;41:1228–39.
314. Grice SJ, Spratling MW, Karmiloff-Smith A, Halit H, Csibra G, de Haan M, Johnson MH. Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. NeuroReport. 2001;12:2697–700.
315. Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F. Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. Developmental Neuropsychology. 2003;23:139–72.
316. Meyer-Lindenberg AKP, Mervis CB, Kippenhan JS, et al. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron. 2004;43:623.
317. Paul BM, Stiles J, Passarotti A, Bavar N, Bellugi U. Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation. Neuroreport. 2002 Jul 2;13(9):1115–9
318. O'Hearn K, Landau B, Hoffman JE. Multiple object tracking in people with Williams syndrome and in normally developing children. Psychol Sci. 2005;16:905–12.
319. Vicari S, Bellucci S, Carlesimo GA. Visual and spatial long-term memory: differential pattern of impairments in Williams and Down syndromes. Dev Med Child Neurol. 2005;47:305–11.
320. Meyer-Lindenberg, A., Mervis, C. B., Sarpal, D., Koch, P., Steele, S., Kohn, P.,… & Mattay, V. S. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. Journal of Clinical Investigation, 115, 1888.
321. Dykens EM. Measuring behavioral phenotypes: provocations from the "new genetics". Am J Ment Retard. 1995;99:522–32.
322. Berry-Kravis E, Hessl DR, Abbeduto L, Reiss A, Beckel-Mitchener A, Urv T. Outcome measures for clinical trials in fragile X syndrome. J Dev Behav Pediatr. 2013;34:508–22.
323. Esbensen AJ, Hooper SR, Fidler D, Hartley S, Edgin J, Liogier d'Ardhuy X, et al. Outcome measures for clinical trials in Down syndrome. American Journal on Intellectual and Developmental Disabilities. 2017;122:247–81.
324. Abbeduto L, Benson G, Short K, Dolish J. Effects of sampling context on the expressive language of children and adolescents with mental retardation. Ment Retard. 1995;33:279–88.
325. Berry-Kravis E, Doll ED, Sterling A, Kover ST, Schroeder SM, Mathur S, Abbeduto L. Development of an expressive language sampling procedure in fragile X syndrome: A pilot study. J Dev Behav Pediatr. 2013;34:245–51.
326. Kover ST, Abbeduto L. Expressive language in male adolescents with fragile X syndrome with and without comorbid autism. J Intellect Disabil Res. 2010;54:246–65.
327. John AE, Rowe ML, Mervis CA. Referential communication skills of children with Williams Syndrome: understanding when messages are not adequate. Am J Int Dev Dis. 2009;114:85–99.
328. Miles S, Chapman R, Sindberg H. Sampling context affects MLU in the language of adolescents with Down syndrome. J Speech Lang Hear Res. 2006;49:325–37.
329. Carey S, Bartlett E. Acquiring a single new word. Pap Rep Child Lang Dev. 1978;15:17–29.
330. Baron-Cohen S, Baldwin DA, Crowson M. Do children with autism use the speaker's direction of gaze strategy to crack the code of language? Child Dev. 1997;6:48–57.
331. Benjamin DP, Mastergeorge AM, McDuffie AS, Kover ST, Hagerman RJ, Abbeduto L. Effects of labeling and pointing on object gaze in boys with fragile X syndrome: An eye-tracking study. Res Dev Disabil. 2014;35:2658–72.
332. Benjamin DP, McDuffie A, Thurman A, Kover ST, Mastergeorge A, Hagerman RJ, Abbeduto L. Effect of speaker gaze on word learning in fragile X syndrome: A comparison with nonsyndromic ASD. Journal of Speech, Language, and Hearing Research. 2015;58:383–95.
333. McDuffie A, Kover ST, Hagerman RJ, Abbeduto L. Investigating word learning in fragile X syndrome: A fast-mapping study. J Autism Dev Disord. 2013;43:1676–91.
334. Thurman A, McDuffie A, Kover ST, Channell MM, Mastergeorge A, Hagerman RJ, Abbeduto L. Use of emotional cues for lexical learning: A comparison of autism spectrum disorder and fragile X syndrome. J Autism Dev Disord. 2015;45:1042–61.
335. Head LS, Abbeduto L. Recognizing the role of parents in developmental outcomes: a systems approach to evaluating the child with developmental disabilities. Ment Retard Dev Disabil Res Rev. 2007;13:293–301.
336. Olsson MB, Hwang CP. Sense of coherence in parents of children with different developmental disabilities. J Intellect Disabil Res. 2002;46:548–59.
337. Baker BL, Blacher J, Olsson MB. Preschool children with and without developmental delay: behaviour problems, parents' optimism and well-being. J Intellect Disabil Res. 2005;49:575–90.
338. Singer GHS. Meta-analysis of comparative studies of depression in mothers of children with and without developmental disabilities. Am J Ment Retard. 2006;111:155–69.
339. Taunt HM, Hastings RP. Positive impact of children with developmental disabilities on their families: a preliminary study. Educ Train Ment Retard Dev Disabil. 2002;37:410–20.

340. Hastings RP, Taunt HM. Positive perceptions in families of children with developmental disabilities. Am J Ment Retard. 2002;107:116–27.
341. Hassall R, Rose J, McDonald J. Parenting stress in mothers of children with an intellectual disability: the effects of parental cognitions in relation to child characteristics and family support. J Intellect Disabil Res. 2005;49:405–18.
342. Stoneman Z, MacLean WE. Ellis' handbook of mental deficiency, psychological theory and research. Mahwah, NJ: Erlbaum; 1997. p. 405–37.
343. Seligman M, Darling RB. Ordinary families, special children: a systems approach to childhood disability. 2nd ed. New York, NY: Guilford Press; 1997.
344. Hodapp RM, Dykens EM. Strengthening behavioral research on genetic mental retardation syndromes. Am J Ment Retard. 2001;106:4–15.
345. Hodapp RM, Ricci LA, Ly TM, Fidler DJ. The effects of the child with Down syndrome on maternal stress. Br J Dev Psychol. 2003;21:137–51.
346. Sellinger MH, Hodapp RM, Dykens EM. Leisure activities of individuals with Prader-Willi, Williams, and Down Syndromes. J Dev Phys Disabil. 2006;18:59–71.
347. Franke P, Maier W, Hautzinger M, et al. Fragile-X carrier females: evidence for a distinct psychopathological phenotype? Am J Med Genet. 1996;64:334–9.
348. Franke P, Leboyer M, Gansicke M, et al. Genotype-phenotype relationship in female carriers of the premutation and full mutation of FMR-1. Psychiatry Res. 1998;80:113–27.
349. Sarimski K. Behavioural phenotypes and family stress in three mental retardation syndromes. Eur Child Adolesc Psychiatry. 1997;6:26–31.
350. van Lieshout CFM, De Meyer RE, Curfs LMG, Fryns J-P. Family contexts, parental behaviour, and personality profiles of children and adolescents with Prader-Willi, fragile-X, or Williams syndrome. J Child Psychol Psychiatry. 1998;39:699–710.
351. von Gontard A, Backes M, Laufersweiler-Plass C, et al. Psychopathology and familial stress – comparison of boys with fragile X syndrome and spinal muscular atrophy. J Child Psychol Psychiatry. 2002;43:949–57.
352. Abbeduto L, Seltzer MM, Shattuck P, et al. Psychological well-being and coping in mothers of youths with autism, Down Syndrome, or fragile X Syndrome. Am J Ment Retard. 2004;109:237–54.
353. Franke P, Leboyer M, Hardt J, et al. Neuropsychological profiles of FMR-1 premutation and full-mutation carrier females. Psychiatry Res. 1999;87:223–31.
354. Freund LS, Reiss AL, Hagerman R, Vinogradov S. Chromosome fragility and psychopathology in obligate female carriers of the fragile X chromosome. Arch Gen Psychiatry. 1992;49:54–60.
355. Roberts JE, Chapman RS, Warren SF. Speech and language development and intervention in Down syndrome and fragile X syndrome. Baltimore, MD: Paul H Brookes Publishing; 2008.

Chapter 14

An Introduction to Congenital and Normal Pressure Hydrocephalus

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Overview

This chapter will provide an overview of cerebrospinal fluid dynamics and then review the literature on childhood and adult forms of hydrocephalus. This review will focus primarily on neurobehavioral presentations associated with congenital hydrocephalus and idiopathic normal pressure hydrocephalus in older adults.

Cerebrospinal Fluid Secretion and Absorption

Hydrocephalus comes from the Greek words "hydro" meaning water, and "cephalus" meaning head. Rekate defined hydrocephalus as "an active distension of the ventricular system of the brain related to inadequate passage of cerebral spinal fluid from its point of production within the ventricular system to its point of absorption into the systemic circulation" [1, 2]. Simply, it is an imbalance between production and absorption of spinal fluid with the CNS. Cerebral spinal fluid (CSF) is produced primarily in a structure known as the choroid plexus. As the neural tube thickens, the blood vessels on the surface of the pia mater penetrate the brain surface, carrying the pia mater with them. Thus, the choroid plexus is formed by a core of blood vessels surrounded by pia which sticks to the ependymal cells lining the ventricles. The ependymal cells are a type of glial cell and are surrounded by capillaries and connective tissue. They form the epithelial lining of the ventricles and spinal cord. The epithelial cells surrounding the blood vessel of the choroid plexus produce CSF. This layer or lining also creates a semipermeable space and acts as a filter regulating what substances enter or leave the ventricular system. Ultimately, spinal fluid is produced as an ultra-filtrate of blood as it passes through vessels lined by these cells [1].

In normal human adults, secretion of CSF occurs at a rate of 0.33 cc per minute (20 cc/hour), resulting in about 500 cc produced per day [3]. Total replacement of CSF occurs every 4–6 h or 5 times per day. Total CSF volume ranges from 140 to 270 ml with higher volumes in adults. The majority of CSF is found in the cerebral and spinal subarachnoid spaces, with only about 30 cc

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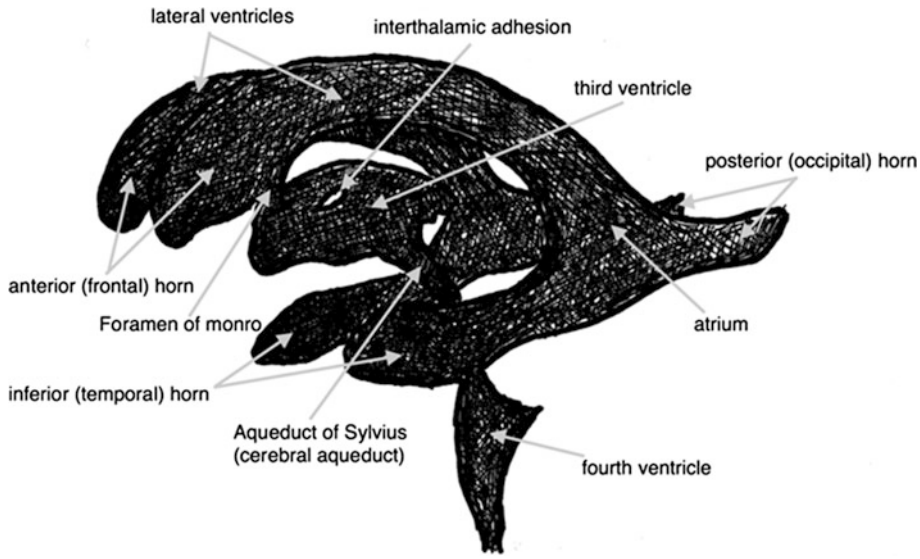

Fig. 14.1 Anatomy of human ventricular system. By author MRM

generally found within the ventricular system of the brain. The majority of "brain" CSF is found in the two large lateral ventricles, which contain sufficient volumes of CSF-producing choroid plexus. The CSF then drains from the two lateral ventricles via the paired Foramen of Monro into the third ventricle. From the third ventricle, CSF drains via the aqueduct of Sylvius into the fourth ventricle and then into the subarachnoid spaces via the foramina of Lushka and Mangendie. CSF primarily leaves the subarachnoid space through arachnoid granulations (i.e., projections of the arachnoid membrane, or "villi") into the venous sinus system of the brain. These villi act as a one-way valve system, permitting CSF to exit the subarachnoid space into the venous sinuses, but preventing blood from entering into the brain subarachnoid spaces. When pressure in the CSF system exceeds venous pressure, CSF will flow into the venous blood of the sinus. The venous blood contains proteins that CSF does not, resulting in an osmotic pressure gradient that aids CSF passage into the venous sinus. Normal resting pressure of CSF is between 5 and 20 cm H_2O in an adult human. CSF can also be reabsorbed in other ways such as through various nerve sheaths exiting the skull as well as through passageways into the lymphatic system. The CSF reabsorbed in these alternate pathways is believed to be a small percentage of total CSF re-absorption; however, in some disease states, including hydrocephalus that is "compensated" the alternate pathways may become of more importance. In an ideal state, secretion of CSF equals absorption via these granulations resulting in normal pressure. See Fig. 14.1 for an illustration of the human ventricular system.

CSF Physiology

Many functions of the CSF are well understood; however, there remain many unanswered questions in this field. We present some common examples of CSF function. CSF can act as a buffer between the brain and the skull [3]. This buffer is especially relevant in traumatic brain injury, where cranial acceleration/deceleration results in brain movement within the skull. The surrounding CSF may act as a protective padding between the brain and the skull. Another function of CSF is to create a space where the cerebral hemispheres remain buoyant thereby reducing effective weight. CSF also disseminates a variety of substances including neurotransmitters, hormones, and electrolytes throughout the nervous system providing signaling and nutrient pathways.

Defining and Classifying Hydrocephalus

Hydrocephalus is an umbrella term that has been defined and classified in many ways over the years. Many of the classifications helped define the disease anatomically. Dandy and Blackfan proposed a classification of hydrocephalus based on the ability of CSF dissolvable dye being able to flow throughout all four ventricles – "communicating" hydrocephalus, versus an inability for the dye to flow throughout the ventricles or subarachnoid space which was called Non-Communicating [4]. Thus communicating hydrocephalus is often synonymous with normal pressure hydrocephalus while non-communicating reflects an obstructive hydrocephalus such as aqueduct stenosis.

Geneticists traditionally classify hydrocephalus into Syndromic and Non-Syndromic types depending on the presence of congenital anomalies [2]. There is no consensus as of yet regarding the classification of patients with genetic syndromes who do not present with major physical abnormalities outside the brain. For example, hydrocephalus due to gene mutations (e.g., L1CAM mutations) has been classified as both Syndromic and Non-Syndromic Hydrocephalus [5, 6]. Because of this lack of consensus, some suggest differentiating between cases of hydrocephalus where the clinical phenotype is either predominantly characterized by abnormal brain findings or accompanied by major physical abnormalities and clinical signs, where hydrocephalus is only part of a condition. In cases where a genetic association or clinical syndrome is identified, hydrocephalus would then be classified according to that syndrome (viz., L1CAM-associated hydrocephalus) [2].

Treatment of Hydrocephalus

Obstructive hydrocephalus treatment involves surgical removal or "bypassing" the obstruction. For example, tumors and cysts may be resected or removed when blocking the Foramen of Monro and CSF flow causing enlarged ventricles. An alternative is endoscopic third ventriculostomy (ETV), which may bypass an obstructed aqueduct of Sylvius by making a passageway out of the third ventricle into the pre-pontine cistern allowing CSF to flow into the subarachnoid space.

Communicating or absorptive hydrocephalus is treated by providing an alternative absorptive surface to reabsorb the CSF. Unfortunately, until the late 1950s, technology was unavailable to provide this relief and hydrocephalus was nearly uniformly fatal. The creation of the "Shunting" device that could be implanted into the brain ventricle and conduct CSF out of the brain through a subcutaneous pathway to another absorptive surface (i.e., peritoneum, pleura, or heart) transformed hydrocephalus from a uniformly fatal disease to nearly 100% curable today. Unfortunately, the shunting device, despite remarkable improvements in technology still can become infected at a relatively high rate, and routinely malfunction – requiring surgical intervention to repair them – that can significantly impact life and lifestyle. Solutions to these problems remain elusive.

Congenital Hydrocephalus

Epidemiology

The incidence and prevalence of hydrocephalus vary based on the population examined and the definition or classification utilized. In surviving neonates, the prevalence of infantile hydrocephalus has been estimated to be 0.57 per 1000 [7] to 0.9 per 1000 [8], which includes all forms (e.g., tumor, infections, inflammation, metabolic, congenital abnormality, and hemorrhage). Population-based studies document evidence of an increase in infantile hydrocephalus from the years 1967–1970 to the years 1979–1982 by 0.15 per 1000 live births [9] that was attributed to increased survival rates of premature neonates [2]. The most recent estimate of prevalence found via online PubMed search was published in 2012 by Munch and colleagues [10]. This 30-year study of idiopathic infantile hydrocephalus in

Denmark documented a prevalence of 1.1 per 1,000 infants.

Primary Etiologies

There are many etiologies of infantile hydrocephalus described in the literature. Of these, the most prevalent causes of congenital hydrocephalus (CH) are those related to developmental malformations, prenatal intraventricular hemorrhage (IVH) [11], and specific gene mutations. Under the umbrella of developmental malformations, Spina bifida (SB) is a congenital condition caused by a neural tube defect occurring anywhere along the spine in which the neural tube does not close during the first 28 days of pregnancy. The severity and number of complications of SB depend on whether or not a fluid sac protrudes through a space in the fetus' back with or without the involvement of the spinal cord. Myelomeningocele (MMC) is the most severe form of SB and is often associated with Chiari II malformation (CM-II), which is believed to be the possible primary mechanism of hydrocephalus in cases of MMC.

There are four types of Chiari malformations, the classification system is based upon the severity of the neuroanatomic presentation, with the most common types, being CM-I and CM-II. CM-II, as mentioned above presents most often with an association to MMC, is more life-threatening and involves a drop of both cerebellar and brainstem tissue below the foramen magnum, resulting in pressure on the pons and fourth ventricle, often hindering passage of CSF into the subarachnoid space [12, 13]. Other potential mechanisms contributing to symptom sequela include extensive distortion of the posterior fossa space, brain stem compression, anomalous venous drainage in the posterior fossa and presence of other CNS abnormalities.

CM-I in contrast typically occurs in isolation and is characterized as the descent of the cerebellar tonsils to any measurement beyond their normal anatomical positioning, below the foramen magnum, without the involvement of other brain structures (i.e., tectum, pons). The presenting clinical features associated with CM-I are typically headache or neck pain, weakness in extremities, sensory loss, ataxic gait, and cranial nerve dysfunction. Treatment often involves decompression surgery to accommodate the herniated cerebellum [13].

The neurocognitive outcomes of MMC, CM-II, and the resulting hydrocephalus have been widely researched. The same cannot be said for CM-I, as there have been relatively few studies with large sample sizes examining cognition in this population to date. A basic PubMed search during the preparation of this chapter's update revealed few peer review articles related to CM-I and cognition. A recent contribution to the CM-I literature is a systemic review by Rogers and colleagues [14] who identified 12 articles meeting their screening criteria for use in their review. The authors explained that from their review, individuals with CM-I most commonly reported and were demonstrated on examination to have problems related to executive functioning. This was followed by deficits in attention, working memory, visuospatial, and visual perceptual abilities. Any delays or problems related to language in children seemed to improve over the course of development, while adults did not report/demonstrate language-related impairments. They also were unaffected on measures of general cognitive functioning, intelligence, learning and memory, and processing speed [14].

Two case studies described women with histories of anxiety who were eventually diagnosed with CM-I and underwent decompression surgery. While surgical intervention did not reduce anxiety, the authors [14] speculated that the underlying anatomical anomaly may have led to or exacerbated the anxiety. In a retrospective study [15], a review of a series of consecutive radiologic studies revealed 35 patients with CM-I, 25% of whom presented with mental retardation, speech delays, and/or epilepsy. They noted that the association between CM-I, cognitive disorders and seizures should not be considered an "incidental finding" [15]. No other data has been published on the cognitive and emotional functioning of this population since this finding years ago.

For a number of years, spina bifida was thought to be the most prevalent cause of congenital hydrocephalus. More recently, intraventricular hemorrhage (IVH) or post-hemorrhagic hydrocephalus in premature infants has been demonstrated to have a much greater occurrence rate as the incidence of MMC has recently dropped propitiously [2, 10]. Hydrocephalus due to IVH most commonly occurs in the periventricular germinal matrix within the caudothalamic groove. This highly vascular region of the premature brain is susceptible to hemorrhage [8, 11] as the walls of these blood vessels lack structural elements and support of external tissue. Following an IVH, hydrocephalus is believed to develop due to occlusion of the arachnoid granulations by the byproducts of the hemorrhage [8] and/or underdeveloped arachnoid granulations during the prenatal period [16]. Ventricular size can increase suddenly or build up over the course of days to weeks following IVH and is seemingly the result of an obstruction of the ventricular outflow tract resulting in dilation of the lateral ventricles. In addition, other lymphatic, perivascular, and dural pathways may be implicated in the mechanism of IVH related hydrocephalus. Studies looking at the role of growth factors have suggested the role of transforming growth factor-beta 1 (TGF-B1), which is elevated in the CSF following IVH, combined with other consequences of IVH, can lead to inflammation of the arachnoid lining (e.g., arachnoiditis) adding to CSF malabsorption [2].

Genetic research in Infantile Hydrocephalus has identified a number of X-linked gene mutations. As referenced previously, the gene L1CAM plays an important role in neuronal migration and axon guidance. When mutated, it can cause several structural malformations that obstruct CSF flow, usually at the level of the Sylvian aqueduct. L1CAM mutations are the most common cause of hydrocephalus associated with stenosis of the aqueduct of Sylvius (HSAS) and are believed to account for 10% of isolated idiopathic hydrocephalus in males. L1CAM associated HSAS has a broad spectrum of disease that often includes X-linked spastic paraplegia and agenesis of the corpus callosum [2].

Fried syndrome, caused by mutations in the AP1S2 gene, is characterized by intellectual disability with prominent basal ganglia iron deposition or calcifications and variable hydrocephalus. The severity and appearance of hydrocephalus on neuroimaging have not been well-defined, but typically presents with aqueductal stenosis in some patients with others showing retrocerebellar or fourth ventricle cysts [2].

Biomarkers

Within the last decade, there has been increasing attention to the identification of specific cerebrospinal fluid (CSF) biomarkers in congenital hydrocephalus (CHC) that may be of potential diagnostic and therapeutic value. Studies have shown alterations in CSF levels of amyloid precursor protein (APP), L1 cell adhesion molecule (L1CAM), and neural cell adhesion molecule 1 (NCAM-1) in infants born premature with post-hemorrhagic hydrocephalus. Cerebrospinal fluid APP levels have also been shown to correlate with ventricular size and potentially correlate with intracranial pressure in these patients. In addition, NCAM-1 and L1CAM have shown similar correlations, though not as robust, as APP. A recent study [17] documented strong correlations with congenital hydrocephalus and the following biomarkers: APP, derivative isoforms of APP (sAPPα, sAPPβ, and $A\beta_{42}$), tau, phosphorylated tau (pTau), and L1CAM. Soluble APPα in particular has shown high sensitivity and specificity for discriminating CHC from normal controls and other neurologic diseases. While sAPPβ, APP, tau, and L1CAM have also demonstrated good sensitivity and specificity, data thus far has been less robust in comparison to sAPPα [17].

Challenges in Assessing Neuropsychological Outcomes

Studies examining neurocognitive functioning in individuals with hydrocephalus have consistently reported worse performance in this group compared with normal controls as well as in individuals with other medical conditions across several domains [7, 18]. An important caveat in reading this literature is that hydrocephalus can be etiologically multifactorial and associated with a variety of specific underlying diseases as described in detail above. It is difficult to separate the effects of the hydrocephalus, as opposed to the effects of the underlying etiology (e.g., intraventricular hemorrhage), comorbidities (e.g., Chiari Malformations) treatments (e.g., shunt revisions) and psychosocial factors (e.g., health disparities), in determining the primary cause of cognitive weakness.

Intellectual Functioning

Prior to the application of CSF shunting to treat hydrocephalus, children who survived had a slowly progressive and/or spontaneously arrested type of hydrocephalus. Of those who survived, only about 38% achieved average intellect [19, 20]. Since the advent of shunting devices, survival and intellect have greatly improved in this population. In a more recent study examining intelligence in children shunted within the first year of life to treat post-hemorrhagic hydrocephalus, the mean WISC-II FSIQ was 83.8 (17.4 SD), while age and education-matched controls had a mean FSIQ of 102.9 (14.7 SD) [21]. Compared to other etiologies of hydrocephalus, children with mild IVH seem to perform in the low average range on standardized intelligence measures. Overall, multiple studies have documented the mean Full Scale IQ remains significantly below that of peers, often 1 to 1.5 standard deviations [21]. Other authors document high occurrence of intellectual disability and other cognitive deficits in premature infants with moderate to severe IVH (grade 3–4), while infants with mild IVH (grade 1–2) are at risk for less severe developmental disabilities. In infants with severe IVH, 75% have required special education services when they reach school age [11, 22].

While there are consistent findings of lower than average intellect in children with hydrocephalus [21, 23, 24], the impact on Verbal and Performance IQ is more controversial. Earlier studies found a significant discrepancy between the Verbal IQ and Performance IQ, consistent with Rourke's model [24] of a nonverbal learning disability in hydrocephalus [12, 25, 26]. The majority of these early studies were limited to children with spina bifida and hydrocephalus. In a recent review of the literature examining cognition in hydrocephalus only eight of 147 studies excluded patients with myelomeningocele (MMC), traumatic brain injury or other neurologic conditions [24]. As noted previously, spina bifida has its own unique morphology separate from hydrocephalus and thus may obscure the true impact of hydrocephalus on cognition. In fact, in more recent studies excluding children with MMC, this VIQ-PIQ discrepancy has not been documented [21, 24]. Thus, etiology may be relevant in determining cognitive outcome. Interestingly, while general intelligence was reduced compared to healthy controls, this PIQ disadvantage was not found in a recent study examining hydrocephalus in young adolescents with spina bifida [7]. The authors suggested that frontal dysfunction, rather than a right hemisphere dysfunction, may actually underlie the intellectual deficit in hydrocephalus.

In general, earlier age of onset results in worse intellectual outcome [21] and intelligence appears to decline with advancing age [24]. Animal experiments indicate that neuronal damage is often progressive in hydrocephalus and not completely reversed by shunting [27]. In terms of the impact of shunt revisions on cognition, studies with lower rates tend not to show a significant impact [21, 24]. The rate of shunt revisions appears to vary greatly across studies, which may account for discrepant findings. In

fact, one study examining primarily children with spina bifida reported a range of revisions from zero to 100. Thus, the etiology itself may impact the number of revisions [28]. Certain conditions such as MMC may result in a more unstable hydrocephalic state, which may uniquely impact cognition.

Executive Functioning and Attention

Most of the neurocognitive research addressing executive functioning in this population has focused on aspects of attention, often in children with spina bifida related hydrocephalus. Most of this research has found a higher susceptibility to distraction in this population compared to peers. Two studies, in particular, found that children with spina bifida and hydrocephalus produce more visual distractibility errors [29] and required more time during focused attention tasks with auditory distracters [30]. Problems have also consistently been seen on tasks requiring focus and shifting of attention [31, 32], while fewer sustained attention deficits have been documented [33]. Some have argued that the attentional dysfunction in hydrocephalus is related to the right posterior attention system, while others have not found support for this theory [24].

In a recent study, 31% of children diagnosed with spina bifida and hydrocephalus met criteria for Attention Deficit Hyperactivity Disorder (ADHD) and 23% met criteria for the Inattentive type [34]. Parents tend to note disinhibition or mental inflexibility on rating scales (such as the Brief Rating Inventory of Executive Function), along with working memory and initiation difficulties [35]. Tarazi and colleagues [36] found increasing deficits reported by parents as children age. They hypothesized that this may reflect a skill maturation deficit due to disruption of frontal lobe functioning at critical times, secondary to the actual hydrocephalus and the impact of revisions and infections. In one case study which included serial assessment of various aspects of attention, the patient displayed reduced functioning prior to shunt revision with improvement in response time and omission errors post revision, though deficits in inhibition were maintained [37]. The timing and number of shunt revisions appear to impact outcome, although the exact threshold is uncertain. In our own laboratory, even subtle adjustments in shunt pressure impact attention negatively [21].

In terms of other executive skills, children with hydrocephalus have been shown to struggle on the planning and organization aspect of the Rey Complex Figure Test (RCFT), hypothesized to reflect executive dysfunction [18, 38]. In some studies, children with hydrocephalus have consistently performed below peers on Similarities, Block Design, Object Assembly, and Picture Completion subtests from the Wechsler Intelligence Tests [7, 21]. Children with hydrocephalus co-occurring with myelomeningocele (MMC) often have problems in performance on paper–pencil measures evaluating attentional abilities [39]. In a study by Lindquist and colleagues comparing children with congenital hydrocephalus, children with MMC and hydrocephalus, and normal controls, both clinical groups performed below the controls on Trail-Making A & B, RCFT, Tower of London, and Verbal Fluency [18].

Memory

Children with congenital hydrocephalus consistently display learning and memory deficits [40]. Results across studies have been mixed regarding whether there is an encoding or retrieval based deficit. For example, several studies have found average recognition performances despite impaired immediate and delayed recall trials [7, 23, 41, 42]. In contrast, other studies have found no benefit from recognition paradigms, suggesting more of an encoding based deficit (consistent with noted attentional dysregulation) [43, 44]. Discrepancies across studies are primarily due to methodological differences. Etiology has varied widely across studies, with some studies assessing

individuals with spina bifida, aqueductal stenosis, and/or hemorrhage hydrocephalus. Other studies set specific, intelligence-based exclusion criteria, with scores ranging from 70 [18] to 90 [41], while others do not address intelligence. Studies that use IQ cutoffs are more likely to report a profile of retrieval deficits [7, 18, 41, 42], while those without IQ cutoffs are more likely to report encoding deficits [10, 43, 44]. Research has also varied with regard to other exclusion criteria. Some studies exclude individuals with psychiatric histories, despite the high rates of depression and ADHD in this population [34].

Language

A review of the literature describes speech disturbances in children with congenital hydrocephalus (CH) as reflecting "a cocktail party syndrome" (CPS) [45, 46]. This effect appears primarily in early studies, especially with myelomeningocele-related hydrocephalus (28–41%) [46], and is associated with lower ranges of intellectual functioning [18]. Patients with CH present with disorders often related to right hemisphere functions, including problems with semantic-pragmatic aspects of language with preserved linguistic skills [40]. Linguistic expression is typically fluent and mostly well structured [47]. However, when talking about stories or situations, children with hydrocephalus tend to become verbose and disorganized while leaving out important details [47]. They omit certain grammatical aspects of language [48] and fail to make semantic and structural links between pieces of stories [49]. In one study, children with hydrocephalus were found to begin to talk about irrelevant subjects with increasing task complexity, whereas normal controls remained focused and responded appropriately [50]. When structured productive language tasks are presented, hydrocephalic children in some instances have demonstrated minimal to no verbal fluency deficits [1, 48], while other studies have shown impaired performances compared to normal peers on fluency tasks with constraints [51].

With advancing age, reading comprehension, receptive language skills, written language, and spoken language deficits emerge [10, 52–56]. Children with hydrocephalus have also been shown to manifest difficulties compared to peers on tasks requiring production of antonyms and synonyms for words [56] and on tasks requiring the ability to break down words phonologically at a basic level of language comprehension [50, 54]. In contrast, children with hydrocephalus have been shown to read single words and nonsense words adequately [56].

Visual Perception and Visuospatial Thinking

As noted previously, early studies suggested that children with hydrocephalus are at highest risk for a nonverbal learning disability based on reports of a Verbal IQ deficit versus Performance IQ strength. More recent studies, especially those examining hydrocephalus without spina bifida, have not found this disparity [7, 21, 23]. In a recent review of this literature [40], children with hydrocephalus displayed variability in visual perception skills. Some abilities, such as facial recognition, appear stronger than others requiring more different spatial demands (e.g., judgment of line orientation). One complication in examining this literature is that many tests of visuospatial processing, such as the Block Design and Picture Arrangement, require speeded responses with a motor component. Many children with hydrocephalus, especially when related to spina bifida, exhibit slowed motor speed processing, thus hindering performance. Additionally, many of these tests also tap executive skills of planning [57].

Subjective parent ratings revealed a high rate of perceived visual perceptual problems, with more than half of parents with children with congenital hydrocephalus reporting problems,

with no age-matched controls being similarly affected. Parent ratings indicated that their children had problems mostly related to shape recognition and simultaneous perception with lesser rates of problems in perception of movement and color perception. Notably, a few children were reported as having problems with object recognition, topographic orientation, and face recognition [58].

Motor

Motor deficits are characteristic of children with hydrocephalus. The severity of motor dysfunction ranges from fine motor deficits to paraplegia and gross gait abnormalities depending on etiology. Gross and fine motor deficits have been demonstrated in young children with spina bifida, post intraventricular hemorrhage (IVH), and aqueductal stenosis (AS) [59, 60]. In general, children with spina bifida tend to have more motor dysfunction than children with periventricular hemorrhagic (VH) related hydrocephalus [61]. In the cases of hemorrhagic and aqueductal stenosis cases, the gait abnormalities occur in almost one-third of children with hydrocephalus. Children with hemorrhagic hydrocephalus tend to have less impairment in overall lower limb function and have better outcomes than children with spina bifida. Motor deficits develop as a consequence of insults to single or multiple areas within the central nervous system [62, 63]. For example, cerebellar dysfunction often seen with Chiari malformations can cause ataxia and oculomotor apraxia when associated with cerebellar vermis malformations [64–66]. These deficits can subsequently cause visuomotor impairments [67]. In spina bifida, spinal lesions affect upper and lower limb function [68]. Pyramidal tract deficiencies result from damage to the cerebral cortex [69]. Behaviorally, this is demonstrated as loss of strength and sluggish reaction times [69, 70]. Children affected by hydrocephalus with resultant motor deficits have been shown to require more practice in learning the daily skills necessary to function in their environments than typically functioning children [71].

Emotional Functioning and Quality of Life

Children with hydrocephalus experience higher rates of depression, anxiety, and attentional deficit disorders. It has been estimated that 44–46% of children with hydrocephalus meet diagnostic criteria for behavioral or emotional disorders or have significant elevations on measures of adjustment [72, 73]. Internalizing difficulties were more commonly found than externalizing difficulties. An incidence of behavioral problems as high as 67% has been documented based on the Connor Rating Scales [74]. Notably, children with lower intelligence scores were more likely to experience behavior problems. An online survey completed by caregivers of children with congenital hydrocephalus (CH) documented a high rate of functional impairment [75]. Notably, 68% of patients with congenital hydrocephalus diagnosed before age 18 months reported not being in a committed relationship and having a history of depression, and 45% received psychiatric treatment. Over 40% of the younger onset patients reported not being employed at the time of the survey as did one-third of the older diagnosed sample. While a significantly lower rate, still 52% of patients diagnosed between 13 and 18 years also reported a history of depression and 45% remained single. Across a sample of 30-year-old women, only 25% reported having children, and many reported being dependent for housing and transportation.

In 2000–2010 follow-up survey of individuals with hydrocephalus of varied etiologies 56% of those survived were employed in open-market jobs or were active students, 23% had sheltered employment, and 21% were unemployed [76]. Males reported significant physical functioning and general health issues compared to healthy controls, while females endorsed role limitations due to physical health problems as well for physical functioning and general health.

More recently, in a long-term follow-up study of CH patients published in 2015 [77], Paulsen and colleagues documented a mortality rate of 48% over a 42–45 year period, with tumor

patients included, and this rate dropped to 39% without tumors. Shunt-related mortality was low at 8%. The quality of life outcome data indicated a high rate of high school graduation with over half socially independent and 42% employed. There continued to be quality of life difficulties with self-report health lower in 6 out of 8 domains on the Short Form Health Survey. In a recent review examining differences in short-term and long-term survival outcomes following ventriculoperitoneal shunt (VPS) placement versus endoscopic third ventriculostomy (ETV), the overall outcomes demonstrated no significant survival advantage between the two procedures, but postoperative complications were greater following VPS in comparison to ETV, 31 and 17%, respectively [78]. A meta-analysis by Cheng and colleagues [79], reported no difference in therapeutic outcomes between ETV and VPS for treatment of non-communicating hydrocephalus, although ETV was associated with lower incidence of postoperative complications, reduced surgery times, and rate of reoperation [79].

Regarding quality of life following shunt placement (beyond the presence of infection), there are certain external factors that are known to moderate a patient's health. Specifically, lower socioeconomic status, poorer family functioning, and lower parental education have been demonstrated as correlating with overall lower quality of life in children with hydrocephalus [80].

Research examining the differences in quality of life over time following either VP shunt or ETV is limited. One study [81] compared quality of life in children with obstructive hydrocephalus who had been treated with either ETV or shunt and concluded that no significant differences were present between the two groups regarding quality of life, though sample size was limited. During our review, we found no systematic longitudinal studies that have evaluated whether or not a direct positive association exists between the improvements in surgical intervention and quality of life outcomes in patients over the past two to three decades.

Summary of Neuropsychological Profile in Congenital Hydrocephalus

In summary, children born with hydrocephalus tend to display mild, diffuse intellectual difficulties. Executive problems, primarily characterized by attention, response inhibition, working memory, and planning deficits are commonly documented in this population. This results primarily in encoding and retrieval-based problems with a relatively consistent finding of benefit from recognition paradigms. Language impairment tends to be subtle, affecting the semantic and pragmatic aspects of language. Visuospatial and planning deficits have consistently been found, although this is difficult to disentangle from the executive difficulties [57]. Deficits in visual perception have also been shown on objective testing [47], as well as on clinical ratings provided by parents [58]. Motor problems include slowed fine motor speed, with greater deficits depending on etiology (i.e., spinal cord and brain stem involvement). Behavioral difficulties tend to include more internalizing problems such as depression and anxiety, along with inattentiveness. Quality of life, while improving in some ways, continues to be challenging for many patients in terms of employment, marriage and overall life satisfaction.

Etiology of Cognitive Impairment

The etiology of this cognitive profile is hypothesized to be related to disruption of periventricular white matter tracks due to enlargement of ventricles [82], which results in the frontal-subcortical profile of cognitive dysfunction. There is also evidence of damage to gray matter structures such as the thalamus and basal ganglia, but to a much lesser extent [5]. In some studies, cognitive impairment has correlated with white

matter neuropathology [83], but not others [84]. Presence of infection, type of infection, etiology, shunt revisions, and age at surgery may all impact cognition [40]. Unfortunately, these differences are often not directly examined in the literature. Furthermore, with advances in technology, the impact of these factors may change. For instance, in early studies, the number of shunt revisions was often very high (>8) [28], while in newer studies shunt revisions are much less common (<5) [21]. Thus, to say shunt revisions did or did not impact outcome may be a factor of patient selection.

Late Life Onset: Idiopathic Normal Pressure Hydrocephalus

Normal Pressure Hydrocephalus (NPH) was first described by Salomon Hakim in 1957 in Colombia as a clinical syndrome of gait instability, memory loss (mild dementia), and incontinence [85]. It is often considered a potentially reversible syndrome if diagnosed early and accurately. iNPH is historically viewed as a type of communicating hydrocephalus in which accumulated CSF equilibrates with absorption, although intracranial pressure (ICP) is slightly elevated and CSF may reach a high normal level. Others have referenced iNPH as an obstructive form of hydrocephalus due to some disruption limiting the flow of CSF from the CNS space. In general, etiology is idiopathic and can be diagnosed in individuals as young as 40, but typically occurs in the 6th to 7th decade. It tends to occur in equally in women and men. A recent systematic review documented a pooled prevalence of 1.3% with higher rates seen in assisted living and extended care facilities [86]. The authors noted the only prospective population-based survey documented an incidence estimated at 1.20 cases/1000 inhabitants/year. Five to 10% of all patients with dementia may suffer from this disorder [87]. Hejl and colleagues found 3% of their 1000 consecutively presenting dementia cases were eventually diagnosed with hydrocephalus and made up 18% of the 185 reversible cases [88]. The rate of iNPH-related dementia is unclear as accurate diagnosis is challenging. Underdiagnosis is thought to be due to the general lack of awareness of iNPH symptoms and the additional confounding problem that the core triad of symptoms (e.g., gait instability, urinary incontinence, and cognitive problems) may manifest in several health complications commonly seen in the elderly [89].

Etiology

Many theories are being explored regarding the pathogenesis of iNPH. In a recent review [90], Keong and colleagues concluded that the exact mechanism remained unclear and is most likely multifactorial. Structural insults (e.g., tissue distortion, interstitial pressure increase), cerebral blood flow disruption (e.g., watershed ischemia, vascular disease), cerebral spinal fluid flow problems (e.g., changes in hydrodynamics), and failure of drainage of vasoactive metabolites (e.g., amyloid beta peptides, tau protein) have all been theorized as playing a role in the emergence of iNPH [90]. The clearance failure theory has raised speculation that shunting may be beneficial in other degenerative dementias such as Alzheimer's disease (e.g., clearance of tau and amyloid in CSF). Unfortunately, a recent double-blinded placebo-controlled trial did not demonstrate any benefit of shunt placement in patients with moderate to severe Alzheimer's disease [91]. Most recently researchers have suggested that iNPH with enlarged ventricles may be part of the presentation of certain cortical dementias such as Alzheimer's disease, Lewy Body dementia, and Progressive Supranuclear Palsy. Espay and colleagues noted that post-shunt responsiveness only persisted in a third of their patients with many receiving the revised diagnosis over time of degenerative disease [92].

Similar to pathogenesis, the understanding of the genetic basis of iNPH is still evolving. A recent study demonstrated that a copy number loss

within intron 2 of the SFMBT1 gene may be a genetic risk factor for shunt-responsive definite iNPH [93]. A total of 8 iNPH-families have been identified in the literature suggesting a familial subgroup of iNPH with potential autosomal dominant inheritance with linkage to 19q12–13.31 [94].

Clinical Diagnosis

Historically, iNPH has been thought of as a rapidly presenting clinical triad (termed Hakim–Adams triad) of incontinence, gait instability, and memory or mental status changes in the context of enlarged lateral ventricles [95, 96]. While useful in alerting clinicians of the potential diagnosis, the NPH triad of symptoms may not always be present as an initial feature and may reflect the later stages of the disease process. For instance, almost half of patients diagnosed with iNPH do not present with incontinence, meet criteria for dementia, or display gross balance disturbance [97]. Many elderly individuals may experience gait problems, incontinence, and confusion for a variety of other reasons. Integration of clinical history, clinical presentation, neuroimaging, and physiological data (i.e., CSF pressure measurement) is required to achieve accurate and reliable diagnosis.

Historically, iNPH has been partly defined as ventriculomegaly out of proportion to cerebral atrophy without documented macroscopic obstruction to the circulation of cerebral spinal fluid [97]. Ventriculomegaly is typically defined as an Evans Index of >0.03, which refers to the ratio of the maximal width of the anterior horns of the lateral ventricles to the maximal width of the skull at the same level. MRI scans are often utilized to document symmetrical ventricular enlargement greater than brain atrophy. More sophisticated ventricular volumetric methods are emerging through the use of imaging software such as the Brain Ventricular Quantification system. Researchers have suggested that specific imaging findings aid in differential diagnosis. For instance a steeper callosal angle at the top of the lateral ventricles in a coronal slice in iNPH than in degenerative disorders [1] and disproportional enlargement of the subarachnoid space in iNPH [98].

While it has a high sensitivity, ventriculomegaly alone is not diagnostic as this is found in other disease processes, such as Alzheimer's and cerebrovascular disease. While sensitivity has been estimated as high as 80%, specificity is estimated at 50% [99]. Understandably, ventriculomegaly is also not consistently predictive of diagnosis or treatment outcome following CSF shunting [100]. In fact, better clinical outcomes have been seen in patients without change in ventricular ratios following intervention [101]. More recently diffusion tensor imaging (DTI) has been examined as an iNPH biomarker. The combination of the Evan's ratio and DTI measures of the splenium of the corpus callosum, posterior limb of the internal capsule, the hippocampus, and the fornix have been proposed as potential promising structural imaging biomarkers of iNPH [102]. Advanced imaging options are being investigated to aid in diagnosis and treatment planning including arterial spin label and phase contrast imaging. While promising, specificity remains marginal [103] at this time.

Specific CSF diagnostic biomarkers have been identified to aid in diagnosis, such as high levels of neurofilament light protein (NFL) and reduced levels of amyloid β 42 (Aβ42). Jeppsson and colleagues [104] confirmed that individuals with iNPH have reduced levels of Aβ42, which is also seen in Alzheimer's disease yet they also found lower levels of Aβ40, Aβ38, and soluble alpha-amyloid precursor proteins (sAPPα, sAPPβ), which is not seen in AD.

In order to improve diagnosis, multidisciplinary teams are often involved in the process of differential diagnosis and identifying patients who may benefit from surgical interventions such as placement of a CSF shunting device. Often patients with suspected iNPH complete a series of assessments including neurological examination, neurosurgery consultation, structural and

functional imaging, physical therapy assessment, and neuropsychological evaluation. The initial neuropsychological assessment is often conducted to aid in differential diagnosis (e.g., AD, vascular parkinsonism, and mixed dementia) when enlarged ventricles are seen on imaging and/or as part of a clinical trial to assess the potential efficacy of surgical placement of a ventriculoperitoneal shunt. For the latter, a cognitive assessment is conducted before and 24 h after a CSF tap or 3–5 days after a lumbar drain is placed for continuous drainage.

Neurocognitive Profile

The prototypical neurocognitive profile is often cited as one of the prominent executive-based subcortical frontal dysfunction leading to impairment across other cognitive domains [95]. This is hypothesized to be primarily related to a metabolic disruption of the periventricular system secondary to ventricular expansion. The disruption includes the cortico-basal ganglia thalamo-cortical loop, with prominent frontal involvement [105]. As a result of this disruption, patients diagnosed with iNPH often present with mental and motor slowing, along with deficits in memory retrieval, visuospatial, construction, concentration, mental flexibility, planning, and problem-solving abilities, but rarely frank cortical features such as anosmia, apraxia or aphasia [106, 107]. While patients with iNPH rarely show signs of major depression, they are often noted to present with apathy, inertia, and slowness [97]. A more recent review by Azab and colleagues [108] concluded that the neurocognitive abnormalities associated with iNPH are thought to be a consequence of a variety of neuroanatomical factors, including brain parenchymal damage, ventricular enlargement, intracranial pressure, the duration of the hydrocephalus, impaired cerebral blood flow, alterations of neuronal cell metabolism, axonal loss, and pathological neurotransmission amongst other synaptic damage.

iNPH is often referred to as a fronto-subcortical dementia [107] although the presentation varies widely. While the traditional subcortical profile is a useful framework, recent literature suggests a diversity of neurocognitive presentations with iNPH. Picascia and colleagues [109] noted that all of their iNPH subjects presented with some form of cognitive impairment, yet they concluded that the entirety of their patient sample could be categorized into the following groups: patients with global cognitive impairment (42%); patients with deficits in attention and executive abilities or fronto-subcortical dysfunction (24%); patients with mild cognitive impairment involving a single domain (17%); and patients with no cognitive impairment (17%). The authors found that cognitive impairment became more severe with older age, increasing disease duration, and increasing severity of motor symptoms, though this is debatable [96]. These authors postulated that early shunt surgery may limit both the progression of motor disturbances and the progression of cognitive deficits.

In a study comparing cognitive performance between healthy controls and iNPH patients, the discriminability efficiency of most neurocognitive tests was rather high, almost 90%. Notably, patients with vascular comorbidity performed worse on cognitive tests but were not different in terms of gait, sleep, or incontinence. Neuropsychological impairment has correlated with impaired gait, incontinence, and sleep disruption [98]. In terms of discriminability, iNPH patients display greater executive dysfunction and less memory impairment when compared with aqueductal stenosis hydrocephalus patients, a form of secondary obstructive hydrocephalus [110]. Anomia or reduced naming has also been found to be more indicative of Alzheimer's disease and poor shunt response [111]. AD should be considered as a diagnostic differential or a comorbid condition when slow progression, enlarged ventricles (e.g., ex vacuo hydrocephalus), insidious onset, and anomia are noted early in the disease course [111]. Interestingly, Savoainen and

colleagues found larger hippocampal volumes in iNPH verses AD patients and a trend towards larger volumes in those patients who benefited from surgery [112]. It is important to consider that AD neuropathology (i.e., amyloid beta) is highly prevalent in iNPH. Some estimates found that 67.6% of iNPH patients and 47% of possible iNPH patients had AD neuropathology present during cortical biopsies. Amyloid beta (Aβ) accumulation due to decreased CSF clearance has been proposed to explain the high co-occurrence of Alzheimer's-like changes in the cortex of iNPH patients and in animal's studies. While some have suggested that Alzheimer's dementia and hydrocephalus are related to CSF circulatory failure with subsequent neurodegeneration, others did not find that Alzheimer's disease pathology impacted clinical outcome following shunting [113].

Treatment

There is no cure for iNPH, but the primary treatment is insertion of a CSF shunting device that transfers CSF into the peritoneal space. Gait improvement following intervention has been documented as high as 80% yet the success rate in terms of cognitive improvement varies greatly across clinics with estimates reported from 26% to 80% [114]. Additionally, studies have indicated that improvement may take 12–24 months [115] and then the improvements may decline again due to comorbid conditions. In a recent meta-analytic review, Peterson and colleagues found statistically significant effects of shunt surgery on global cognition (MMSE), learning and memory (Rey Auditory Verbal Learning Test), and psychomotor speed (Trails A) and to a lesser extent executive abilities (phonemic fluency) [116]. Of note, executive functioning was reported to demonstrate highly variable changes post-shunt with some reporting no change [117] and others reporting improvements [118, 119]. The authors noted the finding of unclear impact on executive functioning may reflect irreversible insult to frontal-subcortical connectivity by the time patients complete surgery.

To date, no diagnostic test or clinical picture can predict response to CSF shunt surgery. Listed prognostic indicators of good shunt outcomes have included shorter duration of cognitive impairment, gait disturbance as the initial symptom, and minimal corpus callosum distortion [101, 120]. Research by Thompson and colleagues [121] suggested that in patients over 80, age did not significantly decrease the chance of a shunt succeeding. In a 2007 review, the following were listed as prognostic indicators of good outcome: onset less than two years prior to intervention, gait disturbance prior to cognitive decline, no alcohol abuse history, large head circumference (e.g., greater than 59 cm in males and 57.5 cm in women), lack of anomia, minimal short-term cognitive disturbance, gait response to lumbar drain trial, and outflow of greater than 18 mm Hg/ml/min during CSF lumbar infusion test [97]. Surprisingly, aside from CSF biomarker and imaging analysis there have been few recent studies examining cognitive outcome predictors.

In a recent review of CSF biomarkers predictors of shunt responsiveness [122] no markers were found to demonstrate high sensitivity or specificity, albeit some are promising. Amyloid β (Aβ), tau, NFL, and LRG were concluded to have the greatest promise as viable predictors of shunt response. $A\beta_{1\text{-}42}$ and total tau protein levels have demonstrated a 80% sensitivity and 82.4% specificity for predicting favorable post-surgical outcomes for iNPH after six months [103].

MRI findings of significant atrophy and white matter hyperintensities have been shown to be prognostic indicators of poor outcome. In contrast, higher presurgical mean ICP wave amplitudes have been documented in cognitive shunt responders [123]. In a review of noninvasive biomarkers, promising sensitivity and specificity rates were found for CSF flow void on MR imaging, SPECT N-acetylaspartate/choline ratio, and phase contrast MR imaging for responsiveness to shunting [124]. Examination of functional

MRI revival patterns on cognitive and motor tasks after CSF drainage have yielded positive results for finger tapping but not cognitive tests [125].

Although research on the natural history of iNPH is rare, a 2014 review examined outcomes in patients who remained unshunted [126]. They found that patients who did not receive surgery demonstrated worsening of symptoms, including cognitive decline, as early as three months post initial evaluation. One study found a 77% improvement in cognition for shunted patients, but only a 9% cognitive improvement in unshunted patients approximately 7 years later. Thus patients with untreated NPH have a high risk of poor cognitive outcome.

In a recent quality of life study [127] slightly fewer than half (e.g., 43%) of patients followed for 1 year post shunting reported a clinically significant improvement in quality of life. Regression analysis revealed the absence of amyloid-B and hyperphosphorylated tau pathology in a frontal biopsy and lower body mass index as poor quality of life predictors. The authors noted, however, that they operationally defined an unfavorable quality of life outcome as a decline or as no change in health-related quality of life (HRQoL) as rated by a questionnaire completed by the patient or an interviewing nurse; because iNPH is a progressive condition, it may have been beneficial to consider the stability of HRQoL a favorable outcome. Furthermore, because of a lack of insight that frequently accompanies cognitive impairment, assessing quality of life based on patient report is particularly difficult. In a recent cost-effectiveness study [128] shunt surgery was found to add an additional 2.2 life years in patients of average 70 years at a relatively low financial cost.

New Treatment Approach: Endoscopic Third Ventriculostomy

Because of the variability in shunt responsiveness detailed above, endoscopic third ventriculostomy (ETV) has been explored as an alternative emerging treatment for iNPH in the hopes of eliminating the need for shunt revisions and possible infection. Ventriculoscopy was first introduced in the early 1900s [129, 130]. One of the first surgeons to employ the procedure was Walter E. Dandy, who performed a choroid plexectomy in an individual with communicating hydrocephalus [130]. The first ETV was performed by W. J. Mixter in the 1920s using an ureteroscope [131]. H. F. McNickle created a new method of performing third ventriculostomy in 1947, which decreased the incidence of complication and increased the rates of success with ETV in cases of hydrocephalus [130]. Despite this finding, the use of the technique was limited due to high complication rates. A new interest came with the development of advanced fiber optic and lens technologies. Improved neuroendoscopes with working ports, good optic resolution, and deflectable tips have made ETV a more precise procedure with improved outcomes [130].

ETV, which avoids the complication of infection or revision, is becoming the treatment of choice for hydrocephalus caused by intraventricular obstruction (e.g., non-communicating hydrocephalus) at the level of the aqueduct of sylvius. In ETV, infection rate is less than 5% of cases [132], but the occurrence of other complications (e.g., hematoma, diabetes, and hygromas) ranges between 6 and 20% [133].

ETV involves a perforation of the floor of the anterior third ventricle creating an internal bypass of aqueductal obstruction. As an initial treatment, surgical response has been documented as high as 90%. In cases presenting with a history of shunt failure, success rates drop to less than 70%, but these patients are subsequently shunt free and rarely require additional surgical intervention. Age is another factor impacting outcome, with higher failure rates reported for infants less than 6 months of age [132] when compared to adolescents and adults.

Despite the growing utilization of this surgical management technique, few studies have been published addressing neuropsychological status before or after a ventriculostomy. A case study

report [134] described a 20-year-old man 7 months post-ETV intervention who displayed memory and executive impairment, along with a significant change in personality involving bulimia, impulsivity, and aggressiveness. This patient, who underwent his first shunt placement at 8 months of age, suffered multiple complications over the years, including 13 shunt revisions. In 2002, another case report [135] described a 45-year-old patient, without prior psychiatric history, who developed a psychotic depression immediately post-treatment. The author theorized that a surgical disruption of the limbic system during endoscopic insertion may have played a role in the development of her psychiatric symptoms. In 2004, a third case report [136] described a 20-year-old male who developed a dense amnesia and bulimia post-stereostatic ETV. In our own study [10, 137] patients with aqueductal stenosis, assessed on average 2 years following ETV intervention, continued to display memory and executive function deficits.

None of these descriptive studies documented presurgical cognitive or psychiatric status. One exception is a 2003 study that presented the cognitive status of six patients ages 25–60 prior to ETV who had a history of late onset idiopathic aqueduct stenosis (LIAS) [138]. Prior to intervention, all displayed a combination of memory and executive dysfunction, with five showing significant improvements post-treatment.

In a 2006 study examining outcome in children [139], IQ development in 23 patients initially treated with ETV for obstructive hydrocephalus prior to 9 months of age was compared to 16 infants treated with a standard shunting device at similar ages and time points. Overall, ETV resulted in slow but adequate development of intellect at age 6 if the initial MRI findings revealed intact cerebral cortex. If the cortex or cerebellum was compromised, ETV was found to be less effective in achieving normal intellectual development compared to those treated with a shunting device. There is a need for longitudinal and treatment outcome studies utilizing this technique.

A meta-analysis conducted by Rasul and colleagues in 2013 [140] included a total of 504 pediatric patients with non-communicating hydrocephalus (366 who underwent ventriculoperitoneal shunt insertion and 138 who underwent ETV). The authors indicated a lack of randomized control studies and identified limited cohort and historically controlled studies that directly compared the effects of shunts versus ETV in non-communicating hydrocephalus. Results suggested that, while some evidence may indicate the superiority of ETV over shunts, "at present there is insufficient evidence to unequivocally recommend one mode of treatment above the other."

In sum, while ETV as an intervention for hydrocephalus holds promise for a reduction in infection and an elimination of the need for shunt revisions, there is a great need for randomized controlled studies and research that document longitudinal surgical, cognitive, and psychiatric outcomes of patients who undergo ETV. Furthermore, future studies should aim to collect premorbid data regarding psychiatric and cognitive functioning in order to better document changes that may result from ETV as the field cannot rely on case studies and anecdotal evidence alone.

Summary

iNPH negatively impacts neurocognitive, emotional, and adaptive functioning. While heterogeneous, the neurocognitive profile associated with adult-onset iNPH is often characterized by significant executive, especially attention, impairment resulting in learning and/or retrieval deficits. In addition, language, spatial, and motor inefficiencies are seen. The visuospatial and language deficits appear to be secondary to executive dysfunction and characterized by reduced command of semantics, speeded fluency, and planning. Rarely is rapid forgetting, anomia or apraxia seen early in the disease presentation. Frontally mediated internalizing symptoms are prominent, especially apathy, anxiety, and depression. Traditional intervention appears to improve cognition, albeit identifying ideal candidates remains elusive due to diagnostic uncertainty, comorbidities and

mediators of change over time in this older cohort. Accumulating longitudinal studies indicate significant aversive impact on cognition if untreated, and improvement, at least briefly, in quality of life following intervention in highly selected patients.

Future research using a standardized unified battery may allow for better predictors of positive cognitive outcomes across studies. Emerging CSF biomarkers and imaging techniques combined with neurocognitive assessment appear promising in identifying ideal surgical candidates. Studies focused on prognostic predictors of cognitive stability or improvement must include uniformed batteries, larger sample sizes, advanced imaging tools, and pathology data. Ongoing psychoeducation of patients, caregivers and physicians regarding early intervention will allow more timely treatment(s), which may improve prognostic abilities and rehabilitation success. Available local resources may vary by geographic location, but we suggest the following print and online resources as starting points for clinicians and parents:

Print Resources

Mohanty, A. (2012). *100 questions and answers about hydrocephalus.* Jones & Bartlett Learning, LLC: Burlington, MA. ISBN:978-0763779900

Mednick, A.S. (2013). *Normal Pressure Hydrocephalus: From diagnosis to treatment*. Addicus Books, Inc.: Omaha, NB. ISBN:978-1-936374-96-0

West, W. & West, E. (2017). *Willow's last surgery: A journey with hydrocephalus*. Create Space independent Publishing Platform. ISBN: 978-1547164912

Online Resources

Hydrocephalus Association: https://www.hydroassoc.org

National Hydrocephalus Foundation: http://nhfonline.org

Pediatric Hydrocephalus Foundation: http://www.hydrocephaluskids.org/wordpress

NIH National institute of Neurological Disorders and Stroke, Hydrocephalus Fact Sheet: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Hydrocephalus-Fact-Sheet

Hydrocephalus Clinical Research Network: http://hcrn.org.

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References

1. Rekate HL. The definition and classification of hydrocephalus: a personal recommendation to stimulate debate. Cerebrospinal Fluid Res. 2008;5:2.
2. Tully HM, Dobyns WB. Infantile hydrocephalus: a review of epidemiology, classification and causes. Eur J Med Genet. 2014;57(8):359–68.
3. Blumenfeld H. Neuroanatomy through clinical cases. Sinauer Assoc. 2010.
4. Dandy WE, Blackfan KD. An experimental and clinical study of internal hydrocephalus. J Am Med Assoc. 2010;61(25):2216–17.
5. Verhagen JM, Schrander-Stumpel CT, Krapels IP, et al. Congenital hydrocephalus in clinical practice: a genetic diagnostic approach. Eur J Med Genet. 2011;54(6):e542–7.
6. Schrander-Stumpel C, Fryns JP. Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. Eur J Pediatr. 1998;157(5):355–62.
7. Hommet C, Billard C, Gillet P, et al. Neuropsychologic and adaptive functioning in adolescents and young adults shunted for congenital hydrocephalus. J Child Neurol. 1999;14(3):144–50.
8. Garton HJ, Piatt JH Jr. Hydrocephalus. Pediatr Clin North Am. 2004;51(2):305–25.
9. Dennis M, Landry SH, Barnes M, Fletcher JM. A model of neurocognitive function in spina bifida over the life span. J Int Neuropsychol Soc. 2006;12(2):285–96.
10. Munch TN, Rostgaard K, Rasmussen ML, Wohlfahrt J, Juhler M, Melbye M. Familial aggregation of congenital hydrocephalus in a nationwide cohort. Brain. 2012;135(Pt 8):2409–15.
11. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010;67(1):1–8.
12. Dennis M, Fitz CR, Netley CT, et al. The intelligence of hydrocephalic children. Arch Neurol. 1981;38(10):607–15.
13. Chisholm BT, Velamoor R, Chandarana PC, Cochrane DK. Anxiety disorder in a case of Arnold-Chiari malformation. J Psychiatry Neurosci. 1993;18:67–8.
14. Rogers JM, Savage G, Stoodley MA. A Systematic review of cognition in Chiari I malformation.

Neuropsychol Rev. 2018. https://doi.org/10.1007/s11065-018-9368-6.
15. Grosso S, Scattolini R, Paolo G, Di Bartolo RM, Morgese G, Balestri P. Association of Chiari I malformation, mental retardation, speech delay and epilepsy: a specific disorder? Neurosurgery. 2001;49:1109–1103.
16. Fox RJ, Walji AH, Mielke B, Petruk KC, Aronyk KE. Anatomic details of intradural channels in the parasagittal dura: a possible pathway for flow of cerebrospinal fluid. Neurosurgery. 1996;39 (1):84–90; discussion 90–81.
17. Limbrick DD Jr, Baksh B, Morgan CD, et al. Cerebrospinal fluid biomarkers of infantile congenital hydrocephalus. PLoS ONE. 2017;12(2): e0172353.
18. Lindquist B, Persson EK, Uvebrant P, Carlsson G. Learning, memory and executive functions in children with hydrocephalus. Acta Paediatr. 2008;97(5):596–601.
19. Laurence KM. The natural history of hydrocephalus. Lancet. 1958;2(7057):1152–4.
20. Laurence KM, Coates S. The natural history of hydrocephalus. Detailed analysis of 182 unoperated cases. Arch Dis Child. 1962;37:345–62.
21. Lacy M, Pyykkonen BA, Hunter SJ, et al. Intellectual functioning in children with early shunted posthemorrhagic hydrocephalus. Pediatr Neurosurg. 2008;44(5):376–81.
22. Takahashi Y. Long-term outcome and neurologic development after endoscopic third ventriculostomy versus shunting during infancy. Child's Nervous System. 2006;22(12):1591–602.
23. Lindquist B, Uvebrant P, Rehn E, Carlsson G. Cognitive functions in children with myelomeningocele without hydrocephalus. Childs Nerv Syst. 2009;25(8):969–75.
24. Dalen K, Bruaroy S, Wentzel-Larsen T, Laegreid LM. Intelligence in children with hydrocephalus, aged 4-15 years: a population-based, controlled study. Neuropediatrics. 2008;39(3):146–50.
25. Donders J, Canady AI, Rourke BP. Psychometric intelligence after infantile hydrocephalus. A critical review and reinterpretation. Childs Nerv Syst. 1990;6(3):148–54.
26. Fletcher JM, Francis DJ, Thompson NM, Davidson KC, Miner ME. Verbal and nonverbal skill discrepancies in hydrocephalic children. J Clin Exp Neuropsychol. 1992;14(4):593–609.
27. Hasan KM, Sankar A, Halphen C, et al. Quantitative diffusion tensor imaging and intellectual outcomes in spina bifida: laboratory investigation. J Neurosurg Pediatr. 2008;2(1):75–82.
28. Dennis M, Jewell D, Drake J, et al. Prospective, declarative, and nondeclarative memory in young adults with spina bifida. J Int Neuropsychol Soc. 2007;13(2):312–23.
29. Horn DG, Lorch EP, Lorch RF Jr, Culatta B. Distractibility and vocabulary deficits in children with spina bifida and hydrocephalus. Dev Med Child Neurol. 1985;27(6):713–20.
30. Tew B, Laurence KM, Richards A. Inattention among children with hydrocephalus and Spina Bifida. Eur J Pediatr Surg. 1980;31(12):381–6.
31. Dennis M, Edelstein K, Hetherington R, et al. Neurobiology of perceptual and motor timing in children with spina bifida in relation to cerebellar volume. Brain. 2004;127(Pt 6):1292–301.
32. Dennis M, Edelstein K, Copeland K, et al. Space-based inhibition of return in children with spina bifida. Neuropsychology. 2005;19(4):456–65.
33. Brewer VR, Fletcher JM, Hiscock M, Davidson KC. Attention processes in children with shunted hydrocephalus versus attention deficit-hyperactivity disorder. Neuropsychology. 2001;15(2):185–98.
34. Burmeister R, Hannay HJ, Copeland K, Fletcher JM, Boudousquie A, Dennis M. Attention problems and executive functions in children with spina bifida and hydrocephalus. Child Neuropsychol. 2005;11(3):265–83.
35. Ries J, Zabel TA, Mahone EM. Parent report of adaptive abilities and executive functioning in children and adolescents with myelomeningocele and hydrocephalus. Arch Clin Neuropsych. 2003;18 (7):762.
36. Tarazi RA, Zabel TA, Mahone EM. Age-related differences in executive function among children with spina bifida/hydrocephalus based on parent behavior ratings. Clin Neuropsychol. 2008;22(4):585–602.
37. Matson MA, Mahone EM, Zabel TA. Serial neuropsychological assessment and evidence of shunt malfunction in spina bifida: a longitudinal case study. Child Neuropsychol. 2005;11(4):315–32.
38. Anderson VA, Anderson P, Northam E, Jacobs R, Mikiewicz O. Relationships Between Cognitive and Behavioral Measures of Executive Function in Children With Brain Disease. Child Neuropsychol. 2002;8(4):231–40.
39. Zielinska D, Rajtar-Zembaty A, Starowicz-Filip A. Cognitive disorders in children's hydrocephalus. Neurol Neurochir Pol. 2017;51(3):234–9.
40. Yeates KO, Fletcher JM, Dennos M. Spina Bifida and Hydrocephalus. In: Morgan JE, Richer JH, eds. Textbook of Clinical Neuropsychology. New York Taylor & Francis; 2008.
41. Iddon JL, Morgan DJR, Loveday C, Sahakian BJ, Pickard JD. Neuropsychological profile of young adults with spina bifida with or without hydrocephalus. J Neurol Neurosurg Psychiatry. 2004;75 (8):1112–8.
42. Yeates KO, Enrile BG. Implicit and explicit memory in children with congenital and acquired brain disorder. Neuropsychology. 2005;19(5):618–28.
43. Scott MA, Fletcher JM, Brookshire BL, et al. Memory functions in children with early hydrocephalus. Neuropsychology. 1998;12(4):578–89.
44. Mataro M, Poca MA, Sahuquillo J, et al. Cognitive changes after cerebrospinal fluid shunting in young

adults with spina bifida and assumed arrested hydrocephalus. J Neurol Neurosurg Psychiatry. 2000;68(5):615–21.
45. Tew B, Laurence KM. The clinical and psychological characteristics of children with the "cocktail party" syndrome. Zeitschrift fur Kinderchirurgie und Grenzgebiete. 1979;28(4):360–7.
46. Hurley AD, Dorman C, Laatsch L, Bell S, D'Avignon J. Cognitive functioning in patients with spina bifida, hydrocephalus, and the "cocktail party" syndrome. Developmental Neuropsychology. 1990;6(2):151–72.
47. Erickson K, Baron IS, Fantie BD. Neuropsychological Functioning in Early Hydrocephalus: Review From a Developmental Perspective. Child Neuropsychol. 2001;7(4):199–229.
48. Donders J, Rourke BP, Canady AI. Neuropsychological functioning of hydrocephalic children. J Clin Exp Neuropsychol. 1991;13(4):607–13.
49. Dennis M, Jacennik B, Barnes MA. The content of narrative discourse in children and adolescents after early-onset hydrocephalus and in normally developing age peers. Brain Lang. 1994;46(1):129–65.
50. Culatta B, Young C. Linguistic performance as a function of abstract task demands in children with spina bifida. Dev Med Child Neurol. 1992;34 (5):434–40.
51. Brookshire BL, Fletcher JM, Bohan TP, Landry SH, Davidson KC, Francis DJ. Specific language deficiencies in children with early onset hydrocephalus. Child Neuropsychol. 1995;1(2):106–17.
52. Barnes MA, Dennis M. Discourse after early-onset hydrocephalus: core deficits in children of average intelligence. Brain Lang. 1998;61(3):309–34.
53. Barnes M, Dennis M, Hetherington R. Reading and writing skills in young adults with spina bifida and hydrocephalus. J Int Neuropsychol Soc. 2004;10 (5):655–63.
54. Barnes MA, Faulkner HJ, Dennis M. Poor reading comprehension despite fast word decoding in children with hydrocephalus. Brain Lang. 2001;76 (1):35–44.
55. Vachha B, Adams R. Language differences in young children with myelomeningocele and shunted hydrocephalus. Pediatr Neurosurg. 2003;39(4):184–9.
56. Barnes MA, Dennis M. Reading in children and adolescents after early onset hydrocephalus and in normally developing age peers: phonological analysis, word recognition, word comprehension, and passage comprehension skill. J Pediatr Psychol. 1992;17(4):445–65.
57. Beebe DW, Ris MD, Brown TM, Dietrich KN. Executive Functioning and Memory for the Rey-Osterreith Complex Figure Task Among Community Adolescents. Applied Neuropsychology. 2004;11(2):91–8.
58. Houliston MJ, Taguri AH, Dutton GN, Hajivassiliou C, Young DG. Evidence of cognitive visual problems in children with hydrocephalus: a structured clinical history-taking strategy. Dev Med Child Neurol. 1999;41(5):298–306.
59. Thompson NM, Fletcher JM, Chapieski L, Landry SH, Miner ME, Bixby J. Cognitive and motor abilities in preschool hydrocephalics. J Clin Exp Neuropsychol. 1991;13(2):245–58.
60. Fletcher JM, Brookshire BL, Landry SH, et al. Behavioral adjustment of children with hydrocephalus: relationships with etiology, neurological, and family status. J Pediatr Psychol. 1995;20 (1):109–25.
61. Pikus HJ, Levy ML, Gans W, Mendel E, McComb JG. Outcome, cost analysis, and long-term follow-up in preterm infants with massive grade IV germinal matrix hemorrhage and progressive hydrocephalus. Neurosurgery. 1997;40(5):983–8; discussion 988–989.
62. Fennell EB, Eisenstadt T, Bodiford C, Rediess S, Mickle J. The Assessment of Neuropsychological Dysfunction in Children Shunted for Hydrocephalus. J Clin Exp Neuropsyc. 1987;9(1):25–6.
63. Shaffer J, Wolfe L, Friedrich W, Shurtleff H, Shurtleff D, Fay G. Developmental expectations: intelligence and fine motor skills. Myelodysplasias and exstrophies: significance, prevention, and treatment. 1986:359–372.
64. Brunt D. Characteristics of Upper Limb Movements in a Sample of Meningomyelocele Children. Percept Mot Skills. 1980;51(2):431–7.
65. Hetherington R, Dennis M. Motor function profile in children with early onset hydrocephalus. Developmental Neuropsychology. 1999;15(1):25–51.
66. Wallace SJ. The effect of upper-limb function on mobility of children with myelomeningocele. Dev Med Child Neurol Suppl. 1973; Suppl 29:84–91.
67. Shawkat FS, Kingsley D, Kendall B, Russell-Eggitt I, Taylor DSI, Harris CM. Neuroradiological and Eye Movement Correlates in Children with Intermittent Saccade Failure: "Ocular Motor Apraxia". Neuropediatrics. 1995;26(06):298–305.
68. Mazur JM, Aylward GP, Colliver J, Stacey J, Menelaus M. Impaired mental capabilities and hand function in myelomeningocele patients. Z Kinderchir. 1988;43(Suppl 2):24–7.
69. Anderson EM, Plewis I. Impairment of a motor skill in children with spina bifida cystica and hydrocephalus: an exploratory study. Br J Psychol. 1977;68(1):61–70.
70. Volpe JJ. Intraventricular hemorrhage in the premature infant–current concepts. Part I. Ann Neurol. 1989;25(1):3–11.
71. Haskell SH. The education of children with physical and neurological disabilities/ Simon H. Haskell and Elizabeth K. Barrett. London; Melbourne: Chapman and Hall; 1993.
72. Connell HM, McConnel TS. Psychiatric sequelae in children treated operatively for hydrocephalus in infancy. Dev Med Child Neurol. 1981;23 (4):505–17.

73. Donders J, Rourke BP, Canady AI. Emotional Adjustment of Children With Hydrocephalus and of Their Parents. J Child Neurol. 1992;7(4):375–80.
74. Lindquist B, Carlsson G, Persson EK, Uvebrant P. Behavioural problems and autism in children with hydrocephalus: a population-based study. Eur Child Adolesc Psychiatry. 2006;15 (4):214–9.
75. Gupta Nalin, Park Jeanna, Solomon Cynthia, Kranz Dory A, Wrensch Margaret, Yvonne WWu. Long-term outcomes in patients with treated childhood hydrocephalus. Journal of Neurosurgery: Pediatrics. 2007;106(5):334–9.
76. Reynolds CR. Behavior Assessment System for Children. In: The Corsini Encyclopedia of Psychology. Wiley; 2010.
77. Paulsen AH, Lundar T, Lindegaard KF. Twenty-year outcome in young adults with childhood hydrocephalus: assessment of surgical outcome, work participation, and health-related quality of life. J Neurosurg Pediatr. 2010;6(6):527–35.
78. Dewan MC, Lim J, Shannon CN, Wellons JC III. The durability of endoscopic third ventriculostomy and ventriculoperitoneal shunts in children with hydrocephalus following posterior fossa tumor resection: a systematic review and time-to-failure analysis. Journal of Neurosurgery: Pediatrics. 2017;19(5):578–84.
79. Cheng H, Hong W, Mei Z, Wang X. Surgical management of non-communicating hydrocephalus in patients: meta-analysis and comparison of endoscopic third ventriculostomy and ventriculoperitoneal shunt. Journal of Craniofacial Surgery. 2015; 1;26(2):481–6.
80. Kulkarni AV, Cochrane DD, McNeely PD, et al. Medical, social, and economic factors associated with health-related quality of life in Canadian children with hydrocephalus. J Pediatr. 2008; 153:689–99.
81. Kulkarni AV, Hui S, Shams I, Donnelly R. Quality of life in obstructive hydrocephalus: endoscopic third ventriculostomy compared to cerebrospinal fluid shunt. Child's Nervous Syst. 2010;26(1):75.
82. Del Bigio MR, Wilson MJ, Enno T. Chronic hydrocephalus in rats and humans: white matter loss and behavior changes. Ann Neurol. 2003;53 (3):337–46.
83. Fletcher JM, Bohan TP, Brandt ME, et al. Morphometric evaluation of the hydrocephalic brain: relationships with cognitive development. Childs Nerv Syst. 1996;12(4):192–9.
84. Hommet C, Cottier JP, Billard C, et al. MRI morphometric study and correlation with cognitive functions in young adults shunted for congenital hydrocephalus related to spina bifida. Eur Neurol. 2002;47(3):169–74.
85. Kondziella D, Sonnewald U, Tullberg M, Wikkelso C. Brain metabolism in adult chronic hydrocephalus. J Neurochem. 2008;106(4):1515–24.
86. Martín-Láez R, Caballero-Arzapalo H, López-Menéndez L, Arango-Lasprilla JC, Vázquez-Barquero A. Epidemiology of idiopathic normal pressure hydrocephalus: a systematic review of the literature. World Neurosurg. 2015;84(6):2002–9.
87. Hakim CA, Hakim R, Hakim S. Normal-pressure hydrocephalus. Neurosurg Clin N Am. 2001;12 (4):761–773, ix.
88. Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. J Neurol Neurosurg Psychiatry. 2002;73 (4):390–4.
89. Brean A, Eide PK. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. Acta Neurol Scand. 2008;118(1):48–53.
90. Keong NC, Pena A, Price SJ, Czosnyka M, Czosnyka Z, Pickard JD. Imaging normal pressure hydrocephalus: theories, techniques, and challenges. Neurosurg Focus. 2016;41(3):E11.
91. Silverberg GD, Mayo M, Saul T, Fellmann J, Carvalho J, McGuire D. Continuous CSF drainage in AD: results of a double-blind, randomized, placebo-controlled study. Neurology. 2008;71 (3):202–9.
92. Espay AJ, Da Prat GA, Dwivedi AK, et al. Deconstructing normal pressure hydrocephalus: ventriculomegaly as early sign of neurodegeneration. Ann Neurol. 2017.
93. Sato H, Takahashi Y, Kimihira L, et al. A segmental copy number loss of the SFMBT1 gene is a genetic risk for shunt-responsive, idiopathic normal pressure hydrocephalus (iNPH): a case-control study. PLoS ONE. 2016;11(11):e0166615.
94. Huovinen J, Kastinen S, Komulainen S, et al. Familial idiopathic normal pressure hydrocephalus. J Neurol Sci. 2016;368:11–8.
95. Shprecher D, Schwalb J, Kurlan R. Normal pressure hydrocephalus: diagnosis and treatment. Curr Neurol Neurosci Rep. 2008;8(5):371–6.
96. Hellstrom P, Edsbagge M, Archer T, Tisell M, Tullberg M, Wikkelso C. The neuropsychology of patients with clinically diagnosed idiopathic normal pressure hydrocephalus. Neurosurgery. 2007;61 (6):1219–26; discussion 1227–1218.
97. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery.* 2005;57(3 Suppl): S4–16; discussion ii-v.
98. Hashimoto M, Ishikawa M, Mori E, Kuwana N. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010;7(1):18.
99. Tarnaris A, Stephenson RF, Cipolotti L. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery. 2007;60(1):E208; author reply E208.
100. Parkkola RK, Komu ME, Kotilainen EM, Valtonen SO, Thomsen C, Gideon P. Cerebrospinal fluid

flow in patients with dilated ventricles studied with MR imaging. Eur Radiol. 2000;10(9):1442–6.
101. McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery. 2005;57(4):699–705; discussion 699–705.
102. Hoza D, Vlasák A, Hořínek D, Sameš M, Alfieri A. DTI-MRI biomarkers in the search for normal pressure hydrocephalus aetiology: a review. Neurosurg Rev. 2015;38(2):239–44.
103. Tarnaris A, Williams MA. Idiopathic normal pressure hydrocephalus: update and practical approach on diagnosis and management. Neurosurgery Quarterly. 2011;21(1):72–81.
104. Jeppsson A, Zetterberg H, Blennow K, Wikkelsø C. Idiopathic normal-pressure hydrocephalus Pathophysiology and diagnosis by CSF biomarkers. Neurology. 2013;80(15):1385–92.
105. Bugalho P, Guimaraes J. Gait disturbance in normal pressure hydrocephalus: a clinical study. Parkinsonism Relat Disord. 2007;13(7):434–7.
106. Iddon JL, Pickard JD, Cross JJ, Griffiths PD, Czosnyka M, Sahakian BJ. Specific patterns of cognitive impairment in patients with idiopathic normal pressure hydrocephalus and Alzheimer's disease: a pilot study. J Neurol Neurosurg Psychiatry. 1999;67(6):723–32.
107. DeVito EE, Salmond CH, Owler BK, Sahakian BJ, Pickard JD. Caudate structural abnormalities in idiopathic normal pressure hydrocephalus. Acta Neurol Scand. 2007;116(5):328–32.
108. Azab WA, Mijalcic RM, Nakhi SB, Mohammad MH. Ventricular volume and neurocognitive outcome after endoscopic third ventriculostomy: is shunting a better option? A review. Child's Nervous System. 2016;32(5):775–80.
109. Picascia M, Minafra B, Zangaglia R, Gracardi L, Pozzi NG, Sinforiani E, Pacchetti C. Spectrum of cognitive disorders in idiopathic normal pressure hydrocephalus. Funct Neurol. 2016;31(3):143.
110. Donnet A, Schmitt A, Dufour H, Giorgi R, Grisoli F. Differential patterns of cognitive impairment in patients with aqueductal stenosis and normal pressure hydrocephalus. Acta Neurochir. 2004;146(12):1301–8.
111. Graff-Radford NR. Normal pressure hydrocephalus. *Neurol Clin.* 2007;25(3):809–832, vii-viii.
112. Savolainen S, Laakso MP, Paljarvi L, et al. MR imaging of the hippocampus in normal pressure hydrocephalus: correlations with cortical Alzheimer's disease confirmed by pathologic analysis. AJNR Am J Neuroradiol. 2000;21(2):409–14.
113. Golomb J, Wisoff J, Miller DC, et al. Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response. J Neurol Neurosurg Psychiatry. 2000;68(6):778–81.
114. Tisell M, Hellstrom P, Ahl-Borjesson G, et al. Long-term outcome in 109 adult patients operated on for hydrocephalus. Br J Neurosurg. 2006;20(4):214–21.
115. McGirt MJ, Woodworth G, Coon AL, Thomas G, Williams MA, Rigamonti D. Diagnosis, treatment, and analysis of long-term outcomes in idiopathic normal-pressure hydrocephalus. Neurosurgery. 2008;62(Suppl 2):670–7.
116. Peterson KA, Savulich G, Jackson D, Killikelly C, Pickard JD, Sahakian BJ. The effect of shunt surgery on neuropsychological performance in normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurol. 2016;263(8):1669–77.
117. Thomas G, McGirt MJ, Woodworth G, et al. Baseline neuropsychological profile and cognitive response to cerebrospinal fluid shunting for idiopathic normal pressure hydrocephalus. Dement Geriatr Cogn Disord. 2005;20(2–3):163–8.
118. Gleichgerrcht E, Cervio A, Salvat J, Loffredo AR, Vita L, Roca M, Manes F. Executive function improvement in normal pressure hydrocephalus following shunt surgery. Behavio Neurol. 21(3–4), 181–85.
119. Hellström P, Edsbagge M, Blomsterwall E, Archer T, Tisell M, Tullberg M, Wikkelsø C. Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus. Neurosurgery. 2008;63(3):527–36.
120. Meier U, Konig A, Miethke C. Predictors of outcome in patients with normal-pressure hydrocephalus. Eur Neurol. 2004;51(2):59–67.
121. Thompson SD, Smith JS, Khan AA, Luoma AMV, Toma AK, Watkins LD. Shunting of the over 80 s in normal pressure hydrocephalus. Acta Neurochir. 2017;159(6):987–94.
122. Attenello FJ, McGirt MJ, Garces-Ambrossi GL, Chaichana KL, Carson B, Jallo GI. Suboccipital decompression for Chiari I malformation: outcome comparison of duraplasty with expanded polytetrafluoroethylene dural substitute versus pericranial autograft. Childs Nerv Syst. 2009;25(2):183–90.
123. Foss T, Eide PK, Finset A. Intracranial pressure parameters in idiopathic normal pressure hydrocephalus patients with or without improvement of cognitive function after shunt treatment. Dement Geriatr Cogn Disord. 2007;23:47–54.
124. Tarnaris A, Kitchen ND, Watkins LD. Noninvasive biomarkers in normal pressure hydrocephalus: evidence for the role of neuroimaging. J Neurosurg. 2009;110(5):837–51.
125. Lenfeldt N, Larsson A, Nyberg L, et al. Idiopathic normal pressure hydrocephalus: increased supplementary motor activity accounts for improvement after CSF drainage. Brain. 2008;131(Pt 11):2904–12.
126. Andren K, Wikkelso C, Tisell M, Hellstrom P. Natural course of idiopathic normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry. 2014;85(7):806–10.
127. Junkkari A, Häyrinen A, Rauramaa T, Sintonen H, Nerg O, Koivisto AM, Roine RP, Viinamäki H,

Soininen H, Luikku A, Jääskeläinen JE. Health-related quality-of-life outcome in patients with idiopathic normal-pressure hydrocephalus–a 1-year follow-up study. Eur J Neurol. 2017;24(1):58–66.
128. Tullberg M, Persson J, Petersen J, Hellström P, Wikkelsø C, Lundgren-Nilsson Å. Shunt surgery in idiopathic normal pressure hydrocephalus is cost-effective—a cost utility analysis Acta Neurochirurgica. 2017; 1–10.
129. Gangemi M, Mascari C, Maiuri F, et al. Longterm outcomes of Endoscopic third ventriculostomy in obstructive hydrocephalus. Minim Invasive Neurosurg. 2007;50:265–9.
130. Jallo GI, Kothbauer KF, Abbott IR. Endoscopic third ventriculostomy. Neurosurg Focus. 2005;19(6):E11.
131. Mixter WJ. Ventriculoscopy and puncture of the floor of the third ventricle. Boston Med Surg J. 1923; 188:277.
132. Di Rocco C, Massimi L, Tamburrini G. Shunts vs endoscopic third ventriculostomy in infants: are there different types and/or rates of complication? Childs Nerv Sys. 2006;22:1573–89.
133. Farin A, Aryan HE, Ozgur BM, et al. Endoscopic third ventriculostomy. J Clin Neurosci. 2006;13(7):763–70.
134. Benabarre A, Ibanez J, Boget T, Obiols J, Martinez-Aran A, Vieta E. Neuropsychological and psychiatric complications in endoscopic third ventriculostomy: a clinical case report. J Neurol Neurosurg Psychiatry. 2001;71:268–71.
135. van Aalst J, Beusl EA, Luijckx GJ. Neuropsychological and psychiatric complications in endoscopic third ventriculostomy. J Neurol Neurosurg Psychiatry. 2002;73(4):460.
136. Bonanni R, Carlesimo GA, Caltagirone C. Amnesia following endoscopic third ventriculostomy: a single case study. Eur Neurol. 2004;51:118–20.
137. Oliveira M, Pyykkonen B, Lacy M, Larson ER, Hunter SJ, Mottlow D, Frim D. Cognitive outcome as a function of endoscopic third ventriculocisternostomy in hydrocephalus. 2007; Presentation at the 35th annual Meeting of the International Neuropsychological Society, Portland, Oregon.
138. Burtscher J, Bartha L, Twerdy K, Eisner W, Benke T. Effect of endoscopic third ventriculostomy on neuropsychological outcome in late onset idiopathic aqueduct stenosis: a prospective study. J Neurol Neurosurg Psychiatry. 2003;74:222–5.
139. Takahaski Y. Long-term outcome and neurologic development after endoscopic third ventriculostomy versus shunting during infancy. Childs Nerv Sys. 2006;22(12):1591–602.
140. Rasul FT, Marcus HJ, Toma AK, Thorne L, Watkins LD. Is endoscopic third ventriculostomy superior to shunts in patients with non-communicating hydrocephalus? A systematic review and meta-analysis of the evidence. Acta Neurochir. 2013;155(5):883–9.

Chapter 15

Learning Disorders

Gayle K. Deutsch and Robert N. Davis

A specific learning disorder (LD) may be present when a child fails to develop adequate core academic skills, such as reading, writing, or calculation, despite adequate instruction and an absence of conditions that may account for the difficulties, such as intellectual disability [1]. The word "specific" in the term "specific learning disorder" indicates that the learning difficulty is not generalized; rather, it is specific to one or more core academic skills. In the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2], LDs are regarded as neurodevelopmental disorders. As such, they involve *inadequate development* of academic skills, rather than representing a *loss* of previously acquired function. Notably, brain lesions may certainly result in cognitive deficits that affect reading, writing, and calculation, but such acquired losses of academic skills would not be classified as specific learning disorders (for a review, see Heilman and Valenstein) [3]. Most research on LDs has involved children, which are the focus of this chapter. For a review of LDs in adults, the interested reader is referred to Mapou [4]. In this chapter, we will first present a conceptual overview of LDs and types of LDs. Second, we will offer recommendations on how to assess children who present with academic skill deficits. Third, we will cover some of the fundamental mechanisms involved in LDs that have been identified in neuropsychological and imaging studies. We will conclude by mentioning some recent interventions that appear promising for remediating academic skill deficits among children with LDs.

History and Background

LDs should be understood to represent unexpected underachievement in one or more areas of core academic skill [1]. The first part of this term, *unexpected*, means that one or more deficits in academic skills exist that would not have been anticipated given the child's history and present circumstances. For example, children with intellectual disability, blindness, or deafness would typically not be expected to achieve reading, writing, and calculation skills to the extent mastered by their unaffected peers. Similarly, a child who has not attended school regularly (for whatever reason), or who has lacked adequate instruction in core academic areas would also not be expected to demonstrate a typical level of achievement. Moreover, children with limited exposure to English should not be regarded as

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having a LD for this reason alone. Historically, a child's level of intellectual functioning (IQ score) was used as a standard to which his or her level of academic achievement was compared. A child of high average intelligence, for example, might be regarded as having a LD if he or she demonstrated reading abilities within the average or low average range. In other words, a certain level of academic achievement was expected based on the child's level of intellectual functioning; deviations from the expected level were regarded as evidence of LD. Often referred to as a discrepancy model of LD (IQ > academic achievement), this perspective is no longer considered valid for various reasons.

As reviewed extensively elsewhere [1, 5], an IQ-achievement disparity is neither necessary nor sufficient for an LD diagnosis. Briefly, children with IQ-achievement discrepancies do not appear to differ in a meaningful way from their low achieving peers (who lack such a discrepancy) with respect to cognitive or neurobiological correlates, genetic factors, etiology, course, or, perhaps most importantly, response to intervention [1]. Moreover, the use of cutoff and/or discrepancy scores is fraught with unreliability and measurement error. Thus, IQ-achievement discrepancy is no longer tenable as a way to conceptualize or identify LDs.

The DSM-5 correctly reflects this shift in thinking about the nature and diagnosis of LD over the past decade. Its predecessor, DSM-IV-TR, conceptualized LDs as "…when the individual's achievement on individually administered, standardized tests in reading, mathematics, or written expression is *substantially below* that expected for age, schooling, and *level of intelligence*" (emphasis added). Furthermore, "*Substantially below* is usually defined as a discrepancy of more than 2 standard deviations *between achievement and IQ*." By contrast, the description and criteria for LDs in DSM-5 makes no mention of the need for a discrepancy between IQ and achievement.

The second part of the term, *underachievement*, refers to the child's substandard mastery of core academic skills. A question then arises as to what constitutes underachievement: how low must performance be for it to be considered problematic? The answer to this question necessarily involves multiple considerations, including not only the magnitude of a child's subpar academic achievement but also consideration of available resources in the child's school environment. Some schools or districts may need to adopt more lenient or restrictive criteria. The DSM-5 describes the degree of underachievement as follows:

> The affected academic skills are substantially and quantifiably below those expected for the individual's chronological age, and cause significant interference with academic or occupational performance, or with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment.

The DSM-5 criteria do not mandate a specific cut score, although they do offer some guidelines:

> Academic skills are distributed along a continuum, so there is no natural cutpoint that can be used to differentiate individuals with and without specific learning disorder. Thus, any threshold used to specify what constitutes significantly low academic achievement (e.g., academic skills well below age expectation) is to a large extent arbitrary. Low achievement scores on one or more standardized tests or subtests within an academic domain (i.e., at least 1.5 standard deviations [SD] below the population mean for age, which translates to a standard score of 78 or less, which is below the 7th percentile) are needed for the greatest diagnostic certainty. However, precise scores will vary according to the particular standardized tests that are used. On the basis of clinical judgment, a more lenient threshold may be used (e.g., 1.0–2.5 SD below the population mean for age), when learning difficulties are supported by converging evidence from clinical assessment, academic history, school reports, or test scores.

Underachievement may be inferred not only from formal test scores, but also from data such as work samples, school grades, and academic history. Additionally, other potential causes of underachievement must be ruled out in order for LD to be diagnosed (which refers back to the "unexpected" portion of the conceptual definition). Although the DSM-5 does not limit the diagnosis to individuals with an IQ-achievement discrepancy, it does exclude high IQ individuals with average achievement scores.

The DSM-5 criteria reflect the known comorbidity of LDs and then separate out the components of reading, math, and written expression. Reading LD co-occurs with math and spelling LD with rates of 11–70% [6]. LDs also co-occur with other conditions, such as ADHD with rates of 30–50% [7].

While psychologists use the DSM-5 to diagnose LD, the reader should be aware of educational definitions and guidelines. According to U.S. federal special education law, the Individuals with Disabilities Education Act (IDEA) defines **specific learning disability as**:

> …a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which disorder may manifest itself in the imperfect ability to listen, think, speak, read, write, spell or do mathematical calculations. Such term includes such conditions as perceptual disabilities, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia. Such term does not include learning problem that is primarily the result of visual, hearing or motor disabilities of mental retardation (now known as intellectual disability), of emotional disturbance, or of environmental, cultural or economic disadvantage.

There are three federal laws that protect individuals with LD.

(1) Individuals with Disabilities Education Act 2004 (IDEA) and the IDE Improvement Act (IDEIA). IDEA has its own procedures for identifying a specific learning disability for the purpose of establishing guidelines for receiving special education services. IDEIA specifies eight areas of achievement and allows for greater flexibility in identifying a LD. It does not require the use of an ability-achievement discrepancy but does permit the use of a child's response to "scientific, research-based interventions" and does permit "other alternative research-based procedures." This information can be found at https://sites.ed.gov/idea.
(2) Section 504 of the Rehabilitation Act of 1973 (Section 504). This applies to some children with LD who need only accommodations and modifications. It is important to note that all students eligible for special education services under IDEA are also eligible under Section 504, but the reverse is not true.
(3) The Americans with Disabilities Act (ADA) is a law that protects individuals with disabilities from discrimination in schools, workplace, and other environments.

Although there are federal laws, it is important to be aware of the state laws where one is practicing. Each state has its own laws for defining special education eligibility requirements. Additionally, under the state, at the local level and further down at the school district level, there can be differences in interpretation of what constitutes a LD designation and what services can be provided based on certain diagnoses. The reader may wish to explore the website http://statelaws.findlaw.com for more information.

The Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) Technical and Interpretive Manual explains the Pattern of Strengths and Weaknesses Discrepancy Analysis (PSW) that is allowed under IDEIA as an alternative research-based procedure [8].

Prevalence Rates of LD

Estimates of the prevalence of LDs vary according to the criteria by which they are defined. The problems that have occurred due to a lack of a clinical consensus in defining what constitutes a LD have also been a factor in operationalizing the presence of LD in epidemiological studies. Additionally, in some studies, LDs are considered as a disorder category and are not fractionated by type. At a very general level, the 2003 National Survey of Children's Health reported an 9.7% lifetime prevalence of LD among children 3–17 years of age [9]. In this study, lifetime prevalence of LD was measured by a survey question: "Has a doctor, health professional, teacher or school official ever told you [name of child] has a learning disorder?" Lifetime prevalence rates differed by sex: 12.2% of boys were reported to have a LD compared to 7.1% of girls [10]. An obvious weakness of this

study is that LDs were operationalized as a survey question in a parent interview. Nonetheless, this study involved 36,579 households in the United States and 12,424 children, thereby reaching a level of population representativeness that is usually impossible except in studies of this scope. In an analysis of data from the preceding survey year (2003), correlates of LD included living in a household with lower education, male gender, increasing age, speaking English as a primary language, living in poverty, parental unemployment, being adopted, presence of a smoker, living in a 2-parent stepfamily situation, higher parental aggravation, and not discussing ideas with the child calmly [10].

Another approach is to examine data on children who receive special education services under Individuals with Disabilities in Education Act IDEA. The most recent available data (2014–2015 school year) show that 4.5% of children in the United States received services due to an LD [11]. This represents a decline of about 2% annually since 2002, which may reflect changes in the diagnostic criteria used, an increase in early childhood education, improvements in reading instruction, and the changes in IDEA 2004 that call for the use of RTI. Despite the noted decline, the National Center for Learning Disabilities estimated that an additional 15% or more of students struggle because their learning and attention problems have not been identified. It should be noted that this value (4.5%) represents a point prevalence figure, i.e., the percentage of children identified as LD and receiving services under IDEA, as contrasted with the lifetime prevalence data reported above in the 2003 National Survey of Children's Health, which is understandably higher.

Prevalence estimates for specific LD types are difficult to summarize succinctly, as various methods for defining the types have been used. It may be stated with reasonable confidence that dyslexia is the most common type of LD. Prevalence rates range from 5 to 12% of school-age children [12–14], and dyslexia affects approximately 80% of children identified as having an LD [15]. These figures are derived almost exclusively from studies of word reading difficulties, as opposed to deficits in reading fluency and/or comprehension. At the present time, no specific prevalence estimates of deficits in reading fluency or comprehension (apart from word-level reading difficulties) are available [1]. Epidemiological studies suggest that males are 1.5–2 times as likely as females to have dyslexia [16].

Math LDs have been found to be present in approximately 1.3–10.3% with a mean estimate of about 5–6% of children. Although there are specific genetic disorders that are more frequent in girls compared to boys, such as Fragile X syndrome and Turner syndrome, gender ratios of normally developing children do not consistently show either a male or female predominance in math LDs [17].

Data are more limited regarding the prevalence of written expression LDs. Cumulative incidence rates ranged from 6.9 to 14.7% depending on which type of research criteria were used to define LD [18]. The three criteria used in a population-based, retrospective birth cohort study that included 5718 children were: (1) a regression-based discrepancy, (2) a non-regression-based discrepancy and (3) low achievement. The low achievement criteria were associated with a larger incidence of LD. They also found that boys were 2–3 times more likely to be affected than girls and gender differences were not dependent on the research criteria used. The gender finders were consistent with a previous study [19].

To this point, we have only discussed LDs in their simplest form, i.e., free from comorbidity with medical and mental health conditions that may adversely affect academic functioning. The neuropsychologist practicing in a medical setting is likely to encounter individuals with diseases affecting the central nervous system (e.g., epilepsy), and who have deficits in academic skills in association with their underlying condition. We believe that a clinical neuropsychologist remains the most appropriate professional to assess the cognitive functioning, including academic skills, of individuals with known or suspected disorders of the central nervous system. It is unlikely that school personnel will have the necessary knowledge of medical conditions and brain functioning to conduct an appropriate evaluation. Moreover, such cases are necessarily

more complicated since the child's academic skill deficits are likely secondary to acquired brain dysfunction–a disease affecting the brain, as opposed to the developmentally based substrate of a typical LD.

Evaluating Children Suspected of LD

We now turn to discussing assessment strategies for the five types of LD that have been identified in empirical research. Three of the types involve reading deficits (word recognition, reading fluency, and reading comprehension). The fourth type involves individuals who struggle with mathematics, including calculation and applied mathematical problem-solving (e.g., story problems). The fifth type involves children who have significant difficulty with written expression, including spelling, handwriting, and written composition [1].

In the context of outpatient neuropsychological evaluation, direct assessment of the academic domains of interest forms the core of the test battery for identification of child at risk for LD. Children with academic achievement problems and a known and/or suspected medical condition affecting cognitive functioning may benefit from a comprehensive neuropsychological evaluation in addition to specific measures of academic achievement. Even if the findings from the neuropsychological portion of the evaluation do not clearly inform the academic issues, such findings may be utilized to understand potential dysfunction of the child's brain. In the case of epilepsy, for example, findings of modality-specific deficits may be helpful for lateralizing the epileptic focus to one cerebral hemisphere. Moreover, findings of academic skill deficits may have implications for inferences regarding lateralized brain dysfunction in epilepsy patients. In one study, for example, epilepsy patients with comorbid reading deficits showed equivalent reductions in verbal and nonverbal memory, regardless of side of seizure onset [20].

At a bare minimum, the individual's level of academic skill should be assessed in each of the five domains identified in the LD literature. The test battery should include measures of word reading, reading fluency, reading comprehension, mathematics, and spelling. There are numerous commercially available test batteries that will satisfy this criterion. We generally prefer the following tests from the Woodcock–Johnson Tests of Achievement – Fourth Edition (WJ-IV) [21]. Another popular achievement battery is the Wechsler Individual Achievement Test – Third Edition (WIAT-IIII) [22].

There are some advantages to using the WJ-IV instead of the WIAT-III. First, the WJ-IV normative sample (n = 7,416) is more than twice the size as the WIAT-III normative sample (n = 3,000). Second, the WJ-IV may be used with individuals ranging in age from 2 to 90 + years (vs. 4–50 years for the WIAT-III). Third, the WJ-IV has three alternate forms whereas the WIAT-III has only a single form. Fourth, we have found the WJ-IV to be faster, and thus less onerous for the child, and easier to administer than the WIAT-III. Fifth, the two batteries compare favorably in terms of psychometric properties, with any major disparities favoring the WJ-IV. The WIAT-III, however, has a better reading comprehension measure, as Passage Comprehension from the WJ-IV is based on the "cloze method" and only requires a single word

Academic skill	WJ-IV test	WIAT-IIII alternate
Oral word reading	Letter-Word identification	Word reading
Reading fluency	Sentence reading fluency oral reading	Oral reading fluency
Reading comprehension	Passage comprehension	Reading comprehension
Calculation	Calculation	Numerical operations
Spelling	Spelling	Spelling
Phonological decoding of print	Word attack	Pseudoword decoding

response. The single word response is more vulnerable to guessing and may not represent the child's true understanding of the text.

In addition to the tests listed above, it is important to include Writing Samples, Applied Problems, and Oral Comprehension from the WJ-IV when possible. Writing Samples provides a more thorough assessment of handwriting and quality of written expression than Spelling alone offers. Applied Problems can be helpful to assess the child's mastery of applied mathematical reasoning. Oral Comprehension is very similar to Passage Comprehension in its processing demands, but all input occurs through the auditory (rather than visual) modality. Better performance on Oral Comprehension than Passage Comprehension would be expected in cases of dyslexia and may be helpful to suggest academic accommodations. Similarly, the three fluency subtests of the WJ-IV (Sentence Reading Fluency, Math Facts Fluency, and Writing Fluency), which collectively form an Academic Fluency composite, may be useful to administer and compare to their untimed counterparts (Letter-Word Identification, Calculation, and Spelling) that collectively form an Academic Skills composite. In cases where the need may exist to suggest extended time on testing, a significant disparity between these two composite scores (Academic Fluency < Academic Skills) provides potentially relevant evidence.

In the case of an individual attending high school or college, a more extensive measure of reading comprehension is desirable, and will likely be necessary should the individual wish to apply for accommodations on tests such as the Scholastic Aptitude Test (SAT). We have found the Nelson–Denny Reading Test (NDRT) [23] to be most suitable for this purpose. Determination of eligibility for extended time on standardized tests often requires evidence that the individual is disproportionately hindered under standard time constraints. Thus, administration of the NDRT Reading Comprehension Test under both standard and extended time formats provides a direct test of this issue. We would recommend using alternate forms for this comparison. For example, one might administer Form G in standard format early in the test session, and then administer Form H in extended time format toward the end of the test session, or even on a separate day.

Depending on the LD being assessed, other tests that examine academic achievement include the Comprehensive Test of Phonological Processing-2nd Edition (CTOPP-2) [24], the Gray Oral Reading Test-5th Edition (GORT-5) [25], the Test of Written Language-4th Edition (TOWL-4) [26], and KeyMath™-3 Diagnostic Assessment [27] and may be considered.

Performance Validity

It has become increasingly apparent over the past decade that children and adolescents do not always put forth adequate or consistent effort during neuropsychological evaluations [28]. Reports from several series of cases have yielded an estimated prevalence rate of 3–5% among pediatric populations for noncredible presentation [29], with rates as high as 15% among a sample of post-secondary students undergoing LD evaluation [30]. Simulator studies have demonstrated that LD is easy to feign [31]. As such, it has been argued that clinicians should routinely include performance validity tests (PVTs) in their pediatric evaluations, including in cases of suspected LD [32]. Children and adolescents may feign a specific LD in order to gain test accommodations, or their parents may be involved in manipulating them to perform in a manner favorable to a diagnosis or test accommodations. In fact, about 10 years ago, a child's parent asked one of the authors (R.D.) to report lower scores than the child had actually produced in order for the child to qualify for special education services at school. There are also less severe, but nevertheless important, cases in which the child and/or his/her parents have no clearly nefarious intentions, but the child simply is not engaged sufficiently in the testing process to produce reliable data [32]. We agree with these authors' position on the importance of performance validity assessment and recommend

the routine use of performance validity testing in one's pediatric evaluations, including cases of known or suspected LD.

The three most extensively researched PVTs in the pediatric population are the Test of Memory Malingering (TOMM) [33], Word Memory Test (WMT) [34], and Medical Symptom Validity Test (MSVT) [35]. The WMT and MSVT require a third-grade reading level when administered in the standard manner on computer, and may be less useful in very young or very impaired children [28]. The TOMM consists entirely of pictorial stimuli, which may make it less vulnerable to confounding due to extremely low reading abilities. However, it appears to be less sensitive to feigning than the WMT or MSVT [29].

We recommend inclusion of at least one free-standing PVT in evaluations of children and adolescents suspected of LD. However, as with adults, additional sources of data should be considered in determining the presence of credible vs. noncredible test performance, including (1) discrepancies between school records and test performance, parent report, or direct observation, and (2) patterns of performance and their consistency with known profiles among individuals with LD. Embedded measures also have the potential to shed light on the credibility of data in pediatric populations, though additional research is needed.

Biological and Neuropsychological Mechanisms

As with all of the LD literature, there is more information known about reading LDs than math and written expression. In the past five to ten years, however, there has been considerable growth in the number of studies focusing on math LDs. This section of the chapter will present information across the LDs but will reflect this disparity. As stated above, there is also comorbidity among the LDs and the disrupted component processes that contribute to LDs. Thus, it is important to consider these relationships when examining the complex and multifactorial neurobiological underpinnings of LDs.

Behavioral and Molecular Genetic Influences

Heritability, environmental, and molecular genetic studies reflect the complexity of multiple genes and environmental risk factors in LD. Estimates from family aggregation studies and twin studies attest to the heritability of LDs. In general, heritability is approximately 0.50 for cognitive abilities [36]. The range of heritability estimates is 40–60% for reading LD [37] across most studies that involve middle and upper SES families but also in a diverse sample [38]. Sizeable heritability estimates have also been obtained for reading comprehension [23], and for measures related to reading fluency, such as rapid naming [24]. Heritability estimates for math range from 0.20 to 0.90 [39, 40]. Heritability estimates for spelling are 0.33–0.70 [41].

Heritability does not explain all of the variance in LDs. The environment plays a role, as well as the interplay between the environment and genes [42] For example, there is evidence that the heritability of reading LD increases as parental education increases [43], that children with reading LD or who are at risk for LD spend less time reading [44] and that parental literacy exposure may contribute to individual reading skill.

Based on targeted and genome-wide studies, reading LD has been linked to nine gene loci, which are abbreviated as DYX1-9, but not all studies have consistent findings [45]. Several candidate genes have also been identified but many of these studies have small effect sizes [37, 42].

There are only two known genome-wide association studies that examined math ability. [46, 47] There was no overlap between the two studies and each had relatively small sample sizes and small effect sizes. The first study found an association between single nucleotide polymorphisms (SNPs) and reading, cognitive ability,

and math skills in children. The second study found that the SNP with the strongest association to math ability had been previously linked to learning difficulties and autism.

Genetic studies of writing have been limited to those that examine spelling as a related cognitive process to dyslexia. One study found an association between a candidate gene for dyslexia, *DCDC2* and spelling [48]. A genome-wide study in Germany [49] found some evidence for an association between one of the known chromosomal risk genes and spelling.

Brain Mechanisms and Correlates of Reading LD

Though most children with LDs do not show overt evidence of brain damage using standard brain imaging techniques, and these measures have not been shown empirically to be diagnostic of LD, there is a growing body of research substantiating the neural mechanisms of LDs using functional and specialized structural brain imaging methods. While early theories regarding the neural basis of dyslexia, dyscalculia, and dysgraphia were based in lesion studies, [50–52] advances in technology have made it possible to investigate brain differences between individuals with and without LD and extend prior research. More recent studies have also attempted to disentangle the effects of experience and the development of compensatory networks from the underlying neurobiological etiology of LDs.

Reading is a complex skill that must be taught and requires phonological processing (i.e., sensitivity to the sound structure of words), orthographic processing (i.e., visual features of words), and semantic processing (i.e., meaning). Therefore, language systems and visual systems of the brain working interactively are needed for the development of reading. Most researchers agree that although developmental dyslexia is a heterogeneous disorder, there is now a consistent and broad area of research that shows a core deficit in developmental dyslexia involves phonological processing. The phonological processing deficit is based on the premise that individuals with dyslexia have impairment in the mental representations and/or processing of speech sounds. Whether it is the representations that are degraded or whether it is an access issue continues to be debated [53].

Rapid automatized naming (RAN) has a strong predictive relationship to reading skill [54]. Some, but not all children with a reading LD will show deficits in both phonological processing and RAN; others may show a deficit in only one area [55]. Whether RAN is dissociable from phonological processing has been another area of debate. Two recent studies have found a neurobiological distinction between RAN and phonological decoding [56, 57]. The first used voxel-based morphometry (VBM) in a large study of Chinese adult readers. Phonological decoding, measured by reading of pronounceable nonwords was related to gray matter volume in the left perisylvian region and naming speed was related to gray matter volume in a more widespread network across the cortex [56]. The second study showed activation in the left parietal region associated with phonological processing measured by reading elisions and blended words, and activation in the right cerebellum associated with RAN [57].

There are other theories regarding brain mechanisms contributing to dyslexia, including the magnocellular theory [58], temporal processing theory [59, 60], and the cerebellar theory [61–63]. With regard to the magnocellular theory there is more recent evidence that impaired visual motion processing may reflect differences in reading experience rather than being the cause of reading LD [64]. The longstanding temporal processing theory imputes a general defect in perceiving rapidly changing auditory signals. The cerebellar theory has shown that impaired motor control of articulation and of the automatization of grapheme-phoneme correspondence contribute to dyslexia.

A variety of functional and structural imaging methodologies, including functional magnetic resonance imaging (fMRI), positron emission topography (PET), VBM, diffusion tensor imaging (DTI), and related techniques such as event-related potentials (ERP) have shown

differences in activation patterns and brain structure, when comparing dyslexic and typically achieving children and adults, in an anterior left frontal region and two posterior left hemisphere regions. More specifically, the left inferior frontal gyrus (IFG; anterior), left temporal parietal, left occipital-temporal regions, and the pathways connecting these regions, mediate speech production, phonological awareness skills, and orthographic processing. These areas are necessary for the development of skilled reading based on studies of dyslexic and typically achieving readers [65].

The left IFG has been associated with articulation and naming [66], the left temporal parietal region with the integration of phonological processing and orthography [67, 68], and the left occipital-temporal regions with processing the visual features of letters and words [69, 70]. This latter area has been termed the visual word form area (VWFA), a part of the left fusiform gyrus, and is activated by visually but not acoustically presented words. It has been hypothesized that a shift occurs from bilateral ventral occipitotemporal cortex to a preponderance of left ventral occipitotemporal involvement in concert with reading development [70, 71].

Meta-analyses of cross-sectional studies comparing children and adults with and without dyslexia using PET and fMRI mostly show hypoactivation in left temporal, parietal, and VWFA regions during reading-related and phonological awareness tasks in both age-matched and reading-matched groups [72–75]. Less consistently, hyperactivation of the left inferior frontal and right hemisphere regions have been reported.

VBM is a method that makes voxel-by-voxel comparisons in the concentration of gray matter between two groups. Reduced gray matter volume in the left parietal region has been found to correspond to areas of reduced activation in participants with dyslexia relative to non-dyslexic participants. Reduced gray matter volumes have also been shown in the left parietotemporal, occipitotemporal areas, and fusiform and lingual gyri in children and adults with reading LD. This difference has also been shown in children who are pre-readers with a familial risk for reading LD [76, 77].

The gray matter findings corroborate the early work of Galaburda [78, 79]. Post-mortem microscopic analysis of brains of individuals with dyslexia revealed abnormalities in the form of ectopias, dyslaminations. Galaburda et al. [80]. extended their research to genetics and animal models that resulted in similar findings.

Diffusion tensor imaging (DTI), a type of structural MRI scan, allows measurement of white matter. For a review of white matter pathways in reading, see Ben-Shachar [81]. Studies looking specifically at white matter pathways using DTI have shown that the left temporoparietal region in children and adults [82–84] yields lower fractional anisotropy (FA) values among poor readers. In children, this area has been identified within the left inferior frontal gyrus [85, 86]. Research using DTI has shown associations between white matter integrity and phonological skills. Another study that traced fibers from the corpus callosum [87] was also consistent with the temporal processing theory of dyslexia, which purports that good readers are better at processing rapidly changing visual and auditory information [58, 88].

In summary, research has shown that reading is a complex skill that lateralizes to language-dominant hemisphere. Areas that are important to the reading network are the inferior frontal, superior and middle temporal, temporoparietal regions along with the VWFA.

Brain Mechanisms and Correlates of Math LD

Development of quantitative abilities includes an abstract sense of numbers and quantity, counting, and calculation, Unlike reading, which must be learned, humans are believed to be born with an innate sense for number estimation and simple calculations [89, 90]. However, there are also higher level math skills that require explicit teaching.

A core deficit in manipulation of quantity has been associated with math LD [91]. This includes problems with processing numerical quantity [92], "number sense," [93] making judgments about quantity and reasoning with symbolic representations of quantity [92, 94]. There are other theories for the etiology of math LDs, including (1) limitations in symbolic processing that limits automatic mapping of symbols to internal representations of size [95], (2) weaknesses in working memory, attention [96, 97], and fact retrieval [98], and (3) a combination of a deficit in the representation and manipulation of the internal number system along with an impairment in working memory and attention (i.e., termed "hybrid" model) [99].

Dehaene and colleagues [100, 101] have postulated that there are three parietal circuits that play a significant role in math skills, including number estimation, calculation, and counting. The three regions are the intraparietal sulcus (IPS) bilaterally, the left angular gyrus (AG), and the posterior superior parietal lobule (PSPL). Although some studies have found that prefrontal regions are involved in an ancillary role and are likely required for working memory [102, 103], the IPS has been shown to activate alone during number detection and number comparison tasks regardless of the modality [104, 105].

Studies with children, adults, and primates have shown that areas within the bilateral IPS are critical for number processing [106–108]. The IPS is activated when performing mental arithmetic (greater activation for subtraction versus multiplication) and number comparison (right hemisphere greater than left hemisphere). IPS activation appears to be specific for processing numbers compared to other categories of information even in subliminal conditions.

Activation of the left AG has been demonstrated in fMRI studies using tasks that require number processing and calculation and may be due to the AG's connections to reading and language systems. Dehaene et al. [101] hypothesize that the left AG contributes to the storing of arithmetic facts – rote arithmetic skills such as multiplication tables – but that it is unlike the IPS in that it does not mediate subtraction tasks, number comparisons, or number representation. Two studies have shown distinct sites along the left AG that subserve subtraction and multiplication in patients with lesions or impairments produced by cortical stimulation [109, 110]. Changes in activation patterns of the left AG have also been associated with math complexity [103].

Finally, the PSPL has shown activation during tasks requiring number comparison [110, 111] number estimation [112], subtraction [113], and counting [114]. This area has also been associated with mediation of visuospatial tasks, attention, eye orientation, and spatial working memory [111, 115].

Functional imaging studies investigating math LD in children and adults have shown either less activation in the IPS [91, 116] or increased IPS activity [117]. The increased activation was hypothesized to be a compensatory mechanism. A study using functional connectivity analyses, (i.e., fMRI that is not task dependent), in children with math LD found hyper-connectivity of the IPS with a bilateral front-parietal network [118].

In a study using VBM in children with math LD, significantly less gray matter volumes were found in the right IPS, anterior cingulum, left IFG, bilateral MFG, left frontoparietal lobe and right parahippocampal gyrus [119]. In another study with children, reduced gray matter volumes were found in the right IPS, fusiform gyrus, parahippocampal gyrus, right anterior temporal cortex, and hippocampi bilaterally [120].

White matter was examined in the same two studies. Reduction in white matter volume was found in the right parahippocampal gyrus [119]. In the second study, there were deficits in the microstructure and long-range white matter projection fibers between the right fusiform gyrus and the right temporoparietal cortex. They also found deficits in several long-range fiber tracts involving the inferior fronto-occipital fasciculus and inferior and superior longitudinal fasciculus [120].

Considered together these studies suggest that there is a distributed network of brain regions in the parietal, ventral temporal-occipital,

prefrontral, and medial temporal lobes that are needed for effective math processing [121–123].

Brain Mechanisms and Correlates of Writing LD

Spelling, composition, and handwriting are the skills needed for writing development [124]. There is less consensus regarding the identification of disorders of written expression compared to reading and math disorders, and many times writing LDs are included with other learning disabilities, particularly reading LD. An LD in writing involves difficulty in handwriting, spelling, and written expression [1]. Berninger [125] stated, "*The hallmark features of dysgraphia, a biologically based learning disability, are impaired orthographic coding and/or grapho-motor planning for sequential finger movements, which together function as the orthographic loop.*" Components of writing are related to reading (mapping of phonology to orthography), but writing is not the inverse of reading [126]. Berninger and colleagues have demonstrated this notion in their work examining the interrelationships of the development of language by eye and language by hand. Their approach to studying language assumes that language is composed of four functional systems in the brain (i.e., language by ear (aural), language by mouth (oral), language by eye (reading) and language by hand (writing). Through the use of structural equation modeling, outcomes of interventions, and functional brain imaging, they have shown that the language by eye and language by hand systems share processes but are distinct and separable skills [127]. Previously, our understanding of brain regions involved in writing was primarily based on lesion studies in individuals with acquired agraphia. There are now structural and functional imaging studies with and without individuals with writing LD, some while they are performing spelling or writing tasks.

Neuropsychological studies of focal brain lesions associated with writing impairments mostly implicated left perisylvian and left superior parietal regions [128]. These studies demonstrated that lesions to the left AG, posterior middle temporal gyrus, inferior temporal gyrus, and inferior occipitotemporal region produced lexical agraphia (greater difficulty spelling irregular words). Damage to the anterior supramarginal gyrus and/or the insula yielded phonological agraphia (greater difficulty spelling unfamiliar but pronounceable words or nonwords) [129, 130]. As Fletcher et al. [1] reported, it is not known whether these same locations were essential for the development of writing, or if they are compromised in individuals with developmental dysgraphia who also had writing problems.

Neuroimaging studies of writing production have shown left hemisphere activation but not in the left AG. Meta-analysis studies examining the results of PET and fMRI in healthy subject found activation in the left ventral occipitotemporal cortex, superior temporal gyrus intraparietal sulcus and inferior frontal gyrus [131]. The second study found significant activations in the superior frontal/sulcus/middle frontal gyrus area, left intraparietal sulcus/superior parietal area and right cerebellum. These were deemed "writing-specific" regions [132].

In an fMRI study of children with writing LD compared to healthy subjects, extensive differences were found across frontal, temporal-occipital and cerebellar regions for sequential finger movements [133]. A later fMRI study with writing pseudo- and real letters showed more widespread brain activation for poor versus good readers and also a correlation between brain activation in the left fusiform gyrus with behavioral writing measures [134]. A combined fMRI and DTI study in children with reading LD, writing LD and healthy controls focused on regions that had been shown to be associated with written word production; the left occipital-temporal gyrus, supramarginal gyrus, precuneus and inferior frontal gyrus [131]. The group with writing LD did not differ in resting state analyses but showed greater functional connectivity and less white matter integrity than the control group [135]. FA extending from the supramarginal gyrus and inferior frontal gyrus correlated with a spelling task. Differences

between the writing LD and reading LD groups were also found across methodologies and behavioral tasks. The finding of greater functional connectivity in writing and reading LD groups was hypothesized as an indicator of neural inefficiency or genetic mechanisms [135].

Treatment

Information regarding intervention programs for each specific LD is outside the scope of the chapter, but we would like the reader to be aware of some background information and resources. It is clear that LDs do not resolve without intervention. Again, most emphasis in this area has focused on treatment for reading LD. Within this area, most interventions have been aimed at improving single word reading. There is consistency across different studies in that children need to have explicit training in phonological awareness skills as a foundation for reading, but there are a variety of treatment types, including classroom intervention, pull-out resource services, computer training, and tutoring, as well as combinations of these approaches. Common school-based interventions are more likely to stabilize reading rather than remediate reading LD [44]. There are many commercial programs available, some which are research-based. Interventions need to be intense, systematic, explicit, and delivered in small groups [136]. Gains have been maintained for about half of the children for at least one year once they have returned to their standard curriculum [44]. Shaywitz [137] advocates for intervention at any age or grade level, but early intervention (6–8 years of age) is key and may prevent further reading problems [138].

Interventions focusing on reading comprehension and fluency are less prevalent than interventions that target phonological awareness and word reading skills. There is some carryover from improvement in phonological awareness and single word reading to reading comprehension, particularly in the early grades [12, 139], but it is important to continue to assist with vocabulary development so as not to hinder reading comprehension, particularly as children advance past the third grade. Despite improvements in word reading and reading comprehension, one of the most difficult areas to remediate is fluency; older children and adults often remain slow and effortful readers [139, 140]. The National Reading Panel [141] reports that effective reading instruction requires the incorporation of phonemic awareness, phonics, fluency, vocabulary, and comprehension.

A meta-analysis of imaging studies that focused on reading interventions reviewed 22 studies, 8 of which had pre-and post-fMRI data that could be analyzed using activation likelihood estimate (ALE) meta-analysis [142]. In most cases, reduced activation for reading LD was found in regions associated with reading with increased activation following intervention. One fMRI study in adolescents with dyslexia found that activation in the inferior frontal gyrus was predictive of greater reading improvement on assessment 2 ½ years later, unrelated to reading remediation [143]. This study did not introduce an intervention but rather attempted to determine which brain regions predicted later improvement regardless of the intervention. The studies reviewed showed evidence of both normalizing changes and compensatory changes.

Interventions for math LD have attempted to target components of math processing which includes number sense, knowledge, and retrieval of math facts, calculations, conceptual knowledge, and procedural knowledge. There is some evidence from a meta-analysis of 15 studies that were either well-controlled experimental or quasi-experimental studies of low achieving math students or students at risk for failure [144] showing that the following led to improvements in mathematics: (1) providing data or recommendations to teachers and students, (2) peer-assisted learning, (3) providing clear, specific feedback to parents on their children's successes, and (4) explicit teacher-led and contextualized teacher-facilitated approaches.

fMRI before and aftermath interventions have shown normalization of activation patterns for children after 8 weeks of 1:1 math tutoring that correlated with behavioral changes [145–149].

After intervention there was a significant reduction of the hyperactivation seen prior to intervention across prefrontal, parietal and ventral temporal-occipital brain regions. Another study using adapted versions of the above tutoring programs analyzed functional connectivity of the intraparietal sulcus with the prefrontal cortex and the ventral temporal-occipital cortex [150]. They also examined AG connectivity with the medial temporal lobe memory system. They found increased IPS connectivity with aforementioned regions in conjunction with improved behavioral performance. AG connectivity was not associated with performance improvement.

Interventions for writing LD mostly focus on spelling and written expression. Williams et al. [151] in an update to their previous review in 2006 [152] examined ten studies in children with reading and writing LDs from kindergarten through grade 12, but most were in grades 2–5, limited to spelling interventions. They concluded that self-study interventions and explicit instruction with practice and immediate corrective feedback helped children improve but not to clinically significant levels.

An intervention that ranged from subword letter formation to word decoding and spelling, to syntax construction, and consisting of 18 computerized lessons over 2–3 months [153] was found to improve spelling and reading skills. This intervention was implemented in a recent DTI and fMRI connectivity study [154]. Subjects were children with writing LD, reading LD and oral and written language LD. Improvement in copying a sentence and dictated spelling were exhibited, and there was some evidence that white matter integrity and gray matter clustering coefficient measures changed after writing instruction.

Combining imaging studies with interventions may lead to a better understanding of what treatments may be most effective and who may benefit from them.

For more specific information regarding interventions for LDs, see Fletcher et al. [1]. and Hale and Fiorello [155]. The latter book has appendices of interventions along with references for each type of LD. For interventions more specifically targeted for adults, the work of Mapou [4] may be consulted. Additionally, many children with LDs require accommodations in addition to interventions. For information regarding accommodations see Lovett and Lewandowski [156].

Summary and Future Directions

In this chapter, we have discussed LDs as unexpected underachievement in one or more academic skills. LDs are best identified through an approach that considers low achievement and failure to respond to instruction. In addition to the specific LD, neuropsychologists need to be aware of medical disorders (such as epilepsy, strokes, multiple sclerosis, etc.) that may result in academic skill deficits. Neuropsychologists remain the most appropriate professionals to consult regarding a child's cognitive functioning in the context of a known or suspected medical disorder.

We have included the new diagnostic criteria from the DSM-5 but the clinician should also be aware of important federal and state educational laws when assessing LDs. Assessment for LD should include a battery of the components of each academic area of reading, math, and writing. There are high comorbidity rates across the LDs as well as attention deficit hyperactivity disorder and if not assessed, weaknesses may go undetermined. PVT's also need to be added to ensure the validity of the test results.

Brain imaging studies have revealed specific neural underpinnings of each LD area. With improved neuroimaging methods, it is apparent that large distributed networks are involved across the whole brain for each specific LD. We are also gaining a better understanding of shared neuronal systems that speak to the comorbidity of these disorders [94]. For example, working memory and executive functions are needed for reading, math, and written language.

The role of molecular genetics in LDs is rapidly expanding and studies are now integrating

behavior, imaging and genetics as a way to optimize diagnostic criteria and to possibly identify those who are at risk for a specific LD [157].

Finally, treatment for LDs is necessary, as they do not remit without intervention. This continues to be an under-developed area, particularly randomized controlled trials comparing interventions. We look forward to continued research that highlights the importance of interventions that work.

References

1. Fletcher JM, Lyon GR, Fuchs LS, Barnes MA. Learning disabilities: from identification to intervention. New York: The Guilford Press; 2007.
2. Association AP. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
3. Heilman KM, Valenstein E. Clinical neuropsychology. 4th ed. Oxford; New York: Oxford University Press; 2003.
4. Mapou RL. Adult learning disabilities and ADHD: research-informed assessment. New York: Oxford University Press; 2009.
5. Dombrowski SC, Kamphaus RW, Reynolds CR. After the demise of the discrepancy: proposed learning disabilities diagnostic criteria. Prof Psychol Res Pr 2004;35(4):364–72.
6. Slot EM, van Viersen S, de Bree EH, Kroesbergen EH. Shared and unique risk factors underlying mathematical disability and reading and spelling disability. Front Psychol. 2016;7:803.
7. Germano E, Gagliano A, Curatolo P. Comorbidity of ADHD and dyslexia. Dev Neuropsychol. 2010;35(5):475–93.
8. Wechsler D. Wechsler intelligence scale for children–Fifth Edition technical and interpretive manual. San Antonio, TX: NCS Pearson; 2014.
9. Bloom B, Dey AN. Summary health statistics for U. S. children: National health interview survey, 2004. Vital Health Stat. 2006;10(227):1–85.
10. Altarac M, Saroha E. Lifetime prevalence of learning disability among US children. Pediatrics. 2007;119(Suppl 1):S77–83.
11. National center for health statistics. Children and youth with disabilities. https://nces.ed.gov/programs/coe/indicator_cgg.asp.
12. Shaywitz S. Overcoming dyslexia: a new and complete science-based program for reading problems at any level. New York: Vintage Books; 2003.
13. Disabilities ICoL. Learning disabilities: a report to the U.S. congress. Washington, DC: US Printing Office; 1987.
14. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Incidence of reading disability in a population-based birth cohort, 1976–1982, Rochester, Minn. Mayo Clin Proc. 2001;76(11):1081–92.
15. Shaywitz SE, Gruen JR, Shaywitz BA. Management of dyslexia, its rationale, and underlying neurobiology. Pediatr Clin North Am. 2007;54(3):609–23, viii.
16. Rutter M, Caspi A, Fergusson D, et al. Sex differences in developmental reading disability: new findings from 4 epidemiological studies. JAMA. 2004;291(16):2007–12.
17. Devine A, Soltesz F, Nobes A, Goswami U, Szucs D. Gender differences in developmental dyscalculia depend on diagnostic criteria. 20160926(0959–4752 (Print)).
18. Katusic SK, Colligan RC, Weaver AL, Barbaresi WJ. The forgotten learning disability: epidemiology of written-language disorder in a population-based birth cohort (1976–1982), Rochester, Minnesota. Pediatrics. 2009;123(5):1306–13.
19. Berninger VW, Nielsen KH, Abbott RD, Wijsman E, Raskind W. Gender differences in severity of writing and reading disabilities. J Sch Psychol. 2008;46(2):151–72.
20. Breier JI, Brookshire BL, Fletcher JM, et al. Identification of side of seizure onset in temporal lobe epilepsy using memory tests in the context of reading deficits. J Clin Exp Neuropsychol. 1997;19(2):161–71.
21. Schrank FA, McGrew KS, Mather N, Woodcock RW. Woodcock-Johnson IV. Rolling Meadows, IL: Riverside Publishing; 2014.
22. Wechsler D. Wechsler individual achievement test. 3rd ed. San Antonio, TX: Pearson; 2009.
23. Brown JI, Fishco VV, Hanna G. Nelson-Denny reading test: manual for scoring and interpretation, forms G & H. Rolling Meadows, IL: Riverside; 1993.
24. Wagner RK, Torgesen JK, Rashcotte CA, Pearson NA. Comprehensive test of phonological processing, 2nd ed. Austin, TX: Pro-Ed; 2013.
25. Wiederholt J, Bryant B. Gray oral reading test-fifth edition (GORT-5): examiner's manual. Austin, TX: Pro-Ed; 2012.
26. Hammill DD, Larsen SC. Test of written language: TOWL4. Pro-ed; 2009.
27. Connolly AJ. KeyMath 3: diagnostic assessment. San Antonio, TX: Pearson; 2007.
28. Kirkwood MW, editor. Validity testing in the assessment of children and adolescents. New York, NY: Guilford Press; 2015.
29. Kirkwood MW. Pediatric validity assessment. NeuroRehabilitation. 2015;36(4):439–50.
30. Harrison AG, Edwards MJ. Symptom exaggeration in post-secondary students: preliminary base rates in a Canadian sample. Appl Neuropsychol. 2010;17(2):135–43.
31. Suhr JA, Harrison AG. Detection of noncredible presentation in learning disorder assessments.

In: 15th Annual AACN Conference, 8 June 2017, Boston, MA; 2017.
32. Harrison AG. Child and adolescent psychoeducational evaluations. In: Kirkwood MW, editor. Validity testing in child and adolescent assessment. New York, NY: Guilford; 2015. p. 185–206.
33. Tombaugh T. Test of memory malingering (TOMM). North Tonawanda, NY: Multi-Health Systems; 1996.
34. Green P. Manual for the word memory test. Edmonton, Alberta, Canada: Green's Publishing; 2003.
35. Green P. Manual for the medical symptom validity test. Edmonton, Alberta, Canada: Green's Publishing; 2004.
36. Plomin R, Haworth CM, Meaburn EL, Price TS, Wellcome Trust Case Control C, Davis OS. Common DNA markers can account for more than half of the genetic influence on cognitive abilities. Psychol Sci. 2013;24(4):562–8.
37. Raskind WH, Peter B, Richards T, Eckert MM, Berninger VW. The genetics of reading disabilities: from phenotypes to candidate genes. Front Psychol. 2012;3:601.
38. Hensler BS, Schatschneider C, Taylor J, Wagner RK. Behavioral genetic approach to the study of dyslexia. J Dev Behav Pediatr. 2010;31(7):525–32.
39. Kovas Y, Plomin R. Learning abilities and disabilities: generalist genes, specialist environments. Curr Dir Psychol Sci. 2007;16(5):284–8.
40. Plomin R, Kovas Y, Haworth CM. Generalist genes: genetic links between brain, mind, and education. Mind Brain Educ. 2007;1(1):11–9.
41. de Zeeuw EL, van Beijsterveldt CE, Glasner TJ, de Geus EJ, Boomsma DI. Arithmetic, reading and writing performance has a strong genetic component: a study in primary school children. Learn Individ Differ. 2016;47:156–66.
42. Peterson RL, Pennington BF. Developmental dyslexia. Annu Rev Clin Psychol. 2015;11:283–307.
43. Friend A, DeFries JC, Olson RK. Parental education moderates genetic influences on reading disability. Psychol Sci. 2008;19(11):1124–30.
44. Torgesen JK. Recent discoveries on remedial interventions for children with dyslexia. In: Snowling MJ, Hulme C, editors. Maiden, MA: Blackwell; 2006.
45. Meaburn EL, Harlaar N, Craig IW, Schalkwyk LC, Plomin R. Quantitative trait locus association scan of early reading disability and ability using pooled DNA and 100 K SNP microarrays in a sample of 5760 children. Mol Psychiatry. 2008;13(7):729–40.
46. Docherty SJ, Kovas Y, Petrill SA, Plomin R. Generalist genes analysis of DNA markers associated with mathematical ability and disability reveals shared influence across ages and abilities. BMC Genet. 2010;11:61.
47. Baron-Cohen S, Murphy L, Chakrabarti B, et al. A genome wide association study of mathematical ability reveals an association at chromosome 3q29, a locus associated with autism and learning difficulties: a preliminary study. PLoS ONE. 2014;9(5):e96374.
48. Lind PA, Luciano M, Wright MJ, Montgomery GW, Martin NG, Bates TC. Dyslexia and DCDC2: normal variation in reading and spelling is associated with DCDC2 polymorphisms in an Australian population sample. Eur J Hum Genet. 2010;18(6):668–73.
49. Konig IR, Schumacher J, Hoffmann P, et al. Mapping for dyslexia and related cognitive trait loci provides strong evidence for further risk genes on chromosome 6p21. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(1):36–43.
50. Dejerine J. Sur un cas de cecite verbale avec agraphie, suivi d'autopsie. Mémoires de la Société Biologique. 1891;3:197–201.
51. Gerstmann J. Syndrome of finger agnosia, disorientation for right and left, agraphia, and acalculia. Arch Neurol Psychiatry. 1940;44:398–408.
52. Hecaen H, Angelergues R, Houillier S. Les varietes cliniques des acalculies aucours des lesions retro-rolandiques: Approche statistique du probleme. Revue Neurologique. 1961;105:85–103.
53. Ramus F. Neuroimaging sheds new light on the phonological deficit in dyslexia. Trends Cogn Sci. 2014;18(6):274–5.
54. Caravolas M, Lervag A, Mousikou P, et al. Common patterns of prediction of literacy development in different alphabetic orthographies. Psychol Sci. 2012;23(6):678–86.
55. Wolf M, Bowers PG. Naming-speed processes and developmental reading disabilities: an introduction to the special issue on the double-deficit hypothesis. J Learn Disabil. 2000;33(4):322–4.
56. He Q, Xue G, Chen C, Chen C, Lu ZL, Dong Q. Decoding the neuroanatomical basis of reading ability: a multivoxel morphometric study. J Neurosci. 2013;33(31):12835–43.
57. Norton ES, Black JM, Stanley LM, et al. Functional neuroanatomical evidence for the double-deficit hypothesis of developmental dyslexia. Neuropsychologia. 2014;61:235–46.
58. Stein J. The magnocellular theory of developmental dyslexia. Dyslexia. 2001;7(1):12–36.
59. Tallal P. Auditory temporal perception, phonics, and reading disabilities in children. Brain Lang. 1980;9(2):182–98.
60. Tallal P, Stark RE, Kallman C, Mellits D. Developmental dysphasia: relation between acoustic processing deficits and verbal processing. Neuropsychologia. 1980;18(3):273–84.
61. Nicolson RI, Fawcett AJ, Berry EL, Jenkins IH, Dean P, Brooks DJ. Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. Lancet. 1999;353(9165):1662–7.
62. Nicolson R, Fawcett AJ, Dean P. Dyslexia, development and the cerebellum. Trends Neurosci. 2001;24(9):515–6.

63. Nicolson RI, Fawcett AJ, Dean P. Developmental dyslexia: the cerebellar deficit hypothesis. Trends Neurosci. 2001;24(9):508–11.
64. Olulade OA, Napoliello EM, Eden GF. Abnormal visual motion processing is not a cause of dyslexia. Neuron. 2013;79(1):180–90.
65. Norton ES, Beach SD, Gabrieli JD. Neurobiology of dyslexia. Curr Opin Neurobiol. 2015;30: 73–8.
66. Fiez JA, Petersen SE. Neuroimaging studies of word reading. Proc Natl Acad Sci USA. 1998;95 (3):914–21.
67. Brunswick N, McCrory E, Price CJ, Frith CD, Frith U. Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: a search for Wernicke's Wortschatz? Brain. 1999;122(Pt 10):1901–17.
68. Paulesu E, Frith U, Snowling M, et al. Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning. Brain. 1996;119(Pt 1):143–57.
69. Cohen L, Dehaene S, Naccache L, et al. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain. 2000;123 (Pt 2):291–307.
70. McCandliss BD, Cohen L, Dehaene S. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cogn Sci. 2003;7(7):293–9.
71. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Functional disruption in the organization of the brain for reading in dyslexia. Proc Natl Acad Sci USA. 1998;95(5):2636–41.
72. Maisog JM, Einbinder ER, Flowers DL, Turkeltaub PE, Eden GF. A meta-analysis of functional neuroimaging studies of dyslexia. Ann NY Acad Sci. 2008;1145:237–59.
73. Richlan F, Kronbichler M, Wimmer H. Functional abnormalities in the dyslexic brain: a quantitative meta-analysis of neuroimaging studies. Hum Brain Mapp. 2009;30(10):3299–308.
74. Richlan F, Kronbichler M, Wimmer H. Meta-analyzing brain dysfunctions in dyslexic children and adults. Neuroimage. 2011;56(3):1735–42.
75. Richlan F. Developmental dyslexia: dysfunction of a left hemisphere reading network. Front Hum Neurosci. 2012;6:120.
76. Raschle NM, Chang M, Gaab N. Structural brain alterations associated with dyslexia predate reading onset. Neuroimage. 2011;57(3):742–9.
77. Black JM, Tanaka H, Stanley L, et al. Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. Neuroimage. 2012;59(3):3021–32.
78. Galaburda AM, Kemper TL. Cytoarchitectonic abnormalities in developmental dyslexia: a case study. Ann Neurol. 1979;6(2):94–100.
79. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. Ann Neurol. 1985;18(2):222–33.
80. Galaburda AM, LoTurco J, Ramus F, Fitch RH, Rosen GD. From genes to behavior in developmental dyslexia. Nat Neurosci. 2006;9(10):1213–7.
81. Ben-Shachar M, Dougherty RF, Wandell BA. White matter pathways in reading. Curr Opin Neurobiol. 2007;17(2):258–70.
82. Beaulieu C, Plewes C, Paulson LA, et al. Imaging brain connectivity in children with diverse reading ability. Neuroimage. 2005;25(4):1266–71.
83. Klingberg T, Hedehus M, Temple E, et al. Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. Neuron. 2000;25(2):493–500.
84. Niogi SN, McCandliss BD. Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. Neuropsychologia. 2006;44(11):2178–88.
85. Deutsch GK, Dougherty RF, Bammer R, Siok WT, Gabrieli JD, Wandell B. Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex. 2005;41(3):354–63.
86. Rimrodt SL, Peterson DJ, Denckla MB, Kaufmann WE, Cutting LE. White matter microstructural differences linked to left perisylvian language network in children with dyslexia. Cortex. 2010;46 (6):739–49.
87. Dougherty RF, Ben-Shachar M, Deutsch GK, Hernandez A, Fox GR, Wandell BA. Temporal-callosal pathway diffusivity predicts phonological skills in children. Proc Natl Acad Sci USA. 2007;104 (20):8556–61.
88. Tallal P, Merzenich MM, Miller S, Jenkins W. Language learning impairments: integrating basic science, technology, and remediation. Exp Brain Res. 1998;123(1–2):210–9.
89. Dehaene S. The number sense. New York: Oxford University Press; 1997.
90. Temple E, Posner MI. Brain mechanisms of quantity are similar in 5-year-old children and adults. Proc Natl Acad Sci USA. 1998;95(13):7836–41.
91. Price GR, Holloway I, Rasanen P, Vesterinen M, Ansari D. Impaired parietal magnitude processing in developmental dyscalculia. Curr Biol. 2007;17(24): R1042–3.
92. Butterworth B, Varma S, Laurillard D. Dyscalculia: from brain to education. Science. 2011;332 (6033):1049–53.
93. Piazza M, Facoetti A, Trussardi AN, et al. Developmental trajectory of number acuity reveals a severe impairment in developmental dyscalculia. Cognition. 2010;116(1):33–41.
94. Ashkenazi S, Black JM, Abrams DA, Hoeft F, Menon V. Neurobiological underpinnings of math and reading learning disabilities. J Learn Disabil. 2013;46(6):549–69.

95. Rousselle L, Noel MP. Basic numerical skills in children with mathematics learning disabilities: a comparison of symbolic vs non-symbolic number magnitude processing. Cognition. 2007;102(3):361–95.
96. Rotzer S, Loenneker T, Kucian K, Martin E, Klaver P, von Aster M. Dysfunctional neural network of spatial working memory contributes to developmental dyscalculia. Neuropsychologia. 2009;47(13):2859–65.
97. Ashkenazi S, Henik A. A disassociation between physical and mental number bisection in developmental dyscalculia. Neuropsychologia. 2010;48 (10):2861–8.
98. Passolunghi MC, Siegel LS. Working memory and access to numerical information in children with disability in mathematics. J Exp Child Psychol. 2004;88(4):348–67.
99. von Aster MG, Shalev RS. Number development and developmental dyscalculia. Dev Med Child Neurol. 2007;49(11):868–73.
100. Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. Cognitive Neuropsychology. 2003;20:487–506.
101. Dehaene S, Molko N, Cohen L, Wilson AJ. Arithmetic and the brain. Curr Opin Neurobiol. 2004;14 (2):218–24.
102. Chochon F, Cohen L, van de Moortele PF, Dehaene S. Differential contributions of the left and right inferior parietal lobules to number processing. J Cogn Neurosci. 1999;11(6):617–30.
103. Menon V, Rivera SM, White CD, Glover GH, Reiss AL. Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage. 2000;12(4):357–65.
104. Eger E, Sterzer P, Russ MO, Giraud AL, Kleinschmidt A. A supramodal number representation in human intraparietal cortex. Neuron. 2003;37 (4):719–25.
105. Pinel P, Dehaene S, Riviere D, LeBihan D. Modulation of parietal activation by semantic distance in a number comparison task. Neuroimage. 2001;14 (5):1013–26.
106. Ansari D. Effects of development and enculturation on number representation in the brain. Nat Rev Neurosci. 2008;9(4):278–91.
107. Brannon EM. The representation of numerical magnitude. Curr Opin Neurobiol. 2006;16(2): 222–9.
108. Cohen Kadosh R, Lammertyn J, Izard V. Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. Prog Neurobiol. 2008;84(2):132–47.
109. Whalen J, McCloskey M, Lesser RP, Gordon B. Localizing arithmetic processes in the brain: evidence from transient deficit during cortical stimulation. J Cogn Neurosci. 1997;9:409–17.
110. Pesenti M, Thioux M, Seron X, De Volder A. Neuroanatomical substrates of arabic number processing, numerical comparison, and simple addition: a PET study. J Cogn Neurosci. 2000;12:461–79.
111. Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron. 2002;33(3):475–87.
112. Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkin S. Sources of mathematical thinking: behavioral and brain-imaging evidence. Science. 1999;284(5416):970–4.
113. Lee KM, Kang SY. Arithmetic operation and working memory: differential suppression in dual tasks. Cognition. 2002;83(3):B63–8.
114. Piazza M, Mechelli A, Butterworth B, Price CJ. Are subitizing and counting implemented as separate or functionally overlapping processes? Neuroimage. 2002;15(2):435–46.
115. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci. 2000;3(3):292–7.
116. Mussolin C, De Volder A, Grandin C, Schlogel X, Nassogne MC, Noel MP. Neural correlates of symbolic number comparison in developmental dyscalculia. 20100305 DCOM-20100527 (1530-8898 (Electronic)).
117. Kaufmann L, Vogel SE, Starke M, Kremser C, Schocke M, Wood G. Developmental dyscalculia: compensatory mechanisms in left intraparietal regions in response to nonsymbolic magnitudes. 20090824 DCOM-20121002(1744-9081 (Electronic)).
118. Jolles D, Ashkenazi S, Kochalka J, et al. Parietal hyper-connectivity, aberrant brain organization, and circuit-based biomarkers in children with mathematical disabilities. Dev Sci. 2016;19(4):613–31.
119. Rotzer S, Kucian K, Martin E, von Aster M, Klaver P, Loenneker T. Optimized voxel-based morphometry in children with developmental dyscalculia. Neuroimage. 2008;39(1):417–22.
120. Rykhlevskaia E, Uddin LQ, Kondos L, Menon V. Neuroanatomical correlates of developmental dyscalculia: combined evidence from morphometry and tractography. Front Hum Neurosci. 2009;3:51.
121. Fias W, Menon V, Szucs D. Core systems of number. Trends Neurosci Educ. 2014;2(2):43–7.
122. Iuculano T. Neurocognitive accounts of developmental dyscalculia and its remediation. Prog Brain Res. 2016;227:305–33.
123. Peters L, De Smedt B. Arithmetic in the developing brain: a review of brain imaging studies. Dev Cogn Neurosci. 2017.
124. Abbott R, Berninger V. Structural equation modeling of relationships among developmental skills and writing skills in primary and intermediate grade writers. J Educ Psychol. 1993;85(3):478–508.
125. Berninger VW. Highlights of programmatic, interdisciplinary research on writing. Learn Disabil Res Pract. 2009;24(2):69–80.

126. Berninger VW, Abbott RD, Jones J, et al. Early development of language by hand: composing, reading, listening, and speaking connections; three letter-writing modes; and fast mapping in spelling. Dev Neuropsychol. 2006;29(1):61–92.
127. Berninger VW, Abbott RD, Abbott SP, Graham S, Richards T. Writing and reading: connections between language by hand and language by eye. J Learn Disabil. 2002;35(1):39–56.
128. Basso A, Taborelli A, Vignolo LA. Dissociated disorders of speaking and writing in aphasia. J Neurol Neurosurg Psychiatry. 1978;41(6):556–63.
129. Henry ML, Beeson PM, Stark AJ, Rapcsak SZ. The role of left perisylvian cortical regions in spelling. Brain Lang. 2007;100(1):44–52.
130. Agraphia Roeltgen D. In: Valenstein KMHE, editor. Clinical neuropsychology. New York: Oxford University Press; 2003. p. 75–96.
131. Purcell JJ, Turkeltaub PE, Eden GF, Rapp B. Examining the central and peripheral processes of written word production through meta-analysis. Front Psychol. 2011;2:239.
132. Planton S, Jucla M, Roux FE, Demonet JF. The "handwriting brain": a meta-analysis of neuroimaging studies of motor versus orthographic processes. Cortex. 2013;49(10):2772–87.
133. Richards TL, Berninger VW, Stock P, Altemeier L, Trivedi P, Maravilla K. Functional magnetic resonance imaging sequential-finger movement activation differentiating good and poor writers. J Clin Exp Neuropsychol. 2009;1–17.
134. Richards TL, Berninger VW, Stock P, Altmeier L, Trivedi P, Maravilla KR. Differences between good and poor child writers on fMRI contrasts for writing newly taught and highly practiced letter forms. Read Writ. 2011;24(5):493.
135. Richards TL, Grabowski TJ, Boord P, et al. Contrasting brain patterns of writing-related DTI parameters, fMRI connectivity, and DTI-fMRI connectivity correlations in children with and without dysgraphia or dyslexia. Neuroimage Clin. 2015;8:408–21.
136. Shaywitz SE, Morris R, Shaywitz BA. The education of dyslexic children from childhood to young adulthood. Annu Rev Psychol. 2008;59:451–75.
137. Shaywitz SE, Shaywitz BA, Fulbright RK, et al. Neural systems for compensation and persistence: young adult outcome of childhood reading disability. Biol Psychiatry. 2003;54(1):25–33.
138. Foorman BR, Francis DJ, Shaywitz SE, Shaywitz BA, Fletcher JM. The case for early reading intervention. In: Blachman BA, editor. Foundations of reading acquisition and dyslexia: implications for early intervention. Mahwah, NJ: Lawrence Erbaum Associates Publishers; 1997. p. 243–64.
139. Torgesen JK, Alexander AW, Wagner RK, Rashotte CA, Voeller KK, Conway T. Intensive remedial instruction for children with severe reading disabilities: immediate and long-term outcomes from two instructional approaches. J Learn Disabil. 2001;34(1):33–58, 78.
140. Hecht SA, Torgesen JK, Wagner RK, Rashotte CA. The relations between phonological processing abilities and emerging individual differences in mathematical computation skills: a longitudinal study from second to fifth grades. J Exp Child Psychol. 2001;79(2):192–227.
141. Langenbereg DN. Report of the national reading panel. Washington DC: National Institute of Child Health and Human Development 2000. Report No.: NIH Pub. No. 00-4754.
142. Barquero LA, Davis N, Cutting LE. Neuroimaging of reading intervention: a systematic review and activation likelihood estimate meta-analysis. PLoS One. 2014;9(1):e83668.
143. Hoeft F, McCandliss BD, Black JM, et al. Neural systems predicting long-term outcome in dyslexia. Proc Natl Acad Sci USA. 2011;108(1):361–6.
144. Baker S, Gersten R, Lee D. A synthesis of empirical research on teaching mathematics to low-achieving students. The Elem Sch J. 2002;103(1):51–73.
145. Fuchs LS, Seethaler PM, Powell SR, Fuchs D, Hamlett CL, Fletcher JM. Effects of preventative tutoring on the mathematical problem solving of third-grade students with math and reading difficulties. Except Child. 2008;74(2):155–73.
146. Fuchs LS, Powell SR, Seethaler PM, et al. The effects of strategic counting instruction, with and without deliberate practice, on number combination skill among students with mathematics difficulties. Learn Individ Differ. 2010;20(2):89–100.
147. Fuchs LS, Geary DC, Compton DL, et al. Effects of first-grade number knowledge tutoring with contrasting forms of practice. J Educ Psychol. 2013;105(1):58–77.
148. Fuchs LS, Powell SR, Seethaler PM, et al. Remediating number combination and word problem deficits among students with mathematics difficulties: a randomized control trial. J Educ Psychol. 2009;101(3):561–76.
149. Iuculano T, Rosenberg-Lee M, Richardson J, et al. Cognitive tutoring induces widespread neuroplasticity and remediates brain function in children with mathematical learning disabilities. Nat Commun. 2015;6:8453.
150. Jolles D, Supekar K, Richardson J, et al. Reconfiguration of parietal circuits with cognitive tutoring in elementary school children. Cortex. 2016;83:231–45.
151. Williams KJ, Walker MA, Vaughn S, Wanzek J. A synthesis of reading and spelling interventions and their effects on spelling outcomes for students with learning disabilities. J Learn Disabil. 2017;50(3):286–97.
152. Wanzek J, Vaughn S, Wexler J, Swanson EA, Edmonds M, Kim AH. A synthesis of spelling and reading interventions and their effects on the spelling outcomes of students with LD. J Learn Disabil. 2006;39(6):528–43.

153. Tanimoto S, Thompson R, Berninger VW, Nagy W, Abbott RD. Computerized writing and reading instruction for students in grades 4 to 9 with specific learning disabilities affecting written language. J Comput Assist Learn. 2015;31(6):671–89.
154. Richards TL, Berninger VW, Yagle KJ, Abbott RD, Peterson DJ. Changes in DTI diffusivity and fMRI connectivity cluster coefficients for students with and without specific learning disabilities in written language: Brain's response to writing instruction. J Nat Sci. 2017;3(4).
155. Hale JB, Fiorello CA. School neuropsychology: a practitioner's handbook. New York: The Guilford Press; 2004.
156. Lovett BJ, Lewandowski LJ. Testing accommodations for students with disabilities: research-based practice. American Psychological Association; 2015.
157. Mascheretti S, De Luca A, Trezzi V, et al. Neurogenetics of developmental dyslexia: from genes to behavior through brain neuroimaging and cognitive and sensorial mechanisms. Transl Psychiatry. 2017;7(1):e987.

Chapter 16

Executive Function Disorders in Pediatric Neuropsychology: Attention-Deficit/Hyperactivity Disorder and Tourette Disorder

Anthony L. Rostain and William C. Culbertson

Introduction

This chapter will review current understanding of two neurodevelopmental disorders involving dysregulation of executive (frontal lobe) functioning: Attention-Deficit/Hyperactivity Disorder (ADHD), and Tourette Disorder (TD). It will describe the clinical phenomenology of these disorders (including co-occurring conditions), recent research into their neurobiological and neuropsychological mechanisms, recommended assessment procedures, medical treatments, and psychosocial interventions.

Attention-Deficit/Hyperactivity Disorder

Children and adolescents presenting with inattention, impulsivity, and hyperactivity constitute a large portion of the behavior problems seen in pediatric practice. Previously referred to as the hyperkinetic syndrome, minimal brain damage, minor cerebral dysfunction, or the hyperactive child syndrome, current views regarding these difficult-to-manage patients emphasize attention deficits in addition to the associated behavior problems which characterize the disorder. Newer conceptualizations of ADHD emphasize the dysregulation of executive functioning that is the hallmark of the disorder and which contributes to both its heterogeneity and its pervasive impact on development. While controversy still surrounds the diagnosis and treatment of attention-deficit disorders, it is generally agreed that there are large numbers of children and adolescents whose inability to sit still, concentrate and complete tasks present numerous challenges for them and for their parents, teachers, and peers. Approximately 5–8% of school-age children suffer from some form of attention-deficit disorder depending upon the method of assessment [1] At present, 3–6% of elementary school children receive psychostimulant medications on a regular basis. There are marked cross-national differences in prevalence rates due to variations in the criteria used to make the diagnosis. Although it is the most widely studied behavior disorder of childhood, its etiology remains unclear, its outcome is variable, and its treatment is both complex and moderately successful. Fortunately, there is a great deal of new scientific evidence regarding its causes, natural course, and treatment outcomes.

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Definition

The most widely used definition of attention-deficit disorders is provided by the *Diagnostic and Statistical Manual*, Fifth Edition (DSM-5) of the American Psychiatric Association [2] which outlines two major dimensions for the disorder:

DSM-5 Diagnostic Criteria for Attention-Deficit/ Hyperactivity Disorder

A. Either (1) or (2)

1. Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level and adversely impacts on social and academic/occupational functioning. Symptoms are not primarily a consequence of oppositional, defiant, or hostile behavior, or are not due to the failure to understand demands. A minimum of five symptoms are required for older adolescents and adults (age equal to or greater than 17 years).

Inattention

a. often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
b. often has difficulty sustaining attention in tasks or play activities
c. often does not seem to listen when spoken to directly
d. often does not follow-through on instructions and fails to finish schoolwork, chores, or duties in the workplace
e. often has difficulty organizing tasks and activities
f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort or persistence
g. often loses things necessary for tasks or activities (e.g., toys, school assignments, mobile telephones, keys, books, or tools)
h. is often easily distracted by extraneous stimuli (for older adolescents and adults, distraction may be due to unrelated thoughts)
i. is often forgetful in daily activities

2. Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with development level and adversely impacts on social and academic/occupational functioning. Symptoms are not primarily a consequence of oppositional, defiant, or hostile behavior, or are not due to the failure to understand demands. A minimum of five symptoms are required for older adolescents and adults (age equal to or greater than 17 years).

Hyperactivity-Impulsivity

a. often fidgets with hands or feet or squirms in seat
b. often leaves seat in classroom or in other situations in which remaining seated is expected (e.g., in the office or workplace)
c. often runs about or climbs excessively in situations in which it is inappropriate (For adolescents or adults, may be limited to subjective feelings of restlessness)
d. often has difficulty playing or engaging in leisure activities quietly
e. is often "on the go" or often acts as if "driven by a motor" (e.g., is unable to remain still for extended periods of time)
f. often talks excessively
g. often blurts out answers before questions have been completed (e.g., completes sentences for others)
h. often has difficulty waiting for his or her turn
i. often interrupts or intrudes on others (for adolescents and adults, may intrude into or take over what others are doing)

B. Several hyperactive-impulsive or inattentive symptoms were evident before the age of 12 years
C. Several inattentive or hyperactive-impulse symptoms are evident in two or more settings (e.g., at school, work, or home)
D. There must be clear evidence that symptoms of inattention and/or hyperactivity-impulsivity disrupt, or reduce the quality of social, academic, or occupational functioning
E. The symptoms do not occur exclusively during the course of a psychotic disorder and are not better accounted for by another mental disorder
F. Presentations of ADHD
    1. Combined Presentation – if both criteria A1 and A2 are met for past 6 months
    2. Predominantly Inattentive Presentation – if only Criterion A1 is met for past 6 months
    3. Predominantly Hyperactive-Impulsive Presentation – if only criterion A2 is met for past 6 months
G. Specify current level of symptom severity: mild, moderate, or severe

Etiology

ADHD is a heterogeneous neurobehavioral disorder with multiple possible causes. Roughly 65–75% of cases are thought to be due to genetics, with the remainder caused by CNS insults from prenatal, perinatal and postnatal sources [3]. Prenatal causes include maternal cigarette smoking (which increases the odds by 2.5 times), maternal alcohol drinking (2.5 odds ratio), premature birth (with an incidence of 45% when intracerebral hemorrhage occurs), maternal respiratory infections, maternal anxiety, and high maternal phenylalanine levels. Perinatal asphyxia or anoxia also increases risk of ADHD. Contrary to popular myth, cocaine or crack exposures do not add risk when other variables are controlled.

Postnatal factors associated with ADHD include head trauma, brain hypoxia, CNS tumors, CNS infection, febrile seizures, lead poisoning, pediatric acute lymphoblastic leukemia (ALL), streptococcal infection and elevated phenylalanine levels.

There is a large and growing body of literature on the genetic basis of ADHD dating back over forty years. Early family, twin, and adoption studies have converged on a mean heritability of 0.75 which places ADHD just below autistic-like traits (0.82–0.87) and schizophrenia (0.80–0.85). Recent family-based and case-control studies of candidate genes have shown a statistically significant correlation between ADHD and variants of seven genes: (1) Serotonin HTR1B Receptor, (2) Serotonin Transporter, (3) Synaptosomal-Associated Protein 25 (SNAP 25), (4) Dopamine β-Hydroxylase, (5) Dopamine Transporter, (6) Dopamine D5 Receptor, and (7) Dopamine D4 Receptor [4, 5].

One common variant of the Dopamine D4 receptor (7-repeat) has been highly studied as it is found to increase the risk for ADHD when coupled with both Dopamine Transporter (SLC6A3 10 repeat) and maternal exposure to smoking. The presence of each of these along with maternal smoking increases the risk of ADHD by 2 ½ to 3 times. The presence of both along with smoking increases the risk to 9 times [6].

Neuroanatomy/Pathophysiology

The most likely neuroanatomic lesions in ADHD involve several circuits in the frontal lobe, anterior and medial to the precentral motor cortex. One of the early regions implicated in the pathogenesis of ADHD was the motor region of the frontal lobes. The motor region is part of a fronto-striatal-thalamic circuit, an architectural portion of the broader cortico-striatal-thalamic-cortical (CSTC) loops [7, 8] consisting of a subcortical feedback loop from the motor and somatosensory areas of the cortex, through restricted portions of the basal ganglia and thalamus, and back to the primary motor cortex and secondary motor areas (premotor and supplementary motor). Disruption of this pathway is hypothesized to be related to hyperactivity [8, 9], motor overflow [10], poor motor

control [11], and weaknesses in visuomotor skills often evidenced by children with ADHD.

In addition to the motor circuit, another series of pathways are thought to be involved in the attentional systems of the brain. The locus coeruleus appears to play a major role in the initiation and maintenance of attention, particularly in response to novel stimuli. Two additional attentional systems appear to be involved: a posterior system which disengages from current environmental stimuli in order to orient to new stimuli and an anterior system which works to integrate the various executive functions of the frontal lobe. For instance, there is evidence that ADHD patients have visual selective attention deficits consistent with posterior system disorder [12]. Disruption of these and other pathways have been implicated in ADHD [13].

Pliszka et al. [14] propose an interesting model in which ADHD is hypothesized to be caused by imbalances in catecholamine functioning throughout several brain regions. The central norepinephrine system (via the locus coeruleus) may be hypoactive, causing insufficient response of the posterior attention system to novel stimuli. The dopaminergically mediated anterior attention system (governing executive function) may also be underactive, leading to poor planning, faulty working memory, lack of attention to details, and inefficient problem-solving. The peripheral epinephrine system is also hypothesized to play a role in mediating the individual's response to psychostimulant medication. The beauty of this multistage model is that it integrates neurochemistry, neuroanatomy, and neurophysiology. It also helps to explain why neurotransmitter studies have failed to show a specific deficiency pattern in patients with ADHD.

Recent reviews [5, 15–17] implicate dysregulation of neural circuits as causative of the symptoms of ADHD. Specifically, the executive fronto-striatal circuit is associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning. The fronto-striatal-motivation/limbic circuits are implicated in symptoms of emotional dyscontrol, motivation deficits, hyperactivity-impulsivity, delay aversion and proneness to aggression. The fronto-cerebellar circuits are associated with motor coordination deficits and problems with the timing and timeliness of behavior. Castellanos and Proal [18] present evidence suggesting that the visual network and the default-mode network are also implicated in ADHD.

The default-mode or "resting brain activation" circuit has been the subject of increasing exploration. It subserves internally oriented, task-irrelevant mental processing such as daydreaming, imagining, remembering, distraction by random thoughts or external events, ruminating, and self-referential thinking [19]. Its activity is suspended (inhibited) when brain networks supporting task-relevant processing (e.g., concentration directed to an external problem-solving task) are activated. For example, the default mode is deactivated when the frontal-parietal control network is activated [20]. Likewise, activation of the salient and ventral networks (networks involved in directing attention to external stimuli that are behaviorally relevant) are anti-correlated with the deactivation of the default-mode network [21]. Decreased suppression of the default-mode network produces attentional lapses, distractibility, and response time variability. A meta-analysis [20] of fMRI task-based studies of children with ADHD revealed hyperactivity in the default-mode network and hypoactivity in task-relevant frontal-parietal executive and ventral attention networks (the latter network is anchored in the temporoparietal junction and ventral frontal cortex). Similarly, Posner and colleagues [22] systematic review of resting connectivity MRI studies involving ADHD age groups (children, adolescents, and adults), revealed three consistent findings: (1) reduced anti-correlation between the activity of the default-mode network and executive control network; (2) lower connectivity within the default-mode network; and (3) reduced connectivity within the cognitive and limbic loops of the frontal-striatal circuits. The latter suggests that dysregulation of cognitive and motivational/emotional behaviors associated with ADHD may be a consequence of abnormal connectivity within the frontal-striatal circuits.

Neuropsychological deficits seen in ADHD suggest the involvement of the prefrontal cortex

(especially in the right hemisphere) where classical studies of patients with damage to this area show patterns of loss of working memory, forgetfulness, increased susceptibility to interference, distractibility, poor concentration, impulsivity, and poor organization. This has led to a growing redefinition of ADHD as a developmental disorder of executive function (EF). These are a wide range of central control processes previously referred to as "frontal lobe functions" that connect, prioritize, and integrate cognitive functions on a moment-by-moment basis. Brain structures and interconnections subserving EF are not fully developed at birth and show continuous development into early adulthood [23]. Maturing depends upon myelinization, synaptic pruning, elaboration of DA and NE systems, and other developmental processes. EF can become impaired developmentally, traumatically, and/or secondary to disease processes.

Neuroimaging findings in ADHD date back to 1990 when Zametkin et al. [24] conducted a PET study of 25 ADHD adults compared with 50 normal controls. ADHD subjects showed 8.1% decreased cortical activity in areas hypothesized to be under-functioning (i.e., premotor cortex, prefrontal cortex, and basal ganglia). Subsequent functional imaging studies have identified under-activation of the frontal networks (fronto-striatal, fronto-parietal, and ventral attention networks) in the performance of tasks assessing inhibitory control, working memory, and attention. The component structures of these networks, particularly the prefrontal and frontal cortices, basal ganglia, parietal lobe, insula, temporal-parietal junction, and cerebellum have been shown to be smaller, under- or overactive, and/or less developed.

In addition, total brain volume for children with ADHD is 3–5% less than children without the disorder, a reduction attributed to decreased grey matter development [5]. Of note, there appears to be a significant delay in age of attainment of peak cortical thickness and cortical surface area, especially as related to the prefrontal cortex, for children with ADHD relative to children without the disorder [25, 26]. Extending the study of developmental trajectories of children and adolescents with ADHD, Shaw and colleagues [27] examined the development of the basal ganglia of children with ADHD from age 4 through 19 years. Noteworthy was the finding that children with ADHD, as contrasted to healthy controls, exhibited a reduction in the basal ganglia surface area at the time of entry into the study. Across development, a significant difference was evident in the growth trajectory of the ventral striatum for the two groups. That is, the non-ADHD group showed an expansion of the surface area of this region with age, whereas, the group with ADHD showed a progressive contraction of the region. The use of psychostimulant medication was found to not alter the progressive contraction. The finding of surface area contraction is consistent with functional under-activation of the ventral striatal region in children with ADHD and its relationship to their insensitivity to delayed reward, motivation deficits and impulsivity [28].

The neurochemical evidence for ADHD is contradictory at best. Urine, serum, and cerebrospinal fluid metabolites of serotonin, norepinephrine, and dopamine are not consistently different in ADHD patients as compared with matched controls. Dopamine β-hydroxylase, monoamine oxidase, and catechol-*O*-methyl transferase are also similar in these two groups. There is some evidence for a decreased turnover of dopamine and for a super-sensitivity to released dopamine in ADHD patients. Pharmacologic studies with dopamine agonists, however, fail to demonstrate a primary deficiency of dopamine. The most significant pharmacologic effects on ADHD symptoms have been found with stimulants such as methylphenidate and dextroamphetamine, both of which work on catecholamine and dopamine metabolism, lending strong support to the role of both in this disorder. In view of the inconsistent findings from neurotransmitter studies, it appears that ADHD involves both complex neuroanatomic and neurochemical alterations in function. As Faraone et al. [5, p. 7] note: "The multifactorial causation of ADHD leads to a heterogeneous profile of psychopathology, neurocognitive deficits, and abnormalities in the structure and function of the brain. Many cases probably

involve dysregulation of the structure and function of the frontal-subcortical-cerebellar pathways that control attention, response to reward, salience thresholds, inhibitory control, and motor behavior. A meta-analysis of peripheral biomarkers in the blood and urine of drug-naive or drug-free patients with ADHD and unaffected individuals found several measures—specifically, noradrenaline, 3-methoxy-4-hydroxyphenyl-ethylene glycol (MHPG), monoamine oxidase (MAO) and cortisol—to be significantly associated with ADHD. Several of these metabolites were also related to response to ADHD medication and symptom severity of ADHD. These results support the idea that catecholaminergic neurotransmitter systems and the hypothalamic–pituitary–adrenal axis are dysregulated in ADHD."

Comorbidity

Attention-deficit disorders are associated with a variety of other childhood psychiatric problems, and numerous psychiatric conditions can present as attention difficulties. Comorbidity has become an important area of research in recent years, as studies reveal that high percentages of children with ADHD also suffer from other disturbances such as oppositional-defiant behavior, conduct disorder and other aggressive behaviors; mood disorders (particularly depression and bipolar affective disorder); anxiety disorders; learning disabilities and language disorders; and among adolescents and young adults, substance abuse and personality disorders. In addition, special populations have high rates of ADHD including patients with Tourette Syndrome, Obsessive-Compulsive Disorder, Autistic Spectrum Disorders, Fetal Alcohol Syndrome, and Posttraumatic Stress Disorder.

Seizure disorders, including petit mal (absence) or partial complex seizures may be mistaken for ADHD. Sensory deficiencies, particularly deafness and partial hearing impairment, can also mimic ADHD. Approximately 40–50% of ADHD children suffer from a learning disability of sufficient magnitude that school performance is negatively affected. A similar percentage show signs of Oppositional-Defiant Disorder, a pattern of constantly challenging rules and of resisting disciplinary measures. When the defiance escalates to the point where major social rules are broken without consideration for the feelings of others (e.g., lying, stealing, fighting, running away), a diagnosis of Conduct Disorder is more likely. In addition to the externalizing problems, other conditions may coexist including depression, bipolar illness, and anxiety. These conditions can exacerbate the child's inattentiveness, or be mistaken for primary attention-deficit/hyperactivity disorders.

Among the impairments caused by ADHD, traffic violations and motor vehicle accidents are of great concern. Health problems such as binge eating, overweight, obesity, hypertension, and smoking have all been associated with premature mortality. Long-term effects in adulthood include reduced educational attainment, lower income, more frequent job changes, unstable interpersonal relationships, higher rates of arrest and convictions, greater suicide attempts and completions, and mental health disorders such as depression, anxiety, posttraumatic stress disorder (PTSD), and substance use disorders [5].

Assessment

The diagnostic evaluation of ADHD begins with a careful description of the problem behaviors. When interviewing parents, it is important that they give examples of situations in which the child is having difficulty. Terms like "hyperactive, disruptive, and impulsive" should be defined as precisely as possible. When parents report that the child will not sit still, will not pay attention, and will not follow instructions, it is helpful to find out when they first became aware of these difficulties. It also helps to clarify if the problems occur both at home and at school. Parents should describe their strategies for handling these behaviors and share their insights into what works and what does not. Relatedly, the

child's response to reward and punishment contingencies, particularly delayed reward, warrants discussion [29]. In addition to the cardinal signs of inattention, impulsivity, and hyperactivity, the clinician should inquire about the degree of oppositional behavior, aggressiveness, moodiness, and temper outbursts which the child is manifesting. Whenever possible, parents should be observed interacting with the child. The clinician should note how the child addresses the parents and whether she/he listens to their instructions and commands. If the child begins to misbehave in the office, this is an opportunity to learn how parents handle oppositional behavior. Structured and semi-structured interview measures (e.g., Structured Clinical Interview for DSM-IV Childhood Diagnoses; KID-SCID) [30] exist which the clinician may find helpful in drawing relevant, reliable and valid diagnostic information.

After thoroughly exploring the presenting problems, a comprehensive history should be obtained including pregnancy; perinatal period; medical history; developmental milestones; speech and language function; sleep pattern; presence of pica, enuresis, or encopresis; early temperament; diet; and medications. Close attention should be paid to potential toxic exposures such as lead and carbon monoxide [31–34]. Social and family history should include an inquiry into the presence of ADHD, learning disabilities, and other psychiatric disturbances in the parents or siblings. Finally, the child's school history should be traced, especially regarding the consistency and nature of the child's behavior and achievement in the early grades. Copies of old report cards and of teachers' descriptions of the child are extremely valuable. It is also important to speak directly to the current teacher to learn about the child's typical behavior in class and to understand how the teacher views and handles the child.

Parent and teacher rating scales (broadband and narrow-band) are extremely useful as adjuncts to the diagnostic interview. There are dozens of instruments available; however, no single scale is perfect nor can any scale "make" a diagnosis of ADHD. Scales offer a relatively quick measure of the child's behaviors as compared with those of age and sex-matched peers. They can also be used to measure the change in targeted areas following the initiation of treatment.

Physical examination of the patient should include a neurodevelopmental assessment. Minor congenital anomalies, neurologic status, speech and language, and overall mental status are important to evaluate. Signs of fetal alcohol effects should be noted, and the presence of unusual physical stigmata is an indication to order chromosome analysis. The neurologic exam should include assessment of involuntary movements, cerebellar functioning, and parietal lobe activity —which are often referred to as the "soft signs" of ADHD. While these are not pathognomonic for ADHD, they can be viewed as markers of neurodevelopmental delay. The child's speech and receptive language abilities are important to screen insofar as communication disorders and learning disabilities can be present in children with ADHD. In addition to overactivity, inattentiveness, and impulsivity, the child's mental status should also be noted for signs of affective disturbance (i.e., anxiety, depression, and irritability), autism and thought disorders, and general intellectual functioning. Standard grade-level screening tests (e.g., Wide Range Achievement Test (5th ed.; WRAT5) [35] and perceptual motor tasks (including drawings) and Beery VMI Developmental Test of Visual-Motor Integration (6th ed.; Berry VMI-6) [36] can provide additional information regarding the child's cognitive abilities. Finally, observing the child's play (using drawings, games, and storytelling) can give the clinician a sense of the child's inner world. The child's ability to relate to adults, to cooperate with the examination, and to pay attention and control himself/herself should be noted in the medical record.

For the most part, medical laboratory tests are of little value in making the diagnosis of ADHD. However, given evidence that patients with mildly elevated lead levels (i.e., 10 μg/dL) may present with ADHD symptoms, plasma lead level, free erythrocyte protoporphyrin, and a

complete blood count should be obtained at the initial visit to rule out lead poisoning and iron deficiency anemia. When there is concern about the presence of absence seizures or other neuropathology, an electroencephalogram (EEG) is indicated. If there is evidence of increased metabolism (e.g., elevated resting heart rate, palpitations, tremors, agitation), a thyroid screening panel and a urine screen for vanillylmandelic acid (VMA) should be obtained to rule out hyperthyroidism and pheochromocytoma, respectively.

Cognitive testing is indicated if there is evidence of learning disabilities or if the clinician wishes to quantify the child's degree of inattentiveness and impulsivity on a laboratory measure. Psychometric tests of intellectual ability and scholastic achievement can pinpoint cognitive difficulties which may be interfering with the child's school performance. Speech and language assessment is indicated for children who appear to have communication problems. Neuropsychological measures of attention and impulsivity are not required, although they may be helpful in assessing the effects of medication and/or of specific environmental interventions.

Treatment: Overview

Multimodal treatment of children with ADHD includes psychoeducation, environmental modification, medication, behavior management, school-based interventions, family therapy, and social competence training. While the precise combination of these interventions will vary depending upon the needs of the child and family, no single treatment approach is sufficient, and that to be effective, treatment must extend over long periods of time [37].

Children belong to several social systems including family, school, peer group, and community. Children with ADHD must also relate to several additional professional helpers (both within and outside the school) including clinicians, psychologists, and other mental health and educational specialists. These professionals need to form cooperative relationships with the family, with the child, and with one another to maximize the chances for successful treatment. This requires close communication and occasional meetings to discuss overall treatment goals and plans for achieving these (Fig. 16.1).

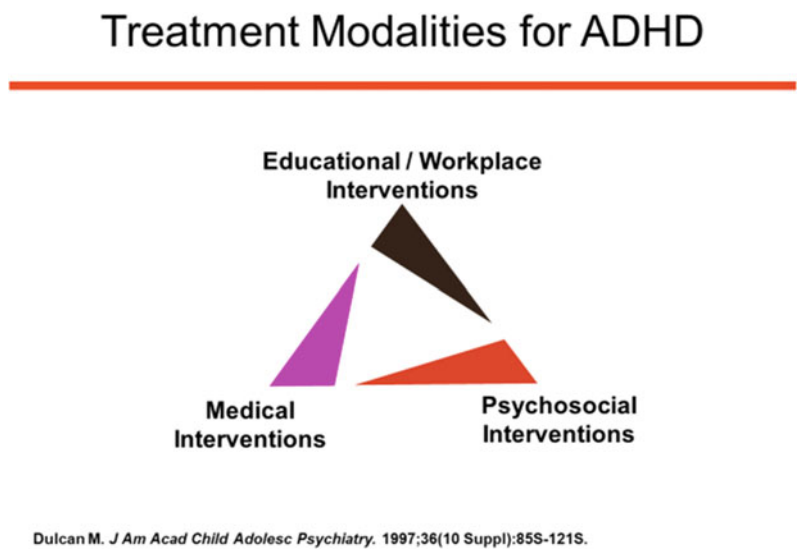

Fig. 16.1 Multimodal treatment of patients with ADHD includes educational or workplace modifications, medications, and psychosocial interventions (e.g. behaviour management, school-based interventions, family therapy, and social competence training). The combination of these interventions should be individualized depending upon the needs of the patient and family. In order to be effective, treatment must extend over long periods of time

A. *Psychoeducation*

The goal of psychoeducation and counseling is to help parents and children cope better with the consequences of having ADHD. Parents and children need reliable information and supportive guidance when confronted with the diagnosis of ADHD. It is important to offer the child and family sufficient time to discuss their concerns and answer their questions. Information should be provided in a comprehensible fashion to clarify misunderstandings or confusion about the facts regarding ADHD. The clinician should emphasize the child's positive traits and the parents' strengths to alleviate feelings of guilt, confusion, and anger. While parents are likely to be relieved to hear that their child's problems are not the result of inadequate parenting; they are also likely to experience grief reactions as they learn more about the implications of the diagnosis. While children may be pleased to hear their problems are not their fault, they are also likely to feel ashamed and resentful about having "something wrong" with them, and they may resist taking their medication or participating in behavioral treatment. It is important for the clinician to monitor the emotional reactions of parents and children, and to be supportive of their efforts to pursue treatment. There are numerous references written for parents that are very helpful in explaining the diagnosis and treatment of ADHD. Support groups for parents of children with ADHD have proliferated in recent years. These groups hold meetings, sponsor lectures, publish newsletters, and offer emotional assistance to families.

B. *Medical Treatment*

While medications have proven to be of short term benefit for children with ADHD, longitudinal studies reveal that medication is only one aspect of treatment and that without behavioral interventions, the child's difficulties at home and at school are likely to persist. The decision to use medication is mediated by several factors including the child's age, severity, and profile of the child's symptoms, comorbidity, and parental attitudes. Children under five years of age are less likely to respond to medications and are at greater risk of having adverse side effects. School-aged children with moderate to severe symptoms of inattention and distractibility (with or without impulsivity and hyperactivity) are very likely to benefit from medication. Children with mild symptoms are also likely to benefit, although it is usually preferable to initiate behavioral treatment prior to starting medication with this group. The presence of other disturbances such as tics, anxiety, aggression or depression tends to influence the choice of pharmacologic agent. Finally, parental attitudes are extremely important to consider when recommending medication. Most parents are ambivalent about starting their child on medication, so it is best to give them ample time to consider the decision carefully. The following guidelines are suggested when instituting a medication regimen: (1) Specify the target behaviors which the medications are intended to ameliorate. Where possible, measure the behaviors; otherwise, use parent and teacher rating scales. (2) Obtain baseline laboratory measures such as CBC, serum electrolytes and liver function tests. (3) Begin with low doses, increase gradually, and aim for the lowest effective dose possible. (4) Follow side effects closely and discontinue the medication if no positive effects are seen or if side effects become severe. (5) Discuss the child reactions to and parents' feelings about the medication. Give support and encouragement if initial results are not as good as expected. (6) Document beneficial and adverse effects on a regular basis.

1. *Psychostimulants*

Modern medicinal use of psychostimulants dates to the 19th century when cocaine was prescribed for a variety of conditions including fatigue and depression. Dr. Charles Bradley first introduced racemic amphetamine sulfate (Benzedrine) as a treatment for severely behaviorally disordered children in 1938. In the 1950s, stimulants were most often used for weight management and as a treatment for narcolepsy. By the 1960s, several types of medication were made available for hyperactivity and impulse control disorders.

Psychostimulants have direct and indirect agonist effects on ∂-adrenergic and β-adrenergic receptors as well as on dopaminergic receptors via three mechanisms: (1) release of stored catecholamines (dopamine and norepinephrine); (2) direct postsynaptic stimulation; and (3) inhibition of presynaptic reuptake of released catecholamine. [Note: methylphenidate works primarily via mechanism 3, whereas amphetamine works via all three mechanisms.]

Meta-analyses have demonstrated that stimulant and non-stimulant medications for ADHD effectively reduce ADHD symptoms in children and adolescents [38, 39]. It is estimated that over 80% of youth with ADHD will demonstrate a positive response to psychostimulants, although it is impossible to predict in advance which medication will produce the best results for any given patient. Clinical effects include: (1) improved behavioral inhibition, and reduced hyperactivity and impulsivity; (2) improved attention/concentration; (3) improved handwriting and fine motor skills; and (4) improved social interactions, especially reduced oppositional behaviors [5, 40].

Standardized measures of cognitive performance with psychostimulants also reveal improvement in attention span, impulse control, short term memory, and problem-solving. These results are seen in both patients with ADHD and normal controls. Cognitive performance of ADHD patients is normalized by medication, but this improvement can be eradicated with improper dosing.

About 5% of patients will experience adverse effects serious enough to warrant discontinuation of the medication. These adverse effects include appetite suppression, gastrointestinal discomfort, sleep disturbance, increased heart rate and blood pressure (clinically insignificant), tics, and minor physical complaints (e.g., headaches, stomach aches). Irritability, dysphoria, heightened anxiety, lack of spontaneity, and oversedation may be seen, but these are often due to overmedication. It appears that a subgroup of children who respond with intense mood lability and dysphoria may be demonstrating early signs of a mood disorder rather than ADHD. This should prompt a change in medication and close monitoring [41].

Extremely serious side effects such as delusions, paranoia, and frank psychosis are rare but can be seen with overdosage and abuse of the medication. In addition, recent concerns have been raised about cardiovascular side effects of stimulants after a rise in sudden deaths in Canada was observed among children and adolescents who had been on these medications. Current recommendations include careful screening for family history of premature deaths from heart disease as well as evidence in the patient of cardiac difficulties or abnormal physical examination.

Clinical and biochemical predictors of non-response or adverse effects to psychostimulants have not been identified, although some authors have noted diminished efficacy of stimulants in ADHD children with symptoms of anxiety. This finding has been challenged in recent studies. On the other hand, it appears that stimulants are helpful in reducing the aggressive behavior of conduct disordered ADHD children.

Discussions with parents and teachers are helpful to identify any incipient problems with the medication. It is also important to decide upon the frequency of medication use. Weekend doses are given for children whose behavior is especially difficult to manage. Weekend medication also assists ADHD children to participate in team sports, church activities, and instructional programs. After a successful response has been recorded, it has become standard practice to switch to long-acting preparations.

It is important to monitor clinical and adverse effects on a regular basis. If the child begins losing weight, the dose and schedule should be revised to optimize appetite around mealtimes. Growth delay, although rarely seen with current dosage recommendations, is an indication for stopping the medication for a time to allow "catch up" growth to take place.

A common side effect seen with stimulants is referred to as "rebound." This usually occurs in the late afternoon or early evening when the medication starts to wear off. Typically, the child becomes restless, hyperactive, inattentive, irritable and prone to temper tantrums and emotional outbursts. Parents should be advised to allow the child to do something enjoyable and to avoid

making too many demands on the child during this time. If the rebound period becomes extremely difficult for the child and family to handle, it may be necessary to adjust or switch medications.

2. *Atomoxetine*

The first FDA approved non-stimulant medication for the treatment of ADHD is atomoxetine (ATX), a norepinephrine reuptake inhibitor that has been demonstrated to have high effect sizes (0.6–1.3) in many studies involving children with ADHD [42, 43]. The advantage of ATX is that it has milder side effects compared to the stimulants and is effective throughout the day and night. Increased CNS norepinephrine levels from ATX are associated with downstream increases in dopamine levels in the frontal cortex without changes in levels found in the nucleus accumbens or the basal ganglia, hence it has few motor side effects and virtually no abuse potential. Side effects include: dizziness, high blood pressure, headache, irritability, nervousness, abdominal pain, nausea, vomiting, loss of appetite, weight loss, dry mouth, constipation, urinary hesitancy, decreased sexual desire, and a very slight chance of reversible hepatic insufficiency. Importantly, ATX has been found to be helpful with ADHD symptoms in patients with comorbid depression and anxiety without any reduction in its effect size [44]. Combining ATX with stimulant medication has been shown to be safe and effective for some but not all patients with partial responses to medication provided via monotherapy [45].

3. *Guanfacine and clonidine*

Guanfacine and clonidine are alpha2-adrenergic agonists that were first introduced as anti-hypertensive agents. Both medications have subsequently been used as adjunctive treatments for ADHD, particularly in combination with psychostimulants. They decrease the tonic and phasic activity of the locus coeruleus, and have direct effects on neurotransmission in the prefrontal cortex, greatly enhancing the effects of norepinephrine and dopamine [9]. They are helpful for patients who are highly aroused, emotionally labile, irritable and explosive, and have proven useful in controlling tics and reducing anxiety, defiance, and aggression. Side effects include sedation, fatigue, dizziness, low blood pressure, slowed heartbeat (bradycardia), dry mouth, indigestion, nightmares insomnia, anxiety depression, and hypertension if discontinued suddenly. Long-acting formulations of both guanfacine and clonidine have been shown to improve symptoms of both impulsivity/hyperactivity and inattention and have received FDA approval for the treatment of ADHD [46–48].

C. *Behavior Management*

Since children with ADHD have trouble controlling their impulses, focusing their attention, and following rules, parents and teachers need to learn basic methods of managing children's behavior. Behavioral management refers to a method of systematically analyzing a child's acceptable and unacceptable behaviors, and of designing programs to maximize the former and minimize the latter. Using techniques such as positive and negative reinforcement, punishments, contracts, response cost, token economies, extinction procedures, environmental manipulation, and stimulus control, parents and teachers can be taught to exert a positive influence on behavior.

The first step in developing a behavioral management program is to specify which behaviors are acceptable and which ones need to be modified. Parents should be asked to make a list of positive and negative behaviors in which the child engages and to rate the relative frequency, duration and/or intensity of each. It is important that parents learn to focus more of their attention on the child's positive behaviors and to "catch them being good" as often as possible. By shifting energy and attention to the child's "good" behaviors, parents will inevitably spend less time harping on the "bad".

The next step is for parents to choose a specific behavior (or behavioral sequence) which they would like to change. They should describe the behavior in ways that can be observed and measured. For example, instead of stating that

the child "takes too long getting dressed in the morning," parents should be able to specify how long it takes for the child to get dressed, and how many verbal and physical reminders the parents provide on average during this time. Most parents will need to buy a stopwatch, observe the child closely, and record the time he/she spends getting dressed versus engaging in other distractions. It is generally best for parents to begin by focusing on a relatively simple behavior which is easy for the child to perform and for the parents to observe and quantify.

Behaviors like getting ready in the morning, doing homework, putting toys away, completing chores, reducing temper tantrums, and getting ready for bed are good for starters. It is also important for parents to consider factors which might prevent the child from successfully accomplishing the task. For example, if homework is difficult for the child to understand because of an aversion to school or a fear of failure, additional support will need to be provided to the child to help him/her to overcome their avoidant behaviors.

Once a target behavior is chosen, parents will need to identify ways to increase the child's motivation to cooperate. Rewards should be given for successful efforts, and penalties should be given for overt resistance or major oppositional behavior. Lack of success despite a clear effort on the part of the child should neither be penalized nor be rewarded. Rewards and punishments should be salient to the child. Rewards include points or stars which can be traded in for a material object, special time ("time in") with a parent or a friend, or "free time" at a favorite activity (Premack principle) such as TV or videogames. Punishments include "time-out;" temporary loss of access to a favorite game, toy, or activity; loss of a privilege; "grounding;" extra chores; and loss of allowance or some other financial penalty. It is helpful to caution parents that children with ADHD tend to lose interest in rewards and penalties rather quickly, so it will be necessary to vary these on a regular basis.

An accounting system must be set up to keep track of the child's performance and to distribute the rewards and penalties in an impartial fashion. It is important that parents not get angry or engage in lengthy discussions with the child when they are administering a penalty. If a "time-out" procedure is being employed, this should be done with relative calm so that the child does not get the impression that the parent dislikes having to carry it out. If the parent can maintain a "matter-of-fact" attitude when a penalty is administered, the potential for secondary gain (i.e., increased attention from the parent) is diminished.

Once parents have decided upon the rewards and penalties, it is advisable for them to draw up a contract. The contract should include the date on which the agreement begins, the specific behaviors which are being targeted for change, the types of rewards and penalties which will be used to enforce the contract, the accounting system which will be used to keep track of rewards and penalties, the time and frequency of rewards, the start and duration of penalties, and the schedule for reviewing the contract. For instance, if a point system is being introduced, it is best to specify how many points the child will receive for performing the desired behavior, how many points he/she will lose for failing to comply, and how the points can be turned into rewards.

Initially, it should be relatively easy for the child to earn enough points to receive a desired reward within a short period of time. Point values can be raised and lowered depending upon the child's willingness to comply. More points should be given for behaviors which the child strongly dislikes (e.g., homework or bedtime) to increase his/her motivation.

The contract should be written in a language that the child can understand and should be posted in a prominent place in the home. Once it has been discussed and reviewed, the contract should be signed by everyone who will be involved in its enforcement (including other adults).

After the contract becomes operational, its efficacy will need to be closely monitored, and its terms will need to be refined and corrected to ensure that it is helping the child achieve the desired behavioral changes. Parents should expect that the contract will work nicely for a

while and that the child will get "bored" with it and will test the parents' determination to enforce it. When this begins to happen, it is imperative that the parents do not give up and abandon the program but that they examine what is going on. If they discover that the child is having trouble earning sufficient points to receive any rewards, either the target behavior is too difficult for the child to perform easily or the reward system may not be of sufficient motivational strength to engage the child. If the child has earned too many points too quickly, it means that the system is not challenging enough. The child should be succeeding at the desired behavior roughly 70–80% of the time. If he/she is succeeding more often, the task should be made more difficult; if less often, it should be made easier.

Although there is often some initial resistance to the new system, most children learn to follow the rules of the contract and feel pleased when they are successful. Some children will have suggestions about rewards or penalties. Adolescents will want to have a voice in determining the specific conditions, so they should be involved early in the process of developing a contract.

Parents who exhibit difficulties with attention, organization, and follow-through may not be able to consistently and effectively implement a behavioral management program. Individuals that are potentially at risk include (a) parents with ADHD, depression and/or other psychiatric issues; (b) single parents; (c) marital couples in conflict; and (d) parents with limited financial and coping resources. These parents will need special assistance and support in developing, monitoring and implementing successful behavioral programs [49].

It should always be kept in mind that the purpose of any behavioral management system is to help the child learn to follow rules and to complete important tasks. This is a major challenge for most children with ADHD, and parents will need to work very diligently to keep a behavioral management program running. Although it takes a great deal of patience, resourcefulness, and perseverance, parents can look forward to significant rewards for the child and the family. If the program succeeds in improving the child's ability to care for himself/herself and in increasing his/her self-control, it will have the added benefits of reducing stress and improving the emotional climate of the family.

Tourette Disorder

Definition

The hallmark characteristics of Tourette Disorder (TD), motor and vocal tics, have interested clinicians and scientists for over a century since their initial description by Gilles de la Tourette in 1885. A tic is a sudden, rapid, involuntary, nonrhythmic repetitive movement, gesture or utterance that typically mimics some fragment of normal behavior.

Simple motor tics are usually fast, darting and meaningless (e.g., shoulder shrugging, eye blinking, head jerking, face grimacing, neck thrusting) whereas complex motor tics are slower and consist of clusters of simple movements or a coordinated sequence of movements that may seem to be purposeful (e.g., hopping, clapping, touching, tapping, poking, smelling, kissing, brushing hair). Occasionally, motor tics lead to secondary injuries such as neck pain or spinal cord damage from severe head tossing; serious eye pain from eye squinting; tooth trauma or fracture due to jaw snapping; serious bruises, sprains or fractures from punching, slapping, or slamming body parts; as well as other forms of self-injurious behaviors [50, 51].

Simple phonic (vocal) tics are similarly fast, darting and meaningless (e.g., coughing, grunting, yelping, humming, sniffing, throat clearing, barking, other animal noises) as compared to complex phonic tics that are linguistically meaningful utterances (including syllables, words, phrases, statements, mutterings, and other expressions of speech). Echolalia (repetition of others' words), palilalia (repetition of one's own words), and coprolalia (uttering obscene words) are common variations of complex phonic tics.

The DSM-5 criteria for Tourette Disorder [2] include:

- Presentation of multiple motor tics and one or more phonic tic. Motor and phonic tic presentation need not be concurrent.
- Tics may wax and wane in severity (frequency) but have persisted for more than 1 year since initial tic onset
- Onset before 18 years
- Disturbance not due to direct effects of substances (e.g., stimulants) or underlying medical condition

Other DSM-5 clinical syndromes involving tics include Transient Tic Disorder; Chronic Motor or Vocal Tic Disorder; and Provisional Tic Disorder. Together, these represent the spectrum of tic disorders of which Tourette Disorder (TD) is the most complex. This section will focus on TD as it is the best studied and most clinically challenging tic syndrome.

Phenomenology

Typically, patients with TD begin to demonstrate symptoms of ADHD (hyperactivity and impulsivity) during early childhood (4–6 years), with simple motor tics manifesting a little later (6–8 years) followed by complex motor tics (8–10 years). Simple phonic tics usually start somewhat later (10–11 years) with complex tics beginning after 12 years old. Over the course of these manifestations, obsessions and compulsions are also very commonly seen. Indeed, the presence of OCD symptoms in patients with ADHD should alert clinicians to the possibility of the emergence of TD during the subsequent clinical course and should prompt an inquiry into the presence of tic symptoms, even those that initially appear to be transient in nature. The gradual unfolding of its clinical manifestations, along with the variety of tics and of associated problems (some of which often seem to overshadow the tics) often cause delays in the diagnosis of TD.

While specific tics are typically of short duration, the pattern of their onset is highly individual. Peterson and Leckman [52] studied the time course of these "tic bouts" and observed a temporal course that waxes and wanes on a daily, weekly, monthly and even yearly basis ("bouts of bouts" and "bouts of bouts of bouts"). While the mechanisms determining the timing of these bouts are not well understood, there are seasonal variations as well as proximal events (e.g., psychosocial stressors) that signal the start and the ending of tic bouts. It is clear, however, that the peak age of tic activity is between 8 and 12 years with a gradual lessening of frequency and intensity of tics during the late adolescent period.

Premonitory urges are aversive focal perceptions or sensations (e.g., increasing tension, pressure, itch) that signal a tic is about to occur [53]. They are usually localized to a specific body part and are seen in about 37% of young children and up to 90% of adolescents [54]. The presence of premonitory phenomena suggests that TD involves an inability to filter and/or suppress internal stimuli and has led some to consider tics themselves to be "involuntary" responses to involuntary sensations [55]. These sensory phenomena are often described as a feeling of mounting inner tension or urge to move ("premonitory urge"), which is transiently relieved by tic expression. Reportedly, many individuals with TS can suppress the expression of a tic, but this inhibition becomes increasingly uncomfortable, leading to the uncontrollable release of the tic [56].

Obsessive-compulsive symptoms associated with TD often present the greatest challenges to clinical care. Common obsessions include mental echolalia, need for exactness or symmetry, aggressive or violent thoughts, obscene thoughts (e.g., exposing oneself, kissing or having sex with others), counting, grouping, and somatic obsessions or bodily sensations. Common compulsions include placing objects just right (symmetry), ordering, arranging, hoarding, touching certain objects (e.g., doorways), tapping, checking and rechecking, smelling, licking, cleaning, washing, and repetitive phrases. More unusual compulsions can include washing and cleaning a car for 7 hours at a time, organizing baseball cards all day long, being unable to drink from a cup that has been touched by someone else, and touching the

burners on a stove in order. The particularities of TD-related OCD symptoms have led to the concept of "tic-like" obsessions and compulsions which can be distinguished from typical symptoms seen in OCD by their somatosensory, visceral quality. A sense of "incompleteness," "imperfection" ("just not right") and "symmetry seeking" behaviors differentiate tic-related OCD from non-tic OCD [50, 57, 58]. From the standpoint of treatment, the OCD symptoms seen in patients with TD are more difficult to treat both medically and psychosocially.

Prevalence and Etiology

The prevalence of transient tic disorders in children is approximately 14% with a slightly higher preponderance in boys (18%) as compared to girls (11%). Chronic motor tics have a reported prevalence of 0.5–2%. The estimated prevalence of TD cited in the literature (0.25–5.7%) is highly variable due to differences in both in epidemiologic study methods and genetic variations across populations [59]. Recent meta-analyses suggest the rate is between 0.6–0.8% [60, 61].

Risk factors for TD include gender (male predominance), perinatal adversity, presence of pervasive developmental disorders, and heredity (population-based heritability estimate = 0.77). Concordance of TD in monozygotic twins is 60–80% and in dizygotic twins is less than 20%; concordance of chronic tics in monozygotic twins is 77–90% and in dizygotic twins is 23%. Genetic risk to first degree relatives of males with TD is > 50% including 18% TD, 31% chronic motor tics, and 7% OCD. Risk to first degree relatives of females with TD is > 30% including 5% TD, 9% chronic motor tics, and 17% OCD [62–64].

Despite compelling evidence from twin and family genetic studies pointing to the heritability of TD, a specific set of genes contributing to the expression of the disorder has not yet been identified. This is due to several factors including difficulty with defining the phenotype, a more complicated mode of inheritance than was initially hypothesized (e.g., genetic imprinting), and the likely heterogeneous location of multiple risk genes on several different chromosomes ("locus heterogeneity"). There have been sporadic reported cases of chromosomal mutations associated with TD, but these are not seen as relevant to most cases in the population. For example, studies have found atypical genes in several TD patients (including chromosomal translocation, point mutation, and missense mutation) at the *SLITRK 1* locus [65–67]. These atypical genes have also been associated with ADHD and OCD. Researchers are now examining the biological activity of this gene which appears to play a role in neuronal migration during the late embryonic period. It appears that the protein expressed by this gene is associated with projection neurons of cortico-striatal-thalamic-cortical (CSTC) circuits, and that plays a significant role in the development of these circuits [68]. While these mutations at the *SLITRK 1* locus are *not* found in most TD patients [69] this line of research may prove helpful in linking specific genetic mechanisms to neurodevelopmental psychopathology in TD and related disorders of CSTC circuitry. The potential contribution of epigenetics to understanding the developmental psychopathology of TD and other neurodevelopmental disorders is leading to new methods for identifying susceptibility gene variants that will be studied via linkage to biobanks, electronic medical records, and neuroimaging genetics consortia like ENIGMA (see http://enigma.ini.usc.edu for more details) [70].

Another proposed etiology for TD and tic disorders is based in neuroimmunology. Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) is marked by the sudden onset of obsessive-compulsive disorder (OCD) or eating restrictions along with comorbid symptoms from two of seven categories: anxiety (especially separation anxiety), emotional lability or depression; irritability, aggression, and/or severely oppositional behaviors; deterioration in school performance (due to ADHD-like behaviors, memory deficits and cognitive changes); sensory or motor abnormalities; and somatic signs and symptoms such as sleep disturbances, enuresis, and urinary frequency [71–73]. Previously, this syndrome was known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection

(PANDAS) [74], but the ensuing scientific controversy regarding its validity as a distinct neuro-immunologic disorder, and the failure to show clear links between Group A beta-hemolytic streptococcal infections and exacerbations of tics or OCD symptoms in identified patients with PANDAS has led to a reconsideration of this condition. Most cases of PANS are thought to be postinfectious in origin, although no single microbe must be identified to make the presumptive diagnosis. In addition to streptococcus, other infectious agents suspected to be linked to PANS include mycoplasma pneumoniae, influenza, Epstein Barr virus, and Borrelia burgdorferi (the causative agent in Lyme disease). Symptoms generally emerge 7–14 days after an acute infection and follow primarily a relapsing/remitting course with symptom flares months to years after the initial flare. The prevailing hypothesis about the pathophysiology of PANS is based on molecular mimicry insofar as antibodies directed against infectious agents such as Group A strep may target brain proteins and either directly stimulate or block receptors of the basal ganglia. In this model, cross-reactive antibodies interfere with neuronal signaling and lead to dopamine system dysregulation which evokes the complex set of clinical symptoms seen in this condition. While the presence of anti-basal ganglia antibodies was reported in early studies of PANDAS, later studies have failed to replicate these findings, hence the current model remains unproven. Treatment approaches for the variety of symptoms associated with PANS include the same behavioral interventions and psychiatric medications employed in non-PANS neuropsychiatric conditions, as well as novel treatments like antibiotics and immunomodulation [71, 73].

Neurobiology

A growing body of scientific research is converging on the role of cortico-striatal-thalamic-cortical (CSTC) circuits in the pathophysiology of tic disorder, TD and related conditions. There are several excellent reviews of progress in this area [53, 70, 75–77] that concisely summarize the complex interaction of disrupted neuronal circuits along with neurotransmitter abnormalities resulting in TD. It is now understood that the basal ganglia (comprised of the striatum, subthalamic nucleus, globus pallidus, and substantia nigra), historically considered to be a subcomponent of the motor system, play a major role in cognitive function and emotional regulation of the organism via rich connections with the frontal cortex and the limbic system (see Fig. 16.2).

The basal ganglia act to enhance desired behaviors and inhibit unwanted or competing behaviors, and these activities are disrupted in tic disorders, TD and related conditions such as OCD and ADHD, all of which can be viewed as disorders of impaired inhibition of unwanted behaviors. Of note is that the circuitry of the basal ganglia and their connections with cortex and thalamus follows a topographic organization that mediates the distinct functions these circuits play. Normal functioning of the CTSC circuits is necessary for healthy behavior and adaptation. Presumably, a wide variety of neuropsychiatric symptoms may emerge from disruptions in these circuits, and the severity and extent of these disturbances may determine the nature and the course of disorders seen. It is beyond the scope of this chapter to describe the neurobiology in detail, however, the following illustration (Fig. 16.3) nicely diagrams key features of the pathophysiology of TD as it is currently understood.

Many neurotransmitters are involved in the functioning of the CTSC including dopamine, glutamate, GABA, serotonin, acetylcholine, norepinephrine and endorphins. While the dopamine system has been the most extensively investigated in TD, it is important to keep in mind that imbalances in any of these transmitters can result in pathology because they interact closely hence disturbances in one chemical can lead to imbalances in the functioning of the others. PET studies of dopaminergic systems have demonstrated increased dopamine receptor density in the ventral striatum of patients with

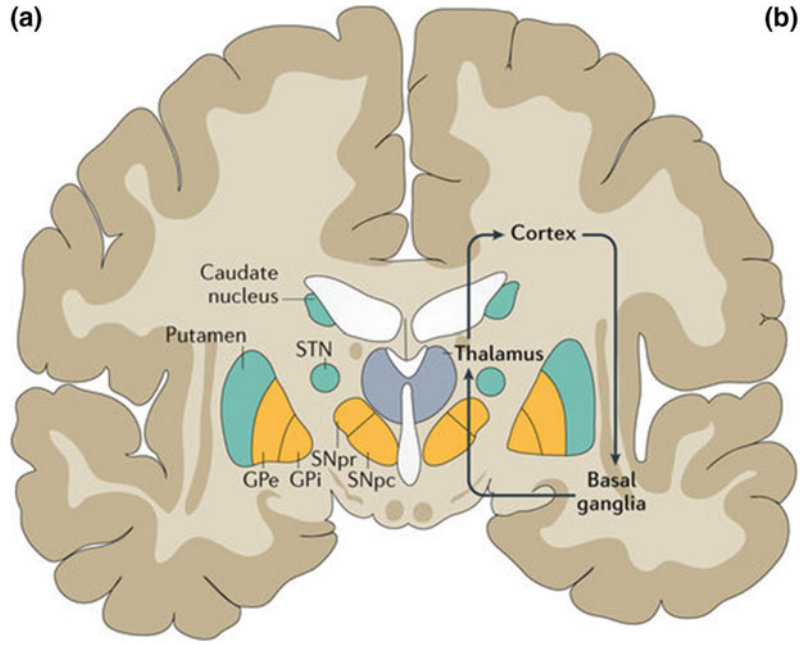

Fig. 16.2 The cortico-striato-thalamo-cortical (CSTC) circuit is a complex interconnection between the cortex, basal ganglia and thalamus, which regulates complex behaviors and involves many neurotransmitters (including dopamine, glutamate and γ-aminobutyric acid (GABA)). An imbalance in one or more of these neurotransmitters might explain some of the characteristics of Gilles de la Tourette syndrome (GTS) (From Robertson et al. 2017, p. 10.)

TD [78] suggesting hyperinnervation in these structures. Other studies have documented high concentrations of dopamine transporters along with increased intrasynaptic dopamine release. Taken together, these and related findings [79] indicate that TD results, in part, from atypical dopamine functioning in the CTSC. Singer [55, p. 154] summarizes the disrupted "tonic-phasic model of dopamine release," a unifying hypothesis, as follows: "Reduction in tonic (basal) dopamine, thought to be due to an overactive dopamine transporter system, could result in a system with high concentrations of dopamine receptors and an increased phasic release of dopamine. If TS is associated with excess nigrostriatal dopaminergic activity, either via supersensitive dopamine receptors, dopamine hyperinnervation, or abnormal presynaptic terminal function, a substantial hyperkinetic effect is expected … Because dopaminergic fibers arise from the ventral tegmental area and form synapses on both pyramidal neurons (stimulate) and interneurons (inhibit) within the prefrontal cortex, we have hypothesized a prefrontal dopaminergic abnormality."

In view of the above, the following is a plausible (albeit simplified) model for understanding the pathophysiology of TD. To start with, during the perinatal period, some genetic defect or vulnerability combines with unknown external factors to disrupt normal CNS development, perhaps the impairment of normal programmed cell death ("developmental apoptosis"). This, in turn, leads to overactivation of the dopamine system (increased dopamine transmission and/or dopaminergic hyperinnervation and/or abnormal presynaptic terminal functioning) especially in the striatum and the limbic system along with deficits in the prefrontal cortex. The result is impairment of CTSC circuits which cause impaired inhibition (tics), decreased restraint or self-control (impulsivity), and impaired executive functioning

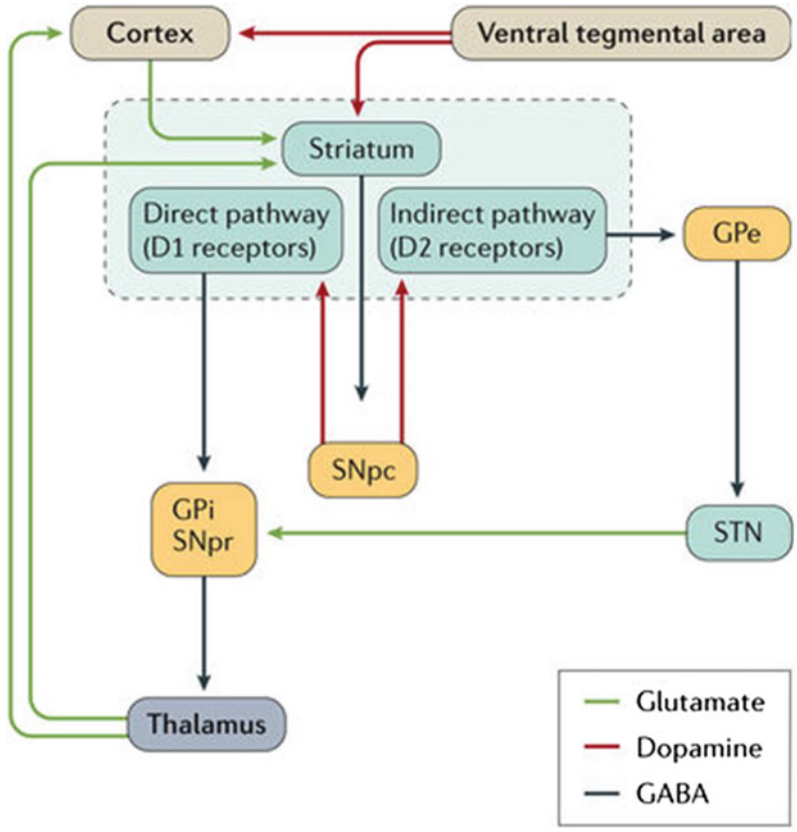

Fig. 16.3 A simplified CSTC circuit includes projections from excitatory glutamatergic pyramidal neurons located in the frontal cortex to GABAergic medium spiny neurons (MSNs) in the striatum. Striatal output pathways include a direct pathway that transmits striatal information monosynaptically to the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNpr) and an indirect pathway that conveys information to these same regions via a disynaptic relay from the globus pallidus externa (GPe) to the subthalamic nucleus (STN). Direct pathway MSNs express dopamine D1 receptors, muscarinic M1 and M4 acetylcholine receptors and the neuropeptide substance P. Indirect pathway MSNs express dopamine D2 receptors, muscarinic M1 receptors, adenosine A_{2A} receptors and enkephalin. Each pathway has an opposing effect on GABAergic GPi and SNpr output neurons: the direct pathway inhibits and the indirect pathway stimulates. Consequently, these pathways have a reverse effect on excitatory projections from thalamic neurons to the frontal cortex and striatum, and, in turn, the facilitation of motor activity. Specifically, activation of the direct pathway facilitates motor activity, whereas activation of the indirect pathway reduces motor activity. The dopaminergic pathway, which is likely to be involved in GTS, is also indicated. SNpc, substantia nigra pars compacta (From Robertson et al. 2017, p. 10.)

(especially in set shifting and attention regulation). While it is still unclear where in these circuits the initial lesions occur, gradually, as these neuronal networks attempt to adapt to environmental stimuli (stressors) and to changes in internal states, symptoms emerge such as impulsivity, poor attentional control, tics, obsessive-compulsive patterns, and emotional dysregulation. Indeed, recent reports suggest that functional disturbances within these fronto-striatal circuits lead to problems with "self-regulatory control" which may form the underpinnings of several childhood psychopathologies including Tourette Disorder, Obsessive-Compulsive Disorder, Trichotillomania, Bulimia Nervosa, Anorexia Nervosa and ADHD [75].

Associated Conditions/Comorbidity

As mentioned above, tic disorders and TD are often accompanied by other psychiatric conditions, most notably ADHD, Obsessive-Compulsive Behavior (OCB), Obsessive-Compulsive Disorder (OCD), anxiety disorders (especially social phobia), mood disorders, Oppositional-Defiant Disorder (ODD), aggressive behavior (notably rage episodes), learning disorders, and disorders of executive functioning.

Approximately 50–70% of patients with TD presenting for treatment exhibit signs of ADHD [80, 81]. Given that the community prevalence rate of ADHD is roughly 5%, its rate among children with tics is roughly *10 times* that of the general population. This high rate of comorbidity is hypothesized to be due to overlapping or shared disruption of the CTSC circuits involved in each disorder (described above). It appears that ADHD accounts for almost all the aggression and delinquency seen in the TD population (i.e., TD-only patients show the same rates of these problems as control population). Academic, social, and occupational difficulties seen in ADHD + TD are virtually identical to those seen in ADHD-only patients. It is well documented that ADHD is highly comorbid with learning disabilities. Interestingly, TD-only patients do *not* have higher rates of LD than the control population. Moreover, ADHD is highly comorbid with affective instability, anxiety, and mood disorders as well as later substance abuse. Finally, ADHD carries significant risk for lifelong psychiatric morbidity in TD. Many of the lifelong difficulties seen in patients with ADHD + TD are attributable to the ADHD. This underscores the importance of inquiring carefully about the presence of ADHD in these patients.

Roughly 60–90% of TD patients exhibit OCB and 40–60% meet criteria for OCD, both of which carry along with them substantial morbidity. Moreover, the additional burdens of obsessiveness and perfectionism have been shown to have a significant negative impact on the quality of life of TD individuals. Indeed, the spectrum of OCB/OCD symptoms constitute the most impairing and treatment-resistant features of complex TD and are highly linked to the most malignant cases [70, 82].

Apart from OCD, children and adolescents with tics and TD are at higher risk for other anxiety disorders and mood disorders, although most studies have been conducted on clinic as opposed to community samples, hence the epidemiology of these conditions in non-clinic samples is not well documented. With respect to patients seen in either specialized or nonspecialized clinics, rates of non-OCD anxiety disorders range from 50 to 67% and of mood disorders (including bipolar disorder) from 23 to 76% depending on the sample studied [83].

Aggressive symptoms in TD have also been reported in both community surveys and clinic studies. A worldwide survey of 3,500 individuals with TD from 22 countries found that 37% reported a history of "anger control problems" and 25% stated these were of ongoing concern [84]. Clinical studies report that anywhere from 25 to 70% of patients with TD have anger control problems including recurrent behavioral outbursts and irritability. The frequent display of explosive anger (rage attacks) is sometimes referred to as "R.A.G.E." or "recurrent anger-generated episodes" [85].

Neuropsychological Functions

Learning, memory and executive functioning disorders have been widely investigated in children with tic disorders and TD, and there is still no clear consensus as to whether neuropsychological deficits are a characteristic of these disorders or are better viewed as a comorbid feature [86]. There is consensus that overall intellectual ability is in the normal range, and evidence suggests there are lower performance IQ scores in this population, but controversy remains regarding the nature of the discrepancies seen between verbal and nonverbal abilities [87]. Part of the difficulty lies in the heterogeneity of population samples, especially with respect to comorbid conditions such as ADHD and OCD. A study by Channon et al. [88] compared 29

patients to 21 controls on a series of neuropsychological tests. Patients were divided into three groups: Tourette Disorder only, TD plus OCD, and TD plus ADHD. Of note, the TD-only group showed impairment in one task involving inhibition and strategy generation, but was otherwise no different from the control group. The TD + ADHD group demonstrated impairment on several executive function measures (inhibition and strategy generation, multitasking, rule following and set shifting) but not on memory and learning. The TD + OCD group did not differ from controls on any neuropsychological measures. Interestingly, the severity of tics did not account for differences in neuropsychological functioning among the TD groups. The lack a of relationship between executive functioning and tic severity for uncomplicated TD (the absence of comorbid psychiatric disorders) has been replicated by others (e.g., [89]). Likewise, support for children, adolescents and adults with TD exhibiting deficits in executive function, particularly inhibitory control, has also been documented in many studies [90, 91]. However, contradictory results for the presence of executive deficits and the relationship of these deficits to tic severity are also evident, [87, 92] highlighting the need for additional studies to disentangle the effects of potentially moderating variables (age, gender, comorbid conditions, intelligence, medication, tic severity, cognitive task employed, type of referral) on executive functioning.

Increasingly, social cognitions and interactions of individuals with TD are being investigated. Most studies have involved adult populations, although children and adolescents are receiving greater attention. Adults with TD have been found to differ from control participants on measures of social cognition assessing perspective-taking and relating emotionally to others, social reasoning and problem-solving, and comprehension of faux pas and nonliteral language (sarcasm and metaphors) [93, 94]. Children and adolescents with TD have been found to struggle with peer bulling and victimization, lower social interaction/competency scores, and increased internalizing behaviors (anxiety/depression) [95–97]. While an earlier study by Channon et al. [98] determined that children with TD did not exhibit deficits in social cognition, two recent investigations [97, 99] do suggest weaknesses in this social domain. Again, there is a need for further studies to determine the presence or absence of deficits in social cognition and related interpersonal behavior for childhood/adolescent TD populations. The important point to keep in mind is that each child with a tic disorder or TD needs to be evaluated individually for the presence of learning, memory and executive functioning difficulties, social problems and the presence of ADHD symptoms since these issues may be a harbinger of other neuropsychological problems.

Clinical Evaluation

The evaluation of patients with tic disorders and TD should include assessment of (1) tic severity and level of impairment, (2) obsessions and compulsions, (3) anxiety and mood symptoms, (4) ADHD symptoms, (5) *oppositional*-defiant and aggressive behaviors, and (6) learning difficulties including academic skill disorders and difficulties with executive functioning [70, 100].

Motor and phonic tics should be delineated and quantified as precisely as possible. The most widely used instrument for doing this is the Yale Global Tic Severity Scale (YGTSS) [101] which identifies the types of tics (motor, phonic/simple, complex), and quantifies each of them on a scale of 0–5 along the following dimensions: number, frequency, intensity, complexity, and interference. From these, motor tic and phonic tic scores (each ranging from 0–25) can be obtained, as can the total tic score (0–50). Scores of > 20 are in the moderate to severe range. It is also possible to quantify the degree of impairment from the tics (0–50). The total Global Severity Score is calculated by combining the total tic and impairment scores.

Obsessions and compulsions are also important to investigate systematically. The Children's Yale–Brown Obsessive-Compulsive Scale (CY-BOCS) [102] is a clinician-administered structured interview that identifies the patient's

major obsessions and compulsions, and then quantifies them on a scale of 0–4 along five dimensions: amount of time spent on obsessions or compulsions, interference with life activities, subjective distress, resistance to obsessions or compulsions, and degree of control the child feels over the obsessions or compulsions. Three scores are obtained: obsession (0–20), compulsion (0–20) and total O-C (0–40) scores, with a total score of greater than 16 being clinically significant.

Anxiety and mood symptoms can be assessed through a standard clinical interview along with standardized instruments such as the Multidimensional Anxiety Scale for Children (2nd ed.; MASC-2) [103] and the State-Trait Anxiety Inventory for Children (STAI-CH) [104], as well as the Children's Depression Inventory (2nd ed.; CDI-2) [105] and the Children's Depression Rating Scale–Revised (CDRS-R) [106]. Attention should be paid to the presence of mood swings and profound irritability which might indicate a disruptive mood dysregulation disorder or the onset of bipolar disorder. ADHD symptoms should be elicited in a similar manner through direct questioning as well as via scales such as the Attention-Deficit Hyperactivity Rating Scale (5th ed.; ADHRS-5) [107], the Conners (3rd ed.; Conners 3) [108], and the Barkley and Murphy Symptom Checklist [109]. Other issues such as oppositional-defiant behavior, serious rule breaking, temper tantrums and aggressive acts toward property and people warrant careful review and evaluation. While there is no indication that children with tic disorders and TS are at higher risk for these disruptive disorders than the general population, it is also the case that severe tics coupled with anxiety and moodiness can result in hostile, aggressive, and explosive acts [90], especially when children already stressed by the demands of school, family and peers have to expend a great deal of energy suppressing their tics or carrying out their compulsive behaviors. These children easily become angered and explosive when they are either frequently interrupted during their compulsive behaviors, or when they are pressured to stop these behaviors and to transition from one activity to another before they feel ready to do so.

Finally, as with all children presenting with atypical neurodevelopment, the presence of learning disorders, including impaired executive functions, should be screened for and carefully evaluated where appropriate. Readers are referred to other sections of this handbook for more details regarding evaluation methods. It is important to remember that proper consideration must be given to the impact of complex tics and OCD symptoms on time-based performance of motor and cognitive tasks [110] since it is very common for timed tests to underestimate the abilities of children and adolescents with tic disorders and TD. It is particularly helpful to assess the level of interference in task performance that is present in the actual testing situation, and to assess how much interference is present in classroom settings and in the home while performing homework and other tasks involving mental effort.

Treatment

Treatment for tic disorders and TD is primarily symptomatic, as there is currently no intervention that can repair the presumably altered neural circuits underlying these conditions. The following section will focus on psychosocial and medical interventions for tics, with a brief discussion of managing the major comorbidities (i.e., ADHD, OCD, and aggression).

A. *Psychosocial interventions*

Family psychoeducation is the first phase of intervention for tics and Tourette Disorder. This includes assisting family members to accept the diagnosis of TS, helping them to learn about TD (e.g., clinical course, complications, neurobiological basis, and treatment approaches) and pointing out helpful resources like the Tourette Syndrome Association (TSA) and other support groups. These resources are especially useful in reducing the stigma associated with chronic tic disorders and TD. It is important to encourage parents to educate those in the child's immediate network (extended family, teachers, friends,

classmates) about the facts regarding TD to reduce negative social consequences (e.g., teasing, bullying, or attempts by adults to discipline the child for exhibiting tics). It is also important to identify local clinical and educational resources that are most likely to be of assistance to the child and family, and to encourage teamwork among these professionals. Setting priorities for treatment and targets for change, assessing patient and family readiness for change, and identifying barriers to successful coping are equally important tasks for clinicians. The goal of psychoeducation is assisting the family to develop effective coping strategies, including forming successful partnerships with helping professionals.

Given the complex interplay of clinical symptom patterns in this disorder, after a comprehensive assessment has been completed it is important to set priorities and realistic expectations for treatment. It is a good idea to focus on the most severe, prominent and impairing symptoms first. For example, if impulsivity and hyperactivity are more disruptive than the tics, focusing on the ADHD symptoms is advisable. It is also helpful to start with the "easier to treat" aspects of the child's presenting problem. In cases where ADHD is of most immediate concern, working on circumscribed issues such as following a simple sequence of behaviors to get ready for school will help the child and family become engaged in treatment and motivated to tackle the more complicated issues. It is worth noting that if tics are not really causing significant problems for the child (i.e., they are not interfering with daily routines, not self-injurious, and are not causing embarrassment or social impairment), they are best left ignored. Parents and other family members may need to be reassured that the tics are not harming the child and that avoiding negative reinforcement is the best way to help their child cope with them.

A promising behavioral intervention for chronic tic disorders that has been shown to be effective in controlled clinical trials of adults and children is habit reversal therapy (HRT) [111–115]. The basic components of HRT are awareness training, competing response training and social support. Awareness training is designed to increase an individual's understanding of his/her own tics through four steps: response description, response detection, early warning procedures, and situational awareness training. Following the awareness training phase, patients are taught to practice competing responses to their tics ("reversal training") to block the performance of tic behaviors. This may involve contracting opposing muscles to those in which an urge to contract is being felt. It may also include "shaping strategies" to enable the child to redirect the tic into a less socially noticeable behavior. Social support is elicited to reinforce proper implementation of competing responses and to remind patients to use these tactics appropriately.

More recently, functional enhancements of HRT have been developed to reduce the frequency and onset of tics and to increase rewards for treatment adherence. Comprehensive behavioral intervention for tics (CBIT) has been shown to be highly effective and is now considered front line treatment for tic disorders and TD [70, 116].

Other psychosocial interventions that have been shown to be helpful in managing ADHD, OCD, and aggressive behaviors utilize cognitive behavioral therapy strategies. For instance, behavioral parent training and family behavioral interventions have been proven to be effective for ADHD symptoms. Parents should be encouraged to set behavioral rewards and consequences to promote self-control, self-regulation, and inhibition in children. School-based interventions and summer recreational programs have also been shown to be effective for ADHD. Executive function difficulties (e.g., organization, planning, set shifting) and attention deficits may be helped via environmental redesign, accommodations, and ongoing assistance with challenging tasks. CBT techniques such as self-monitoring, self-evaluation, and self-management procedures can assist older children and adolescents to gain greater self-control.

Symptoms of OCD, particularly compulsive behaviors, are best treated with a modified form of CBT [117]. The neurobiological and self-reinforcing aspects of tic-like obsessions and compulsions make them more difficult to treat

than non-tic-related OCD. Since many OCD behaviors are an outgrowth of the chronic tic disorder, clinicians need to spend time at the outset assessing the child's view of these behaviors and helping the child to choose which are most important for him or her to master and change. It is also important to address barriers to treatment (e.g., negative self-efficacy and learned helplessness) since many children who come to treatment have already tried unsuccessfully to alter their rituals and compulsions.

Problem-solving strategies for addressing oppositional-defiant behavior, anger outbursts, and hostility-aggression are best introduced using a family systems model of care. Approaches like collaborative problem-solving model [118] have shown some promise in reducing oppositional and aggressive behaviors in inflexible children. Unlike traditional contingency management approaches for negativistic behaviors, these strategies introduce an understanding of the neurobiological underpinnings of many behaviors (e.g., compulsions, fixations) into the treatment model. For instance, it is important for the family to introduce methods for helping the child self-soothe and shift focus when they are becoming frustrated, to identify important triggers of the challenging behaviors, to redirect the child's attention and behavior to positive goals, and to minimize, where possible, negative emotional interactions that serve to reinforce defiance and aggression.

B. *Medications*

Tics should be treated medically only if they are causing pain or injury, social or emotional problems and/or marked functional impairments. The medications most commonly used for tics are dopamine blocking agents (i.e., neuroleptics/antipsychotics) and alpha2-adrenergic agonists (clonidine and guanfacine). While the precise mechanisms of action of these agents is beyond the scope of this chapter, it is important to note that the differences in these two classes of medications permits them to be used together.

Dopamine-blocking antipsychotic medications were first shown to be effective in the treatment of tics in the mid-1960s, when haloperidol was first reported to be successful in many case studies. Subsequent controlled clinical trials demonstrated the efficacy of haloperidol, pimozide, fluphenazine and the substituted benzamides (tiapride, sulpiride, and amisulpride) in reducing the severity, intensity, and frequency of tics. Of these, only pimozide and haloperidol are FDA approved. In Europe, tiapride is the preferred dopamine blocking medication because it does not interfere with cognitive functioning. Mounting concern about the side effects of these typical antipsychotics (e.g., akathisia, dystonia, parkinsonism, tardive dyskinesia, sedation, dysphoria, cognitive blunting, and increased appetite) led to the search for equally effective alternative dopamine-blocking agents. The introduction of second-generation or "atypical" antipsychotics has led to greater use of these agents due to their more favorable side effects profile. Second-generation antipsychotics include risperidone, aripiprazole, ziprasidone, olanzapine, quetiapine, and metoclopramide. While evidence for their efficacy in TD is greatest for risperidone and aripiprazole, only the latter has received FDA approval [119]. While these newer medications may have fewer side effects, the evidence for the efficacy is not as well established leading some practitioners to favor the typical antipsychotics [120, 121].

The alpha2-adrenergic agonists have been shown to be reducing the symptoms of ADHD and can be combined with stimulant medications in comorbid TD and ADHD without exacerbating tics. For the most part, alpha2-adrenergic agonists are only helpful in reducing tics in patients with TD + ADHD [122]. The most common side effects encountered are sedation, fatigue, dry mouth, orthostatic hypotension and depression. Rarely, bradycardia and rhythm disturbances can occur, hence ECG monitoring is recommended.

Additional medications that have proven helpful in the treatment of tics include benzodiazepines (e.g., clonazepam), dopamine antagonists (tetrabenazine, piquindone, and inosine), dopamine agonists (pergolide, amantadine, selegiline, and pramipexole), botulinum toxin injections, and antiepileptics (topiramate, gabapentin, levetiracetam, and carbamazepine). More recently, donezepil, nicotine, opioid agonists (naloxone and

naltrexone), calcium channel blockers (verapamil, nifedipine, and flunarizine), benzamide, propranolol, odansetron, and delta-9-tetrahydrocannabinol have also shown promise as anti-tic medications, although their use remains investigational [70].

Medications for obsessive-compulsive symptoms (OCS) associated with TD include selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine) and serotonin–norepinephrine inhibitors (SNRIs) (e.g., clomipramine). In general, OCS are less responsive to medications in patients with tic disorders and TD. Moreover, these agents may produce worsening of tics, behavioral activation (including insomnia, motor restlessness, impulsiveness, and disinhibition) agitation, hypomania and even mania. Other side effects seen with SSRIs include nausea, stomach ache, heartburn, decreased appetite, diarrhea, fatigue, and decreased sexual functioning. Augmentation strategies for the treatment of OCS include using medications such as risperidone, buspirone, and the tricyclic antidepressants, although all have potential side effects that need to be monitored.

ADHD symptoms in patients with tic disorder or TD can be treated effectively with stimulants, alpha2-adrenergic agents or atomoxetine. Earlier caution about the worsening of tics from stimulant medications has been challenged by more recent studies. The Tourette Syndrome Study Group [123] conducted a multisite study of 136 children with chronic tics and ADHD and found no greater worsening of tics in subjects receiving methylphenidate alone than those receiving placebo, clonidine or the combination of methylphenidate and clonidine. The other major finding of this study was that the combined medication group did best in terms of ADHD symptom reduction. Alpha2-adrenergic agents, already discussed in the section on ADHD, can improve attention and impulsivity as well as tics. Atomoxetine, also discussed before, has been shown to be effective in reducing tics in children with comorbid ADHD [124].

The pharmacologic treatment of aggression must be preceded with a comprehensive diagnostic evaluation. The presence of bipolar disorder, ADHD, and disruptive behavior disorders (e.g., conduct disorder, oppositional-defiant disorder and intermittent explosive disorder) will help to determine the best strategy for medication usage. Depending on the nature of the aggressive behavior and the comorbid conditions present, any number of agents might be employed including SSRIs, SNRIs, atypical antipsychotics, mood stabilizers, alpha2-adrenergic agonists, and stimulant medications, either alone or in combination.

C. *Somatic Treatments*

Experimental somatic treatments for intractable TD include deep brain stimulation (DBS) [125] repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT). DBS, a reversible neurosurgical procedure, was shown to improve medically intractable tics when the electrodes are placed in the midline thalamic nuclei, with up to 62% improvement seen in a case series of 18 adult patients [126]. An RCT of this placement of DBS electrodes also yielded positive results [127]. Unfortunately, there have been no carefully controlled randomized studies to determine the optimal placement of electrodes (among nine proposed sites), nor to evaluate whether the risks (infection, stroke, neurological sequelae, blurred vision) merit the benefits of treatment. Therefore, it is important to exhaust all other pharmacologic options before proceeding with DBS [128].

Kwon et al. [129] conducted an open-label trial of rTMS (10 treatments over 2 weeks) in 10 boys with TD and found an average reduction of YGTSS scores of 34%. Le et al. [130] conducted a similar study with 25 boys and girls who received 20 daily sessions of rTMS and found improvements in both tic ratings and ADHD, depression and anxiety measures. Neither of these studies was sham (placebo) controlled, hence their results are promising but inconclusive at best [131]. A significant improvement in YGTSS total, motor, and phonic scores was evident at both 6-months and maintained at 12-months. Scores did not differ across areas targeted for DBS

Case studies have reported positive results from ECT for severe TD, but it is important to

note that there have been no randomized trials conducted documenting the usefulness of ECT. With greater evidence for their efficacy, and with clearer guidelines delineating appropriate indications for their use, it is likely that these somatic treatments will become an important treatment option especially for adults with severe and intractable TD [70, 131].

Prognosis/Long-term Outcomes

In general, the prognosis for TD is very good [70, 82, 132]. Up to 50% of children will completely outgrow their symptoms by adulthood with little or no long-term consequences. Approximately 40% will have substantial improvement in their tics in later life, and up to 10% will continue to have impairing symptoms in adulthood. At present, there is no way to predict the course of the illness into adulthood, nor is it clear what the impact of treatment is on the natural history of TD. Less favorable outcome is predicted by the following factors: adverse perinatal events; comorbid developmental, learning and mental disorders; chronic physical illness; unstable and unsupportive family environments; and exposure to psychoactive drugs and alcohol. The most serious sequelae of TD include treatment-resistant OCD, major mental disorders (e.g., depression, bipolar disorder), character pathology (personality disorders), substance abuse; physical injuries, and chronic under- or unemployment. A significant minority of patients with comorbid mental disorders will require ongoing psychosocial treatment and social services, not unlike some of the patients first described by Gilles de la Tourette in 1885. It is also clear that negative societal attitudes and beliefs about this disorder can worsen the burden of illness on individuals and their families. Hence, it is important for clinicians to address stigma and to support the efforts of patients with TD to live in the world with hope and dignity. Organizations such as the Tourette Syndrome of America can also play a vital role in helping patients and families feel connected to a larger community of support.

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References

1. Roberts W, Milich R, Barkley RA. Primary symptoms, diagnostic criteria, subtyping and prevalence of ADHD. In: Barkley RA, editor. Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment. 4th ed. New York, NY: Guilford Press; 2014.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
3. Nigg J. What causes ADHD?. New York, NY: Guilford Press; 2006.
4. Bralten J, Franke B, Waldman I, et al. Candidate genetic pathways for attention-deficit/hyperactivity disorder (ADHD) show association to hyperactive/impulsive symptoms in children with ADHD. J Am Acad Child Adolesc Psychiatry. 2013;52(1204):12.e1.
5. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primer. 2015;1:1–22.
6. Neuman RJ, Lobos E, Reich W. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. Biol Psychiatry. 2007;61:1320–8.
7. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci. 1986;9:357–81.
8. Zhu Y, Yang D, Ji W. The relationship between neurocircuitry dysfunctions and attention deficit hyperactivity disorder: a review. BioMed Res Int. 2016;1–7. http://dx.doi.org/10.1155/2016/3821579.
9. Arnsten AFT. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J Clin Psychiatry. 2006;67:7–12.
10. Gaddis A, Rosch KS, Dirlikov B, et al. Motor overflow in children with attention-deficit/hyperactivity disorder is associated with decreased extent of neural activation in the motor cortex. Psychiatry Res. 2015;233:488–95.
11. Gilbert DL, Issacs KM, Augusta M, Macneil LK, Mostofsky SH. Motor cortex inhibition: a marker of ADHD behavior and motor development in children. Neurology. 2011;76:615–21.
12. Armstrong CL, Hayes KM, Martin R. Neurocognitive problems in attention deficit disorder: alternative concepts and evidence for impairment in inhibition of selective attention. Ann NY Acad Sci. 2001;931(1, theme issue):196–215.

13. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci. 2012;35:73–89.
14. Arnsten AFT, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation and emotion: disruption in neurodevelopmental psychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2012;51:356–67.
15. Pennington BF. Explaining abnormal behavior: a cognitive neuroscience perspective. New York, NY: Guilford Press; 2014.
16. Wasserstein J, Stefanatos GA. Re-examining ADHD as corticostriatal disorder: implications for understanding common comorbidities. ADHD Rep. 2016;24:1–10.
17. Castellanos FX, Proal E. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. Trends Cogn Sci. 2011;16:7–26.
18. Pliszka SR, Glahn DC, Semrud-Clikeman M, et al. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naïve or in long-term treatment. Am J Psychiatry. 2006;164:942–8.
19. Pliszka SR. Neuroscience for the mental health clinician. 2nd ed. New York, NY: Guilford Press; 2016.
20. Cortese S, Kelly C, Chabernaud C, et al. Neuroscience of ADHD: a meta-analysis of 55 fMRI studies. J Am Psychiatry. 2012;169:1–28.
21. Farrant K, Uddin LQ. Asymmetric development of dorsal and ventral attention networks in the human brain. Dev Cogn Neurosci. 2015;12:165–74.
22. Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev. 2014;24:3–15.
23. Zillmer EA, Spiers MV, Culbertson WC. Principles of neuropsychology. 2nd ed. Belmont, CA: Waldworth; 2008.
24. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. New Engl J Med. 1990;323:1361–6.
25. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Nat Acad Sci. 2007;104:19649–54.
26. Shaw P, Malek M, Watson B, Sharp W, Evans A, Greenstein D. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012;72:191–7.
27. Shaw P, De Rossi P, Watson B, et al. Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2014;53:780–90.
28. Plichta MM, Scheres A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI. Neurosci Biobehav Rev. 2014;38:125–34.
29. Willcutt EG. Theories of ADHD. In: Barkley RA, editor. Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. 4th ed. New York, NY: Guilford Press; 2015. p. 391–404.
30. Hien D, Matzner FJ, First MB, Spitzer RL, Williams J, Gibbon M. Structured clinical interview for DSM-IV childhood diagnoses (KID-SCID). New York, NY: Biometrics Research; 1994.
31. Khan K, Sharief N. Chronic carbon monoxide poisoning in children. Acta Paediatrica. 1995; 84:742.
32. Armstrong CL, Cunningham J. Functional and developmental effects of environmental CO toxicity in children. In: Penney D, editor. Carbon monoxide toxicity. Boca Raton, FL: CRC Press; 2007.
33. Daneshparvar M, Mostafavi SA, Jeddi MZ, et al. The role of lead exposure on attention-deficit/hyperactivity disorder in children: a systematic review. Iran J Psychiatry. 2016;11:1–14.
34. Nigg JT, Elmore AL, Natarajan N, Friderici KH, Nikolas MA. Variation in an iron metabolism gene moderates the association between blood lead levels and attention-deficit/hyperactivity disorder in children. Psychol Sci. 2016;27:257–69.
35. Wilkinson GS, Robertson GJ. Wide range achievement test. 5th ed. New York, NY: Pearson Inc.; 2017.
36. Beery KE, Buktenica NA, Beery NA. Beery VMI developmental test of visual-motor integration. 6th ed. North Tonawanda, NY: Multi-Health Systems; 2010.
37. Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1997;36(-suppl):85S–121S.
38. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry. 2010;19:353–64.
39. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC Med. 2012; 10:99–114.
40. Barkley RA, editor. Attention Deficit Hyperactivity disorder: a handbook for diagnosis and treatment. 4th ed. New York, NY: Guilford Press; 2014.
41. Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128:1007–22.
42. Tanaka Y, Rohde LA, Jin L, Feldman PD, Upadhyaya HP. A meta-analysis of the consistency of atomoxetine treatment effects in pediatric patients with attention-deficit/hyperactivity disorder from 15 clinical trials across four geographic regions. J Child Adolesc Psychopharmacol. 2013;23: 262–70.

43. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009–2011: focus on clinical efficacy and safety. J Psychopharmacol. 2014;28:204–11.
44. Clemow DB, Bushe CJ. Atomoxetine in patients with ADHD: a clinical and pharmacological review of the onset, trajectory, duration of response and implications for patients. J Psychopharmacol. 2015;29:1221–30.
45. Treuer T, Shur-Fen Gau S, Mendez L, et al. A systematic review of combination therapy with stimulants and atomoxetine for attention deficit/hyperactivity disorder, including patient characteristics, treatment strategies, effectiveness, and tolerability. J Child Adolesc Psychopharmacol. 2013; 23:179–93.
46. Biederman J, Melmed RD, Patel A, McBurnett K, Donahue J, Lyne A. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. CNS Spectrums. 2008;13:1047–55.
47. Jain R, Segal S, Kollins SH, Khayrallah M. Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:171–9.
48. Faraone SV, McBurnett K, Sallee FR, Steeber J, Lopez FA. Guanfacine extended release: a novel treatment for attention-deficit/hyperactivity disorder in children and adolescents. Clin Ther. 2013; 35:1778–93.
49. Evans SW, Owens JS, Bunford N. Evidenced-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2014;43:527–51.
50. Leckman JF. Phenomenology of tics and sensory urges. In: Martino D, Leckman JF, editors. Tourette syndrome. New York, NY: Oxford University Press; 2013. p. 3–25.
51. Martino D, Madhusudan N, Zis P, Cavanna AE. An introduction to the clinical phenomenology of Tourette syndrome. Int Rev Neurobiol. 2013; 112:2–25.
52. Peterson BS, Leckman JF. The temporal dynamics of tics in Gilles de la Tourette syndrome. Biol Psychiatr. 1998;44:1337–48.
53. Cavanna AE, Black KJ, Hallett M, Voon V. Neurobiology of the premonitory urge in Tourette syndrome: pathophysiology and treatment implications. J Neuropsychiatr Clin Neurosci. 2017; 29:95–104.
54. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. Psychosom Res. 2009;67:497–501.
55. Singer HSS. Tourette's syndrome: from behaviour to biology. Lancet Neurol. 2005;4:149–59.
56. Leckman JF, King RA, Bloch MH. Clinical features of Tourette syndrome and tic disorders. J Obsessive-Compuls Rel Dis. 2014;3:372–9.
57. Leckman JF, Walker WK, Goodman WK, Pauls DL, Cohen DJ. 'Just right' perceptions associated with compulsive behaviors in Tourette's syndrome. Am J Psychiatry. 1994;151:675–80.
58. Worbe Y, Mallet L, Goldmard J-L, et al. Repetitive behavior in patients with Gilles de la Tourette Syndrome: tics, compulsions, or both? PLOS One. 2010;5(9):e12959.
59. Robertson MM. A personal 35-year perspective on Gilles de la Tourette syndrome: prevalence, phenomenology, comorbidities, and coexistent psychopathologies. Lancet Psychiatr. 2015;2:68–87.
60. Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringsheim T. Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol. 2012;47:77–90.
61. Scharf JM, Miller LL, Gauvin CA, Alabiso J, Mathews CA, Ben-Shlomo Y. Population prevalence of Tourette syndrome: a systematic review and meta-analysis. Mov Dis. 2015;30:221–8.
62. Pauls DL, Fernandez TV, Mathews CA, State MW, Scharf JM. The inheritance of Tourette disorder: a review. J Obsessive Compuls Relat Disord. 2014; 3:380–5.
63. Browne HA, Hansen SN, Buxbaum JD, et al. Familial clustering of tic disorders and obsessive-compulsive disorder. JAMA Psychiatry. 2015; 72:359–66.
64. Mataix-Cols D, Isomura K, Pérez-Vigil A, et al. Familial risks of Tourette syndrome and chronic tic disorders: a population-based cohort study. JAMA Psychiatry. 2015;72:787–93.
65. Abelson JF, Kwan KY, O'Roak BJ, et al. Sequence variants in SLITRK1 are associated with Tourette's syndrome. Science. 2005;310:317–20.
66. O'Roak BJ, Morgan TM, Fishman DO, et al. Additional support for the association of SLITRK1 var321 and Tourette syndrome. Mol Psychiatry. 2010;15:447–50.
67. Karagiannidis I, Rizzo R, Tarnok Z, et al. Replication of association between a SLITRK1 haplotype and Tourette syndrome in a large sample of families. Mol Psychiatry. 2012;17:665–8.
68. Stillman AA, Krsnik Z, Sun J, et al. Developmentally regulated and evolutionarily conserved expression of SLITRK1 in brain circuits implicated in Tourette syndrome. J Comp Neurol. 2009;513: 21–37.
69. Scharf JM, Moorjani P, Fagerness J, et al. Lack of association between SLITRK1 var321 and Tourette syndrome in a large family-based sample. Neurology. 2008;70:1495–6.
70. Robertson MM, Eapen V, Singer HS, et al. Gilles de la Tourette syndrome. Nat Rev Dis Primers. 2017;3:1–20.
71. Murphy TF, Gerardi DM, Leckman JF. Pediatric acute-onset neuropsychiatric syndrome. Psychiatr Clin North Am. 2014;37:353–74.

72. Chang K, Frankovich J, Cooperstock M, et al. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS consensus conference. J Child Adolesc Psychopharmacol. 2015;25:3–13.
73. Thienemann M, Murphy T, Leckman J, et al. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part I—psychiatric and behavioral interventions. J Child Adolesc Psychopharmacol. 2017;27:566–73.
74. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998; 155:264–71.
75. Marsh R, Maia TV, Peterson BS. Functional disturbances within frontostriatal circuits across multiple childhood psychopathologies. Am J Psychiatry. 2009;166:664–74.
76. Jackson GM, Draper A, Dyke K, Pépés SE, Jackson SR. Inhibition, disinhibition, and the control of action in Tourette syndrome. Trends Cogn Sci. 2015;19:655–65.
77. Polyanska L, Critchley HD, Rae CL. Centrality of prefrontal and motor preparation cortices to Tourette, syndrome revealed by meta-analysis of task-based neuroimaging studies. NeuroImage Clin. 2017;16:257–67.
78. Albin RL, Koeppe RA, Bohnen NI, et al. Increased ventral striatal monoaminergic innervation in Tourette syndrome. Neurology. 2003;61:310–5.
79. Buse J, Schoenefeld K, Münchau A, Roessner V. Neuromodulation in Tourette syndrome: dopamine and beyond. Neurosci Behav Rev. 2013; 37:1069–84.
80. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community-based study. Neurol Clin. 2002;59:414–20.
81. O'Rourke JA, Scharf JM, Platko J, et al. The familial association of Tourette's disorder and ADHD: the impact of OCD symptoms. Am J Med Genet B Neuropsychiatr Genet. 2011;156:432–8.
82. Hassan N, Cavanna AE. The prognosis of Tourette syndrome: implications for clinical practice. Funct Neurol. 2012;27:23–7.
83. Shaw ZA, Coffey BJ. Tics and Tourette syndrome. Psychiatr Clin North Am. 2014;37:269–86.
84. Freeman R, Fast D, Burd L, Kerbeshian J, Robertson M, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol. 2000;42:436–47.
85. Budman CL, Rockmore L, Bruun RD. Aggressive symptoms in Tourette's syndrome. In: Kurlan R, editor. Handbook of Tourette's syndrome and related tic and behavioral disorders. 2nd ed. New York, NY: Marcel Dekker; 2005. p. 127–54.
86. Como PC. Neuropsychological function in Tourette's syndrome. In: Kurlan R, editor. Handbook of Tourette's syndrome and related tic and behavioral disorders. 2nd ed. New York, NY: Marcel Dekker; 2005. p. 237–52.
87. Morand-Beaulieu S, Leclerc JB, Valois P, Lavoie ME, O'Connor KP, Gauthier B. A review of the neuropsychological dimension ns of Tourette syndrome. Brain Sci. 2017;7:106. https://doi.org/10.3390/brainsci7080106.
88. Channon S, Pratt P, Robertson MM. Executive function, memory and learning in Tourette's syndrome. Neuropsychology. 2003;17:247–54.
89. Eddy CM, Rickard HE, Cavanna AE. Executive functions in uncomplicated Tourette syndrome. Psychiatry Res. 2012;200:46–8.
90. Morand-Beaulieu S, Grot S, Lavoie J, Leclerc JB, Luck D, Lavoie ME. The puzzling question of inhibitory control in Tourette syndrome: a meta-analysis. Neurosci Biobehav Rev. 2017;80: 240–62.
91. Yaniv A, Benaroya-Milshtein N, Steinberg T, Ruhrrman D, Apter A, Lavidor M. Specific executive control impairments in Tourette syndrome: the role of response inhibition. Res Dev Dis. 2017;61:1–10.
92. Jeter CB, Patel SS, Morris JS, Chuang AZ, Butler IJ, Sereno AB. Oculomotor executive function abnormalities with increased tic severity in Tourette syndrome. J Child Psychol Psychiatry. 2015;56: 193–202.
93. Eddy CM, Cavanna AE. Altered social cognition in Tourette syndrome: nature and implications. Behav Neurol. 2013;7:15–22.
94. Eddy CM, Macerollo A, Martino D, Cavanna AE. Interpersonal reactivity differences in Tourette syndrome. Psychiatry Res. 2015;228:922–35.
95. Zinner SH, Conelea CA, Glew GM, Woods DW, Budman CL. Peer victimization in youth with Tourette syndrome and other chronic tic disorders. Child Psychiatry Human Dev. 2012;43:124–36.
96. Hirschtritt ME, Lee PC, Pauls DL, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiatry. 2015;72:325–33.
97. McGuire JF, Hanks C, Kewin AB, Storch EA, Murphy TK. Social deficits in children with chronic tic disorders: phenomenology, clinical correlates and quality of life. Compr Psychiatry. 2013; 54:1023–31.
98. Channon S, Sinclair E, Waller D, Healey L, Robertson MM. Social cognition in Tourette's syndrome: intact theory of mind and impaired inhibitory functioning. J Autism Dev Disord. 2004;34:669–77.
99. Güler AS, Berkem M, Yazgan Y, Kalaça S. Cognitive flexibility and social responsiveness in children and adolescents with Tourette syndrome. Child Psychiatry Human Dev. 2015;46:940–50.

100. Specht MW, Chang SW. Tourette's disorder and other tic disorders. In: Reddy LA, Weissman AS, Hale JB, editors. Neuropsychological assessment and intervention for youth: an evidence-based approach to emotional and behavioral disorders. Washington, DC: American Psychological Association; 2013. p. 201–24.
101. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry. 1989;28:566–73.
102. Scahill L, Riddle MA, McSwiggin-Hardin M, et al. The children's Yale Brown obsessive compulsive scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36:844–52.
103. March JS. Multidimensional anxiety scale for children, 2nd ed. North Tonawanda, NY: Multi-Health Systems; 2013.
104. Spielberger CD, Edwards CD, Montouri J, Lushene R. The state-trait anxiety inventory for children (STAI-CH). Menlo Park, CA: Mind Garden Inc.; 1970.
105. Kovacs M. Children's depression inventory. 2nd ed. North Tonawanda, NY: Multi-Health Systems; 2010.
106. Poznanski EO, Mokros HB. Children's depression rating scale, revised (CDRS-R). Torrance, CA: WPS; 1996.
107. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD rating scale for children and adolescents: checklists, norms, and clinical interpretation. 5th ed. New York, NY: Guilford Press; 2016.
108. Conners CK. Conners, 3rd ed (Conners 3). North Tonawanda, NY: Multi-Health Systems; 2008.
109. Barkley RA, Murphy KR, Fischer M. Adult ADHD symptom checklist. Adult ADHD: what the science says. New York, NY: Guilford Press; 2008.
110. Khalifa N, Eklund S. Fine motor functioning and perception in children with Tourette syndrome. J Childhood Dev Disord. 2017;3:1–7.
111. Piacentini J, Chang S. Habit reversal training for tic disorders in children and adolescents. Behav Modif. 2005;29:803–22.
112. Frank M, Cavanna AE. Behavioural treatments for Tourette syndrome: an evidence-based review. Behav Neurol. 2013;27:105–17.
113. Fründt O, Woods D, Ganos C. Behavioral therapy and Tourette syndrome and chronic tic disorders. Neurol Clin Pract. 2017;7. https://doi.org/10.1212/CPJ.0000000000000348.
114. McGuire JF, Picentini J, Brennan EA, et al. A meta-analysis of behavior therapy for Tourette syndrome. J Psychiatr Res. 2014;50:106–12.
115. McGuire JF, Ricketts EJ, Piacentini J, Murphy TK, Storch EA, Lewin AB. Behavior therapy for tic disorders: an evidenced-based review and new directions for treatment research. Curr Dev Disord Rep. 2015;2:309–17.
116. Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010;303:1929–37.
117. Conelea CA, Walther MR, Freeman JB, et al. Tic-related obsessive-compulsive disorder (OCD): phenomenology and treatment outcome in the pediatric OCD treatment study II. J Am Acad Child Adolesc Psychiatry. 2017;53:1308–16.
118. Greene RW, Ablon JS. Treating explosive kids: the collaborative problem solving approach. New York, NY: Guilford Press; 2006.
119. Budman C. The role of atypical antipsychotics for treatment of Tourette's syndrome: an overview. Drugs. 2014;74:1177–93.
120. Srour M, Lesperance P, Richer F, Chouinard S. Psychopharmacology of tic disorders. J Canad Acad Child Adolesc Psychiatry. 2008;17:150–9.
121. Thomas R, Cavanna AE. The pharmacology of Tourette syndrome. J Neural Transm. 2013;120:689–94.
122. Weisman H, Qureshi IA, Leckman JF, Scahill L, Bloch MH. Systematic review: pharmacological treatment of tic disorders - efficacy of antipsychotic and alpha-2 adrenergic agonist agents. Neurosci Biobehav Rev. 2013;37:1162–71.
123. Tourette Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002;58:527–36.
124. Spencer TJ, Sallee FR, Gilbert DL. Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome. J Atten Disord. 2008;11:470–81.
125. Martinez-Ramirez D, Simenez-Shahed J, Leckman JF, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome. JAMA Neurol. 2018. https://jamanetwork.com/journals/jamaneurology/fullarticle/2669923.
126. Servello D, Porta M, Sassi M, Brambilla A, Robertson MM. Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. J Neurol Neurosurg Psychiatry. 2008;79:136–42.
127. Maciunas RJ, Maddux BN, Riley DE, et al. Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette's syndrome. J Neurosurg. 2007;107:1004–14.
128. Andrade P, Visser-Vandewalle V. DBS in Tourette syndrome: where are we standing now? J Neural Trans (Vienna). 2016;123:791–6.
129. Kwon HJ, Lim WS, Lim MH, et al. 1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette's syndrome. Neurosci Lett. 2011;492:1–4.
130. Le K, Liu L, Sun M, Hu L, Xiao N. Transcranial magnetic stimulation at 1 Hertz improves clinical symptoms in children with Tourette syndrome for at least 6 months. J Clin Neurosci. 2013;20:257–62.
131. Kious BM, Jimenez-Shahed J, Shprecher DR. Treatment-refractory Tourette syndrome. Progress Neuro-Psychopharmacol Biol Psychiatry. 2016;70:227–36.
132. Bloch MH, Peterson BS, Scahill L, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med. 2006;160:65–9.

Part IV
Aging

Chapter 17

Dementia

Christine E. Whatmough

Introduction

Dementia is a condition of persistent decline in multiple mental domains essential to normal daily living. There are several major syndromes of dementia, each with particular domains of impairment which are predominant in the early stages. These primary domains are memory, language, attention, and social functioning. Other areas which can be affected include semantic knowledge, visuospatial skills, executive functions, and emotion or personality [1]. For a diagnosis of dementia, impairment must be severe enough to alter a person's former level of functioning, and not be present only in the course of delirium. Although the preponderance of cases of dementia occurs in the elderly, dementia is not limited to any age bracket and does occur in the young and middle aged.

Some dementias are associated with a particular pathological entity which distinguishes it from the others, such as Pick's bodies in frontal lobe dementia or prions in Creutzfeldt–Jakob disease. In other cases, similar pathology is common to several dementias but in different brain regions such as tau inclusions which first appear in the medial temporal cortex in Alzheimer's dementia but in the frontal cortex in frontotemporal dementia [2]. The cognitive and behavioral symptoms of dementia are a reflection, not of the specific histopathology but rather of the localization of the degenerative process [3]. For instance, frontotemporal dementia (FTD) can be seen in patients with microvacuolation of the superficial layers of the frontal cortex or by the presence of Pick's bodies in the same cortical layers of the frontal and temporal cortex [4].

In this chapter, five dementias are presented: Alzheimer's disease (AD), dementia with Lewy bodies, Parkinson's disease dementia, Binswanger's disease (a vascular dementia), and transmissible spongiform encephalopathies (prion diseases), as well as mild cognitive impairment. Frequently the pathologies of two dementias (e.g., AD and vascular dementia) cooccur so that there is a fair percentage of patients who have mixed dementias. This is illustrated in Fig. 17.1 where the postmortem diagnosis [5] of 382 patients from a dementia brain bank illustrates the frequency of overlap in pathology. A high degree of overlap has also been shown in studies of prevalence of dementia types antemortem [6]. It is difficult to establish the prevalence of the different dementias partly not only because of this overlap but also because different diagnostic criteria are often used [7, 8]. The order in magnitude of prevalence, however, is more or less agreed upon and is dependent upon the age of onset. Among dementia cases with onset after the age of 65 years

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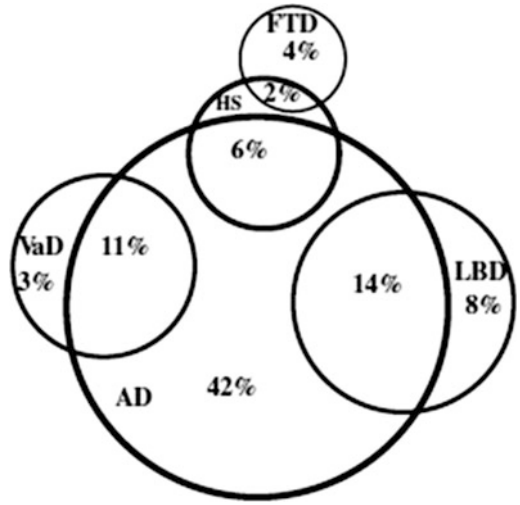

Fig. 17.1 The relative prevalence of dementia diagnosis postmortem from the State of Florida Brain Bank. All had been diagnosed with dementia antemortem. AD, Alzheimer's disease; FTD, frontotemporal dementia; HS, hippocampal sclerosis; LBD, Lewy body dementia; VaD, vascular dementia. Percentages and overlaps of $\leq 1\%$ are not indicated. Sample readings: of the whole sample, 42% were AD only, 11% were mixed AD–VaD, and 3% were VaD only. Based on Table 2 of Barker et al. [5] and used with permission

Alzheimer's disease is by far the most frequent, occurring either alone, or as part of a mixed dementia, in up to 75% of all dementias [9]. The next most prevalent dementia is variously reported to be either some form of vascular dementia or dementia with Lewy bodies which clinics may find account for 15–20% of dementias; FTD accounts for between 5 and 6% of dementia patients. Parkinson's disease dementia is frequently a mixed dementia [10], and prion dementias are rare. Among cases of dementia with an onset under the age of 65, AD is less prevalent composing about 33% of dementias [11], and the onset of a vascular dementia, FTD, or dementia with Lewy bodies is more common in this age-group.

The search for a cure for any of the dementias is ongoing. A small percentage of elderly patients who experience cognitive deficits, however, suffer from conditions that can be halted, and occasionally mental functions can be restored. The most commonly occurring causes of these "reversible" conditions are normal pressure hydrocephalus, vitamin B_{12} and thiamine deficiencies, hypothyroidism, and depression. Obstructive sleep apnea and certain regimes of medication can also result in cognitive deficits similar to those in early dementia. Because the cognitive deficits in these conditions overlap with first deficits in the major dementias much of the workup to diagnosis carried out by the physician is done to eliminate these factors as possible causes. These treatable conditions are, however, rare and represent less than 5% of dementias [12].

Neuropsychological Testing of Dementias

It is recommended that neuropsychological testing (NPT) be an integral part of the clinical diagnosis of dementia [13]. The contribution of neuropsychological evaluation to patient care in the context of dementia is varied. In some cases, such as that of suspected Alzheimer's dementia (AD), cognitive deficits are the first and only identifiable symptom of the disease. Here the neuropsychological evaluation will be of primary importance in arriving at a diagnosis. It contributes, first, to determining whether subjective complaints relate to a measurable cognitive loss

and, second, to distinguishing between the major types of dementia. In other instances of suspected dementia, there may be an established disease with neurological signs such as in Parkinson's disease or motor neuron disease, which may or may not be accompanied by cognitive deficits or dementia. Here again the NPT can contribute to the diagnosis of dementia. The NPT is of value, not only to the physician but also to patients and caregivers in enabling them to make informed decisions about the vocational and functional impacts of cognitive deficits [13]. Finally, in cases of frontal-type behavior where there is unusual deportment, recognition that there is a physiological basis for the strange behavior can provide some emotional support for loved ones and help caregivers better understand the challenges that need to be managed in the care of the patient.

Resources, however, are frequently limited and physicians must rely on short cognitive batteries or screens to assess the mental status of dementia patients. Several tests and cognitive batteries each with their relative strengths have been developed to this end. The most commonly reported screening measure of cognitive function is the Mini-Mental State Examination (MMSE) [14] which provides a rapid assessment of general cognitive performance and helps to situate the relative impairment of a patient within a context of normal cognitive functions. Its strength is its rapidity, and it is best in detecting AD-type deficits and in assessing moderate and mild cases of the disease (MMSE scores of 10–25). It is less useful for evaluating severely demented individuals, and in detecting mild cognitive impairment (MCI), as people with MCI often score in the normal range (26 or better). For patients in the very low end, a good measure is the Global Deterioration Scale (GDS) [15]. GDS scores range from 1 (normal) to 7 (late dementia). Both the Mattis Dementia Rating Scale (DRS) [16, 17] and the Clinical Dementia Rating Scale (CDR) [18] are effective in following longitudinal decline. The Initiation/Perseveration subscale of the DRS is particularly appreciated for discerning frontal lobe and subcortical deficits which in turn are helpful in predicting everyday functioning. The CDR range most commonly used rates patients from 0 (no dementia) to 3 (severe dementia). The CDR takes approximately 30–45 min to administer and involves interviews with both the patient and an informant. It is frequently used in research because the rating of "0.5: questionable dementia" can be used as an approximation for a diagnosis of mild cognitive impairment. Recently, several new tests have been specifically developed to evaluate cases in which cognitive deficits appear mild on the MMSE. Two in particular, the MoCA (Montreal Cognitive Assessment) [19] and the DemTect [20], are discussed under section "Mild Cognitive Impairment." It should be remembered that all of these tests evaluate cognitive functions at one point in time. They will not necessarily detect fluctuations in cognition which is a diagnostic feature of some syndromes. Furthermore, mood changes and psychosis are core features of some of the major dementia syndromes and patients in early stages of these dementias can often score in the normal range on these tests.

A vast amount of information has been acquired through the use of brain imaging with regard to the structural and functional consequences of different dementia syndromes. Surprisingly, however, in most cases, cerebral imaging is used not to diagnose dementia but to exclude other possible causes of mental decline such as tumors, normal pressure hydrocephalus, and cerebral vascular events. This is because structural and metabolic differences between dementia patients and control groups in brain imaging studies do not translate into segregated values, except in the case of people with very advanced forms of dementia and for whom behavioral data would be sufficient for diagnosis. There are some exceptions to this general rule and they will be raised in context.

Alzheimer's Disease

The most common form of dementia is Alzheimer's disease (AD). In 1906, Alois Alzheimer presented a three-page paper which identified an "unusual disease of the cerebral cortex" in a

woman, Auguste D., who had died at the age of 55 years [21]. Over the period of 10–15 years prior to death, the disease had progressively caused memory loss, aphasia, disorientation, auditory hallucinations, and severe behavioral disturbances that impaired social functioning. Alzheimer identified several brain abnormalities postmortem. The cortex was thinner than normal and there were senile plaques which had, until then, been found only in the elderly. Using a new stain his investigation revealed neurofibrillary tangles within the neurons.

Alzheimer's disease was thus first identified in a patient who would today be termed a case of early-onset AD and the term AD was associated for many years mainly with "presenile dementia." As late as 1956, this identification of AD as something different from dementia in the elderly is brought out by the diverging opinion of Raskin and Ehrenberg [22] that "we believe AD is an entity that does not depend on the presenile age of the patient but can occur at any age." In their review they go on to point out that it had been found both in people too young or too old to be called presenile. They supported their conclusions for AD's presence in the elderly by behavioral and neuropathological studies of 270 hospital cases of patients aged 60–97 years.

The general course of cognitive deterioration in AD is one of slow loss during the early and the very late stages with more rapid changes in the middle stages [23, 24]. Storandt et al. found that a median survival time from diagnosis of AD in a mild form (mean age 72.0 years, CDR 1) was 6.9 years and that from diagnosis of mild cognitive impairment was 8.7 years (mean age 75.3 years, CDR 5). There are no focal neurological signs or metabolic deficiencies at onset, the symptoms being principally cognitive. In later stages, there can be motor dysfunction, myoclonus, and seizures.

Pathology: The neuropathology associated with AD postmortem has been well documented by Braak and Braak [25] who found that the neurofibrillary tangles (NFTs) appear in a predictable order within the brain which they identify as six stages. NFTs first appear within the transentorhinal region (Stages I and II), an area which receives input from the association areas of the neocortex and transmits it to the entorhinal cortex and ultimately the hippocampus. Braak and Braak call Stages I and II the silent stages of AD because when NFT lesions are confined to this area, there are no symptoms of dementia. Stages III and IV, a time of incipient AD, are characterized by a proliferation of NFTs in not only the transentorhinal/entorhinal region but also the hippocampus. Braak and Braak [26] maintain that it is the severing of the reciprocal links between the hippocampus and the trans/entorhinal region which creates the amnesic syndrome. In Stages V and VI, NFTs appear in the neocortex, first in the association cortices of the temporal and frontal lobes working progressively, from a functional point of view, backward into the secondary and then primary sensory and motor areas. Since the association cortices are the storage sites of the highest levels of representation, their devastation produces the manifestations of agnosia, aphasia, and apraxia which become apparent in the AD patient.

Amyloid deposits are also present in the AD brain and occur in a specific order [27]. There is, however, incomplete congruence between the appearance of plaques and NFTs. Furthermore, moderate loads of plaques can be found in elderly people who do not display the cognitive deficits of AD.

Besides these cortical pathologies, there is a marked loss of neurons within two specific basal forebrain structures, the nucleus basalis of Meynert and the nucleus locus coeruleus. These subcortical losses result in decreases in the cholinergic (ACh) and noradrenergic neurotransmitters. The reduction in ACh in AD has led to the cholinergic hypothesis of AD [28]. Most pharmaceutical treatments for AD have been designed to increase the availability of acetylcholine in the central nervous system, and they have been shown to have mild effects on behavior. For instance, cholinesterase inhibitors (ChI) can maintain levels of cognitive performance in early AD with variable impact and for a variable length of time, and improve many behavioral disturbances such as agitation, apathy, hallucinations, and aberrant motor behavior [28].

Magnetic resonance (MR) imaging reveals severe medial temporal (parahippocampal,

hippocampal) atrophy with milder frontoparietal and temporal atrophy in early phases of AD. With time there is a progressive widening of the sulci and enlargement of the ventricles. FDG-PET reveals a progression in hypometabolism that largely parallels the progression of neuropathology [29]. In mild stages, hypometabolism is restricted to the posterior cingulate cortex, then to the temporoparietal cortex, and then with increasing disease severity, hypometabolism becomes characteristic of the frontal lobes and some subcortical areas.

Risk factors: The greatest risk factor for AD is age, with the risk of developing the disease increasing exponentially after the age of 80 years [30]. People with 6 years or less of education are also at increased risk, and many studies [31] have found that the prevalence of AD is greater in elderly women than in elderly men. Besides these unmodifiable factors, there is good evidence that a sedentary lifestyle, hypertension, high cholesterol, and head injury with loss of consciousness all increase the risk of dementia [32].

Alzheimer's disease can be transmitted genetically in an autosomal dominant pattern as a result of mutations to one of three genes: amyloid precursor protein gene (*APP*) and the presenilin genes (*PSFN1* and *PSFN2*). Genetic transmission by these genes, however, accounts for less than 1–2% of the prevalence of AD [33]. A much commoner genetic factor arises from variations in apolipoprotein E gene (*ApoE*) [34]. Carriers of the ε4 allele of *ApoE*, which represent 15% of Europeans and Americans of European descent, are at increased risk of Alzheimer's disease. The degree of risk is greater for those who are homozygous for ε4 (OR = 17.9) than for those with only one ε4 allele (OR = 4.2) [35].

Neuropsychology of AD

Key features: The earliest and most obvious impairment in AD is a failure to form new memories. This is referred to by different professionals variously as "short-term memory loss," "learning deficit," or "episodic memory impairment." Here we will follow the terminology of neuropsychology and call it an impairment in memory acquisition or an episodic memory impairment, which is actually a failure of long-term memory processes. We will reserve the term "short-term memory" for the even shorter time span involved in working memory and measured with digit and word span tasks. The memory impairment in AD is considered a long-term memory deficit because it becomes evident only when there is either a delay or an interference between acquisition and recall [36].

This incapacity to acquire new information has a tremendous impact on daily life. Although habitual routines can remain for a time, the lack of a more exact memory quickly renders the patient dependent on others to organize and direct their daily living. Evidence that there has been a decline from the patient's previous level of functioning is a necessary contribution for diagnosis. Incidents indicating memory decline may be reported in a multitude of ways: failure to remember appointments, PIN numbers, or people's names; failure to remember how to use a credit card; leaving the stove element on after use; frequently losing household items such as keys; getting lost; and inattentive driving.

Memory: Memory impairment is the first and foremost deficit in AD and a number of standard tests will bring this out. On the MMSE, AD patients generally do poorly on orientation for time because the date and time of year are pieces of information which are constantly changing and require frequent updating. They also do poorly on orientation for place if testing takes place in an unfamiliar setting. Besides orientation, they also fail at an early stage on the MMSE delayed recall of three words. The MMSE is, however, a screening tool and fixed cut-off scores for dementia can produce both false positives (diagnosing dementia when there is none) and false negatives (missing dementia when it is present). Standard memory tests which can be used to test verbal memory are the Logical Memory sub-tests of the Wechsler Memory Scale (WMS) and list learning tests such as the Rey auditory verbal learning task (RVLT) [37], the California verbal list learning test (CVLT) [38], and the selective reminding task of Buschke [39]. AD patients perform at floor on these tasks

Table 17.1 Representative data from the memory clinic of a Canadian hospital: median (range)

	MMSE	LM	RVLT	Fluency	BNT
Younger groups, 64–77 years					
Normal	29 (28–30)	23.5 (12–35)	44 (33–57)	18.5 (13–27)	56 (41–60)
MCI	28 (26–30)	**9** (4–38)	**29.5** (16–43)	12.5 (10–43)	48 (32–60)
MCI-to-AD	**25** (22–29)	**5** (1–24)	**25 (16–33)**	**11** (6–16)	52 (16–60)
AD	**25** (20–30)	**2** (0–15)	**23 (14–31)**	**11** (4–21)	42 (16–60)
Older groups, 78–91 years					
Normal	29 (27–30)	24.5 (14–36)	43 (33–69)	16 (9–22)	53.5 (40–60)
MCI	27 (24–30)	14.5 (2–24)	**28** (19–38)	13 (8–18)	49 (33–60)
MCI-to-AD	27 (23–30)	**7** (0–19)	**28** (11–41)	11 (3–18)	**36** (4–60)
AD	**24** (15–29)	**4** (0–18)	**22** (10–36)	**8** (2–15)	**37** (16–58)

There are 18–21 people in each group. Each group is matched to its respective normal age-group for age, gender, and years of education with one exception; there are more males in the older MCI group than in the older normal group (72% vs. 40%). Scores in bold indicate a median value below the range of the normal elderly. The MCI patients, when tested between 12 and 42 months later (median = 20 months), were still MCI. The MCI-to-AD group were diagnosed with AD between 9 and 19 months later (median = 13 months). The data for the AD group contributed to their diagnosis. LM, sum of logical memory tasks 1 and 2 of WMS; RVLT, sum of five trials of Rey verbal learning task; Fluency is for animals; BNT, Boston Naming Task.

within the first few years of onset. The few elements that the patient does recall are usually the last items on the list, a recency effect that can be ascribed to relative preservation of short-term or working memory.

In Table 17.1, we provide representative data from patients diagnosed with either AD or MCI at the Memory Clinic of the Sir Mortimer B. Davis Jewish General Hospital (Montreal) and of normal elderly volunteers (NEVs). The NEVs had no dementia at the time of testing nor up until at least 3 years later and they are matched to the patient groups for age, gender, and education. Two MCI groups are presented and are discussed later. The data for the AD patients are drawn from the neuropsychological evaluation which contributed to their diagnosis. As can be seen, half of the AD patients had MMSE scores in the range of the MCI and many in the range of the normal elderly and yet performed very poorly on the episodic memory tasks (LM and RVLT) and poorly on the language/semantic tasks (BNT and animal fluency).

AD patients are also impaired in visual memory tasks such as the Benton's Visual Retention Test [40] or the Visual Reproduction subtest of the WMS [41] with the former being the most often cited [42]. Unlike certain types of amnesia with an acute onset, AD patients are poor not only on delayed recall – What did you hear (or see)? – but also at recognition memory – Did you see (or hear) this item or that one? This will be apparent on the recognition portion of the WMS Hard Pairs association learning and the CVLT-recognition subtest. Their errors in recognition tasks are most often false positives.

Previously well-established memories for past public or personal events (retrograde or remote memory) can be preserved in the initial stages or reveal a small gradient (better memory for the more distant past). As the disease progresses, however, memory for public events becomes equally poor across the decades [34]. This loss becomes apparent in natural situations when the patient can, for instance, no longer remember the names or number of grandchildren, or who is the current political leader of the country.

In contrast to AD patients' poor performance on almost all memory tasks which involve a delay or an interfering task, mild AD patients have forward and backward digit spans which are in the range of healthy elderly people. Backward digit span, however, which requires the spatial manipulation of information, becomes diminished with moderate levels of dementia [43].

Confrontation naming: Memory deficits alone are not sufficient for diagnosis and there must also be deficits in either one or two other

cognitive domains such as language, executive function, praxis, visuospatial, or constructional capacities. Of these, the most frequently noted secondary deficit is word finding difficulties. This is evident in the patients' discourse and on tasks of confrontation naming. A commonly used naming task is the Boston Naming Task (BNT) which can be used in either its reduced 30-item or 15-item version [44]. The errors produced by the patients are usually either semantic approximations or paraphrases (bear – "an animal, or, a dog," scissors – "for cutting") or no response. In confrontation naming tasks, there is greater difficulty in naming biological items such as fruits and vegetables, and animals than in naming man-made objects such as pieces of clothing, tools, or pieces of furniture [45]. This category effect increases as overall naming ability decreases and appears to arise from the greater visual and semantic overlap within biological categories than within manufactured categories so that AD patients also have difficulty naming musical instruments which have strong within-category resemblances (e.g., violin, guitar, cello) [46].

Naming impairments in the case of AD patients appear to arise from a general semantic memory deficit [47] and AD patients are not helped by semantic cueing (e.g., it is a wild animal) or even phonemic cueing (e.g., it starts with the letter "B"). Instead, cueing tends to confuse them. Other tasks of semantic memory in which they do poorly are the category fluency tasks (name as many animals as you can in a minute) which is more impaired than letter fluency. When evaluating semantic memory, it is important to take into account the age of the patient. As can be seen in Table 17.1, even in the normal elderly, there is a decrease in semantic memory scores (fluency and BNT) after the age of 80.

Discourse and thinking: In mild stages, speech is grammatically correct but simple in structure with reduced content and a certain anomia. The AD patient's vocabulary is reduced and there is frequent use of vague terms such as "stuff," "guy," and "things." Although syntax and grammar are preserved at first [48], studies carried out to evaluate their level of comprehension have revealed that they have difficulty understanding complex sentences [43] or providing the gist or lesson of a short story [49]. Part of their poor comprehension can be attributed to their diminished semantic knowledge which is particularly poor for abstract words such as "worth" or "honor" [50]. Poor abstract thinking can be measured on the Similarities section of the Wechsler Adult Intelligence Scale (WAIS).

Attention and executive function: As a group, mild AD patients have focused reaction times (RTs) which are slower yet within the range of the normal elderly. This can be seen in tasks of simple RTs (press the key when an "x" appears) and choice RTs (press the right key when an "x" appears and press the left key when an "o" appears). Attention deficits, however, become evident when the patient is required to either inhibit a prepotent response such as in the Stroop task or divide attention between two tasks [51, 52] such as crossing out certain figures on paper while listening for the name of a specific city among a list. Executive deficits are an early feature of AD and can be seen in poor performance on Trail B but not A of the Trail Making task and on the Wisconsin Card Sorting Task [33].

Visuospatial or visuoconstructional impairments: Mild AD patients can often perform within normal limits on tasks which require copying simple designs (the pentagons on the MMSE, designs from the Visual Retention Test). They are poor, however, in direct copy of more complex designs such as those of the WMS Visual Reproduction task or the Rey figure and they have trouble producing conceptually based pictures in tasks such as freehand drawing of a clock or a house. Their memory for visual material is as poor as it is for verbal material. This can measured with the Benton Visual Retention task or the Weschler Memory Scale [53]. Mental spatial rotation is also impaired early in the course of AD [54].

In mild to middle stages, apraxic impairments can be observed in difficulties manipulating tools and in dressing. Formal tests reveal that they are poor at both imitating meaningless hand gests

and performing conceptually based gests such as demonstrating use of an object or acting out its use in pantomime [55].

Areas Relatively Preserved

In early phases of the disease, there are some areas of cognition which remain relatively preserved. These include short-term memory as measured by digit span (forward), word span, and Corsi block span [42]. Digit span backward may also be preserved in mild cases. Single-word reading of regular (e.g., boat) and exception words (e.g., yacht) is good in mild AD patients, while moderate AD patients begin to regularize exception words presented in isolation (e.g., yacht – yachet). Mild AD patients have been shown to be able to learn new motor routines and undergo the effects of perceptual and cognitive priming, all demonstrations of a preserved implicit memory system [56].

Symptoms Associated with Age of Onset in AD

Several studies have compared the cognitive profile of AD patients in whom onset is before the age of 65 years with those with a later onset and have found significant differences. The most common finding has been that early-onset (EO-AD) patients perform relatively worse on attention and executive tasks than do late-onset (LO-AD) patients. In particular, EO-AD patients do not show the preserved digit span seen in LO-AD patients [57–61]. Their poor performance on short-term memory tasks such as the Brown–Peterson Paradigm has been correlated with left frontal glucose hypometabolism [57]. EO-AD, patients also tend to decline more rapidly in the early stage [60, 62] and have been found to do worse than LO-AD patients on graphomotor tasks such as simple designs (copying loops) and complex designs and to exhibit apraxia more frequently [59]. They also perform worse on language tasks of reading, writing, spontaneous speech, and comprehension, and are poorer on written picture description.

LO-AD patients, on the other hand, are worse than EO-AD patients on long-term memory and semantic tasks such as the Similarities subtest of the WAIS and on confrontation naming tasks (BNT) [61, 63]. One study also found the LO-AD patients to be worse on visuoconstruction tasks [64]. We have found that there is an effect of age even among old and older LO-AD patients. In 65- to 77-year olds, semantic memory appears better preserved initially (see Table 17.1) than in 78- to 88-year olds but it declines rapidly over the initial 18-month period. The older patients (80+ years) score poorly on both episodic and semantic memory tasks and their scores on both types of memory tasks decline in parallel. Finally one study has found that very late-onset AD patients (older than 90 years) had marked sleep–wake disturbances, whereas earlier onset AD patients had greater memory, orientation, and inappropriate behaviors [65]. The authors suggest that the additional symptoms of very old patients may be due to vascular factors. Sevush [61] performed a factor analyses of scores of EO-AD and LO-AD patients and found that EO-AD patients scored lower on a factor weighted more heavily on reading, digit span, left/right discrimination, writing, spontaneous speech, and comprehension, whereas LO-AD patients scored lower on a second factor which included long-term memory, orientation, object naming, and abstraction.

The rare patients with presenilin mutations often develop dementia before the age of 60 years. These patients frequently have frontal deficits that resemble those of frontotemporal dementia patients [66] and often develop seizures, paraparesis, and myoclonus.

Emotional and Psychotic Symptoms

Depression in and of itself can result in some memory problems similar to those in early AD. At the same time, depressive symptoms are also often present in the early stages of AD and so

should not rule out the possibility of a diagnosis of AD [67]. As the disease progresses, some AD patients display an apathetic indifference, and anosognosia develops in some patients that is not related to depression but is associated with apathy [68]. Several scales and inventories are used equally to measure depressive symptoms. Among the most frequently cited are the Geriatric Depression Scale [69], Beck Depression Inventory [70], and the Hamilton Depression Rating Scale [71].

Delusions have been found to be present in 30–70% of AD patients [72]. Typically, they are persistent and paranoid in nature. The most common fixed delusions are either that someone is stealing from them or that they are in danger. Other typical delusions are that their family is going to abandon them or that there is a stranger living in their home. Misidentification syndromes, such as Capgras syndrome, are present in about 15% of cases [73]. Unlike schizophrenia, hallucinations are usually in the visual modality (in 82% of AD patients with psychosis) and often involve the patient talking to people not present; auditory hallucinations are rarer (35%) [74]. In general the presence of hallucinations and delusions presages a more rapid cognitive decline in AD [72].

In some patients, social functioning can remain acceptable for a long time, outliving vital memories. The patient's persistent sense of moral decorum can be seen in cases where, for example, a woman refuses to be helped to be dressed by her husband because she no longer believes they are married.

Posterior Cortical Atrophy

Posterior cortical atrophy (PCA) is an early-onset dementia (in the fifties or sixties) frequently considered a variant of AD. Compared with the typical AD pattern of pathology, PCA is associated with more NFTs in the primary and secondary visual cortex (Brodmann's areas 17 and 18) and less in the hippocampus [75]. In vivo imaging indicates greater occipito-parietal atrophy than in AD with relatively preserved mesiotemporal areas and a characteristic occipito-parietal hypoperfusion [76]. When compared with typical AD patients, some PCA patients have been found to have greater atrophy in the right association visual cortex and lesser atrophy in the left hippocampus [77].

Key features: As might be expected, PCA patients display a posterior type cognitive profile and are more impaired on visuospatial tasks than on verbo-semantic tasks. Frequently their first complaints are of reading and writing difficulties, getting lost, or not recognizing objects. Upon testing, a variety of visuospatial deficits may be found: elements of Balint's syndrome such as inability to move the eyes voluntarily to a target or reach for one as well as simultanagnosia (inability to appreciate multiple visual stimuli simultaneously), apperceptive agnosia, visual and dressing apraxia, and environmental disorientation [76]. Elements of Gerstmann's syndrome such as dysgraphia, acalculia, and left/right orientation are also frequently present. Although there may be visual field deficits, there are no primary ophthalmologic causes. PCA patients do have memory impairments on delayed recall but they are not as severe as in AD patients of similar disease duration and MMSE scores [78, 79]. They also have better language skills than does the typical AD patient and demonstrate better insight into their condition and greater rates of depression [80].

The feature which best distinguishes the PCA patients from the more typical AD patients is their difficulty in processing compound stimuli (simultanagnosia) [79]. This can be seen in their verbal description of a complex picture such as the Cookie Theft Picture from the Boston Diagnostic Aphasia Examination [81]. The PCA patient distinguishes individual elements of the picture very slowly and is very poor at taking in the overall scene. Other tasks at which they are particularly poor are recognizing fragmented figures and discerning both levels of Navon letters [79]. Navon letters are large letters formed of smaller letters. When asked to report what they see when viewing a Navon letter, PCA patients report the individual small letters but fail to perceive the larger letter that they make up, even after cueing. AD patients on the other hand tend to

see the large letter first but will see the smaller letters if cued to them. PCA patients also perform poorly on copy of the Rey–Osterrieth Complex Figure and simple tests of vision [78].

Up to 25% of PCA patients experience visual hallucinations and it has been found that the patients with hallucinations more frequently have parkinsonism, myoclonic jerks, and REM sleep disorder which suggests the involvement of thalamocortical circuits [82].

Dementia with Lewy Bodies (DLB)

DLB is also termed Lewy body disease, Lewy body dementia, diffuse Lewy body disease, and Lewy body variant of AD.

The second most common form of dementia after AD is dementia with Lewy bodies (DLB) representing up to 20% of dementia cases. Several factors set it apart from AD. First, it occurs significantly more often in men than in women [5] and its symptoms are more severe and aggressive in men than in women. The course of DLB from onset to death is 1–5 years, much shorter than in AD. Onset before the age of 70 years is more frequent and this early onset is associated with more rapid progression. Unlike AD, neurological signs, in the form of parkinsonism, are one of three possible diagnostic features. By definition, these signs, usually gait disturbance or balance difficulties, must appear either simultaneously or within 1 year before or after the appearance of cognitive or psychiatric symptoms.

Postmortem studies have revealed that, although DLB is rarely misdiagnosed when recognized, it is frequently missed [83]. This may be due to the fact that DLB and AD pathology frequently co-occur (see Fig. 17.1), or that DLB is less known, or that the typical picture presented for DLB does not apply to all [84]. Proper discernment of the signs of DLB and its diagnosis, however, is particularly important because DLB patients can suffer severe negative effects from the administration of neuroleptics to treat psychotic features, whereas they benefit from ACh inhibitors, possibly more than do AD patients [85].

Pathology: Lewy bodies, the pathological element from which DLB derives its name, were first identified in 1912 by the neurologist Friedrich Lewy and, at that time, were associated with Parkinson's disease. They are neuronal cytoplasmic inclusions which are found in nuclei of the brain stem (dorsal vagal nuclei, locus coeruleus, and substantia nigra) in Parkinson's disease (PD) and in the basal forebrain, limbic regions (amygdala, transentorhinal cortex, and cingulate), and neocortex of PD patients who develop dementia. One consequence of cell loss in the nucleus basalis of Meynert and the septal forebrain is that it creates a severe disruption of the cholinergic system which in turn affects attentional capacities. One imaging study [86] using voxel-based morphometry (VBM) indicated that DLB patients have greater temporal, parietal, and occipital lobe atrophy than do Parkinson disease dementia patients, but less frontal and temporal lobe atrophy than do AD patients.

Key features: Diagnostic criteria for DLB [84] indicate that two out of three core features should be present for a diagnosis of probable DLB. These are spontaneous parkinsonism, visual hallucinations, and fluctuations in attention or cognition. In general, the presence of psychotic symptoms in DLB, as in AD, presages a more rapid progression of the disease [87].

The principal psychotic feature of DLB is visual hallucinations (VH) occurring in over 80% of patients. The hallucinations are well formed and recurrent, and are of people or animals who speak or interact with the patient. For example, a patient may complain of a small dog nipping at his heels. Although the hallucinations are unpleasant, they do not terrify the patient and in some cases the patient has sufficient insight to acknowledge that they are unreal. Although they can be present in patients taking levodopa medication for parkinsonism symptoms, this is not a necessary condition [88]. Patients who experience VH often also have greater visual spatial impairments than do others.

Table 17.2 Percentage of AD and DLB patients who endorsed four specific items on the Mayo fluctuations scale

Four-item DLB fluctuations composite	AD, % yes	DLB, % yes
1. Are there times when the patient's flow of ideas seems disorganized, unclear or not logical? Yes, no, don't know	58.6	85.7
2. How often is the patient drowsy and lethargic during the day, despite getting enough sleep the night before? (a) All the time or several times a day * (b) Once a day or less	27.1	72.9
3. How much time does the patient spend sleeping during the day (before 7:00 pm)? (a) 2 h or more* (b) Less than 2 h	27.1	67.1
4. Does the patient stare into space for long periods of time? Yes, no, don't know	12.9	34.3

DLB patients (63%) and AD patients (12%) endorsed three or four items on this scale. AD, Alzheimer's disease patients; DLB, Dementia with Lewy bodies; % yes, affirmative response to Yes/No or to *specified items.

Other psychotic features such as depression or delusions can be present in DLB. A suggestive feature of DLB is sleep disturbance; informants frequently report that even before the diagnosis of DLB, the patient exhibited signs of REM sleep disorder such as thrashing about or loudly vocalizing during sleep. One study [89] found that of 100 DLB patients, 56 showed some form of misidentification syndrome such as misidentifying people (e.g., thinking a child is one's spouse), places (this house is my company), or objects. Of these, 17 people had either Capgras syndrome, in which patients confirm that one person has been replaced with an identical duplicate, or phantom boarder syndrome, in which patients confirm that a stranger is living in their house. Delusions, most frequently of theft, were significantly more common among women than men. In this same study, dysphoria was present in 45% of patients and there was no gender bias for this trait.

Of the three core features, the presence of fluctuations in cognition and attention is the most difficult to ascertain. Changes in the level of attentiveness can occur over very short periods such as within the time of an interview or over longer periods such as days. They may be reported as episodes of going blank or of times when there was a spontaneous recall of information that had been forgotten. Although there are semi-structured interviews that can be carried out with informants [90], responses to them do not always distinguish between the fluctuations seen in AD and those in DLB. Fluctuations in AD, in general, are much milder and are noted most often in the midst of carrying out a task and can frequently be characterized as times of confusion resulting from memory failure. Fluctuations in DLB, on the other hand, are not memory related and not particularly influenced by the level of activity. Ferman et al. [91] carried out an extensive interview with informants for AD and DLB patients and found four questions to be particularly helpful in distinguishing between DLB and AD patients. The questions, presented in Table 17.2, are related to levels of arousal, such as daytime sleeping, drowsiness, and staring blankly into space, and to cognitive confusion. The study found that 63% of DLB informants responded positively to three or four of these questions, whereas only 12% of AD informants responded at that level.

Cognition: The principal areas of cognitive impairment in the early stages of DLB are attention, executive function and visual perception. Memory deficits and language impairments are not always present in the early stages of DLB, but they quickly develop to a degree that DLB patients soon resemble AD patients in these domains. DLB patients, however, show better recognition memory than do AD patients on tasks such as the Benton Visual Retention Test or the RVLT. The digit span of DLB patients is similar to that of mild AD patients and is within the low range of age-matched non-demented people.

DLB patients have worse attention impairments than do AD patients so that whereas AD

patients will be impaired primarily on category fluency tasks, DLB patients perform poorly on both letter fluency and category fluency tasks.

DLB have severe visual spatial/visual constructional impairments. Unlike mild AD patients, DLB patients are poor even at copying a clock, the pentagons, or other simple designs such as the outlined cross or the block designs from the Wechsler Intelligence Scale for Children. They also have difficulty distinguishing overlapping figures. Because of their poor performance on these more basic visual tasks, it is difficult to evaluate whether their poor performance on visual memory tasks is more impaired in that domain than in the verbal.

DLB patients have basic attentional and psychomotor deficits which in turn become deficits in performing tasks of executive function. DLB patients have been found to do significantly worse than AD patients on the Initiation/Perseveration subset of the Mattis Dementia Rating Scale, whereas the AD patients do worse than the DLB patients on the Memory subset of tasks [92]. DLB patients also do poorly on both Trails A and B and on the Wisconsin Card Sorting Task.

Although we have brought out the tasks in which AD and DLB patients differ, it should be remembered that AD pathology co-occurs with DLB pathology more often than not (see Fig. 17.1). The relative rate at which either pathology invests the brain will have its effect on the cognitive profile; so, for example, if an individual is severely amnestic due to AD, attentional fluctuations will be difficult to discern.

Parkinson's Disease Dementia (PDD)

When Parkinson first wrote of "trembling palsy" in 1812 he had noted that the senses and intellect were uninjured. By the end of the nineteenth century, however, several had reported behavioral and cognitive changes in Parkinson disease. These included depression, irritability, poor memory, and dementia [93]. Today it is generally held that 20–40% of PD patients develop dementia [94], although some have put the prevalence as high as 70% [95].

In Parkinson disease (PD) there is a severe loss of pigmented cells in the substantia nigra entailing a dopamine deficiency throughout the brain. There is also cell loss in the locus coeruleus, the nucleus basalis of Meynert, the Raphe nuclei, and the dorsal vagal nuclei resulting in further disruptions to cholinergic, noradrenergic, and serotonergic neurotransmitter systems. Lewy bodies are found in all these areas of cell loss. The additional diagnosis of dementia in PD can be associated with either DLB pathology, AD pathology, or both. AD pathology appears to exacerbate the condition of PD patients so that mild levels of both conditions (Lewy bodies and AD) can have a greater effect on cognition than either alone [95–97].

Cognitive impairments are common in PD, even in the initial stages. One study carried out comprehensive neuropsychological testing with PD patients and it revealed that at first diagnosis, 62% of PD patients display impaired performance on at least one cognitive task and 10% of the original cohort were demented 3.5 years later. Patients who were older at disease onset and had non-tremor dominant motor phenotype were more likely to develop dementia. Other studies have found an annual conversion rate to dementia of 5–10% in PD patients.

Impairments in executive functions or on frontal lobe tasks have been attributed both to the degeneration of the medial substantia nigra with loss of nigral projections of dopamine to the limbic and frontal areas, and to cholinergic deficiency. Executive deficits are probably more a result of cholinergic dysfunction than cortical cell loss.

Several studies have found that there is a close relationship between Braak and Braak morphological stages for AD (NFT pathology) and cognitive status as measured by MMSE in PD patients [95, 98, 99]. As a result it has been suggested that it is the isocortical and limbic pathology and not the subcortical pathology that is relevant to the development of dementia. It should be remembered, however, that the MMSE

does not measure the things thought to be dominant in subcortical dementias such as hallucinations and mood changes. As such these studies are probably confirming the fact that AD pathology can be comorbid with DLB pathology and that the pattern of AD pathology has the stronger influence on purely cognitive functions than does that of Lewy bodies.

Key features: With the advent of a consensus for diagnosing DLB, several studies have been undertaken to distinguish the cognitive and psychiatric profiles of DLB and PDD patients. As of yet, only minimal differences have been found. The general conclusions of these studies are that PDD and DLB are the same syndrome with different time courses with respect to motor signs. In PDD, motor signs are present for at least a few years, and in some cases for several years, before the diagnosis of dementia. The key symptoms of PDD, like DLB, are both psychotic and cognitive and are more likely to result in nursing home placement than are motor symptoms.

Mood and psychosis: Depression and depressive features are common in PDD. Psychotic symptoms in PDD are similar to those of DLB patients. They come in the form of illusions, a false sense of presence, hallucinations, or delusions. Hallucinations and delusions are recurring, and either stable in nature or progressive. Auditory hallucinations can occur, but unlike in schizophrenia they frequently occur along with a visual hallucination (e.g., a person appears and talks to the patient). Psychosis in PDD has been associated with the presence of Lewy bodies, imbalances in neurotransmitters, and/or visuospatial processing deficits [100].

Cognition: The predominant cognitive deficit reported in PD patients is in the domain of executive function (initiating responses, planning, and set shifting). PD patients make an increased number of errors on the Wisconsin Card Sorting Task (WCST). Their errors are both perseverative and non-perseverative, indicating that they have difficulty in forming sets [101]. Interestingly there have been incidental reports that at times PD patients can verbalize correct responses but not execute them, suggesting a disconnect between thought and action. Areas of cognition that are relatively preserved include language functions, orientation, cued recall, and recognition memory [102].

PD patients with the additional diagnosis of dementia display aphasic features. They also manifest visuoconstructional and visuoperceptual deficits which can be observed in the clock-drawing task. Although most studies have found PDD and DLB to be nearly identical in all respects, one study found sexual disinhibition, alexia, and naming problems to be more common in DLB than in PDD [94].

A question of interest with PD and PDD patients has been whether they exhibit not only slowed motor responses but also slowed cognitive processing (bradyphrenia). Ballard et al. [103] compared the performance of DLB, PDD, PD, AD, and normal elderly controls on tasks of simple and choice RT. Although PD patients were slower on simple and choice RTs, the difference between these two scores, which can be considered a measure of central (or cognitive) processing speed, was found not to be significantly different from that of controls. PDD patients and DLB patients, however, not only were much slower on both tasks but also were disproportionately slower on the choice RT task, indicating slowed mental processing. These tests also looked at the variability in response times and found greater fluctuations in both PDD and DLB than in AD, PD, and controls. This study looked at the effect of the presence of parkinsonism on cognition. Interestingly, the presence or the absence of parkinsonian symptoms and the level of parkinsonism severity correlated strongly with central processing time in a combined DLB/PDD group but not in PD patients. An increase in central processing time is characteristic of other types of patients with striatofrontal dysfunction such as in progressive supranuclear palsy [104].

In a clinical setting it is difficult to evaluate central processing time when the patients have motor deficits. Motor speed can be measured with finger tapping, cancellation, and pegboard tasks. Psychomotor speed is usually evaluated with the digit-symbol task, color dots of the Stroop, or Trail A of the Trail Making task. Separating the influence of motor impairments

on mental processing, however, can be best done with computer tasks with increasing levels of task requirements (e.g., simple and choice RT, visual search). While these tasks are frequently used in experimental settings, there are no established norms for the various age-groups.

As with DLB patients, PDD patients initially may not have marked memory deficits but they do develop to the point that they resemble AD patients in encoding impairments with the possible exception that PDD patients can have better recognition memory than do AD patients and commit fewer intrusion and false-positive errors [105, 106].

Binswanger's Dementia

Subcortical Arteriosclerotic Encephalopathy

A good number of individuals have dementia related to strokes, and in these the cognitive changes reflect the neuroanatomy of the strokes themselves. In addition, there are individuals (often with hypertension) who develop cognitive changes even without a single overt stroke episode. Their imaging, particularly MRI, reveals marked changes in deep white matter, thought to be responsible for the cognitive alterations. This vascular syndrome has been termed Binswanger's dementia. Binswanger's dementia (BD) develops slowly and intermittently over several years [107]. Patients are typically in their seventies or eighties when first diagnosed. In this form of vascular dementia there is ischemic injury to small vessels in deep white matter. These injuries lead to demyelination and are discernable as bilateral white matter hypodensities on CT scans and as multiple diffuse signals on T2 on MR imaging in the periventricular regions. The presence of these imaging signs, however, is not sufficient for diagnosis of BD. The behavioral effects of damage to axons in this area are thought to result from the disconnection of subcortical structures and the cortical surface [108].

Key features: Cognitive deficits are not an early prominent symptom of BD. Instead the first symptoms of BD are mood changes and neurological signs [109].

Mood: In some cases the patient first manifests a state of mania or is characterized by emotional incontinence. Displays of a wide range of emotion have been reported including episodes of elation, euphory, rage, weeping, forced laughing or crying, anxiety, irritation, and indifference [110]. The early manic phase may develop into an abulia; depression is also common in BD patients, as is personal neglect.

Psychosis: Lawrence [111] made an incidental finding of increased obsessional behavior in BD. They found that six of seven BD patients had marked obsessional symptoms and the seventh case displayed mild obsessional behavior. This contrasted with only 5 of 11 AD patients who exhibited mild examples of obsessional behavior. The behaviors of the BD patients included increased orderliness, fixed routines, and checking rituals. Unlike the classical obsessive–compulsive disorder, it was not egodystonic in the BD patients; they had no desire to change their behavior and were resistant to change. The authors of this study suggest that this obsessional behavior may be evidence of dysfunction of basal ganglia and frontal areas in BD patients.

Neurological signs: Neurological signs are frequent and reflect diffuse vascular damage. Pseudobulbar palsy (dysarthria and swallowing difficulties), gait disturbances due to increased muscle tone, and parkinsonism are seen.

Cognition: Although there can be amnestic intervals, memory impairments are not prominent in BD. In some cases, aphasia and psychomotor slowing is present.

Transmissible Spongiform Encephalopathies (Prion Diseases)

Transmissible spongiform encephalopathies (TSEs) arise from the replication of an abnormal isoform of the naturally occurring prion protein PrP. As this abnormally shaped protein, or prion,

replicates, it causes a characteristic vacuolation of primarily gray matter brain tissue from which comes the name of spongiform encephalopathy. These vacuoles are visible only at the microscopic level and there are no specific structural irregularities on the MR image except perhaps some atrophy. Most often TSEs, or prion diseases, occur sporadically, but they can be transmitted through direct contact with contaminated instruments or infected body tissue or fluids (iatrogenic), and there are prion diseases that are inherited in an autosomal dominant pattern. Although prion diseases are extremely rare, they became the subject of worldwide attention when a new variant of Creutzfeldt–Jakob disease, a TSE, was recognized in 1996. This variant is thought to have been acquired by the consumption of beef from cattle which had been fed offal contaminated with bovine spongiform encephalopathy, "mad cow disease" [112]. Pathological review of tissue obtained by biopsy and autopsy remains the only way to confirm this diagnosis.

Creutzfeldt–Jakob disease: CJD is the most common TSE with an incidence of 1 person/million/year. Most cases of CJD occur sporadically (sCJD), but there is an inherited form, fCJD, and the variant form, vCJD, referred to above. Onset in 80% of cases of sCJD occurs between the ages of 50–70 years [113], but there have been cases in which onset was in the teens or after 80 years of age. In 25% of cases, there is a prodromal stage in which there are symptoms of fatigue, sleep problems, decreased appetite, weight loss, asthenia, or anxiety. Patients usually present with either symptoms of cognitive impairment such as visual deficits or neurological signs, commonly cerebellar ataxia. At this point the disease takes a very rapid course of mental and neurological decline and death occurs on average within 4 or 5 months.

Key features: A typical EEG, motor signs, and stimulus-provoked myoclonus are among the diagnostic signals of sCJD, but the overriding distinguishing feature of the disease is the rapidity with which it progresses. Initially the EEG [114] has a slow background rhythm which is followed later by a pattern of repetitive high-voltage sharp wave discharge. This pattern may initially be unilateral but soon becomes bilateral. Cognitive impairments quickly become pervasive; whether in the domains of memory, language, or executive function, there is no area of relative strength. The end state of patients is typically one of akinetic mutism.

Psychotic features, which are rare as a first symptom, develop in 42% of sCJD patients [115], usually within the first 100 days. A wide range of paranoid and persecutory delusions as well as vivid auditory and visual hallucinations can be present. Sadness, depression, and withdrawal frequently characterize these patients during the first weeks. In some cases, the patients are first treated for these mood changes before a diagnosis of CJD is established.

Familial CJD: Cases of familial CJD make up only 10% of cases of CJD and have a different time course than do those of sCJD. Onset is generally 12 years earlier than in sCJD (35–60 years) and the disease is of a slightly longer duration (M = 13 months). Although cognitive impairments are pervasive in all domains, one study found some minor differences which distinguished it from sCJD or vCJD. In the early months of the disease, only a minority of fCJD patients manifested a confrontation naming deficit and they did not display as severe a perceptual impairment as vCJD [116] patients.

New variant CJD: Most cases of vCJD have been found in Great Britain and other European countries, or among people who have visited these countries. The disease typically has occurred at an even younger age than familial cases (mean age 25 years, range 12–74) and has had a course of approximately 13 months [115], which is longer than that for sCJD.

The initial symptoms of vCJD have been psychiatric and sensory abnormalities or cerebellar signs. Prior to presentation, relatives had frequently noted a personality change characterized by withdrawal and depression. Insomnia and daytime sleepiness, anorexia, and weight loss were noted to be common. EEG was normal in vCJD [112] until late in the course of the disease. As the disease progressed, some patients have

manifested highly complex delusions which could last for hours at a time. In similar fashion to other TSEs, cognitive deficits in the domains of memory and executive function quickly became pervasive. One study [116] found that naming deficits were worse in vCJD than in fCJD but that visuoperceptual impairments were less common in vCJD than in fCJD or sCJD.

There are other inherited TSEs found in a few kindreds across the world. Among them are fatal familial insomnia and Gerstmann–Straussler–Scheinker disease.

Fatal familial insomnia (FFI): FFI was formally recognized in 1992 and is classified by some as a variant of fCJD. The thalamus is prominently involved in FFI which is visible on MR imaging as a hyperintensity in the thalamus. Onset usually occurs when the patient is in his/her forties (range 20–63 years) and disease duration is usually 13–15 months but ranges from 6 to 24 months.

The distinctive features of FFI are nocturnal insomnia and a profound disruption of the sleep–wake cycle. Other core features are abnormal polysomnogram and markedly impaired attention. Hallucinations, parasomnias, and dysautonomia can be present episodically.

After the manifestation of sleep symptoms, cognitive impairments most often appear in the form of mild amnesia, attentional, and concentration deficits. As the disease progresses, FFI patients become confused and disoriented, and the end course of the disease is one of stupor and coma.

Gerstmann–Straussler–Scheinker (GSS): The first family described with GSS had symptoms of progressive cerebellar ataxia and cognitive decline. GSS typically begins in fifth or sixth decade but may be present as young as 25 years. Disease duration varies widely from 3 months to 13 years. The early cognitive deficits that have been noted are memory impairment, learning difficulties, dysphasia, attention span, and slow central processing time. Mood changes which have been reported range from aggressivity, irritability, emotional lability to apathy, and withdrawal [117]. EEG is normal in GSS [112].

Mild Cognitive Impairment [Similar to Cognitively Impaired, No Dementia (CIND)]

Given the insidious onset of dementia, it is not surprising that the clinical community has developed a diagnostic construct termed mild cognitive impairment (MCI) which situates a patient on a continuum somewhere between normal aging and dementia. Mild cognitive impairment refers to a state in which cognitive deficits are milder than in dementia and not sufficiently severe to disrupt daily living. Recognition of MCI in a patient is considered a diagnosis of significance because in most cases it is a prodromal state of dementia. The annual conversion rate of MCI patients to AD has been observed to be 8–10% [118]. Some MCI patients, however, do not progress to dementia, either recovering somewhat or remaining cognitively stable over a period of as many as 10 years.

MCI deficits are often too minor to be detected with the MMSE (see Table 17.1) and new screening tests have been developed to rapidly detect milder impairments [13]. Two in particular are the Montreal Cognitive Assessment (MoCA) [19] and DemTect [119]. They both take about 10 min to administer and have high rates (%) of sensitivity/specificity (MoCA: 90/87; DemTect: 80/92). The authors of the MoCA recommend that it be administered to patients with both cognitive and functional complaints and scores above 25 on the MMSE, and to people with cognitive complaints only.

In Table 17.1, data from two groups of patients classed here as MCI are presented ("MCI" and "MCI-to-AD"). The data are taken by chart review over a 10-year period (1995–2005); a variety of terms were used initially to diagnose the patients: MCI, dementia borderline, age-associated cognitive decline, CIND, or vascular cognitive impairment. An observation about this data underlines the difficulty in predicting whether an MCI patient will progress to AD within 1 year. It is that although as a group the progressors clearly have lower scores than the non-progressors on the four memory tasks, the

ranges of scores of the groups greatly overlap with each other and even with normal elderly.

Key features: For the most part when MCI patients progress to dementia, it is either to AD, a frontotemporal dementia, or a vascular dementia. The cognitive deficits of MCI patients often presage the type of dementia they will develop and some have found it useful to further breakdown MCI into subgroups which anticipate future progression. Currently the subgroups most often used are amnestic MCI (aMCI), multi-domain MCI, and single-domain non-memory MCI. The aMCI patient is characterized by measurable deficits in acquiring new memories and is most likely to develop AD. Multi-domain MCI patients are more likely to develop some form of vascular dementia or a frontotemporal dementia. A typical single-domain non-memory MCI is the patient who scores well on memory tasks but has marked word-finding difficulties. This patient might progress to primary progressive aphasia and eventually semantic dementia. These subdivisions should not belie the fact that attentive testing of MCI patients has revealed that the deficits of most MCI patients are heterogeneous. For instance, besides memory deficits, aMCI patients frequently have subtle deficits in executive function and attention, as well as language impairments apparent only with clinical testing.

Conclusion

Research into neurodegenerative syndromes began essentially in the nineteenth century and has since made steady progress in better defining the behavioral, neurological, and pathological features of the various dementia syndromes. In turn this research into deficient forms of brain function has provided us with a better understanding of the interactivity which underlies normal brain function. It is only recently, however, that research has begun to consider the real possibility of developing feasible preventative or remedial therapies and treatments for the major forms of dementia.

Most standard neuropsychological tests were originally conceived of for the purposes of experimental research (e.g., Stroop), and neuropsychology has been a central component of dementia research since its inception. In the future, experimental neuropsychology will continue to be instrumental in developing finer tuned approaches and tests with the goals of better differentiating the dementia syndromes and discovering the basis of mind–brain correlation. In view of this close historic relationship between neuropsychology and research, the effective clinician will be avid for the latest developments in the field which will help to refine his/her contribution to patient care.

References

1. Cummings J, Benson DF, LoVerme S Jr. Reversible dementia. Illustrative cases, definition, and review. J Am Med Assoc. 1980;243:2434–9.
2. Espinoza M, de Silva R, Dickson DW, Davies P. Differential incorporation of tau isoforms in Alzheimer's disease. J Alzheimer's Dis. 2008;14:1–16.
3. Kurz AF. Uncommon neurodegenerative causes of dementia. Int Psychogeriatr. 2005;17(Suppl 1): S35–49.
4. Arvanitakis Z, Graff-Radford N. Focal degenerative dementia syndromes. Clin Geriatr Med. 2001;17:303–18.
5. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002;16:203–12.
6. Chertkow H. Diagnosis and treatment of dementia: introduction. Introducing a series based on the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia. CMAJ. 2008;178:316–21.
7. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med. 1997;337:1667–74.
8. Verhey FR, Lodder J, Rozendaal N, Jolles J. Comparison of seven sets of criteria used for the diagnosis of vascular dementia. Neuroepidemiology. 1996;15:166–72.
9. Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. Neurology. 1994;44:1593–600.
10. Feldman H, Kertesz A. Diagnosis, classification and natural history of degenerative dementias. Can J Neurol Sci. 2001;28(Suppl 1):S17–27.

11. Mendez MF. The accurate diagnosis of early-onset dementia. Int J Psychiatry Med. 2006;36:401–12.
12. Houston WS, Bondi MW. Potentially reversible cognitive symptoms in older adults. In: Attix DK, Welsh-Bohmer KA, editors. Geriatric neuropsychology: assessment and intervention. New York, NY: Guilford Press; 2006. pp. 103–29.
13. Jacova C, Kertesz A, Blair M, et al. Neuropsychological testing and assessment for dementia. Alzheimer's Dementia. 2007;3:299–317.
14. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
15. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982;139:1136–9.
16. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellek L, Karasu TB, editors. Geriatric psychiatry: a handbook for psychiatrists and primary care physicians. New York, NY: Grune & Stratton Inc; 1976. pp. 77–121.
17. Mattis S. Dementia rating scale (DRS). Odessa, FL: Psychological Assessment Resources; 1988.
18. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566–72.
19. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
20. Troyer AK. DemTect effective in screening for mild cognitive impairment and mild dementia. Evid Based Ment Health. 2004;7:70.
21. Morris RG, Salmon DP. The centennial of Alzheimer's disease and the publication of "Uber eine eigenartige Erkankung der Hirnrinde" by Alois Alzheimer. Cortex. 2007;43:821–5.
22. Raskin N, Ehrenberg R. Senescence, senility, and Alzheimer's disease. Am J Psychiatry. 1956;113:133–7.
23. Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry. 1994;151:390–6.
24. Storandt M, Grant EA, Miller JP, Morris JC. Rates of progression in mild cognitive impairment and early Alzheimer's disease. Neurology. 2002;59:1034–41.
25. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol. 1991;82:239–59.
26. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol Aging. 1995;16: 271–8, discussion 278–84.
27. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging. 1997;18:351–7.
28. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry. 1999;66:137–47.
29. Choo IH, Lee DY, Youn JC, et al. Topographic patterns of brain functional impairment progression according to clinical severity staging in 116 Alzheimer disease patients: FDG-PET study. Alzheimer Dis Assoc Disord. 2007;21:77–84.
30. Mcdowell I, Hill G, Lindsay J, et al. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. Neurology. 1994;44:2073–80.
31. Rocca WA, Amaducci LA, Schoenberg BS. Epidemiology of clinically diagnosed Alzheimer's disease. Ann Neurol. 1986;19:415–24.
32. Patterson C, Feightner JW, Garcia A, et al. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. CMAJ. 2008;178: 548–56.
33. Welsh-Bohmer KA, Warren LH. Neurodegenerative dementias. In: Attix DK, Welsh-Bohmer KA, editors. Geriatric neuropsychology: assessment and intervention. New York, NY: Guilford Press; 2006. pp. 56–88.
34. Salmon DP, Bondi MW. The neuropsychology of Alzheimer's disease. In: Nussbaum PD, editor. Handbook of neuropsychology and aging. New York, NY: Plenum Press; 1997. pp. 141–58.
35. Fields RB. Geriatric head injury. In: Nussbaum PD, editor. Handbook of neuropsychology and aging. New York, NY: Plenum Press; 1997. pp. 280–97.
36. Squire LR. Memory and brain. New York, NY: Oxford University Press; 1987.
37. Rey A. L'Examen clinique en psychologie. Paris: Presses universitaires de France; 1964.
38. Delis DC, Kramer JH, Kaplan EF, Ober BA. California verbal learning. Research Manual ed. San Antonio, TX: The Psychological Corporation, Harcourt Brace Jovanovich; 1987.
39. Buschke H. Cued recall in amnesia. J Clin Neuropsychol. 1984;6:433–40.
40. Benton AL. Revised visual retention test. 4th ed. New York, NY: The Psychological Corporation; 1974.
41. LaRue A, Swanda R. Neuropsychological assessment. In: Nussbaum PD, editor. Handbook of neuropsychology and aging. New York, NY: Plenum Press; 1997. pp. 360–84.
42. LaRue A. Aging and neuropsychological assessment. New York, NY: Plenum Press; 1992.
43. Lambon Ralph MA, Patterson K, Graham N, et al. Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55 cases. Brain. 2003;126:2350–62.
44. Kaplan EF, Goodglass H. The assessment of aphasia and related disorders. 2nd ed. Philadelphia, PA: Lea and Feiberg; 1983.

45. Whatmough C, Chertkow H, Murtha S, et al. The semantic category effect increases with worsening anomia in Alzheimer's type dementia. Brain Lang. 2003;84:134–47.
46. Dixon MJ, Bub DN, Chertkow H, Arguin M. Object identification deficits in dementia of the Alzheimer type: combined effects of semantic and visual proximity. J Int Neuropsychol Soc. 1999;5:330–45.
47. Chertkow H, Bub D. Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? Brain. 1990;113(Pt 2):397–417.
48. Nebes RD. Alzheimer's disease: cognitive neuropsychological aspects. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. New York, NY: McGraw-Hill; 2007. pp. 545–50.
49. Chapman SB, Zientz J, Weiner M, et al. Discourse changes in early Alzheimer disease, mild cognitive impairment, and normal aging. Alzheimer Dis Assoc Disord. 2002;16:177–86.
50. Fung TD, Chertkow H, Murtha S, et al. The spectrum of category effects in object and action knowledge in dementia of the Alzheimer's type. Neuropsychology. 2001;15:371–9.
51. Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. Attentional control in Alzheimer's disease. Brain. 2001;124:1492–508.
52. Levinoff EJ, Li KZ, Murtha S, Chertkow H. Selective attention impairments in Alzheimer's disease: evidence for dissociable components. Neuropsychology. 2004;18:580–88.
53. Wechsler D. Manual for the Wechsler memory scale-revised. San Antonio, TX: The Psychological Corporation; 1987.
54. Armstrong CL, Cloud B. The emergence of spatial rotation deficits in dementia and normal aging. Neuropsychology. 1998;12:208–17.
55. Benke T. Two forms of apraxia in Alzheimer's disease. Cortex. 1993;29:715–25.
56. Heindel WC, Butters N, Salmon DP. Impaired learning of a motor skill in patients with Huntington's disease. Behav Neurosci. 1988;102:141–7.
57. Kalpouzos G, Eustache F, de la Sayette V, et al. Working memory and FDG-PET dissociate early and late onset Alzheimer disease patients. J Neurol. 2005;252:548–58.
58. Suribhatla S, Baillon S, Dennis M, et al. Neuropsychological performance in early and late onset Alzheimer's disease: comparisons in a memory clinic population. Int J Geriatr Psychiatry. 2004;19:1140–7.
59. Reid W, Broe G, Creasey H, et al. Age at onset and pattern of neuropsychological impairment in mild early-stage Alzheimer disease. A study of a community-based population. Arch Neurol. 1996;53:1056–61.
60. Jacobs D, Sano M, Marder K, et al. Age at onset of Alzheimer's disease: relation to pattern of cognitive dysfunction and rate of decline. Neurology. 1994;44:1215–20.
61. Sevush S, Leve N, Brickman A. Age at disease onset and pattern of cognitive impairment in probable Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 1993;5:66–72.
62. Rosselli MC, Ardila AC, Moreno SC, et al. Cognitive decline in patients with familial Alzheimer's disease associated with E280a presenilin-1 mutation: a longitudinal study. J Clin Exp Neuropsychol. 2000;22:483–95.
63. Grosse DA, Gilley DW, Wilson RS. Episodic and semantic memory in early versus late onset Alzheimer's disease. Brain Lang. 1991;41:531–7.
64. Filley CM, Kelly J, Heaton RK. Neuropsychologic features of early- and late-onset Alzheimer's disease. Arch Neurol. 1986;43:574–6.
65. Hori K, Oda T, Asaoka T, et al. First episodes of behavioral symptoms in Alzheimer's disease patients at age 90 and over, and early-onset Alzheimer's disease: comparison with senile dementia of Alzheimer's type. Psychiatry Clin Neurosci. 2005;59:730–5.
66. Mendez MF, McMurtray A. Frontotemporal dementia-like phenotypes associated with presenilin-1 mutations. Am J Alzheimer's Dis Other Demen. 2006;21:281–6.
67. Rockwood K, Bouchard RW, Camicioli R, Léger G. Toward a revision of criteria for the dementias. Alzheimer's Dementia. 2007;3:428–40.
68. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A diagnostic formulation for anosognosia in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2006;77:719–25.
69. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17:7–49.
70. Beck AT, Beck RW. Screening depressed patients in family practice. A rapid technic. Postgrad Med. 1972;52:81–5.
71. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6:278–96.
72. Scarmeas N, Brandt J, Albert M, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. Arch Neurol. 2005;62:1601–8.
73. Harciarek M, Kertesz A. The prevalence of misidentification syndromes in neurodegenerative diseases. Alzheimer Dis Assoc Disord. 2008;22:163–9.
74. Leroi I, Voulgari A, Breitner JC, Lyketsos CG. The epidemiology of psychosis in dementia. Am J Geriatr Psychiatry. 2003;11:83–91.
75. Tang-Wai DF, Graff-Radford NR, Boeve BF, et al. Clinical, genetic, and neuropathologic characteristics of posterior cortical atrophy. Neurology. 2004;63:1168–74.
76. Mendez MF, Ghajarania M, Perryman KM. Posterior cortical atrophy: clinical characteristics and differences compared to Alzheimer's disease. Dement Geriatr Cogn Disord. 2002;14:33–40.

77. Whitwell JL, Jack CR Jr, Kantarci K, et al. Imaging correlates of posterior cortical atrophy. Neurobiol Aging. 2007;28:1051–61.
78. Charles RF, Hillis AE. Posterior cortical atrophy: clinical presentation and cognitive deficits compared to Alzheimer's disease. Behav Neurol. 2005;16:15–23.
79. McMonagle P, Deering F, Berliner Y, Kertesz A. The cognitive profile of posterior cortical atrophy. Neurology. 2006;66:331–8.
80. Mendez MF, Shapira JS, Clark DG. "Apperceptive" alexia in posterior cortical atrophy. Cortex. 2007;43:264–70.
81. Goodglass H, Kaplan E. The assessment of aphasia and related disorders. Philadelphia, PA: Lea and Febiger; 1976.
82. Josephs KA, Whitwell JL, Boeve BF, et al. Visual hallucinations in posterior cortical atrophy. Arch Neurol. 2006;63:1427–32.
83. Weisman D, Cho M, Taylor C, et al. In dementia with Lewy bodies, Braak stage determines phenotype, not Lewy body distribution. Neurology. 2007;69:356–9.
84. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimer's Dis. 2006;9:417–23.
85. Aarsland D, Mosimann UP, McKeith IG. Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol. 2004;17:164–71.
86. Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. Neurology. 2007;69:747–54.
87. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry. 2005;162:2022–30.
88. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006;66:93–8.
89. Nagahama Y, Okina T, Suzuki N, et al. Classification of psychotic symptoms in dementia with Lewy bodies. Am J Geriatr Psychiatry. 2007;15:961–7.
90. Walker MP, Ayre GA, Cummings JL, et al. The clinician assessment of fluctuation and the one day fluctuation assessment scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry. 2000;177: 252–6.
91. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology. 2004;62:181–7.
92. Connor DJ, Salmon DP, Sandy TJ, et al. Cognitive profiles of autopsy-confirmed Lewy body variant vs pure Alzheimer disease. Arch Neurol. 1998;55:994–1000.
93. Pollock M, Hornabrook RW. The prevalence, natural history and dementia of Parkinson's disease. Brain. 1966;89:429–48.
94. Galvin JE. Cognitive change in Parkinson disease. Alzheimer Dis Assoc Disord. 2006;20:302–10.
95. Jellinger KA. The morphological basis of mental dysfunction in Parkinson's disease. J Neurol Sci. 2006;248:167–2.
96. Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci. 2006;248:255–8.
97. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology. 2003;60:1586–90.
98. Bancher C, Braak H, Fischer P, Jellinger KA. Neuropathological staging of Alzheimer lesions and intellectual status in Alzheimer's and Parkinson's disease patients. Neurosci Lett. 1993;162:179–82.
99. Braak H, Braak E, Yilmazer D, et al. Pattern of brain destruction in Parkinson's and Alzheimer's diseases. J Neural Transm. 1996;103:455–90.
100. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS. NIMH work group. Mov Disord. 2007;22:1061–8.
101. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. Brain. 1986;109(Pt 5):845–83.
102. Jacobs DM, Stern Y, Mayeux R. Dementia in Parkinson disease, Huntington disease, and other degenerative conditions. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. New York, NY: McGraw-Hill; 2007. p. 579–87.
103. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology. 2002;59:1714–20.
104. Dubois B, Pillon B, Legault F, et al. Slowing of cognitive processing in progressive supranuclear palsy. A comparison with Parkinson's disease. Arch Neurol. 1988;45:1194–9.
105. Helkala EL, Laulumaa V, Soininen H, Riekkinen PJ. Different error pattern of episodic and semantic memory in Alzheimer's disease and Parkinson's disease with dementia. Neuropsychologia. 1989;27:1241–8.
106. Kuzis G, Sabe L, Tiberti C, et al. Explicit and implicit learning in patients with Alzheimer disease and Parkinson disease with dementia. Neuropsychiatry Neuropsychol Behav Neurol. 1999;12:265–9.
107. Forstl H, Howard R, Levy R. Binswanger's clinical and neuropathological criteria for "Binswanger's disease". J Neurol Neurosurg Psychiatry. 1991;54:1122–3.
108. McPherson SE, Cummings JL. Vascular dementia: clinical assessment, neuropsychological features, and treatment. In: Nussbaum PD, editor. Handbook

of neuropsychology and aging. New York, NY: Plenum Press; 1997. pp. 177–88.
109. Bowler JV, Hachinski V. Vascular dementia. In: Feinberg TE, Farah MJ, editors. Behavioral neurology and neuropsychology. New York, NY: McGraw-Hill; 2007. pp. 589–603.
110. Mahler ME, Cummings JL. Behavioral neurology of multi-infarct dementia. Alzheimer Dis Assoc Disord. 1991;5:122–30.
111. Lawrence RM. Is the finding of obsessional behaviour relevant to the differential diagnosis of vascular dementia of the Binswanger type? Behav Neurol. 2000;12:149–54.
112. Weihl CC, Roos RP. Creutzfeldt–Jakob disease, new variant Creutzfeldt–Jakob disease, and bovine spongiform encephalopathy. Neurol Clin. 1999;17:835–59.
113. Brown P, Cathala F, Castaigne P, Gajdusek DC. Creutzfeldt–Jakob disease: clinical analysis of a consecutive series of 230 neuropathologically verified cases. Ann Neurol. 1986;20:597–602.
114. McConnell HW, Snyder PJ, Valeriano J. Electroencephalography of the elderly. In: Nussbaum PD, editor. Handbook of neuropsychology and aging. New York, NY: Plenum Press; 1997. pp. 422–8.
115. Wall CA, Rummans TA, Aksamit AJ, et al. Psychiatric manifestations of Creutzfeldt-Jakob disease: a 25-year analysis. J Neuropsychiatry Clin Neurosci. 2005;17:489–95.
116. Cordery RJ, Alner K, Cipolotti L, et al. The neuropsychology of variant CJD: a comparative study with inherited and sporadic forms of prion disease. J Neurol Neurosurg Psychiatry. 2005;76:330–6.
117. Collins S, McLean CA, Masters CL. Gerstmann–Straussler-Scheinker syndrome, fatal familial insomnia, and kuru: a review of these less common human transmissible spongiform encephalopathies. J Clin Neurosci. 2001;8:387–97.
118. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology. 2003;61:1179–84.
119. Kalbe E, Kessler J, Calabrese P, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry. 2004;19:136–43.

Chapter 18

Theoretical Perspectives on Cognitive Aging

Ayanna K. Thomas, Jennifer B. Dave, and Baily M. Bonura

Physical and psychological deterioration have long been considered the inevitable outcome of senescence [1]. For most, childhood development involves increasing efficiency in cognition and abstraction ability. Many of these abilities peak in the middle of our second decade, followed by a slow loss of cognitive efficiency that may accelerate during the fifth decade [2]. However, the impact of aging on various skills is far from uniform. Further, a subset of the neuro-typical aging population does not demonstrate cognitive impairment, suggesting that the idea of the inevitability of cognitive decline may be tenuous. Social and broader environmental context may account for the range in age-related cognitive changes across different samples of older adults.

In the first edition of the chapter, we focused primarily on age-related cognitive changes from a so-called "life span" perspective, in the absence of life course (i.e., environmental) influences. In this second edition, we pick up where we left off, by again examining age-related cognitive changes but in a broader context of the course of life. Such a perspective is often taken by clinical practitioners in assessment and treatment of age-related cognitive deficits (e.g., in clinically estimating baseline or premorbid levels of functioning). However, systematic integration of the interaction between life course factors and the snapshot of cognition in older adults from a single neuropsychological evaluation is absent from the scientific literature. Therefore, the primary goal of this chapter is to present current thinking and research that examines the relationship among lifestyle factors, environmental influences, and cognitive aging, and how such a relationship may impact the understanding of neuropsychological assessment profiles from a single time point.

Since the publication of the previous version of this chapter, there has been a flurry of research designed to understand how experiences across the lifespan as well as genetic predisposition can impact cognition in older adults. Not surprisingly, such an approach is challenging and can result in overly complex and uninformative theoretical models. In addition, conclusions based on this approach are often limited because follow-up assessments are constrained by narrow time frames or focus on a narrow range of abilities. However, for all of these challenges, we suggest that taking a life course perspective to understand age-related changes in cognition at one-time point is a more appropriate approach because such a perspective can identify both long-term risks and protective factors in association with age-related cognitive changes.

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By taking a life course perspective and basing new models of cognitive aging on this perspective, researchers may begin to study cognitive functioning in older adults for what it is – a dynamic, heterogeneous process. Thus, as researchers and clinicians, we begin to understand the snapshot of cognitive functioning, as reflecting the accumulation of experiences and we begin to understand how those experiences shape neurologic and cognitive adaptations over the life course [3, 4]. Before reviewing specific theories of cognitive aging, we discuss the basics of age-related neurologic changes. Following our discussion of neurological changes, we then present traditional models of Cognitive Aging. This discussion examines neuropsychological assessment within specific models of Cognitive Aging. What will be clear from this discussion is that traditional models do not account for the variability in performance demonstrated by older adults. More recent models that take a life course perspective are then presented and used as a bridge to understanding how cognition changes as a function of life course factors.

Neurologic Changes Associated with Cognitive Aging

Age-related changes in the brain are associated with cognitive decline, such as control and maintenance of attention [5], maintenance and manipulation of information in working memory [6, 7], and deficits in encoding and retrieval of information from long-term memory [8, 9]. The cognitive changes that accompany advancing age result from several neurophysiological changes. Neuroimaging studies have documented numerous changes in the structure and function of the aging brain [10]. Cross-sectional and longitudinal studies of brain volume show linear and curvilinear changes in grey matter volume, as well as curvilinear changes in white matter volume, with volume decreasing as we age [6, 11, 12, 13]. These changes are more apparent in the prefrontal and the medial temporal regions. Research has also demonstrated age-related decreases in the connectivity of major white matter tracts. The most pronounced changes occur in anterior and subcortical regions [14, 15].

Neuronal shrinkage [16, 17], a breakdown in myelin integrity [18, 19], and neurochemical changes [20] also accompany normal aging. For example, positron emission tomography (PET) studies in humans have revealed relatively linear declines during adulthood in serotonin receptors in the cortex, in dopamine receptors in the prefrontal cortex and striatum, and in dopamine transporters in the striatum [21]. These changes have been correlated with changes in cognitive functioning and have their greatest impact in the prefrontal cortex (PFC), where speed of processing may be most critical. In addition to changes in neuronal transmission in the PFC, functional imaging studies revealed age-related decline in blood flow to the prefrontal cortex, with blood flow used as a proxy for neuronal activity [22]. This research suggests that cognitive changes related to the frontal lobes and specifically the PFC should be more pronounced than those associated with other brain regions [23].

In the next section, we will consider these neurological changes in the context of traditional life span models of cognitive aging. These models have generally taken a cross-sectional approach, comparing young adults to older adults, and predicting cognitive functioning at a single time point. Neuropsychological assessment of older adult cognition is highly influenced by this approach to understanding cognition. Such an approach has been greatly informative, and several important models have emerged that successfully account for some patterns of age-related changes in cognition.

Life Span Models of Cognitive Aging

Three prominent life span models of cognitive aging that have been theorized to explain normal decline in cognition include the speed of processing theory, the inhibitory deficits hypothesis, and self-initiated processing deficits theory. Each

of these is described below. Supportive evidence from clinical neuropsychological tests and their normative data is also noted.

Speed of Processing

One dominant theory suggests that nearly all age-related variance on almost any kind of cognitive task, ranging from memory to reasoning, can be explained by the rate at which the individual makes speeded comparisons on perceptual speed tasks. Perceptual speed tasks are simple paper-and-pencil measures that require the individual to make rapid perceptual same/different judgments about pairs of digits or letter strings or two similar symbols. Speed of processing is measured by the number of comparisons correctly made in a fixed period of time, typically somewhere between 1 and 3 min [24].

The processing speed theory assumes that cognitive operations are limited by general processing constraints and variations in the efficiency or effectiveness of completion of specific processes. In other words, the theory assumes that the ability to process information from the environment becomes less efficient as we age. Therefore, with increasing age, the capacity and mental energy, or cognitive resources, required to perform information processing routines becomes limited. It is assumed that general limitations frequently impose constraints on many types of processing (i.e., encoding) and hence, they have consequences for the performance of a large variety of cognitive tasks. A reduction with increased age in the speed of many cognitive operations is hypothesized to be a major contributor to the adult age differences found on many measures of cognition [25–31].

The processing speed theory also assumes that both a limited time mechanism and a simultaneity mechanism are responsible for the relations between processing speed and measures of cognitive functioning. The basic idea underlying the limited time mechanism is that slower speed of executing many processing operations means that less processing can be completed in a given amount of time. This limited time mechanism suggests that the processing of information occurs in discrete steps, and a response latency represents the sum of the durations of the individual steps. According to the processing speed theory, as we age, we may spend more time executing early operations associated with a particular cognitive task, restricting time available for later processing. One method of illustrating the hypothesized relation between limited time and cognitive operations involves manipulating the amount of time available to process the stimulus.

Alternatively, the key assumption in the simultaneity mechanism is that a slower speed of processing results in less information available for simultaneous processing. The concept of working memory is another way of referring to the amount of simultaneously active information, and there are many reports of age-related declines in measures of working memory. When the rate of executing operations is slow, relevant information is less likely to be useful because it may be impoverished by the time preceding operations are completed [32]. Salthouse proposed that even on untimed tasks such as the Wisconsin Card Sorting Task (WCST), slower processing speed may adversely affect performance. For instance, slower processing speed may result in a decrease in the amount of information that is simultaneously active, which may correspond to less working memory capacity.

Diagnostic Tests: Changes in the PFC accompany aging and those changes affect performance on a variety of neuropsychological measures that have been used to support the processing speed framework [33–35]. Examples of some of the tests are the Controlled Oral Word Association Test (COWAT) [36, 37], the WCST [38], and the Digit Symbol Coding Test from the Wechsler Adult Intelligence Scales [39–41]. The COWAT involves orally producing as many words as possible that begin with a specified letter in 1 min. Important abilities measured by this test include initiating mental searches, maintaining these searches, and inhibiting irrelevant responses [42]. Interestingly, the COWAT has been found to map onto different areas in functional imaging, including the left dorsolateral prefrontal cortex,

anterior cingulate, and left inferior frontal gyrus [43]. Thus, one would expect that, because these frontal areas decline in normal aging, there would be a decline on COWAT. Indeed that is the case. For example, Tombaugh, Kozak, and Rees [44] reported a mean decrease of four to five words per decade after the age of 59 years for individuals with normal cognition.

The WCST measures the ability to display flexibility in the face of changing schedules of reinforcement. In this task, individuals are asked to match stimulus cards with target cards according to a particular rule but are not informed of the rule. The rule must be inferred based on trial-by-trial feedback, and the rules change at regular intervals. Several executive functioning abilities are measured in the task, including perseveration or inhibition of responses that were previously correct, and deductive reasoning in the number of categories achieved. Because this task places demands on one's cognitive load, the relatively worse performances seen in normal aging in perseverations and number of categories achieved could reflect decreased capacity for simultaneous processing of information.

Finally, Digit Symbol Coding is a test of complex attention and psychomotor speed. The task has a "key" of numbers with corresponding symbols. Participants use this key to fill in the missing symbol in a square with a corresponding (given) number. Depending on the test version, participants are either given 90 or 120 s, and older adults robustly perform more slowly than their younger counterparts.

These three neuropsychological tests are relevant exemplars of those that assess changes in cognitive behavior as a function of age. Additionally, the speed of processing framework successfully accounts for age-related decrements on these tasks.

Inhibitory Deficit Hypothesis

In addition to processing speed, research suggests that older adults may manifest inhibitory deficits in working memory. Hasher and Zacks [45] proposed the inhibitory deficit framework, which suggests that an efficient (fast and accurate) mental life requires the ability to limit activation to information most relevant to one's goals. Three functions of inhibition were proposed: controlling *access* to attention's focus, *deleting* irrelevant information from attention and working memory, and *suppressing* or *restraining* strong but inappropriate responses. The inhibitory deficit hypothesis has generally been supported by findings from a variety of experimental paradigms, including negative priming [46, 47], text processing [48], and speech production [49]. Further, evidence from experimental tasks demonstrates that the PFC is particularly important for efficient inhibitory processes in working memory [50, 51].

A central component of the concepts of access, deletion, and suppression or restraining is the notion of cognitive control in working memory. Thus, when discussing the inhibitory deficit hypothesis of cognitive aging, we must also understand how and why working memory is affected. Working memory can be conceptualized in two important ways: (1) as the amount of online cognitive resources available at any given moment to process information and (2) as the amount of mental energy available to perform online mental operations [52]. In other words, working memory allows humans (and other species) to maintain a limited amount of information in an active state for a brief period of time and to manipulate that information [52]. Thus, the online manipulation of material may be a cornerstone of higher cognitive processes, such as reasoning, decision-making, problem-solving, and language understanding (e.g., [53, 54]).

We typically measure working memory by asking participants to both *store* and *process* information simultaneously. An example of a common working memory task would be constructing a "mental map" of an area while receiving directions on how to find a particular house there. Typically, the amount of information kept active, or "online," ranges from 1 to 10 items whereas the duration of that storage ranges from 0 to 60 s. Changes in working memory are tied to cognitive aging and can be examined through both a *capacity* metaphor (amount of resources) and an

energy metaphor (processing resources). Regardless of the metaphor, as it relates to age-related decline, cognitive functioning will depend on the resources of the individuals involved and, critically, on the demands made by the subcomponents of the task. When those demands are minimal, age deficits should also be minimal [55]. However, age deficits should increase as the cognitive demands of the task increase [45].

The inhibitory deficit hypothesis employs the *capacity* metaphor and assumes that success in *active* mental processing (mediated by working memory) may require the inhibition of irrelevant information. An inhibitory mechanism may serve to limit entrance into working memory only to information that is along the "goal path" of comprehension. That is, the inhibitory mechanism may act to suppress or delete irrelevant information from working memory. Older adults however may be less likely to inhibit such unwanted thoughts as compared to younger adults. Thus, according to the inhibitory deficit hypothesis, the online processing of information is reduced because the resources needed for that processing are cluttered by irrelevant thoughts and mental processes in older adults.

Hasher and Zacks [45] present compelling evidence demonstrating that older adults are more likely to maintain disconfirmed antecedent information that they heard earlier than are younger adults, and that this irrelevant information affects subsequent cognitive performance. Inefficient inhibition will enable the initial entrance into working memory of information that is off the goal path. Inhibitory deficits will also result in the prolonged maintenance of such information in working memory. At least three categories of off-goal-path thoughts may be identified: irrelevant environmental details, personal memories or concerns, and goal-irrelevant interpretations.

Experimentally, researchers have demonstrated that older adults have difficulties inhibiting irrelevant information from the focus of attention. For example, in a standard working memory capacity experiment, participants are presented with lists in increasing order of length, from shortest to longest (e.g., [56]) setting the stage for recall of the longest lists to be vulnerable to disruption from any non-suppressed materials from earlier lists. When the longest sets are given first to younger and older adults, age differences in span are reduced and can even be eliminated (see [57–59]). According to Lustig, Hasher, and Zacks [60] the typical age differences seen on working memory span tasks seem to be the product of a reduced ability to delete or suppress no longer relevant materials, rather than of age differences in *processing resources* (see also [61–63]).

Diagnostic Tests: Inhibitory deficits have been tied to changes in the PFC and have also been shown in people with frontal lesions. Such tasks that require inhibition include the COWAT, the Stroop Test, and Digit Span [64]. For example, repetitions, intrusions, or rule violations in the COWAT are tallied to signify perseveration (the uncontrollable repetition of a particular response) or inhibition problems. Inhibitory problems also are demonstrated when individuals provide words beginning with a letter different from the specified letter of interest.

The Stroop Test typically has three parts: word reading, color naming, and color-word interference. Different versions exist, yet the important aspects of the test involve either the length of time it takes to complete each section or the number of items completed in a certain time limit. The typical finding is that individuals require more time to complete the interference portion. The Stroop test is generally thought to measure conflict resolution. Time to resolve conflict has been explained in terms of inhibition, automaticity through practice, failure to enhance relevant task goals, and attention [42, 65, 66, 67]. In patient samples, poor performance on the Stroop test has been correlated with damage to the frontal lobe. Studies of lesion patients have implicated different areas of frontal damage, including medial and posterior areas [68, 69]. In normal cognitive aging, older adults have exhibited greater interference effects as compared to younger adults [70]. On the Victoria Stroop Test, a shortened version of the original, age effects on accuracy are present, even after controlling for baseline cognitive slowing [71].

Digit Span from the Wechsler Adult Intelligence Scale (WAIS, multiple versions [64]); is

composed of three sections in the most current version (WAIS-IV): Digits Forward, Backward, and Sequencing. Digits Forward require the participant to remember and reproduce in the order that the digits were read aloud by the examiner. Digits Backward and Sequencing tasks require the participant to reorder presented digits in reverse or in ascending order. These tasks measure general attention and short-term memory. However, Digits Backward and Sequencing also measure mental tracking abilities. For all of these tasks, with continuously correct responses, the total number of items in the set is increased. Thus, individuals are required to maintain a goal state, and that maintenance is directly related to frontal functioning. A subtle decrease in performance is demonstrated when young adults (under age 55) are compared to older adults (over age 55) (see WAIS norms). Finally, inhibitory deficits may play a role in age-related impairment on the WCST [42], discussed above.

Self-Initiated Processing Deficits

The speed of processing and inhibitory deficit models are considered domain-general theories. Both posit that all age-related changes in cognition can be explained by changes in an ability that is shared by the various types of tasks for which age-related impairment is demonstrated. However, there is a large body of research that suggests that aging accompanies a set of independent changes, where one area of cognition may be impaired while others are spared. Consistent with this domain-specific approach to cognitive aging, neuropsychological assessment of neuro-typical older adults suggests more pronounced decrements in performance of tasks associated with episodic tests of memory [72, 73]. A convergent pattern is demonstrated by older adults on memory performance associated with neuropsychological testing [74]. Episodic memory can be thought of as memory for the information that was previously encountered, and memory for the context in which that information was encountered. Research has consistently demonstrated episodic memory deficits in older adults [75].

Craik, Byrd [76] and colleagues have proposed that older adults may fail to use effective encoding strategies to effectively bind contextual details to previously encountered information (for review, see [77]). That is, older adults may demonstrate a deficit in self-initiated processes at encoding that may result in domain-specific cognitive changes in episodic memory. These memory and neurologic deficits might better be understood within the framework of "self-initiated processing," a domain-specific approach to understanding cognitive aging. According to this view, these deficits reduce the kinds of self-initiated activities that are required for efficient task completion at both during learning and at retrieval. Thus, older adults may have more difficulty in generating elaborate and distinctive memory traces.

More recently, Thomas and colleagues have provided substantial evidence to suggest that deficits in self-initiated processes at retrieval, or during task completion, may also result in age-related differences in memory performance. For example, Bulevich and Thomas [78] found that older adults relied on less effective retrieval strategies unless encouraged to do otherwise either indirectly, through the demands of the task, or directly, through instruction. The reliance on less demanding retrieval processes resulted in a greater proportion of errors in an eyewitness memory paradigm. Thomas and colleagues [78–83] have consistently demonstrated that older adults default to less cognitively demanding processes unless encouraged to engage in more challenging processing. Defaulting to less demanding processes has resulted in more errors in map learning [82], an over-reliance on heuristics in problem-solving [83], and an increase in false memory susceptibility [80]. Further, the dominance of cognitively less effortful processes has been related to changes in frontal functioning. Across all of these studies, Thomas and colleagues showed that age-related differences may be reduced or even eliminated when older adults were provided with substantial contextual support for retrieval. That is, by providing external support to supplement self-initiated processes, in a variety of experimental tasks, older adults perform similarly to younger adults.

It is important to note that the tasks that benefit most from contextual and environmental support are those associated with episodic memory. Research suggests that episodic memory is supported by the medial temporal lobe (MTL) [84–86]. The MTL, and specifically the hippocampus, demonstrate changes as a function of age; however, those changes are not as pronounced as those found in the frontal cortex. Interestingly, fMRI techniques have demonstrated that older adults showed decreased activation in the MTL during the encoding phase of an episodic memory task as compared to younger adults [87]. It has been suggested that the MTL operates by forming associations between sensory, cognitive, emotional, and other content that characterize episodic memories [88, 89]. Thus, the MTL might serve to develop numerous associations that can be influential at retrieval. Without these associations, older adults may have reduced ability to access encoded memories. As such, they may benefit from environmental support.

Older adults seem to benefit from both adjustments to working memory capacity (as suggested by the inhibitory deficit hypothesis) and to environmental support (as suggested by the self-initiated processing deficit hypothesis). These two hypotheses are not necessarily in conflict, yet the inhibitory deficit hypothesis might be a subcomponent of the latter. Research suggests that processing resource limitations, as hypothesized by the self-initiated processing deficit hypothesis, may be reduced by providing external environmental support during online memory processes of encoding and retrieval.

The Big Picture: "Life Course" Models and the Influence of Environment on Cognitive Aging

The previously highlighted models of processing speed deficit, inhibitory deficit, and self-initiated processing deficit can be thought of as resource dependent, which emphasizes the importance of resource limitations in accounting for age-related differences on cognitive tasks and neuropsychological assessments. The models discussed tend to relate these theoretical resources to biological changes in the PFC and MTL. Although these models can be used to account for the observed behavior found on neuropsychological tests used to assess cognitive function in older adults at a single time point, it should be clear from the review to this point that no one theory has yet to adequately explain the complex pattern of cognitive change and increased cognitive variability seen in neuro-typical, non-dementing older adults.

Life course models of cognitive aging include environmental factors and genetic predisposition factors to better predict age-related changes in cognition. These so-called compensation models predict recruitment of different networks and/or brain regions to handle cognitive operations as we age. Uniting resource and compensatory models in order to better understand age-related changes in cognition allows for more precise diagnosis of pathological changes in cognition and better-targeted interventions and support for predicted neuro-typical cognitive decline. In the next section, we will present two compensation models which include compensatory mechanisms based on environment and experience factors. Following the discussion of these two models, we will present a discussion about several important factors that have been shown to impact the increasing variability often found in the cognitive performance of older adults. The reader will note that many of these factors are accounted for in more recent compensation life course models of cognitive aging.

Cognitive Reserve

The concept of Cognitive Reserve (CR) postulates that individual differences in the cognitive processes and neural networks underlying task-performance allows for variability and individual differences in both age-related cognitive decline and compensation and coping in the context of brain damage [90]. CR is an active model that

postulates a flexible and agile brain that attempts to cope with damage or age-related neurological changes by using preexisting cognitive resources or by enlisting compensatory processes [91]. As opposed to assuming some fixed cutoff at which functional impairment occurs, CR suggests that the manifestation of cognitive impairment is dependent on compensatory and coping strategies instituted by the brain.

The examination of CR in older adults has focused on whether older adults recruit different neural networks when completing cognitive tasks as compared to younger adults. The most straightforward form of compensation occurs when greater use of alternate networks by older adults is associated with age-invariant performance. In this situation, alternate networks may be recruited to compensate for age-related neural changes. However, recruitment of additional or different networks may not always accompany preserved task-performance. Research has demonstrated that older adults may recruit compensatory networks but still perform worse than younger adults [92].

Measurement of CR has been notoriously challenging. Standard proxies for CR include education [93], IQ [94], literacy [95, 96], occupational attainment [97], engagement in leisure activities [98, 99], and the integrity of social network [100]. These indices are imprecise because they may relate to cognitive performance for other reasons than reserve. However, a recent series of studies quantified CR as variance in episodic memory performance that remains after accounting for demographic factors and structural brain changes [101–103]. This "residual" method defines CR as the discrepancy between observed performance and expected level of performance based on pathology. In this method, individuals who perform better than predicted will have high CR, and individuals who perform worse than predicted will have low reserve. Using this method, Reed et al. [101] demonstrated that higher levels of the residual reserve variable were associated with a lower likelihood of mild cognitive impairment, a reduced risk of dementia conversion over three years, less of a decline on a composite measure of executive functioning, and a moderation of the association between memory performance and change in executive functioning over three years.

The Scaffolding Theory of Aging and Cognition—Revised

The Scaffolding Theory of Aging and Cognition (STAC) [104], aimed to explain age differences in cognitive function by incorporating the effects of a broad range of adverse biological and neurophysiological factors that have been associated with normal aging. The STAC model assumes that, relative to younger adults, non-demented older adults are affected by varying degrees of neural degradation. Functional deterioration has also been well documented and is incorporated into the STAC model. Changes in cognitive functioning are the result of neural and functional deterioration. According to the STAC model, such age-related cognitive changes result in compensatory scaffolding, which operates to counteract the adverse effects of neural and functional decline. Compensatory scaffolding is demonstrated by the recruitment of additional brain regions or by over-activation of specific regions by older adults as compared to younger adults in the context of various cognitive tasks. Meta-analytic evidence has now verified the pervasiveness and reliability of age-related over-activation of prefrontal and parietal regions when older adults are compared to younger adults across a wide range of cognitive task domains including perceptual, memory, and executive function tasks [105]. The model also suggests that it is possible to improve compensatory scaffolding by explicit interventions such as exercise, intellectual engagement, and social engagement.

A revised model of STAC (STAC-r), presented in 2014 [106], incorporated early life experiences as factors that likely influence brain structure and brain function. This model is presented in Fig. 18.1. This important revision to the model allows for the incorporation of the *rate of change* of cognitive function in conjunction with the *level* of cognitive functioning. Rate of change provides a metric of the steepness of cognitive

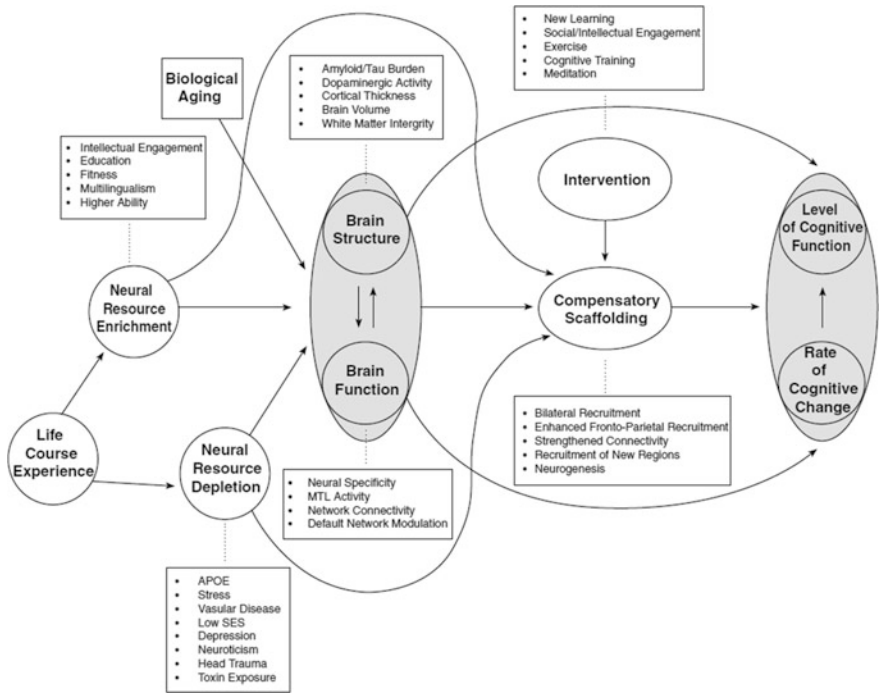

Fig. 18.1 A life course model of the Scaffolding Theory of Aging and Cognition (STAC-R)

decline over time, which is predicted to influence the level of cognitive function. As it relates to standard neuropsychological assessment of older adults, clinicians often accumulate data on the level of cognitive functioning; however, it is unclear as to whether rate of change, as predicted by prior experiences, systematically influences the interpretation of such assessment data. The STAC-r model, and the authors of this chapter suggest that both rates of change and level of functioning are important in understanding older adult cognition.

As can be seen in Fig. 18.1, the STAC-r model includes two experience-based constructs that are predicted to influence brain structure and functioning. *Neural resource enrichment* includes influences that act to enhance brain structure or function. Recent correlational-based research suggests that individuals who are engaged in intellectual and social activities in middle and late adulthood fare better cognitively than less engaged peers [107–112]. There is also evidence to suggest that high levels of education and quality of education may be protective of cognitive functioning [113–116]. A host of other life course factors has also been implicated in preserving cognitive functioning. For example, cardiovascular health and physical fitness [117–119], bilingualism [120–122], and multilingualism [123] have all been identified as having beneficial outcomes for cognitive aging.

The second construct proposed in the STAC-r model, *neural resource depletion*, encompasses negative influences on brain structure and neural function. The presence of the APOE-4 gene increases the risk of Alzheimer's disease, and thus is included as a neural resource depletion factor [124]. Amyloid and tau deposition [125], which are comprised of the plaques and tangles associated with Alzheimer's disease (AD), also have been associated with decrements in cognitive functioning in non-demented older adults [126–128]. Vascular risk factors [129–132], major depression [133], and chronic stress [134] have also been associated with age-related cognitive impairment.

Individual Differences, Environmental Factors, and Treatment

Here, we focus on three specific areas in which individual differences may affect one's cognitive trajectory. Specifically, we discuss sex, depression, and stereotype threat.

Sex as an Important Individual Difference Factor

Several studies have revealed the effects of estrogen use on tests of verbal memory, suggesting differences between men and women in some cognitive domains [134–137]. Researchers suggest that the effects of estrogen on cognition might be tied to the PFC [138] and hippocampal grey matter volume [139]. Neuropsychological measures associated with the PFC have confirmed the benefit of estrogen, with estrogen use being related to improved performance on the WCST [140]. Research has also demonstrated differential age-related brain changes in males as compared to females [141]. As one example, Cowell and colleagues [142] found greater age-related reductions in brain volume for both frontal and temporal lobes in males than in females. As it relates to cognitive assessments, numerous studies have demonstrated greater age-related cognitive decline in males than in females in both cross-sectional and longitudinal studies (e.g., [143–145]). Interestingly, similar results have been found in two studies of spatial memory in rhesus monkeys [146]. Lacreuse and colleagues [147] suggested that biological rather than sociocultural factors may underlie the gender differences in age-related decline. A number of other studies, however, have failed to find significant gender differences in rates of cognitive aging (e.g., [148, 149, 150, 151, 152, 153, 154, 155, 156).

Depression

Mood state may also exert influence on cognitive performance. There is a growing body of literature that suggests that late-life depression, and more specifically new, late-onset depression, is frequently associated with cognitive dysfunction (as measured by neuropsychological performance; for review [156]) Treatment for depression, both medical and psychological, is available and effective in a large proportion of older adults with depression. However, cognitive dysfunction can persist even after successful treatment of the depressive episode, sometimes improving slightly, but often not returning to premorbid levels [157, 158]. Even if there is an apparent resolution of a depressive episode and subsequent return to premorbid cognition levels, these individuals remain at an increased risk for dementia after a 2- to 4-year follow-up [159]. Given the risk of more permanent cognitive changes during and following depression, it is unclear whether depression plays a causal role or is a reaction to early changes perceived by the individual.

Alternatively, both depression and cognitive changes could be symptoms of cerebrovascular changes. Vascular depression (sometimes called "subcortical ischemic depression") is a condition in which cerebrovascular lesions or other vascular risk factors (such as diabetes, hypertension, etc.) can "predispose, precipitate, or perpetuate" depressive symptoms [160]. Thus, causality and directionality have not been definitively determined. Some researchers have indicated that vascular depression looks similar to medial frontal lobe syndrome and frontal-subcortical deficits, in which there is functional impairment (IADLs) and psychomotor retardation or lassitude (i.e., slowness or difficulty initiating activities) [161].

Although the literature is not entirely consistent, some typical neuropsychological changes are exhibited in depressed older adults. Using a comprehensive neuropsychological battery, Butters et al. [161], found that compared to age-matched controls, non-demented depressed older adults had worse cognitive performance in the domains of information processing speed, memory, visuospatial abilities, executive function, and language. However, further analyses indicated that information processing speed (as measured by Grooved Pegboard, Digit Symbol,

and Trails A) was the deficit underlying dysfunction in all of the cognitive domains. Other studies have shown similar deficits in executive function and information processing speed [161]. Therefore, according to Salthouse's processing speed hypothesis, slowness would be an expected result of aging, and these deficits thus manifest to an even greater extent in older adults with depression or vascular depression.

Practical issues are associated with assessing and diagnosing mood disorders in older adults. First, accurate diagnosis of depression is necessary. Practitioners may overlook a diagnosis of depression because of possible age differences in the manifestation of the disease. Specifically, older adults may experience fewer symptoms than do younger adults [162]. In addition, symptoms may differ. The elderly might not endorse sadness but instead experience greater amounts of fatigue and loss of interest [163]. Practitioners should also know the base rates of depression in the elderly: estimates suggest older adult rates of major depressive disorder vary from 1–4%, sub-syndromal or minor depression rates range from 4–13% and dysthymia rates are about 2% [156]. Given the overlap of late-life depression and vascular problems, practitioners should assess vascular health during the intake interview. Finally, because of the likelihood that cognitive problems will persist to some degree even after treatment of the depressive episode, patients should continue to be assessed on a regular basis.

Stereotype Threat

Clinical assessment should also consider how the nature of assessment in and of itself can impact cognitive performance. In Western culture, individuals in old age are stereotyped as being forgetful. The presence of this stereotype leaves older adults (i.e., 55+ years old) at risk of experiencing *stereotype threat* (see [164]). An individual may experience stereotype threat when she encounters situations in which she feels she might confirm the stereotype. The effects of stereotype threat on cognition can be likened to a self-fulfilling prophecy, in which individuals behave in a manner that causes them to fulfill an expectation. This is evident in older adults, who, after confronting stereotypes about their memory in the context of laboratory experiments, underperform on a wide range of veridical memory tasks that measure accurate recollection (for a review [165]). Further, this effect is strongest for older adults with certain characteristics. One such characteristic is level of education, as those who are highly educated have shown the greatest substandard performance when experiencing stereotype threat [166] (but see [167, 168]). Another characteristic is age. The negative effects of stereotype threat are more pronounced in older adults who are closer to middle age than elderly [169, 170]. Thus, susceptibility to stereotype threat can be moderated by certain individual difference factors.

It is easy to imagine how neuropsychological testing may engender the experience of stereotype threat. As such, it is paramount for clinicians to understand the effect that this social contextual factor can have on cognitive performance. Research suggests that negative effects of threat may be reduced if older adults are educated about the nature of stereotype threat, or if they are given information about the objective difficulty of the task [171]. Regardless of the approach to reducing the possibility of experiencing threat, clinicians should understand how threat can influence performance and may wish to consider performance on assessments within this context.

Conclusions and New Directions

This chapter reviews the nature of demonstrated deficits in performance on various neuropsychological domains as a function of normal aging. From a neuropsychological standpoint, older adults will demonstrate deficits in performance in various domains, ranging from perceptual speed

tasks (i.e., WAIS Coding) to episodic memory tasks (i.e., WMS Logical Memory). The goal for cognitive aging researchers is to develop a theory that accounts for all of these changes. Such a theory would allow for systematic tests of methods that could be used in compensating for the inevitable, but variable, decline in cognitive functioning.

Traditional models of cognitive aging have been extremely useful in generating testable hypotheses and moving the field forward. They have laid a solid foundation for moving to more complex but likely more informative models that bring together cognitive resources with cognitive compensation. More recent life course models make predictions regarding the impact of early, mid, and later life experiences on cognitive change and compensation. These models also comprehensively integrate lifestyle factors into current conceptualization of cognitive aging. Lifestyle factors that have been implicated in reducing age-related cognitive decline include cognitive and social engagement, musical training, physical exercise, and improvements in diet [172, 173]. Additional research has examined the effect of medications, including over-the-counter and prescribed medications and dietary supplements; however, these treatments are not reviewed in this chapter.

Research over the last 40 years has painted a rather complex picture of cognitive aging. We now are beginning to understand the important relationship between changes in the brain associated with normal aging and the resulting behavioral manifestations. In the first edition of this chapter we argued for an increase in interdisciplinary research to better understand the complexity of the global phenomenon of cognitive aging. We again put forth this call. Interdisciplinary research directed at understanding the relationship between biological, social, and cognitive aging will result in more effective treatments for the growing aging population. Through our interdisciplinary lens, we better understand the weaknesses and holes in our present conceptualization of cognitive aging.

References

1. Schaie K. The course of adult intellectual development. Am Psychol. 1994;49:304–13.
2. Salthouse TA. Selective review of cognitive aging. J Int Neuropsychol Soc. 2010;16(5):754–60. https://doi.org/10.1017/s1355617710000706.
3. Elder GH Jr, Shanahan MJ. The life course and human development. In: Damon W, Lerner RM, editors. Handbook of child psychology, vol. 1: theoretical models of human development. 1st ed. Hoboken, NJ: John Wiley & Sons; 2006. p. 665–715.
4. Park S, Kwon E, Lee H. Life course trajectories of later-life cognitive functions: does social engagement in old age matter? Int J Environ Res Public Health. 2017;14(4):393. https://doi.org/10.3390/ijerph14040393.
5. Allen PA, Weber TA, Madden DJ. Adult age differences in attention: filtering or selection? J Gerontol. 1994;49:P213–22.
6. Hasher L, Zacks RT. Working memory, comprehension, and aging: a review and a new view. San Diego, CA: Academic Press; 1988.
7. Verhaeghen P, Salthouse TA. Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models. Psychol Bull. 1997;122:231–49.
8. Balota DA, Dolan PO, Duchek JM. Memory changes in healthy older adults. In: Tulving E, Craik FI, editors. The Oxford handbook of memory. New York, NY: Oxford University Press; 2000. p. 395–409.
9. Craik FI, Byrd M, Swanson JM. Patterns of memory loss in three elderly samples. Psychol Aging. 1987;2:79–86.
10. Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci. 2012;13:491–505.
11. Raz N. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging: linking cognitive and cerebral aging. New York, NY: Oxford University Press; 2005. p. 19–52.
12. Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, Alzheimer Disease Neuroimaging Initiative. Critical ages in the life course of the adult brain: nonlinear subcortical aging. *Neurobiol Aging*. 2013;34:2239–47.
13. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehav Rev. 2006;30:730–48.
14. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex. 2005;2005(15):1679–89.
15. Bennett IJ, Madden DJ. Disconnected aging: cerebral white matter integrity and age-related

differences in cognition. Neuroscience. 2014;12: 187–205.
16. Anderson B, Rutledge V. Age and hemisphere effects on dendritic structure. Brain J Neurol. 1996; 119:1983–90.
17. Swaab D, Hofman M, Lucassen P, Salehi A, Uylings HB. Neuronal atrophy, not cell death, is the main hallmark of Alzheimer's disease. Neuro-biol Aging. 1994;15:369–71.
18. Armstrong CL, Traipe E, Hunter JV, van Buchem MA. Age related, regional, hemispheric, and medial-lateral differences in myelin integrity in vivo in the normal adult brain. Am J Neuroradiol. 2004;25:977–84.
19. Waldemar G. Functional brain imaging with SPECT in normal aging and dementia: methodological, pathophysiological and diagnostic aspect. Cerebrovasc Brain Metab Rev. 1995;7:89–130.
20. Bäckman L, Lindenberger U, Li S-C, Nyberg L. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci Biobehav Rev. 2010;34:670–7.
21. Klostermann EC, Braskie MN, Landau SM, O'Neil JP, Jagust WJ. Dopamine and frontostriatal networks in cognitive aging. Neurobiol Aging. 2012;33:623.e15–24.
22. Cabeza R, Nyberg L, Park DC. Cognitive neuroscience of aging. 2nd ed. Oxford: Oxford University Press; 2017.
23. Raz N, Gunning-Dixon FM, Head D, Dixon JA. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology. 1998;12:95–114.
24. Salthouse TA. The nature of the influence of speed on adult age differences in cognition. Dev Psychol. 1994;30:240–59.
25. Salthouse TA. Adult age and the speed-accuracy trade-off. Ergonomics. 1979;22:811–21.
26. Salthouse TA. Anticipatory processing in transcription typing. J Appl Psychol. 1985;70:264–71.
27. Salthouse TA. Speed of behavior and its implications for cognition. In: Birren JE, Schaie KW, editors. Handbook of the psychology of aging. 2nd ed. New York: Van Nostrand Reinhold; 1985. p. 400–26.
28. Salthouse TA. Cognitive facets of aging well. Gener J Am Soc Aging. 1991;15:35–8.
29. Salthouse TA, Babcock RL, Shaw RJ. Effects of adult age on structural and operational capacities in working memory. Psychol Aging. 1991;6:118–27.
30. Salthouse TA, Legg S, Palmon R, Mitchell DR. Memory factors in age-related differences in simple reasoning. Psychol Aging. 1990;5:9–15.
31. Salthouse TA, Mitchell DR. Effects of age and naturally occurring experience on spatial visualization performance. Dev Psychol. 1990;26:845–54.
32. Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychol Rev. 1996;103:403–28.
33. Buchsbaum BR, Greer S, Chang W-L, Berman KF. Meta-analysis of neuroimaging studies of the Wisconsin Card-Sorting Task and component processes. Hum Brain Mapp. 2005;25:35–45.
34. Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, Miyashita Y. Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat Neurosci. 1998;1:80–4.
35. Sumitani S, Tanaka T, Tayoshi S, Ota K, Kameoka N, Ueno S, Ohmori T. Activation of the prefrontal cortex during the Wisconsin Card Sorting Test as measured by multichannel near-infrared spectroscopy. Neuropsychobiology. 2006;53:70–6.
36. Volz H-P, Gaser C, Hager F, Rzanny R, Mentzel H-J, Kreitschmann-Andermahr I, Sauer H. Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test–a functional MRI study on healthy volunteers and schizophrenics. Psychiatry Res Neuroimaging. 1997;75:145–57.
37. Benton AL, Hamsher K. Multilingual aphasia examination. 2nd ed. Iowa City: AJA Association; 1989.
38. Berg EA. A simple objective technique for measuring flexibility in thinking. J Gen Psychol. 1948;39:15–22.
39. Salthouse TA. What do adult age differences in the Digit Symbol Substitution Test reflect? J Gerontol. 1992;47:P121–8.
40. Salthouse TA. Influence of processing speed on adult age differences in working memory. Acta Physiol. 1992;79:155–70.
41. MacDonald SW, Hultsch DF, Strauss E, Dixon RA. Age-related slowing of digit symbol substitution revisited: what do longitudinal age changes reflect? J Gerontol B Psychol Sci Soc Sci. 2003;58: P187–94.
42. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York, NY: Oxford University Press; 2012.
43. Phelps EA, Hyder F, Blamire AM, Shulman RG. FMRI of the prefrontal cortex during overt verbal fluency. Neuroreport Int J Rapid Commun Res Neurosci. 1997;8:561–5.
44. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999;14:167–77.
45. Hasher L, Zacks RT. Working memory, comprehension, and aging: a review and a new view. San Diego, CA: Academic Press; 1998.
46. Kane MJ, Hasher L, Stoltzfus ER, Zacks RT, Connelly SL. Inhibitory attentional mechanisms and aging. Psychol Aging. 1994;9:103–12.
47. Tipper SP. Mechanisms of visual selective attention. Can Psychol/Psychologie Canadienne. 1991;32:640–2.
48. Hamm VP, Hasher L. Age and the availability of inferences. Psychol Aging. 1992;7:56–64.

49. Arbuckle TY, Gold DP. Aging, inhibition, and verbosity. J Gerontol. 1993;48:P225–32.
50. Dempster FN. The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. Dev Rev. 1992;12:45–75.
51. Harnishfeger KK, Bjorklund DF. A developmental perspective on individual differences in inhibition. Learn Individ Differ. 1994;6:331–55.
52. Baddeley A. Working memory. New York, NY: Clarendon Press/Oxford University Press; 1986.
53. Carpenter PA, Just MA, Shell P. What one intelligence test measures: a theoretical account of the processing in the Raven Progressive Matrices Test. Psychol Rev. 1990;97:404–31.
54. Jonides J. Working memory and thinking. In: Smith EE, Osherson DN. Thinking: an invitation to cognitive science, vol. 3. 2nd ed. Cambridge, MA: The MIT Press; 1995. p. 215–65.
55. Riby LM, Perfect TJ, Stollery BT. The effects of age and task domain on dual task performance: a meta-analysis. Eur J Cogn Psychol. 2004;16:868–91.
56. Daneman M, Carpenter PA. Individual differences in working memory and reading. J Verbal Learn Verbal Behav. 1980;19:450–66.
57. Lustig C, May CP, Hasher L. Working memory span and the role of proactive interference. J Exp Psychol Gen. 2001;130:199–207.
58. May CP, Hasher L, Kane MJ. The role of interference in memory span. Mem Cogn. 1992;27:759–67.
59. Rowe G, Hasher L, Turcotte J. Age differences in visuospatial working memory. Psychol Aging. 2008;23:79–84.
60. Lustig C, Hasher L, Zacks RT. Inhibitory deficit theory: Recent developments in a "new view". In: Gorfein DS, MacLeod CM, editors. The place of inhibition in cognition. Washington, DC: American Psychological Association; 2007. p. 145–62.
61. Bunting M. Proactive interference and item similarity in working memory. J Exp Psychol Learn Mem Cogn. 2006;32:183–96.
62. Friedman NP, Miyake A. The relations among inhibition and interference control functions: a latent-variable analysis. J Exp Psychol Gen. 2004;133:101–35.
63. Hedden T, Park DC. Contributions of source and inhibitory mechanisms to age-related retroactive interference in verbal working memory. J Exp Psychol Gen. 2003;132:93–112.
64. Wechsler D. Cognitive, conative, and non-intellective intelligence (1950). In: Notterman JN, editor. The evolution of psychology: fifty years of the American psychologist. Washington, DC: American Psychological Association; 1997. p. 1922–32.
65. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev. 2006;16:17–42.
66. MacLeod CM. Half a century of research on the Stroop effect: an integrative review. Psychol Bull. 1991;109:163–203.
67. Posner MI, Snyder CRR. Attention and cognitive control. New York, NY: Psychology Press; 2004.
68. Vendrell P, Junque C, Pujol J, Jurado MA, Molet J, Grafman J. The role of prefrontal regions in the Stroop task. Neuropsychologia. 1995;33:341–52.
69. Stuss D, Floden D, Alexander M, Levine B, Katz D. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia. 2001;39:771–86.
70. Wecker NS, Kramer JH, Wisniewski A, Kaplan E. Age effects on executive ability. Neuropsychology. 2000;14:409–14.
71. Troyer AK, Leach L, Strauss E. Aging and response inhibition: normative data for the Victoria Stroop Test. Aging Neuropsychol Cogn. 2006;13:20–35.
72. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41:49–100.
73. Ronnlund M, Nyberg L, Backman L, Nilsson L-G. Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. Psychol Aging. 2005;20:3–18.
74. Salthouse TA. Relations between cognitive abilities and measures of executive functioning. Neuropsychology. 2005;19:532–45.
75. Grady CL, Craik FI. Changes in memory processing with age. Curr Opin Neurobiol. 2000;10(2):224–32.
76. Craik FIM, Byrd M. Aging and cognitive deficits: the role of attentional resources. In: Craik FIM, Trehub SE, editors. Aging and cognitive processes. New York: Plenum; 1982. p. 191–211.
77. Old SR, Naveh-Benjamin M. Differential effects of age on item and associative measures of memory: a meta-analysis. Psychol Aging. 2008;23:104–18.
78. Bulevich JB, Thomas AK. Retrieval effort improves memory and metamemory in the face of misinformation. J Mem Lang. 2012;67:45–58.
79. Thomas AK, Bulevich JB. Effective cue utilization reduces memory errors in older adults. Psychol Aging. 2006;21:379–89.
80. Thomas AK, McDaniel MA. Frontal functioning impacts the effectiveness of encoding processes in reducing false memories. Aging Neuropsychol Cogn. 2013;20:443–70.
81. Thomas AK, Bonura BM, Taylor HA, Brunye TT. Metacognitive monitoring in visuo-spatial working memory. Psychol Aging. 2012;27:1099–110.
82. Thomas AK, Bonura BM, Taylor HA. The influence of semantic relationships on older adult map memory. Psychol Aging. 2012;27:657–65.
83. Thomas AK, Millar PR. Reducing the framing effect bias in older adults by encouraging analytical processing. J Gerontol B Psychol Sci Soc Sci. 2012;67B:139–49.
84. de Haan M, Mishkin M, Baldeweg T, Vargha-Khadem F. Human memory development

and its dysfunction after early hippocampal injury. Trends Neurosci. 2006;29:374–81.
85. Kramer JH, Rosen HJ, Du A-T, Schuff N, Hollnagel C, Weiner MW, Delis DC. Dissociations in hippocampal and frontal contributions to episodic memory performance. Neuropsychology. 2005;19:799–805.
86. Lancelot C, Ahad P, Noulhiane M, Hasboun D, Baulac M, Samson S. Loss of memory for auditory-spatial associations following unilateral medial temporal-lobe damage. Neuropsychologia. 2005;43:1975–82.
87. Daselaar S, Veltman D, Rombouts S, Raaijmakers JGW, Jonker C. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain J Neurol. 2003;126:43–56.
88. Alvarez P, Zola-Morgan S, Squire LR. Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. J Neurosci. 1995;15:3796–807.
89. Eichenbaum H. Learning from LTP: a comment on recent attempts to identify cellular & molecular mechanisms of memory. Learn Mem. 1996;3:61–73.
90. McCune B. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873–904.
91. Stern Y. What is cognitive reserve? theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002;8:448–60.
92. Reuter-Lorenz P. New visions of the aging mind and brain. Trends Cogn Sci. 2002;6:394.
93. Stern YP, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol. 1992;32:371–5.
94. Alexander GE, Furey ML, Grady CL, Pietrini P, Brady DR, Mentis MJ, Schapiro MB. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. Am J Psychiatry. 1997;154:165–72.
95. Manly JJ, Touradji P, Tang MX, Stern Y. Literacy and memory decline among ethnically diverse elders. J Clin Exp Neuropsychol. 2003;25:680–90.
96. Manly JJ, Schupf N, Tang M-X, Stern Y. Cognitive decline and literacy among ethnically diverse elders. J Geriatr Psychiatry Neurol. 2005;18:213–7.
97. Richards M, Sacker A. Lifetime antecedents of cognitive reserve. J Clin Exp Neuropsychol. 2003;25:614–24.
98. Staff RT, Murray AD, Deary IJ, Whalley LJ. What provides cerebral reserve? Brain. 2004;127:1191–9.
99. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology. 2001;57:2236–42.
100. Scarmeas N, Zarahn E, Anderson KE, Habeck CG, Hilton J, Flynn J, Stern Y. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. Arch Neurol. 2003;60(3):359–65.
101. Reed BR, Dowling M, Farias ST, Sonnen J, Strauss M, Schneider JA, Mungas D. Cognitive activities during adulthood are more important than education in building reserve. J Int Neuropsychol Soc. 2011;17:615–24.
102. Reed BR, Mungas D, Farias ST, Harvey D, Beckett L, Widaman K, DeCarli C. Measuring cognitive reserve based on the decomposition of episodic memory variance. Brain. 2010;133:2196–209.
103. Zahodne LB, Manly JJ, Brickman AM, Siedlecki KL, DeCarli C, Stern Y. Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. J Int Neuropsychol Soc. 2013;19(8):854–62.
104. Park DC, Reuter-Lorenz PA. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009;60:173–96.
105. Spreng RN, Wojtowicz M, Grady CL. Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. Neurosci Biobehav Rev. 2010;34(8):1178–94. https://doi.org/10.1016/j.neubiorev.2010.01.009.
106. Rueter-Lorenz PA, Park D. How does it STAC up? Revisiting the scaffolding theory of aging and cognition. Neuropsychol Rev. 2014;24(3):355–70.
107. Amieva H, Mokri H, Le Goff M, Meillon C, Jacqmin-Gadda H, Foubert-Samier A, Dartigues J. Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain. 2014;137:1167–75. https://doi.org/10.1093/brain/awu035.
108. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. Neurology. 2009;73(5):356–61. https://doi.org/10.1212/wnl.0b013e3181b04ae3.
109. Plassman BL, Williams JW, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med. 2010;153(3):182–U188.
110. Reed BR, Dowling M, Farias ST, Sonnen J, Strauss M, Schneider JA, Mungas D. Cognitive activities during adulthood are more important than education in building reserve. J Int Neuropsychol Soc. 2011;17(4):615–24. https://doi.org/10.1017/s1355617711000014.
111. Singh-Manoux A, Richards M, Marmot M. Leisure activities and cognitive function in middle age: evidence from the Whitehall II study. J Epidemiol Community Health. 2003;57(11):907–13.
112. Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. J Am Med Assoc. 2002;287(6):742–8.
113. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the

relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. Lancet Neurolology. 2006;5:406–12.
114. Christensen H, Batterham PJ, Mackinnon AJ, Anstey KJ, Wen W, Sachdev PS. Education, atrophy, and cognitive change in an epidemiological sample in early old age. Am J Geriatr Psychiatry. 2009;17(3):218–26.
115. Karlamangla AS, Miller-Martinez D, Aneshensel CS, Seeman TE, Wight RG, Chodosh J. Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. Am J Epidemiol. 2009;170(3):331–42. https://doi.org/10.1093/aje/kwp154.
116. Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB. Predictors of maintaining cognitive function in older adults: the Health ABC study. Neurology. 2009;72(23):2029–35. https://doi.org/10.1212/wnl.0b013e3181a92c36.
117. Head D, Bugg JM, Goate AM, Fagan AM, Mintun MA, Benzinger T, Morris JC. Exercise engagement as a moderator of the effects of APOE genotype on amyloid deposition. Arch Neurol. 2012;69(5):636–43. https://doi.org/10.1001/archneurol.2011.845.
118. Erickson KI, Gildengers AG, Butters MA. Physical activity and brain plasticity in late adulthood. Dialogues Clin Neurosci. 2013;15(1):99–108.
119. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. Neurology. 2010;75(16):1415–22.
120. Bialystok E, Craik FIM, Luk G. Bilingualism: consequences for mind and brain. Trends Cogn Sci. 2012;16(4):240–50. https://doi.org/10.1016/j.tics.2012.03.001.
121. Gold BT, Kim C, Johnson NF, Kryscio RJ, Smith CD. Lifelong bilingualism maintains neural efficiency for cognitive control in aging. J Neurosci. 2013;33(2):387–96. https://doi.org/10.1523/jneurosci.3837-12.2013.
122. Schweizer TA, Ware J, Fischer CE, Craik FIM, Bialystok E. Bilingualism as a contributor to cognitive reserve: evidence from brain atrophy in Alzheimer's disease. Cortex. 2012;48(8):991–6. https://doi.org/10.1016/j.cortex.2011.04.009.
123. Alladi S, Bak TH, Duggirala V, Surampudi B, Shailaja M, Shukla AK, Kaul S. Bilingualism delays age at onset of dementia, independent of education and immigration status. Neurology. 2013;81(22):1938–44.
124. Landau SM, Marks SM, Mormino EC, Rabinovici GD, Oh H, O'Neil JP, Jagust WJ. Association of lifetime cognitive engagement and low beta-amyloid deposition. Arch Neurol. 2012;69(5):623–9. https://doi.org/10.1001/archneurol.2011.2748.
125. Mielke MM, Haughey NJ, Bandaru VV, Zetterberg H, Blennow K, Andreasson U, et al. Cerebrospinal fluid sphingolipids, beta-amyloid, and tau in adults at risk for Alzheimer's disease. Neurobiol Aging. 2014. https://doi.org/10.1016/j.neurobiolaging.2014.05.019.
126. Rodrigue KM, Kennedy KM, Devous MD Sr, Rieck JR, Hebrank AC, Diaz-Arrastia R, Park DC. Beta-amyloid burden in healthy aging: regional distribution and cognitive consequences. Neurology. 2012;78(6):387–95. https://doi.org/10.1212/wnl.0b013e318245d295.
127. Rodrigue KM, Kennedy KM, Park DC. Beta-amyloid deposition and the aging brain. Neuropsychol Rev. 2009;19(4):436–50. https://doi.org/10.1007/s11065-009-9118-x.
128. Mielke MM, Haughey NJ, Bandaru VV, Zetterberg H, Blennow K, Andreasson U, Carlsson CM. Cerebrospinal fluid sphingolipids, beta-amyloid, and tau in adults at risk for Alzheimer's disease. Neurobiol Aging. 2014;35(11):2486–94. https://doi.org/10.1016/j.neurobiolaging.2014.05.019.
129. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, DeCarli C. Midlife vascular risk factor exposure accelerates structure brain aging and cognitive decline. Neurology. 2011;77(5):461–8. https://doi.org/10.1212/wnl.0b013e318227b227.
130. de Frias CM, Schaie KW, Willis SL. Hypertension moderates the effect of APOE on 21-year cognitive trajectories. Psychol Aging. 2014;29(2):431–9. https://doi.org/10.1037/a0036828.
131. Bender AR, Raz N. Age-related differences in memory and executive functions in healthy APOE epsilon 4 carriers: the contribution of individual differences in prefrontal volumes and systolic blood pressure. Neuropsychologia. 2012;50(5):704–14. https://doi.org/10.1016/j.neuropsychologia.2011.12.025.
132. Honjo K, Black SE, Verhoeff NP. Alzheimer's disease, cerebrovascular disease, and the β-amyloid cascade. Can J Neurol Sci. 2012;39(6):712–28.
133. Brickman AM, Muraskin J, Zimmerman ME. Structural neuroimaging in Alzheimer's disease: do white matter hyperintensities matter? Dialogues Clin Neurosci. 2009;11(2):181–90.
134. Cowell PE, Turetsky BI, Gur RC, Grossman RI, Shtasel DI, Gur RE. Sex differences in aging of the human frontal and temporal lobes. J Neurosci. 1994;14:4748–55.
135. Kampen DL, Sherwin BB. Estradiol is related to visual memory in healthy young men. Behav Neurosci. 1996;110:613–7.
136. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry. 2001;158:227–33.
137. Bean LA, Ianov L, Foster TC. Estrogen receptors, the hippocampus, and memory. Neuroscientist. 2014;20:534–45.
138. Keenan P, Ezzat W, Ginsburg K, Moore G. Prefrontal cortex as the site of estrogen's effect on

cognition. Psychoneuroendocrinology. 2001;26: 577–90.
139. Albert K, Hiscox J, Boyd B, Dumas J, Taylor W, Newhouse P. Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017;56:1–6. https://doi.org/10.1016/j.neurobiolaging.2017.03.033.
140. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. Am J Psychiatry. 1996;153:974–84.
141. Meinz EJ, Salthouse TA. Is age kinder to females than to males? Psychon Bull Rev. 1998;5:56–70.
142. Barrett-Connor E, Kritz-Silverstein D. Gender differences in cognitive function with age: the Rancho Bernardo study. J Am Geriatr Soc. 1999;47:159–64.
143. Larrabee GJ, Crook TH. Do men show more rapid age-associated decline in simulated everyday verbal memory than do women? Psychol Aging. 1993;8:68–71.
144. Wiederholt W, Cahn D, Butters NM, Salmon DP, Kritz-Silverstein D, Barrett-Connor E. Effects of age, gender and education on selected neuropsychological tests in an elderly community cohort. J Am Geriatr Soc. 1993;41:639–47.
145. Zelinski EM, Stewart ST. Individual differences in 16-year memory changes. Psychol Aging. 1998;13:622–30.
146. Lacreuse A, Kim CB, Rosene DL, Killiany RJ, Moss MB, Moore TL, Herndon JG. Sex, age, and training modulate spatial memory in the rhesus monkey (Macaca mulatta). Behav Neurosci. 2005;119:118–26.
147. Lacreuse A, Herndon JG, Killiany RJ, Rosene DL, Moss MB. Spatial cognition in rhesus monkeys: male superiority declines with age. Horm Behav. 1999;36:70–6.
148. Aartsen MJ, Martin M, Zimprich D. Gender differences in level and change in cognitive functioning: results from the longitudinal aging study Amsterdam. Gerontology. 2004;50:35–8.
149. Barnes L, Wilson R, Schneider J, Bienias JL, Evans DL, Bennett DA. Gender, cognitive decline, and risk of AD in older persons. Neurology. 2003;60:1777–81.
150. de Frias C, Nilsson L-G, Herlitz A. Sex differences in cognition are stable over a 10-year period in adulthood and old age. Aging Neuropsychol Cogn. 2006;13:574–87.
151. De Luca CR, Wood SJ, Anderson V, Buchanan JA, Proffitt TM, Mahony K, Pantelis C. Normative data from the Cantab. I: development of executive function over the lifespan. J Clin Exp Neuropsychol. 2003;25:242–54.
152. Herlitz A, Nilsson L-G, Backman L. Gender differences in episodic memory. Mem Cogn. 1997;25:801–11.
153. Larrabee GJ, Trahan DE, Curtiss G, Levin HS. Normative data for the Verbal Selective Reminding Test. Neuropsychology. 1988;2:173–82.
154. Singer T, Verhaeghen P, Ghisletta P, Lindenberger U, Baltes PB. The fate of cognition in very old age: six-year longitudinal findings in the Berlin Aging Study (BASE). Psychol Aging. 2003;18:318–31.
155. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. J Int Neuropsychol Soc. 2002; 8:341–8. https://doi.org/10.1017/S135561770102015X.
156. Alexopoulos GS. Depression in the elderly. Lancet. 2005;365:1961–70.
157. Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, Reynolds CF. Changes in cognitive functioning following treatment of late-life depression. Am J Psychiatry. 2000;157: 1949–54.
158. Nebes RD, Pollock BG, Houck PR, Butters MA, Mulsant BH, Zmuda MD, Reynolds CF. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized double-blind clinical trial with nortriptyline and paroxetine. J Psychiatr Res. 2003;37:99–108.
159. Krishnan KRR, Taylor WD, McQuoid DRE, MacFall JR, Payne ME, Provenzale JM, Steffens DC. Clinical characteristics of magnetic resonance imaging–defined subcortical ischemic depression. Biol Psychiat. 2004;55:390–7.
160. Butters MA, Whyte E, Nebes RD, Begley AE, Dew MA, Mulsant BH, Becker JT. The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry. 2004;61:587–95.
161. Lesser IM, Boone KB, Mehringer CM, Wohl MA, Miller BL, Berman NG. Cognition and white matter hyperintensities in older depressed patients. Am J Psychiatry. 1996;153:1280–7.
162. Blazer DG, Burchett B, Service C, George LK. The association of age and depression among the elderly: an epidemiologic exploration. J Gerontol. 1991;46:M210–5.
163. Newmann JP, Engel RJ, Jensen JE. Changes in depressive-symptom experiences among older women. Psychol Aging. 1991;6:212–22.
164. Steele CM, Aronson J. Stereotype threat and the intellectual test performance of African Americans. J Pers Soc Psychol. 1995;69(5):797–811. https://doi.org/10.1037/0022-3514.69.5.797.
165. Barber SJ, Mather M. Stereotype threat in older adults: when and why does it occur and who is most affected? The Oxford handbook of emotion, social cognition, and problem solving in adulthood, New York, NY: Oxford University Press; 2014. p. 302–19. http://dx.doi.org/10.1093/oxfordhb/9780199899463.013.008.
166. Hess TM, Hinson JT, Hodges EA. Moderators of and mechanisms underlying stereotype threat effects on older adults' memory performance. Exp Aging Res. 2009;35(2):153–77. https://doi.org/10.1080/03610730802716413.

167. Andreoletti C, Lachman ME. Susceptibility and resilience to memory aging stereotypes: education matters more than age. Exp Aging Res. 2004;30 (2):129–48. https://doi.org/10.1080/03610730490274167.
168. Smith AM, Gallo DA, Barber SJ, Maddox K, Thomas AK. Stereotypes, warnings, and demographic characteristics influence older adults' susceptibility to associative false memory errors. The Gerontologist. 2017;57:S206–15.
169. Eich TS, Murayama K, Castel AD, Knowlton BJ. The dynamic effects of age-related stereotype threat on explicit and implicit memory performance in older adults. Soc Cogn. 2014;32(6):559–70.
170. Hess TM, Hinson JT. Age-related variation in the influences of aging stereotypes on memory in adulthood. Psychol Aging. 2006;21(3):621–5. https://doi.org/10.1037/0882-7974.21.3.621.
171. Thomas AK, Dubois SJ. Reducing the burden of stereotype threat eliminates age differences in memory distortion. Psychol Sci. 2011;22(12):1515–7. https://doi.org/10.1177/0956797611425932.
172. Mella N, Grob E, Döll S, Ghisletta P, de Ribaupierre A. Leisure activities and change in cognitive stability: a multivariate approach. Brain Sci. 2017;7:27.
173. Reid AG, Rakhilin M, Patel AD, Urry HL, Thomas AK. New technology for studying the impact of regular singing and song learning on cognitive function in older adults: a feasibility study. Psychomusicology: Music, Mind, and Brain. 2017;27(2):132–44.

Chapter 19

Neuropsychology of Movement Disorders and Motor Neuron Disease: Parkinson's Disease, Progressive Supranuclear Palsy, Essential Tremor, Huntington's Disease, and Amyotrophic Lateral Sclerosis

Alexander I. Tröster, Sarah J. Pulaski, and Steven Paul Woods

Introduction

Movement disorders fall into two broad categories: Hypokinetic and hyperkinetic. Hypokinetic disorders involve a paucity of voluntary movement and are exemplified by Parkinson's disease and related Parkinsonian disorders such as progressive supranuclear palsy and multiple system atrophy; by contrast, hyperkinetic disorders are characterized by excessive involuntary movements, a classic example of which is Huntington's disease (HD). These disorders all involve basal ganglia and/or cerebellum, and the cortical–basal ganglionic–thalamic–cortical pathophysiologies of the various disorders have been well described [1]. Motor neuron disorders are not classified as movement disorders. These disorders are grouped into upper and lower motor neuron disorders. Signs such as weakness, increased muscle tone, and hyperreflexia characterize upper motor neuron disease, whereas lower motor neuron disease is characterized by weakness, loss of reflexes, loss of muscle tone, fasciculations, and muscular atrophy. Although patients afflicted by motor neuron disease may have difficulty moving their limbs due to weakness (for example, brushing their teeth due to upper extremity proximal weakness) they do not have a movement disorder per se. The best-known motor neuron disease is amyotrophic sclerosis (ALS), or Lou Gehrig's disease. This chapter describes the more important movement and motor neuron disorders, specifically Parkinson's disease, progressive supranuclear palsy, essential tremor, Huntington's disease, and ALS, and highlights the pathophysiology and neurobehavioral features of each condition.

Parkinson's Disease

Biological Underpinnings

Parkinson's disease (PD) is a hypokinetic movement disorder characterized by tremor, bradykinesia, rigidity, and eventually postural instability. Worldwide prevalence estimates of PD range from 18 to 418 per 100,000 [2] and age-specific prevalence increases until the ninth decade [3]. Annual incidence of PD has been estimated at 11 per 100,000, with incidence increasing from 0 per 100,000 among those 0–

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29 years old to 93 per 100,000 among those 70–79 years old [4]. Numerous environmental risk factors for PD have been identified: exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (a designer drug that is a dopaminergic toxic compound, MPTP), herbicides, pesticides, manganese, iron, and drinking of well water [5]. There appears to be no one gene responsible for PD but studies have identified genetic loci responsible for some forms of familial or sporadic Parkinsonism. Linkage studies have identified five genetic loci (genes, if identified, in parentheses) associated with autosomal dominant inheritance patterns of Parkinsonism: PARK 1 (alpha-synuclein; SNCA), PARK 3, PARK 4 (alpha-synuclein; SNCA), PARK 5 (ubiquitin C-terminal hydrolase L1; UCHL1), and PARK 8 (leucine-rich repeat kinase 2; LRRK2). Two loci are associated with Parkinsonism possibly inherited in an autosomal dominant manner (PARK 10, PARK 11). Four loci have been linked to autosomal *recessive* forms of Parkinsonism: PARK 2 (Parkin), PARK 6 (PINK1), PARK 7 (DJ-1), and PARK 9. The various loci have all been mapped to chromosomes 1, 2, 4, 6, or 12. Only one locus (PARK 10) has been linked to sporadic, late-onset PD. Additionally, cognitive decline in PD has been linked to mutations in the glucosylceramidase beta (GBA) gene associated with Gaucher's disease, and polymorphisms (the H1/H1 haplotype) in the microtubule-associated protein tau(MAPT) gene.

Aspects of Diagnosis

The evolution of the neuroanatomical pathology of PD, progressing from brain stem to neocortex, has been described by Braak and colleagues [6]. Progression through Stages 3–6 is related to increasing cognitive impairment [7]. PD involves dopaminergic cell loss from the substantia nigra, and dopamine depletion in the striatum is greater in the putamen than the caudate. Neurobehavioral changes are probably attributable to mesocortical and mesolimbic, rather than nigrostriatal, dopaminergic system abnormalities [8, 9], and to non-dopaminergic cell loss in the locus coeruleus (noradrenergic), the dorsal raphe nuclei (serotonergic), the nucleus basalis of Meynert (cholinergic), and the dorsal vagal nucleus [10–13]. Another neuropathological substrate of PD is the presence of Lewy bodies in the brainstem. The role of Lewy bodies in the expression of dementia in PD, and whether the clinical entities of dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) are neuropathologically and neuropsychologically different remains debated [14, 15]. Although there remains no definitive evidence of human-to-human transmission of clinical PD, the stereotypical progression of α-synuclein pathology in most PD patients has led to speculation that α-synuclein deposition in PD may proceed via cell-to-cell transmission similar to transmission of pathological prion proteins in human transmissible spongiform encephalopathies [16, 17].

Neuropsychological Mechanisms

Attention and Executive Functions

Whereas patients with early PD perform normally on span tasks [18, 19], they do poorly on tasks demanding of efficient manipulation of information within working memory (e.g., Digit Ordering) [20]. Impairments are also observable on many tasks (e.g., Stroop task, visual search, Trail making) requiring divided or selective attention and both limited attentional resources and attentional set shifting may underlie poor performance [21, 22]. Patients typically show impairments on visual search and cancelation tasks. Working memory deficits in PD have been attributed to reduced capacity of the system [20], difficulty manipulating information within working memory [23], and difficulty inhibiting responses [24, 25]. Executive functions, including planning, conceptualization, flexibility of thought, insight, judgment, self-monitoring, and regulation, are often compromised early on in PD. Studies evaluating planning in PD using the Tower of Hanoi or its variants report that PD patients show normal accuracy (number of moves) but a slowness in problem-solving [26], while some also demonstrate impaired planning accuracy [27, 28]. Studies

using card sorting tests, such as the Wisconsin Card Sorting Test (WCST), typically report that patients with PD, especially early on in the disease course, have difficulty with one or more of set formation, set maintenance, and set shifting [29, 30]. Set loss, as opposed to a shifting deficit, is more likely to be observed later in PD [31, 32]. Set-shifting ability, in particular, appears to be a critical determinant of whether patients demonstrate difficulty on various executive function tasks [33] and patients with PD have particular difficulty with extradimensional (i.e., switching to a novel classification rule) as opposed to intradimensional (i.e., generalizing an existing classification rule to a novel stimulus class) set shifting [34]. Studies using gambling tasks to evaluate decision-making, judgment, and impulsivity have yielded inconsistent results. Czernecki and colleagues [35] found that patients' performance on the gambling task did not improve across assessments, suggesting a failure to benefit from experience—but, deficits on the gambling task may only be observable when patients are on dopaminomimetic medications [36]. The neural basis of executive deficits is being elucidated with functional neuroimaging. Positron emission tomography (PET) has revealed reduced blood flow in the globus pallidus [37], the caudate, and the dorsolateral frontal cortex of PD patients compared to controls in response to activation with the Tower of London task [38], which is improved by levodopa [39]. In the very early stages of PD, dopaminomimetics may, however, lead to executive dysfunction: for example, reversal errors may be related to the hyperdopaminergic state of the relatively intact hemisphere resulting from dopaminergic replacement therapy in patients with early PD and unilateral motor symptom onset [40]. Executive deficits have also been linked to cholinergic deficits observed on functional neuroimaging [41].

Motor Skills and Information Processing Speed

Diminished information processing speed in post-encephalitic Parkinsonism was already recognized in the 1920s, when the term bradyphrenia was coined [42], and bradyphrenia is particularly evident in demented patients with PD. Early in the disease, processing speed may be ameliorated by dopaminomimetic medications [43]. Motor symptoms such as bradykinesia, rigidity, and tremor are a hallmark of PD, but patients do not have an apraxia. Motor learning (such as on the pursuit rotor task) may or may not be impaired [44, 45].

Language

Motor speech abnormalities (e.g., dysarthria) are common in advanced PD. Despite the absence of aphasia, subtle alterations in performance on language tasks are observable in patients with PD, perhaps secondary to diminished attention, working memory, or inefficient information processing strategy development and deployment.

Visual confrontation naming is preserved in PD [46, 47], but rare studies report subtle naming impairments [48, 49] and naming becomes more compromised in patients with obvious cognitive impairment [50]. Lexical and semantic verbal fluency is often intact in patients without dementia [47]. Two verbal fluency tasks especially sensitive to PD are alternating word fluency (requiring retrieval of consecutive words from alternate semantic or letter categories) [51] and verb fluency tasks requiring naming of actions [52]. Phonemic and semantic verbal fluency impairments, when observed, may be related to general retrieval deficits [53] or to a deficit in an underlying process such as switching but not semantic clustering (i.e., respectively, disengaging from one category of words to produce those from another category, and the production of consecutive words from the same semantic or phonemic category) [54, 55]. Subtle impairments may also be observed in syntactic comprehension and production [56], and underlying mechanisms include grammatical processing deficits [57, 58], slowed information processing [59], and diminished attention [60, 61].

Learning and Memory

Impairments in episodic memory may be evident in the earliest stages of the disease and at diagnosis [62, 63]. Learning of new information is

slowed in PD [64]. Free recall is impaired, and while recognition is relatively preserved [65], it is not necessarily intact [66]. As cognitive impairment progresses in PD, both recall and recognition are compromised [67]. The relative preservation of recognition compared to recall is often interpreted to mean that patients with PD have retrieval deficits, but it is clear that patients may also have encoding difficulties [68, 69], and the rate with which a semantic encoding strategy evolves across word list learning trials is slow [68, 70]. In contrast to semantic encoding, serial encoding appears to be preserved [68, 70], as are serial position effect [71]. A possible explanation for these findings is that serial encoding reflects the use of an externally imposed strategy, whereas semantic encoding relies on self-initiated strategies diminished in PD [72]. Retention of word lists over time is usually normal [73], and intrusion errors (production of non-list words during recall) are typically semantically related to the words on the list and qualitatively similar to those of normal elderly [73, 74].

Recollection of information from the past (remote memory) is typically preserved [75, 76] and only rarely are subtle abnormalities revealed [77, 78]. Patients with PD also demonstrate deficits on numerous experimental memory tasks putatively sensitive to frontal dysfunction such as conditional associative learning [79], source memory [80], metamemory [81], recency discrimination [82], temporal ordering [83], subject-ordered pointing [84], and aspects of prospective memory, that is, for intended, future actions [85]. Findings with respect to non-declarative memory in PD are inconsistent. The most recent studies provide evidence of abnormal semantic priming [86], and the possibility that these abnormalities may be related to information processing speed, slowed lexical access, and dopaminergic abnormalities [87, 88].

Visuoperception

Visuospatial deficits are quite common in PD and occur independent of motor deficits [89, 90]. Similarly, although impaired saccadic eye movements may contribute to visuoperceptual impairments, they cannot fully account for them [91]. Facial matching tasks reveal impairments in PD [46] and the facial recognition impairment in PD is related to configural, but not componential visuoperceptual processing difficulties [92]. Another visuospatial task free of motor demands is one requiring patients to match lines of similar spatial orientation. Two studies found that PD patients make more serious errors than healthy controls, e.g., confusing an oblique line with one from the same quadrant that was displaced by two or three 18° segments from the target line and mismatching horizontal lines.

Assessment of Functional Status in PD

Declines in functional status, or the ability to independently complete basic and instrumental activities of daily living, often occurs with progression of PD. While neuropsychological measures do not provide direct assessment of functional status, they assist with identification of cognitive dysfunction associated with such declines. The severity of motor symptoms of PD correlates with functional status in *physical* (i.e., basic) activities of daily living. By contrast, executive dysfunction correlates with declines in *instrumental* activities of daily living that allow individuals to live independently [93].

Establishing the degree of impairment in instrumental activities of daily living (IADL) is especially necessary when attempting to distinguish those individuals with PD with mild cognitive impairment (PD-MCI) and dementia [93]. Current criteria for the diagnosis of PDD require the presence of significant functional declines secondary to cognitive impairments, whereas a diagnosis of PD-MCI requires that cognitive impairments do not result in significant functional declines.

Traditionally, determinations of a PD patient's ability to perform IADL have been made using information obtained in interviews with family members or caregivers, indirect methods (e.g., cognitive testing), or functional rating scales intended for use in populations with other dementias. These approaches suffer from

significant weaknesses: indirect methods and interviews may underestimate disability and dysfunction. By contrast, functional rating scales not specific to PD fail to properly account for the functional impact of motor symptoms and thus may overestimate dysfunction. Two new PD-specific instruments, the PD-Cognitive Function Rating Scale (PD-CFRS) and the Brief Penn Daily Activities Questionnaire (PDAQ) have been developed to assess functional status in PD. These two scales appear to be sensitive to cognition-associated functional changes in PD [93].

The PD-CFRS is a 5-min questionnaire designed to explore a range of functions thought to be sensitive to the early and mild cognitive impairments in PD [94, 95]. The scale is comprised of 12 items administered via interview to a knowledgeable informant. The items included address a range of potential instrumental cognitive problems observed in the two weeks before evaluation. All 12 questions use examples to explore whether the patient has had trouble performing an activity (0 = none; 1 = some of the time; 2 = most of the time; 8 = the subject has never done the activity in the past) such as handling money, domestic economy, handling personal mail, controlling drug treatment schedule, arranging holidays or meetings, organizing daily activities, using home electronic appliances, understanding how to use public transportation, solving unexpected events, oral expression, comprehension of written material, and handling the cell phone. The maximum score is 24 and is obtained by summing the ratings. Those items rated as never done in the past are omitted from the sum total. The original validation study demonstrated that the PD-CFRS is a reliable and valid instrument that sensitively captures and measures relevant functional changes related to cognitive impairment in PD. Good discriminant validity was found in cognitive impairment across all stages of PD [93–95]. A cutoff score of $\geq$3 was found to be optimal for detecting functional impairment in patients with PD-MCI. A prospective multicenter responsiveness study showed that an increase of 2 points in the PD-CFRS after 6 months was associated with a clinically significant worsening of cognitive functional status [95].

The PDAQ for PD is a 15-item scale assessing IADL that are specific and sensitive to cognitive abilities in PD including items such as ability to read, keep track of time, follow instructions, remember an errand list, count money, multi-task, and learn new gadgets, among others. Like the PD-CFRS, it is administered in interview format to knowledgeable informants. Items are scored from 0 ("cannot do") to 4 ("none") with a maximum of 60 points, with higher scores indicating better functioning. Initial validation results suggest that the PDAQ for PD has good discriminant validity across stages of cognitive impairment in PD and correlates highly with global cognitive performance [93].

Neuropsychiatric Features

Depression is common in PD, occurring in about half of all patients—one meta-analysis reported a prevalence rate of 42% in studies using Diagnostic and Statistical Manual criteria [96]. Yet, anxiety and depression are often unrecognized by clinicians treating PD [97], and even when recognized, depression may be inadequately treated. One study observed that only one-third of depressed PD patients were receiving antidepressant treatment, and that, among those with persistent depression, only 11% had been tried at antidepressant dosages within the highest recommended ranges [98]. Despite the considerable prevalence of depression in PD, suicide is uncommon and perhaps rarer in PD than among elderly in general [99]. The most frequently used antidepressants in PD are the selective serotonin reuptake inhibitors (SSRIs) [100]. Dopamine agonists such as pramipexole [101], the tricyclic nortriptyline [102, 103], and cognitive behavioral therapy [104] may also alleviate depression in PD.

Probably almost 50% of patients with PD have significant symptoms of anxiety. As many as 75% of those patients with PD *and* depression may have a comorbid anxiety disorder [105]. The prevalence of anxiety disorders (vs. symptoms) in PD ranges from 5 to 40% [106], though one recent study reported current and lifetime

prevalence rates above 40% [107]. One study found that almost 20% of PD patients had generalized anxiety, 20% had a social phobia, and 20% experienced social anxiety [108]. Most patients might have anxiety disorders that do not clearly fit DSM criteria for a specified anxiety disorder [107]. Recurrent panic attacks may occur in up to 24% of patients treated with levodopa [109] and a considerable number of patients have symptoms of OCD [110].

In addition to depression and anxiety, impulse control disorders (ICDs) and related disorders may occur in as many as 15–20% of PD patients treated with dopaminergic medication, especially dopamine agonists [111]. In PD, ICDs may manifest as compulsive buying, gambling, sexual behavior, eating, and punding (i.e., repetitive, stereotyped behaviors that are seemingly aimless, e.g., sorting objects such as buttons) in hobbyism (i.e., excessive engagement in hobby-related activities such as building models, sewing, painting, etc.). Current research suggests that age and sex may be potential risk factors for the development of ICDs in PD, with a disproportionately greater number of ICDs manifested in younger males with PD [111].

Although traditional instruments such as the Beck Anxiety Scale and State-Trait Anxiety Inventory have often been used in PD, the overlap of symptoms between PD and anxiety disorders (e.g., restlessness, feeling flushed, and tremulousness) and consequent potential overdiagnosis of anxiety disorders has led to development of a scale specifically for use in PD. The Parkinson Anxiety Scale (PAS) is a 12-item observer or patient-rated scale developed to assess for the presence of persistent, episodic anxiety, and avoidance behavior in individuals with PD. The diagnostic properties of both the observer-rated and self-rated scales suggest that the persistent anxiety subscale correlates with generalized anxiety disorder, the episodic anxiety subscale with panic disorder, and the avoidance subscale with agoraphobia and social phobia. Initial validation results suggest that the PAS has good internal consistency and excellent interrater and test–retest reliability [112].

A scale assessing impulsive and compulsive behaviors specifically in PD has also been developed. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) is a patient-rating scale comprised of four primary questions on a 5-point Likert scale (pertaining to commonly reported thoughts, urges, and behaviors associated with ICDs), each applied to the four ICDs (compulsive buying, gambling, eating, and sexual behavior), as well as three related disorders (medication use and hobbyism/punding) [113]. Patients are instructed to answer questions based on behaviors that occurred in the preceding 4 weeks or any 4-week period in the lifetime. Scores for each ICD and related disorders range from 0 to 16 (with the exception of hob byism/punding ranging from 0 to 32), with higher scores indicating greater severity of symptoms. Initial validation results indicate that the QUIP-RS has adequate sensitivity and specificity, as well as good interrater and test–retest reliability, suggesting that it can be used to support diagnosis of ICD and related disorders, as well as to monitor change and severity over time.

Progressive Supranuclear Palsy

Biological Underpinnings and Diagnosis

Formerly known as Steele–Richardson–Olszewski Syndrome [114, 115], progressive supranuclear palsy (PSP) is a neurodegenerative atypical Parkinsonism that is primarily characterized by vertical gaze palsy and postural instability (commonly associated with backward falls), along with several other supporting symptoms such as akinesia/rigidity, retrocollis, pseudobulbar palsy, and neuropsychological impairment [116]. The most widely used clinical criteria were proposed by the National Institute of Neurological Disorders and Stroke and Society for PSP (NINDS-SPSP) and a diagnosis of probable PSP required demonstration of vertical supranuclear gaze palsy, in addition to postural

instability and falls within the first year of symptom onset. The diagnosis of possible PSP required the presence of either supranuclear gaze palsy or a combination of slow vertical saccades and postural instability with falls within the first year. The just-published International Parkinson and Movement Disorder Society criteria [117] are more complex and include progression of symptoms. They require sporadic occurrence, age 40 or older at onset of first PSP symptom, and a gradual progression of PSP symptoms. Different symptoms in the domains of oculomotor dysfunction, postural instability, akinesia, and cognitive dysfunction (core features) offer different levels of certainty of diagnosis, and supportive clinical and neuroimaging findings are also outlined in the criteria.

Both the incidence and prevalence of PSP are estimated to be 5 persons per 100,000 and neither is strongly associated with any demographic or genetic risk factors, with the exception of older age [118]. PSP is considered a tauopathy and shares some pathological and clinical features with cortical basal ganglionic degeneration, as well as frontotemporal dementia (e.g., primary progressive aphasia). Although signs of PSP may be evident as early as age 40, formal diagnosis typically occurs after age 60, with particularly high incidence rates after age 80 [119]. At present there are no effective pharmacological or neurosurgical treatments available for patients with PSP and survival rates range from approximately 5 to 10 years after diagnosis [120].

PSP is classified among the "tauopathies," with tau-positive neurofibrillary tangles and neuropil threads, tufted astrocytes, and coiled oligodendroglial bodies being the most distinctive neuropathological features of the disease [121]. These histopathological features are most commonly in subcortical regions, such as the midbrain (e.g., red nucleus), subthalamic nucleus, basal ganglia (e.g., substantia nigra and striatum), and brainstem (e.g., pontine reticular formations). Neuronal loss and atrophy of the frontal cortex, including both prefrontal and motor regions, may also be present. Considering the prevalence of dopaminergic receptors and cholinergic interneurons in these affected regions, it is not surprising that PSP is also associated with moderate-to-severe deficiencies in these neurotransmitter systems [122].

With conventional neuroimaging techniques, midbrain and brainstem atrophic features such as "hummingbird", also known as the "penguin" sign, and "morning glory" sign (on MRI), or the "pimple" sign of midbrain hypometabolism (on PET) may sometimes be present, but require subjective determination by a radiologist. Increasingly, advanced neuroimaging methods are being utilized to quantify morphologic changes associated with PSP. Voxel-based morphometric (VBM) studies have documented prominent and consistent atrophy of gray and white matter in brainstem structures, variable atrophy of the cerebellum and subcortical structures, and prominent frontal cortical atrophy with involvement of the insular cortex [123]. Using MR volumetry, volume loss of the brainstem and midbrain appear to be prominent features of PSP, while volume loss of the cerebellum is noted inconsistently. Subcortical volume loss has commonly been noted in the basal ganglia and thalamus. Consistent with findings using VBM, studies using MR volumetry have observed a similar distribution of reduced cortical volume predominantly in a frontal distribution. Using diffusion-weighted MR imaging (DWI) and diffusion tensor imaging (DTI), damage to the cerebellar outflow tracts has been consistently found in PSP and supported involvement of the cerebellum in the cognitive, affective, and motor symptoms associated with PSP. Using DWI and DTI, brainstem changes have been described in the pontine white matter, while cortical diffusion changes impact frontal white matter. In contrast, few DWI and DTI studies have reported altered diffusion in subcortical structures [123].

Neuropsychological Mechanisms

Neuropsychological impairment is frequently observed in PSP and, unlike many other movement disorders, cognitive deficits are explicitly mentioned as a supportive feature in the

diagnostic criteria for PSP [116, 117]. An early onset of cognitive deficits may be a harbinger of more rapid disease progression and mortality [124]. The prevalence of dementia in PSP is estimated to range between 50 and 80% [125], but may be less prevalent in a subset of patients with more traditional Parkinsonian features (in a clinical phenotype referred to by some as "PSP-parkinsonism"), such as levodopa-responsive tremor and asymmetric onset of motor symptoms [126]. The neuropsychological profile associated with PSP is commensurate with its frontostriatal neuropathogenesis and is typically marked by prominent executive dysfunction and bradyphrenia [127]. Several neuropsychological tests are useful in identifying cognitive impairments in PD and atypical Parkinsonian disorders, such as PSP. However, as shown in Table < InternalRef RefID="19.1, neuropsychological tests appear more helpful in differentiating PD from atypical Parkinsonian disorders than in differentiating among atypical Parkinsonian disorders, especially corticobasal syndrome from PSP and MSA [128, 129].

Attention and Executive Functions

Although basic verbal attentional skills are generally within normal limits, deficits in visual attention are common in PSP [130]. Executive dysfunction is also a prominent feature of PSP and is hypothesized to arise from a deafferentation of the basal ganglia and prefrontal cortex [127], although both frontal and subcortical regions are likely implicated. A broad range of dysexecutive signs may be present, including deficits in planning, problem-solving [131], and cognitive flexibility [132]. Deficits in problem-solving and cognitive flexibility may be more vulnerable to decline in PSP as compared to PD and MSA [133]. Various frontal release signs can also be observed in patients with PSP; for example, the "applause sign" (i.e., perseveration of clapping to command) may be evident in as many as three-quarters of PSP patients [124] and reliably differentiates PSP from PD and FTD [134].

Motor Skills and Information Processing Speed

Bradykinesia and bradyphrenia are among the most prevalent and severe neurocognitive deficits associated with PSP [135] and should be considered when interpreting deficits in higher level cognitive functions. Impairment is observed on simple tests of motor skills, such as finger tapping, as well as on more complex tasks involving motor sequencing [131]. Patients with PSP may also display ideomotor apraxia, although to a

Table 19.1 Neuropsychological tests determined to be moderately (20–29% overlap between groups' score distributions) to very (less than 20% overlap) useful (Lee et al. 2012) in distinguishing between PD and atypical Parkinsonian disorders

Conditions differentiated	PSP	CBS	MSA
PD	Semantic fluency, phonemic fluency, alternating semantic fluency, Wisconsin Card Sorting Test (categories, errors, perseverative errors), Trail Making Test Part A, frontal assessment battery, JLO, Digit Span, orientation choice reaction time *(all worse in PSP)*	Orofacial and ideomotor apraxia *(both worse in CBS)*	Trail Making Test Part B, Stroop *(both worse in MSA)*
PSP	–	None	–
MSA	Semantic fluency, phonemic fluency, alternating phonemic fluency, alternating semantic fluency, Wisconsin Card Sorting Test (errors and categories), JLO, Addenbrooke's cognitive examination (ACE) *(all worse in PSP)*	Orofacial apraxia *(worse in CBS)*	–

Abbreviations: PD: Parkinson's Disease, PSP: Progressive Supranuclear Palsy, MSA: Multiple System Atrophy, CBS: Corticobasal Syndrome

lesser extent than that which is present in patients with cortical basal ganglionic degeneration [136].

Language

Speech abnormalities such as dysarthria and hypophonia occur earlier [137] and are more common in PSP as compared to other movement disorders [138]. Impairment in verbal fluency follows the classic "subcortical" pattern of letter fluency being more affected than category fluency [139], although the effects of PSP on action (verb) fluency [52] will be important to determine since PSP is associated with greater deficits in naming verbs versus noun [140]. When present, deficits in confrontation naming of nouns may be attributable to visual misperceptions, rather than semantic memory deficits per se [141].

Learning and Memory

Episodic memory deficits are present in PSP, but the severity of these deficits is considerably less when compared to PDD, DLB, and AD [142]. The memory impairment profile is largely consistent with that which is observed in other movement disorders, such as HD and PD (see above). Remote memory is largely unaffected [30], but tests of recent episodic memory reveal a mixed encoding/retrieval profile whereby free recall is impaired, but recognition discrimination is generally within normal limits [143]. Non-declarative learning and memory deficits are observed for measures of procedural learning [135] but not on tasks of perceptual priming [135].

Visuoperception

Oculomotor deficits are a hallmark of PSP, with impairment in voluntary vertical eye movements considered a primary diagnostic feature. Other neuro-ophthalmological abnormalities may include blepharospasm and reduced blinking frequency, all of which may interfere with higher level spatial cognition. Visuoperceptual abilities are also affected in PSP, including visual search and scanning [133], orienting [139], tracking, and attention, which may be associated with greater severity of oculomotor deficits [144].

Neuropsychiatric Features

Apathy has consistently been identified as the most common neuropsychiatric symptom in patients with PSP, perhaps reflecting pathology within medial prefrontostriatal loops (see Joel, 2001) [145]. With some prevalence estimates near 90% [146], apathy is far more common and severe in PSP as compared to PD, which is more likely to present with depression, hallucinations, and delusions [147]. Although apathy is sometimes misdiagnosed as depression, the latter does not present as a prominent neuropsychiatric feature of PSP [146]. Paralleling the above-described deficits in inhibitory cognitive processes, individuals with PSP also exhibit elevated behavioral signs of disinhibition [147]. As many as three-quarters of patients with PSP may evidence changes in "personality" [124], which can include increased irritability [147]. When combined with patients' limited insight regarding their cognitive and behavioral deficits [148], these neuropsychiatric symptoms may greatly exacerbate caregiver stress and burden.

Essential Tremor

Biological Underpinnings and Diagnosis

Perhaps the most prevalent movement disorder is essential tremor (ET), which is estimated to occur in between <0.5 and 4% of the general adult population [149]. ET is characterized by an action tremor (i.e., a 4–12 Hz tremor that emerges during voluntary motion or sustained extension of a limb) that is typically evident in the upper extremities, but may also be observed in the head and/or voice [150]. Although intention and/or resting tremor may also be evident, action tremor is the modal clinical presentation of ET. The tremor is typically bilateral (although often asymmetrical), slowly

progressive, and of long duration (e.g., >5 years), with onset normally after age 65. ET is generally considered a monosymptomatic condition, such that the presence of other abnormal neurological signs is exclusionary; however mild-to-moderate cerebellar signs (e.g., ataxia, dysarthria, and nystagmus) are also present in some cases.

Historically, it was widely believed that ET was without a neuropathological substrate. Over the past 10 years, however, an emergent body of evidence suggests that ET is associated with neuropathophysiological changes in the cerebellothalamocortical loop. Cerebellar degeneration in ET is characterized by the loss of Purkinje cells and an associated elevation in torpedoes (i.e., fusiform swellings consisting of neurofilaments) [151]. Lewy bodies may also be evident in the locus ceruleus, but are unlikely to co-occur with cerebellar degeneration, perhaps arguing for some heterogeneity in the neuropathophysiology of the disorder [151]. Patients with ET also demonstrate lower N-acetylaspartate (NAA; a marker of neuronal injury) [152] and higher regional blood flow bilaterally in the cerebellum [153]. Whether these alterations translate into neurodegenerative changes that are viewable with structural imaging techniques remain uncertain [154]. Frontal and parietal abnormalities on DTI correlate with executive and visuospatial dysfunction in ET [155].

Despite its long-held classification as a "benign" movement disorder, it has become increasingly clear that ET is often accompanied by a variety of non-motor complications that are consistent with the disorder's cerebello- thalamocortical substrates. Individuals with ET report significant decline in the independent performance of both physical (e.g., self-care) and instrumental (e.g., communication) activities of daily living [156]. In fact, as many as 75–95% of ET experience at least one significant disability related to their ET symptoms [157]. Moreover, ET is associated with reduced general health status [158], as well as lower physical and mental health-related quality of life [159]. Functional disability, poorer health status, and lower health-related quality of life are associated with more severe motor symptoms [160], older age [159], affective distress [157], and cognitive impairment [161].

Neuropsychological Mechanisms

Prevalence estimates of cognitive impairment rates vary somewhat across the literature, but mild-to-moderate deficits are observed in approximately 50% of individuals with ET. Although ET cases with later tremor onset (>65 years of age) demonstrate an almost two-fold risk of incident dementia [162], there is no known specific dementia syndrome that accompanies ET. In fact, while ET is associated with lower performance on the Mini-Mental State Examination (MMSE) as compared to healthy adults at a group level [163], MMSE scores below commonly used dementia cut points in ET are rare in the absence of a comorbid neurodegenerative condition. However, more subtle impairments may be evident in several different ability areas, including attention and executive functions, language, memory, information processing speed, and visuoperception.

Attention and Executive Functions

Several studies have shown mild impairment on measures of complex auditory attention and working memory in ET, such as digit span [164] and selective attention [165]. Deficits in sustained visual attention are also evident, including on measures of letter cancelation [166] and continuous performance tasks [166]. Speeded measures of divided attention (e.g., Trail making Test, Part B), prepotent response inhibition (e.g., Stroop Color-Word Test), and cognitive flexibility (e.g., design fluency) are also sensitive to ET [167]. Findings regarding higher level executive functions, such as abstraction, verbal and nonverbal concept formation, and planning, are mixed across the ET literature. For example, several studies report that ET is associated with an increased number of perseverative responses on the Wisconsin Card Sorting Test [166],

whereas others do not [168]. When present, deficits in attention and executive functions may be predictive of problems in day-to-day life; for example, Woods et al. (2008) [161] reported that executive dysfunction (i.e., impairment on the Stroop Color-Word Test) was a unique predictor of poorer physical health status in ET, above-and-beyond that which was explained by motor symptoms.

Motor Skills and Information Processing Speed

Not surprisingly, ET is associated with deficits on tasks of basic motor skills [169], including fine-motor speed and coordination [165]. As is true in other movement disorders, deficits in basic motor skills should be taken into account when interpreting higher level cognitive impairments in patients with ET. Impairment is observed on measures of psychomotor processing speed, including simple tasks such as Trail making Test, Part A [163], as well as more complex measures like Symbol Search [164]. Deficits are also apparent on non-motor measures of information processing, including the Color trial of the Stroop Test [165, 168].

Language

While gross aphasia is rare in ET and, if present, should raise questions regarding alternate or comorbid conditions, milder abnormalities in speech and language are nevertheless quite prevalent in clinic samples. As noted above, some patients may present with a vocal tremor or dysarthria, with the latter being more common in patients who have undergone thalamic deep brain stimulation [170]. Mixed findings exist regarding whether ET is associated with impairment in confrontation naming [163, 171]. Formal neuropsychological evaluation will commonly reveal impairment in verbal fluency, including both letter [167] and semantic trials [165]. Qualitative analysis may show an increased rate of perseverative responses on letter fluency [168], but whether the global fluency deficit reflects impairment in basic motor speech, slowed information processing, a degradation of semantic stores, and/or inefficient a lexicosemantic switching/retrieval is not yet known.

Learning and Memory

Consistent with other movement disorders (e.g., PD), deficits in list learning and recall may be observed in patients with ET. Early evidence suggests that impairment is evident in both immediate and delayed free recall [172], as well as on recognition [165, 168]. Although no detailed component process analysis has been published, such findings are commensurate with a primary encoding deficit; for example, several studies have reported a profile of impaired immediate and delayed recall (with no rapid forgetting) on list learning and passage [163–165]. In contrast, deficits in visual memory are less [165, 166].

Visuoperception

Deficits in facial recognition [172] and judgment of line orientation [168] may be evident. On the other hand, few patients with ET are impaired in the Visual Organization Test [168, 172]. While deficits in spatial cognition are not commonly associated with cerebellar dysfunction, there is more recent evidence to that effect [173, 174] and they are documented in other movement disorders, such as HD [175].

Neuropsychiatric Factors

Although research in this area is still sparse, it appears that ET is also associated with increased rates of neuropsychiatric distress. Several studies have reported elevated symptoms of depression [172] and anxiety in ET, including social phobia [176]. The overall severity of current depressive symptoms in ET is comparable to that which is observed in PD, but patients with ET may express slightly fewer somatic complaints [177]. Nevertheless, depression is a unique predictor of lower psychosocial health status in ET, even after considering the effects of ET disease severity [161]. Studies regarding the prevalence,

predictors, and consequences of psychiatric comorbidity in ET are clearly indicated.

Huntington's Disease

Biological Underpinnings

Huntington's disease (HD) is a heritable neurodegenerative disorder characterized by a debilitating constellation of symptoms that include involuntary movements (e.g., chorea and dystonia), dementia, and marked neuropsychiatric changes [178]. HD arises from a mutation on chromosome 4 that typically involves more than 40 repeats of the CAG trinucleotide, although individuals with 36–40 repeats may also become symptomatic [179]. HD is transmitted in an autosomal dominant pattern of inheritance, meaning that offspring of a parent with HD has a 50% chance of inheriting the disease. The prevalence of HD is approximately 6 per 100,000 in the general population, with the highest rates being among Caucasians [180]. Diagnosis is typically made in mid-life (late 30s and early 40s), but persons with a greater number of CAG repeats are at risk of earlier onset, with approximately 5% of cases presenting during childhood or adolescence [181, 182]. A prodromal phase of HD has also been described, whereby some individuals evidence subtle neural changes, cognitive impairment, and psychiatric features prior to receiving a formal diagnosis. There are no effective treatments available to slow the progress of HD and life expectancy from the time of diagnosis ranges from approximately 15 to 20 years [183].

Diagnosis

The neuropathology of HD primarily involves significant and early loss of medium spiny neurons in the caudate [184], but multiple aspects of the basal ganglia and frontostriatal loops are also affected, including the putamen, substantia nigra, and globus pallidus [145]. Caudate atrophy is nevertheless the most striking neuropathological feature of HD and may even be present to a milder degree in the presymptomatic phase of the disorder. Atrophy of the frontal and temporal cortices can also be observed in HD, particularly among individuals with advanced disease [185]. Functional neuroimaging data show that the prefrontal cortex is hypometabolic at rest in HD [186], whereas increased BOLD signal is evident in the frontal and parietal cortices during the performance of demanding cognitive tasks, perhaps reflecting the recruitment of compensatory networks [187].

Neuropsychological Mechanisms

Given the relatively selective involvement of the basal ganglia, HD has long been considered a prototype of the "subcortical" dementias [188], with prominent cognitive deficits in the areas of executive functions, speeded information processing, episodic memory retrieval, procedural learning, emotion processing, and social cognition. A subset of individuals evidence mild neuropsychological impairments in these cognitive domains during the prodromal phase of HD (i.e., prior to the onset of motor symptoms) [175], which tend to intensify as the diagnosis nears [189]. Cognitive deficits continue to advance in prevalence and magnitude in the early stages of HD [190] and invariably progress to frank dementia.

Attention and Executive Functions

Both basic (e.g., digits forward) and complex (e.g., digits backward) attentional abilities are impaired in HD [191]. With regard to the latter, deficits are apparent in a wide range of functions, including working memory and the divided, sustained and selective aspects of attention, and even on tasks that are typically considered less demanding attentional tasks (e.g., bimanual motor tapping) [193]. Executive dysfunction also runs the gamut of ability areas, such as cognitive

flexibility [194], planning [195], problem-solving, and abstraction [196], which are associated with both striatal and cortical abnormalities [197]. As compared to healthy older adults and patients with PD, individuals with HD demonstrate riskier decision-making style on a laboratory gambling task, performance on which is marked by a tendency to seek higher immediate rewards despite the risk of more severe long-term penalties. Risky decision-making is strongly related to deficits in conceptualization and episodic memory, but not to caregiver reports of disinhibition or dysexecutive symptoms [198].

Motor Skills and Information Processing Speed

Although choreiform movements are the most readily recognizable symptom of HD, other movement abnormalities may develop, such as dystonia, dyskinesia, and motor impersistence. On neuropsychological tests, patients with HD display progressive slowing of motor, complex psychomotor, and non-motor cognitive processes [191]. Increased variability in the timing of motor functions, but not necessarily accuracy, may emerge prior to diagnosis [199]. Indeed, mild bradyphrenia and bradykinesia may be present in the preclinical phase of the disease and tend to show a more gradual decline than do memory and executive impairments, which can progress quickly around the time of diagnosis, perhaps related to basal ganglia degeneration [200]. Cognitive slowing is already observed in the premanifest stages of HD and is often a significant predictor of functional status in HD (e.g., driving status) [182]. The word reading component of the Stroop test may be more sensitive to cognitive decline in HD than the interference component probably because there is a failure to automatize simpler psychomotor tasks in HD.

Language

Motor speech abnormalities, most notably dysarthria, are frequently observed even in the early stages of HD [201]. Although less prominent than in AD, HD is associated with deficits in confrontation naming, which are largely driven by visuoperceptual errors [202] and may progress with advancing disease [191]. Contrary to traditional beliefs about discrepant phonemic versus semantic fluency impairment in "subcortical dementias," individuals with HD typically evidence comparable impairment on letter and category cued verbal fluency tasks [203], suggesting a primary lexicosemantic retrieval deficit. This impairment is hypothesized to be driven by difficulties in the complex process of switching between lexicosemantic categories (i.e., disengaging from one semantic cluster, searching for and identifying another appropriate cluster, and then retrieving words from that cluster) rather than a degradation of the semantic memory stores [204].

Learning and Memory

Episodic memory functions are among the earliest and most severely affected cognitive abilities in HD [196]. The profile of learning and memory impairment in HD has been characterized as a primary retrieval deficit, such that patients' free recall is moderately to severely impaired, but their ability to accurately recognize previously presented material is only mildly affected [73]. It deserves mention, however, that a recent meta-analysis suggested that this classic retrieval profile may only be apparent in individuals with mildly symptomatic disease [205], whereas patients with more advanced disease demonstrate broader learning and memory impairment. Relative to AD, patients with HD demonstrate superior novel recognition discrimination [206], generate significantly fewer cued-recall intrusions [207], and do not show a strong temporal gradient on tests of retrograde amnesia [208]. HD is also associated with impairments on measures of implicit memory, including perceptual, motor, and cognitive skill learning, which are typically unaffected in AD [209].

Visuoperception

Abnormal neuro-ophthalmological signs, including increased errors and latencies on anti-saccadic movements, may be an early

biomarker of HD [210]. Several aspects of spatial cognition are also affected in HD. For example, Bylsma and colleagues [211] demonstrated that patients with HD were impaired in the personal orientation (i.e., egocentric) aspects of a route-walking task, perhaps reflecting deficits in mental rotation. As compared to AD, individuals with HD are slower on tasks of mental rotation, but make significantly fewer errors [212]. Impairment may also be seen on measures of spatial orienting [213], as well as on tests of space and object perceptions [191].

Neuropsychiatric Features

Neuropsychiatric symptoms are salient in HD and are an important predictor of functional status [214]. Depression is perhaps the most prevalent psychiatric comorbidity and is present in approximately 40–50% of patients [215]. Individuals in the early stages of the disease appear to be at particular risk of depression [216]. Suicidal ideation (9–23%) [216], attempts, and completions (5–10%) [217] are unusually high in HD as compared to other neurological disorders [216]. Risk of suicidality may be greater in individuals with histories of psychiatric disorders and those without significant psychosocial responsibilities [218]. Anxiety and apathy [219], as well as "personality changes," such as increased aggression [215] and irritability [219] are also prevalent in HD, whereas symptoms of obsessive–compulsive disorder, delusions, and hallucinations are less frequently observed [219].

Deficits in social cognition and emotion processing are also observed in individuals with HD, with emotion processing impairments manifesting early in the disease course, even during the preclinical phase [182]. Perhaps the most prominent difficulties with emotion processing in HD are related to cross-modal impairments in recognition/interpretation of visual (e.g., facial expression, body language) and auditory (e.g., vocal intonation) communication of negative emotions including disgust, fear, and anger [182, 192]. While most research to date has investigated emotion processing in HD using emotion recognition paradigms, more recent research investigating spontaneous, instructed (i.e., directed), and imitated emotional expression in HD have provided evidence for possible impairments in expressive communication as well [220]. Research investigating the possible underlying mechanisms for reduced emotional expression in HD has found that these deficits are more likely to be associated with impaired motoric control of facial muscles necessary for emotional expression, rather than alexithymia. In contrast, studies investigating interoceptive emotional experience and emotional awareness in HD have yielded inconsistent results, with some suggesting intact emotional awareness [220] and others finding evidence for possible alexithymia [221]. In addition to impairments in emotion processing, individuals with HD also demonstrate reduced social cognition including deficits in tasks of "Theory of Mind" including recognition of socially inappropriate behavior, sarcasm, and intentions.

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

History and Diagnosis

Charcot in the 19th century described the syndromic features of amyotrophic lateral sclerosis (ALS), a progressive, fatal, neurodegenerative disease affecting upper and lower motor neurons. Neuropathological findings of ALS are found throughout the brain, brainstem motor nuclei, cranial nerves, and spinal cord. In the spinal cord, hallmark features include atrophy of the anterior horn cells, sclerosis of the lateral columns, and atrophy of spinal nerve endings that innervate muscles [222]. Bunina bodies, a pathological feature of ALS, are found in the brain and spinal cord, while the brain is marked by loss of Betz cells in the motor cortex, cytoplasmic inclusions comprised of TDP-43 (also found in individuals with frontotemporal dementia), atrophy in the frontal and temporal cortices, atrophy of the corticospinal tract, and generalized white matter volume loss. The majority of patients present with motor neuron

symptoms at disease onset and, progressively, develop impairments in speech, swallowing, breathing, use of upper and lower limbs, and eventually paralysis. Three neurological presentations are identified. The bulbar onset variant presents with prominent dysarthria and/or dysphagia, and these patients may have disease that affects lower or upper motor neurons, and, thus, may demonstrate features of bulbar palsy (facial weakness, limited palatal movement and lingual atrophy, weakness and fasciculation) and/or pseudobulbar palsy (emotional lability, dysarthria, and brisk jaw jerk). Persons with cervical onset can also show upper and/or lower motor neuron involvement and have upper limb signs such as proximal or distal weakness. Lumbar onset patients have involvement of lower motor neurons and proximal weakness of the lower extremities or foot drop.

ALS is now recognized as a multisystem disorder because a significant number of patients (as many as 15%) develop features of a frontotemporal dementia (and the observation that a significant number of patients with frontotemporal dementia develop motor neuron disease has raised debate about whether the two conditions anchor the extremes of a single disease spectrum). These cognitive changes, less well studied than the motor neuron symptoms, are observed in 10–75% of patients and not predicted by region of motor disease [222, 223]. Most often evident is executive dysfunction (manifest in poor planning, abstraction, and word search) [224]. Compromises in visuospatial, language, and memory functions are more inconsistently observed. The presence of a frontotemporal dementia or executive dysfunction is associated with reduction in the mean survival time by 12 months [222]. Behavioral changes characterized by affective and personality changes have also been noted (e.g., obsessiveness, irritability, pathological laughing, or crying), and their presence also negatively impacts mean survival time. Moreover, cognitive and behavioral symptoms can begin prior to, concurrently, or following motor neuron denervation, with the estimated interval between onset of frontotemporal dementia and the diagnosis of ALS ranging from less than 2 years to more than 7 years. Indeed, some have proposed a categorization of ALS dependent upon the presence of cognitive and behavioral features: ALS, ALS with cognitive impairment, ALS with behavioral impairment, and ALS with FTD, but this fails to consider patients with both cognitive and behavioral abnormalities. Some studies have reported relatively normal cognition even in patients with late-stage ALS and severe physical disability [225].

Biological Underpinnings

ALS has an incidence of about 1.5–2.5 per 100,000 per year and a prevalence of 6 per 100,000 [226]. Mean age of onset is 55 years and ranges between 40 and 70 years, with sporadic adolescent and young adult onset [222]. At least eight familial variants of ALS (ALS 1–8) have been identified, of which two are inherited in autosomal recessive manner and the remainder in autosomal dominant manner. However, 90% of ALS cases are sporadic and likely reflecting a combined environmental and genetic etiology [227].

Neuropsychological Mechanisms

Attention and Executive Functions

Simple attention functions are typically preserved, but as tasks make greater demands on working memory, deficits are more readily (but not universally) identified in ALS. For example, digit span backward has been shown to be sensitive to ALS, whereas digit span forward is intact [228]. Impairment in selective attention is also demonstrable in ALS [229], but performance on complex tasks such as the Stroop task and Paced Auditory Serial Addition Test (PASAT) may [230] or may not be identified [231–234]. Tasks considered to tap a variety of executive functions are those most consistently demonstrating impairments in ALS, although there is some inconsistency with regards to

impairment on specific tests. For example, a majority of studies has demonstrated ALS patients to be impaired on conceptualization and set-shifting tasks such as card sorting tasks [230, 235–238] but a few studies have failed to reveal such impairments [232, 233, 239]. Patients with cognitive impairments tend to have greater frontotemporal white matter changes than ALS patients without cognitive impairment [239], and patients with dementia have greater frontal [240] and temporal lobe volume reductions than patients without dementia [241]. Similarly, cognitively compromised patients with ALS have greater frontal lobe pathology than cognitively intact patients [242]. These structural correlates of cognitive impairment do not, however, explain the heterogeneity of cognitive impairment in ALS. There is preliminary evidence that genetic factors might play a role, but this remains far from clear. For example, patients with familial ALS with a mutation in the superoxide dismutase 1 (SOD1) gene are less likely to have dementia [243] and perform better on neuropsychological tests than do patient with sporadic ALS or other forms of familial ALS [244]. Some patients with ALS and dementia may have mutations in the progranulin gene, also implicated in some forms of frontotemporal dementia [245]. Location of the onset of disease may also partly explain variability in cognitive dysfunction [246]. For example, patients with pseudobulbar symptoms may also have impairments in planning as revealed by the Tower of Hanoi [247]. Deficits in nonverbal (figural) fluency have also been reported in one study [238].

Motor Skills and Information Processing Speed

Information processing speed may be reduced in some patients if one considers the PASAT as demanding of processing speed [230]. Others have found psychomotor speed to be relatively preserved [248]. Reaction time is reduced in some patients [238].

Language

As noted earlier, deficits in verbal fluency are those cognitive deficits observed with greatest consistency in ALS. Although both letter and semantic fluencies can be affected by ALS, some have argued that letter fluency is more consistently impaired [222, 231]. This is consistent with the presumed frontal dysfunction hypothesis of verbal fluency based on functional neuroimaging findings [249], because letter fluency is more demanding than semantic fluency of self-initiation of systematic word retrieval strategies. The findings that ALS (with dementia) may especially compromise verb as opposed to noun processing [222, 250, 251], and action naming more than object naming [252], are also consistent with frontal dysfunction. Visual confrontation naming in contrast to verbal fluency has been only inconsistently reported to be impacted by ALS [228, 236].

Learning and Memory

Deficits in learning and memory have only been observed inconsistently in ALS, and deficits in immediate recall are more likely to be seen than in delayed recall [224]. Deficits have been observed in prose [234], verbal paired associate learning [237], and picture recall [232], as well as recall of word lists [236]. Although some have suggested that a retrieval deficit underlies recall impairments, one study has found that cuing during encoding but not retrieval facilitates recall in ALS, suggesting that encoding deficits play a role in memory deficits [253]. That is, shallow encoding may be sufficient to sustain recognition but not free recall. There is general agreement that rapid rates of forgetting suggestive of consolidation deficits are not observed in ALS.

Visuoperception

With the exception of one study that found poorer performance by ALS (especially bulbar

onset) patients than healthy controls on the Motor-Free Visual Perception Test [254], studies have found visuoperceptual and spatial skills to be preserved in ALS. Adequate performances have been observed on tests such as the Money Road Map test [237], Facial Recognition [234], Judgment of Line Orientation [236], and position discrimination [231].

Neuropsychiatric Factors

Studies employing structured interviews have found a prevalence of major depression in about 5% of patients with ALS, and hopelessness (in 20–30%) and end of life concerns may be more common in ALS than depression [255]. In addition, many patients have reactive depression symptoms after diagnosis. Frontal syndromes consistent with frontotemporal dementia occur in about 5% of persons with ALS [223]. Apathy appears especially common, while disinhibition is rarer. Sixty-three percent of patients may exhibit apathy, irritability, inflexibility, restlessness, and disinhibition [224, 252], and apathy and disturbances of conduct may be more common among patients with bulbar onset ALS [252]. Pseudobulbar signs such as pathological laughing and crying also occur in ALS.

Conclusions

Amyotrophic lateral sclerosis is considered a motor neuron disease whereas Parkinson's disease, progressive supranuclear palsy, essential tremor, and Huntington's disease are considered movement disorders. Neuropsychologically, despite their different neuropathologies, these disorders have in common a predominant impairment in executive functions and working memory among patients who have cognitive impairment. Indeed, in PSP and PD, executive dysfunction may be one of the earliest features of the diseases. The neuropathological and radiographic correlates of cognitive dysfunction in the disorders are, in most cases, quite well established. By contrast, much work remains to be done to understand the heterogeneity of cognitive impairments among patients with a given disorder and the potential genetic contributions to this heterogeneity. In addition, few studies have addressed cognitive rehabilitation in these disorders, particularly in comparison to other interventions such as occupational and speech therapies. Such cognitive and behavioral interventions will be critical to develop and evaluate in movement and motor neuron disorders so as to enhance patient quality of life.

References

1. Israel Z, Bergman H. Pathophysiology of the basal ganglia and movement disorders: from animal models to human clinical applications. Neurosci Biobehav Rev. 2008;32:367–77.
2. Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology. 1993;12:195–208.
3. Tanner CM, Goldman S, Ross GW. Etiology of Parkinson's disease. In: Jankovic JJ, Tolosa E, editors. Parkinson's disease & movement disorders. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 90–103.
4. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology. 1999;52:1214–20.
5. Seidler A, Hellenbrand W, Robra BP, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology. 1996;46:1275–84.
6. Braak H, Tredici KD, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197–211.
7. Braak H, Rub U, Del Tredici K. Cognitive decline correlates with neuropathological stage in Parkinson's disease. J Neurol Sci. 2006;248:255–8.
8. Mattay VS, Tessitore A, Callicott JH, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol. 2002;51:156–64.
9. Mentis MJ, McIntosh AR, Perrine K, et al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. Am J Psychiatry. 2002;159:746–54.
10. Bohnen NI, Kaufer DI, Hendrickson R, Constantine GM, Mathis CA, Moore RY. Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia. J Neurol Neurosurg Psychiatry. 2007;78:641–3.

11. Dubois B, Danze F, Pillon B, Cusimano G, Lhermitte F, Agid Y. Cholinergic-dependent cognitive deficits in Parkinson's disease. Ann Neurol. 1987;22:26–30.
12. Mayeux R, Stern Y, Cote L, Williams JB. Altered serotonin metabolism in depressed patients with Parkinson's disease. Neurology. 1984;34:642–6.
13. Stern Y, Mayeux R, Cote L. Reaction time and vigilance in Parkinson's disease: possible role of altered norepinephrine metabolism. Arch Neurol. 1984;41:1086–9.
14. Kaufer DL, Tröster AI. Neuropsychology of dementia with Lewy bodies. In: Goldenberg G, Miller BL, editors. Handbook of clinical neurology: neuropsychology and behavioral neurology. 3rd ed. Amsterdam: Elsevier; 2008.
15. Tröster AI. Neuropsychological characteristics of dementia with lewy bodies and Parkinson's disease with dementia: differentiation, early detection, and implications for "mild cognitive impairment" and biomarkers. Neuropsychol Rev. 2008.
16. Irwin DJ, Lee VM, Trojanowski JQ. Parkinson's disease dementia: convergence of α-synuclein, tau, and amyloid-β pathologies. Nat Rev Neurosci. 2013;14:626–36.
17. Kovacs GG. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. Int J Mol Sci. 2016;17:E189.
18. Huber SJ, Shuttleworth EC, Paulson GW, Bellchambers MJ, Clapp LE. Cortical vs subcortical dementia: neuropsychological differences. Arch Neurol. 1986;43:392–4.
19. Sullivan EV, Sagar HJ. Nonverbal recognition and recency discrimination deficits in Parkinson's disease and Alzheimer's disease. Brain. 1989;112:1503–17.
20. Gabrieli JDE, Singh J, Stebbins G, Goetz CG. Reduced working memory span in Parkinson's disease: evidence for the role of a frontostriatal system in working and strategic memory. Neuropsychology. 1996;10:322–32.
21. Dujardin K, Degreef JF, Rogelet P, Defebvre L, Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol. 1999;246:783–8.
22. Woodward TS, Bub DN, Hunter MA. Task switching deficits associated with Parkinson's disease reflect depleted attentional resources. Neuropsychologia. 2002;40:1948–55.
23. Lewis SJ, Cools R, Robbins TW, Dove A, Barker RA, Owen AM. Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. Neuropsychologia. 2003;41:645–54.
24. Kensinger EA, Shearer DK, Locascio JJ, Growdon JH. Working memory in mild Alzheimer's disease and early Parkinson's disease. Neuropsychology. 2003;17:230–9.
25. Rieger M, Gauggel S, Burmeister K. Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. Neuropsychology. 2003;17:272–82.
26. Morris RG, Downes JJ, Sahakian BJ, Evenden JL, Heald A, Robbins TW. Planning and spatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51:757–66.
27. Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-dependent fronto-striatal planning deficits in early Parkinson's disease. Neuropsychology. 1995;9:126–40.
28. Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain. 1988;111:941–59.
29. Bondi MW, Kaszniak AW, Bayles KA, Vance KT. Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. Neuropsychology. 1993;7:89–102.
30. Pillon B, Dubois B, Ploska A, Agid Y. Severity and specificity of cognitive impairment in Alzheimer's, Huntington's, and Parkinson's diseases and progressive supranuclear palsy. Neurology. 1991;41:634–43.
31. Bowen FP, Kamienny RS, Burns MM, Yahr M. Parkinsonism: effects of levodopa treatment on concept formation. Neurology. 1975;25:701–4.
32. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. Brain. 1986;109:845–83.
33. Cronin-Golomb A, Corkin S, Growdon JH. Impaired problem solving in Parkinson's disease: impact of a set-shifting deficit. Neuropsychologia. 1994;32:579–93.
34. Robbins TW, Owen AM, Sahakian BJ. The neuropsychology of basal ganglia disorders: an integrative cognitive and comparative approach. In: Ron MA, David AS, editors. Disorders of brain and mind. Cambridge, UK: Cambridge University Press; 1998. p. 57–83.
35. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia. 2002;40:2257–67.
36. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia. 2003;41:1431–41.

37. Owen AM, Doyon J, Dagher A, Sadikot A, Evans AC. Abnormal basal ganglia outflow in Parkinson's disease identified with PET: implications for higher cortical functions. Brain. 1998;121:949–65.
38. Dagher A, Owen AM, Boecker H, Brooks DJ. Mapping the network for planning: a correlational PET activation study with the Tower of London task. Brain. 1999;122:1973–87.
39. Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain. 2002;125:584–94.
40. Tomer R, Aharon-Peretz J, Tsitrinbaum Z. Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. Neuropsychologia. 2007;45:357–67.
41. Bohnen NI, Kaufer DI, Hendrickson R, et al. Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. J Neurol. 2006;253:242–7.
42. Naville F. Les complications et let sequelles mentales de l'encephalite epidemique. Encephale. 1922;17:369–375, 423–336.
43. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev. 2006;30:1–23.
44. Harrington DL, Haaland KY, Yeo RA, Marder E. Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. J Clin Exp Neuropsychol. 1990;12:323–39.
45. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. J Neurosci. 1989;9:582–7.
46. Levin BE, Llabre MM, Weiner WJ. Cognitive impairments associated with early Parkinson's disease. Neurology. 1989;39:557–61.
47. Lewis FM, Lapointe LL, Murdoch BE. Language impairment in Parkinson's disease. Aphasiology. 1998;12:193–206.
48. Globus M, Mildworf B, Melamed E. Cerebral blood flow and cognitive impairment in Parkinson's disease. Neurology. 1985;35:1135–9.
49. Matison R, Mayeux R, Rosen J, Fahn S. "Tip-of-the-tongue" phenomenon in Parkinson disease. Neurology. 1982;32:567–70.
50. Beatty WW, Monson N. Lexical processing in Parkinson's disease and multiple sclerosis. J Geriatr Psychiatry Neurol. 1989;2:145–52.
51. Zec RF, Landreth ES, Fritz S, et al. A comparison of phonemic, semantic, and alternating word fluency in Parkinson's disease. Arch Clin Neuropsychol. 1999;14:255–64.
52. Piatt AL, Fields JA, Paolo AM, Koller WC, Tröster AI. Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. J Clin Exp Neuropsychol. 1999;21:435–43.
53. Randolph C, Braun AR, Goldberg TE, Chase TN. Semantic fluency in Alzheimer's, Parkinson's, and Huntington's disease: dissociation of storage and retrieval failures. Neuropsychology. 1993;7:82–8.
54. Tröster AI, Fields JA, Testa JA, et al. Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. Neuropsychologia. 1998;36:295–304.
55. Troyer AK, Moscovitch M, Winocur G, Leach L, Freedman M. Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease. J Int Neuropsychol Soc. 1998;4:137–43.
56. Murray LL. Spoken language production in Huntington's and Parkinson's diseases. J Speech Lang Hear Res. 2000;43:1350–66.
57. Cohen H, Bouchard S, Scherzer P, Whitaker H. Language and verbal reasoning in Parkinson's disease. Neuropsychiatry Neuropsychol Behav Neurol. 1994;7:166–75.
58. Ullman MT, Corkin S, Coppola M, et al. A neural dissociation within language: evidence that the mental dictionary is part of declarative memory, and that grammatical rules are processed by the procedural system. J Cogn Neurosci. 1997;9:266–76.
59. Grossman M, Zurif E, Lee C, et al. Information processing speed and sentence comprehension in Parkinson's disease. Neuropsychology. 2002;16:174–81.
60. Grossman M, Cooke A, DeVita C, et al. Grammatical and resource components of sentence processing in Parkinson's disease: an fMRI study. Neurology. 2003;60:775–81.
61. Lee C, Grossman M, Morris J, Stern MB, Hurtig HI. Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. Brain Lang. 2003;85:347–56.
62. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127:550–60.
63. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005;65:1239–45.
64. Faglioni P, Saetti MC, Botti C. Verbal learning strategies in Parkinson's disease. Neuropsychology. 2000;14:456–70.
65. Beatty WW, Staton RD, Weir WS, Monson N, Whitaker HA. Cognitive disturbances in Parkinson's disease. J Geriatr Psychiatry Neurol. 1989;2:22–33.
66. Whittington CJ, Podd J, Kan MM. Recognition memory impairment in Parkinson's disease: power and meta-analyses. Neuropsychology. 2000;14:233–46.
67. Tierney MC, Nores A, Snow WG, Fisher RH, Zorzitto ML, Reid DW. Use of the Rey Auditory

Verbal Learning Test in differentiating normal aging from Alzheimer's and Parkinson's dementia. Psychol Assess. 1994;6:129–34.
68. Buytenhuijs EL, Berger HJ, Van Spaendonck KP, Horstink MW, Borm GF, Cools AR. Memory and learning strategies in patients with Parkinson's disease. Neuropsychologia. 1994;32:335–42.
69. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for impaired encoding and retrieval memory profiles in Parkinson disease. Cogn Behav Neurol. 2004;17:195–200.
70. Berger HJ, van Es NJ, van Spaendonck KP, et al. Relationship between memory strategies and motor symptoms in Parkinson's disease. J Clin Exp Neuropsychol. 1999;21:677–84.
71. Stefanova ED, Kostic VS, Ziropadja LJ, Ocic GG, Markovic M. Declarative memory in early Parkinson's disease: serial position learning effects. J Clin Exp Neuropsychol. 2001;23:581–91.
72. Taylor AE, Saint-Cyr JA. The neuropsychology of Parkinson's disease. Brain Cogn. 1995;28:281–96.
73. Massman PJ, Delis DC, Butters N, Levin BE, Salmon DP. Are all subcortical dementias alike? verbal learning and memory in Parkinson's and Huntington's disease patients. J Clin Exp Neuropsychol. 1990;12:729–44.
74. Rouleau I, Imbault H, Laframboise M, Bedard MA. Pattern of intrusions in verbal recall: comparison of Alzheimer's disease, Parkinson's disease, and frontal lobe dementia. Brain Cogn. 2001;46:244–9.
75. Fama R, Sullivan EV, Shear PK, et al. Extent, pattern, and correlates of remote memory impairment in Alzheimer's disease and Parkinson's disease. Neuropsychology. 2000;14:265–76.
76. Leplow B, Dierks C, Herrmann P, Pieper N, Annecke R, Ulm G. Remote memory in Parkinson's disease and senile dementia. Neuropsychologia. 1997;35:547–57.
77. Sagar HJ, Cohen NJ, Sullivan EV, Corkin S, Growdon JH. Remote memory function in Alzheimer's disease and Parkinson's disease. Brain. 1988;111:185–206.
78. Venneri A, Nichelli P, Modonesi G, Molinari MA, Russo R, Sardini C. Impairment in dating and retrieving remote events in patients with early Parkinson's disease. J Neurol Neurosurg Psychiatry. 1997;62:410–3.
79. Pillon B, Deweer B, Vidailhet M, Bonnet AM, Hahn-Barma V, Dubois B. Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on 'strategic' processes? Neuropsychologia. 1998;36:1–9.
80. Hsieh S, Lee C-Y. Source memory in Parkinson's disease. Percept Mot Skills. 1999;89:355–67.
81. Ivory S-J, Knight RG, Longmore BE, Caradoc-Davies T. Verbal memory in non-demented patients with idiopathic Parkinson's disease. Neuropsychologia. 1999;37:817–28.
82. Fischer P, Kendler P, Goldenberg G. Recency-primacy recognition in Parkinson's disease. J Neural Transm. 1990;2:71–7.
83. Cooper JA, Sagar HJ. Incidental and intentional recall in Parkinson's disease: an account based on diminished attentional resources. J Clin Exp Neuropsychol. 1993;15:713–31.
84. West R, Ergis AM, Winocur G, Saint-Cyr J. The contribution of impaired working memory monitoring to performance of the self-ordered pointing task in normal aging and Parkinson's disease. Neuropsychology. 1998;12:546–54.
85. Kliegel M, Phillips LH, Lemke U, Kopp UA. Planning and realisation of complex intentions in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005;76:1501–5.
86. Copland D. The basal ganglia and semantic engagement: potential insights from semantic priming in individuals with subcortical vascular lesions, Parkinson's disease, and cortical lesions. J Int Neuropsychol Soc. 2003;9:1041–52.
87. Angwin AJ, Chenery HJ, Copland DA, Murdoch BE, Silburn PA. The speed of lexical activation is altered in Parkinson's disease. J Clin Exp Neuropsychol. 2007;29:73–85.
88. Castner JE, Copland DA, Silburn PA, Coyne TJ, Sinclair F, Chenery HJ. Lexical-semantic inhibitory mechanisms in Parkinson's disease as a function of subthalamic stimulation. Neuropsychologia. 2007;45:3167–77.
89. Lee AC, Harris JP, Calvert JE. Impairments of mental rotation in Parkinson's disease. Neuropsychologia. 1998;36:109–14.
90. Levin BE, Llabre MM, Reisman S, et al. Visuospatial impairment in Parkinson's disease. Neurology. 1991;41:365–9.
91. Bodis-Wollner I. Neuropsychological and perceptual defects in Parkinson's disease. Park Relat Disord. 2003;9:S83–9.
92. Cousins R, Hanley JR, Davies AD, Turnbull CJ, Playfer JR. Understanding memory for faces in Parkinson's disease: the role of configural processing. Neuropsychologia. 2000;38:837–47.
93. Marras C, Tröster AI, Kulisevsky J, Stebbins GT. The tools of the trade: a state of the art "how to assess cognition" in the patient with Parkinson's disease. Mov Disord. 2014;29:584–96.
94. Kulisevsky J, Fernandez de Bobadilla R, Pagonabarraga J, Martinez-Horta S, Campolongo A, Garcia-Sanchez C, Pascual-Sedano B, Ribosa-Nogué R, Villa-Bonoma C. Measuring functional impact of cognitive impairment: validation of the Parkinson's disease cognitive functional rating scale. Park Relat Disord. 2013;19:812–7.
95. Kulisevsky J, Pagonabarraga J. Neurocognitive screening and assessment in Parkinsonism. In: Tröster AI, editor. Clinical neuropsychology and cognitive neurology of Parkinson's disease and

other movement disorders. Oxford: Oxford University Press; 2015. p. 27–50.
96. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, etiology, and treatment of depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2001;13:187–96.
97. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Park Relat Disord. 2002;8:193–7.
98. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16:178–83.
99. Myslobodsky M, Lalonde FM, Hicks L. Are patients with Parkinson's disease suicidal? J Geriatr Psychiatry Neurol. 2001;14:120–4.
100. Weintraub D, Morales KH, Moberg PJ, et al. Antidepressant studies in Parkinson's disease: a review and meta-analysis. Mov Disord. 2005;20:1161–9.
101. Barone P, Scarzella L, Marconi R, et al. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: A national multicenter parallel-group randomized study. J Neurol. 2006;253:601–7.
102. Menza M, Dobkin RD, Marin H, et al. The impact of treatment of depression on quality of life, disability and relapse in patients with Parkinson's disease. Mov Disord. 2009.
103. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009;72:886–92.
104. Dobkin RD, Allen LA, Menza M. Cognitive-behavioral therapy for depression in Parkinson's disease: a pilot study. Mov Disord. 2007;22:946–52.
105. Schiffer RB, Kurlan R, Rubin A, Boer S. Evidence for atypical depression in Parkinson's disease. Am J Psychiatry. 1988;145:1020–2.
106. Walsh K, Bennett G. Parkinson's disease and anxiety. Postgrad Med J. 2001;77:89–93.
107. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Mov Disord. 2009.
108. Stein MB, Heuser IJ, Juncos JL, Uhde TW. Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry. 1990;147:217–20.
109. Vazquez A, Jimenez-Jimenez FJ, Garcia-Ruiz P, Garcia-Urra D. "Panic attacks" in Parkinson's disease: a long-term complication of levodopa therapy. Acta Neurologica Scandanavica. 1993;87:14–18.
110. Alegret M, Junque C, Valldeoriola F, Vendrell P, Marti MJ, Tolosa E. Obsessive-compulsive symptoms in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001;70:394–6.
111. Weintraub D. Dopamine and impulse control disorders in Parkinson's disease. Ann Neurol. 2008;64:S93–100.
112. Leentjens AF, Dujardin K, Pontone GM, et al. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Mov Disord. 2014;29:1035–43.
113. Weintraub D, Mamikonyan E, Papay K, et al. Questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale. Mov Disorders. 2012;27:242–7.
114. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol. 1964;10:333–359.
115. Richardson JC, Steele J, Olszewski J. Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia: a clinical report on eight cases of "heterogeneous system degeneration". Trans Am Neurol Assoc. 1963;88:25–29.
116. Litvan I, Agid Y, Jankovic J, et al. Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). Neurology. 1996;46:922–30.
117. Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord. 2017;32:853–64.
118. Nath U, Ben-Shlomo Y, Thomson RG, et al. The prevalence of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in the UK. Brain. 2001;124:1438–49.
119. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. Neurology. 1997;49:1284–8.
120. Burn DJ, Lees AJ. Progressive supranuclear palsy: where are we now? Lancet Neurol. 2002;1:359–69.
121. Dickson DW, Rademakers R, Hutton ML. Progressive supranuclear palsy: pathology and genetics. Brain Pathol. 2007;17:74–82.
122. Warren NM, Burn DJ. Progressive supranuclear palsy. Pract Neurol. 2007;7:16–23.
123. Stezin A, Lenka A, Jhunjhunwala K, Saini J, Pal PH. Advanced structural neuroimaging in progressive supranuclear palsy: where do we stand? Park Relat Disord. 2017;36:19–32.
124. Kaat LD, Boon AJ, Kamphorst W, Ravid R, Duivenvoorden HJ, van Swieten JC. Frontal presentation in progressive supranuclear palsy. Neurology. 2007;69:723–9.
125. Tröster AI, Fields JA. Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, and related disorders of the frontostriatal system. In: Morgan JE, Ricker JH, editors. Textbook of clinical

neuropsychology. New York: Psychology Press; 2008. p. 536–77.
126. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005;128:1247–58.
127. Albert ML, Feldman RG, Willis AL. The 'subcortical dementia' of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1974;37:121–30.
128. Lee W, Williams DR, Storey E. Cognitive testing in the diagnosis of parkinsonian disorders: A critical appraisal of the literature. Mov Disord. 2012;27:1243–54.
129. Tröster AI, Garrett R. Parkinson's disease and other movement disorders. In: Morgan JE, Ricker JH, editors. Textbook of neuropsychology, 2nd ed. Suffolk: Taylor & Francis Group, in press.
130. Rafal RD, Posner MI, Friedman JH, Inhoff AW, Bernstein E. Orienting of visual attention in progressive supranuclear palsy. Brain. 1988;111(Pt 2):267–80.
131. Monza D, Soliveri P, Radice D, et al. Cognitive dysfunction and impaired organization of complex motility in degenerative parkinsonian syndromes. Arch Neurol. 1998;55:372–8.
132. Millar D, Griffiths P, Zermansky AJ, Burn DJ. Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. Mov Disord. 2006;21:199–207.
133. Soliveri P, Monza D, Paridi D, et al. Neuropsychological follow up in patients with Parkinson's disease, striatonigral degeneration-type multisystem atrophy, and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 2000;69:313–8.
134. Dubois B, Slachevsky A, Pillon B, Beato R, Villalponda JM, Litvan I. "Applause sign" helps to discriminate PSP from FTD and PD. Neurology. 2005;64:2132–3.
135. Grafman J, Litvan I, Stark M. Neuropsychological features of progressive supranuclear palsy. Brain Cogn. 1995;28:311–20.
136. Soliveri P, Piacentini S, Girotti F. Limb apraxia in corticobasal degeneration and progressive supranuclear palsy. Neurology. 2005;64:448–53.
137. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain. 2008;131:1362–72.
138. Cordato NJ, Halliday GM, Caine D, Morris JG. Comparison of motor, cognitive, and behavioral features in progressive supranuclear palsy and Parkinson's disease. Mov Disord. 2006;21:632–8.
139. Rosser A, Hodges JR. Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1994;57:1389–94.
140. Cotelli M, Borroni B, Manenti R, et al. Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. Neuropsychology. 2006;20:558–65.
141. Podoll K, Schwarz M, Noth J. Language functions in progressive supranuclear palsy. Brain. 1991;114 (Pt 3):1457–72.
142. Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2003;74:1215–20.
143. Pillon B, Gouider-Khouja N, Deweer B, et al. Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry. 1995;58:174–9.
144. Bak TH, Caine D, Hearn VC, Hodges JR. Visuospatial functions in atypical parkinsonian syndromes. J Neurol Neurosurg Psychiatry. 2006;77:454–6.
145. Joel D. Open interconnected model of basal ganglia-thalamocortical circuitry and its relevance to the clinical syndrome of Huntington's disease. Mov Disord. 2001;16:407–23.
146. Litvan I, Mega MS, Cummings JL, Fairbanks L. Neuropsychiatric aspects of progressive supranuclear palsy. Neurology. 1996;47:1184–9.
147. Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2001;13:42–9.
148. O'Keeffe FM, Murray B, Coen RF, et al. Loss of insight in frontotemporal dementia, corticobasal degeneration and progressive supranuclear palsy. Brain. 2007;130:753–64.
149. Benito-Leon J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol. 2006;2:666–78; quiz 662 p following 691.
150. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? estimates of the prevalence of essential tremor throughout the world. Mov Disord. 1998;13:5–10.
151. Louis ED, Vonsattel JP. The emerging neuropathology of essential tremor. Mov Disord. 2008;23:174–82.
152. Pagan FL, Butman JA, Dambrosia JM, Hallett M. Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology. 2003;60:1344–7.
153. Wills AJ, Jenkins IH, Thompson PD, Findley LJ, Brooks DJ. A positron emission tomography study of cerebral activation associated with essential and writing tremor. Arch Neurol. 1995;52:299–305.

154. Martinelli P, Rizzo G, Manners D, et al. Diffusion-weighted imaging study of patients with essential tremor. Mov Disord. 2007;22:1182–5.
155. Bhalsing KS, et al. White matter correlates of cognitive impairment in essential tremor. Am J Neuroradiol. 2015;36:448–53.
156. Rajput A, Robinson CA, Rajput AH. Essential tremor course and disability: a clinicopathologic study of 20 cases. Neurology. 2004;62:932–6.
157. Louis ED, Barnes L, Albert SM, et al. Correlates of functional disability in essential tremor. Mov Disord. 2001;16:914–20.
158. Busenbark KL, Nash J, Nash S, Hubble JP, Koller WC. Is essential tremor benign? Neurology. 1991;41:1982–3.
159. Lorenz D, Schwieger D, Moises H, Deuschl G. Quality of life and personality in essential tremor patients. Mov Disord. 2006;21:1114–8.
160. Troster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. Park Relat Disord. 2005;11:367–73.
161. Woods SP, Scott JC, Fields JA, Poquette A, Troster AI. Executive dysfunction and neuropsychiatric symptoms predict lower health status in essential tremor. Cogn Behav Neurol. 2008;21: 28–33.
162. Bermejo-Pareja F, Louis ED, Benito-Leon J. Risk of incident dementia in essential tremor: a population-based study. Mov Disord. 2007;22:1573–80.
163. Benito-Leon J, Louis ED, Bermejo-Pareja F. Population-based case-control study of cognitive function in essential tremor. Neurology. 2006;66:69–74.
164. Higginson CI, Wheelock VL, Levine D, King DS, Pappas CT, Sigvardt KA. Cognitive deficits in essential tremor consistent with frontosubcortical dysfunction. J Clin Exp Neuropsychol. 2008:1–6.
165. Tröster AI, Woods SP, Fields JA, et al. Neuropsychological deficits in essential tremor: an expression of cerebello-thalamo-cortical pathophysiology? Eur J Neurol. 2002;9:143–51.
166. Duane DD, Vermilion KJ. Cognitive deficits in patients with essential tremor. Neurology. 2002;58:1706.
167. Gasparini M, Bonifati V, Fabrizio E, et al. Frontal lobe dysfunction in essential tremor: a preliminary study. J Neurol. 2001;248:399–402.
168. Sahin HA, Terzi M, Ucak S, Yapici O, Basoglu T, Onar M. Frontal functions in young patients with essential tremor: a case comparison study. J Neuropsychiatry Clin Neurosci. 2006;18:64–72.
169. Heroux ME, Parisi SL, Larocerie-Salgado J, Norman KE. Upper-extremity disability in essential tremor. Arch Phys Med Rehabil. 2006;87:661–70.
170. Putzke JD, Uitti RJ, Obwegeser AA, Wszolek ZK, Wharen RE. Bilateral thalamic deep brain stimulation: midline tremor control. J Neurol Neurosurg Psychiatry. 2005;76:684–90.
171. Lacritz LH, Dewey R Jr, Giller C, Cullum CM. Cognitive functioning in individuals with "benign" essential tremor. J Int Neuropsychol Soc. 2002;8:125–9.
172. Lombardi WJ, Woolston DJ, Roberts JW, Gross RE. Cognitive deficits in patients with essential tremor. Neurology. 2001;57:785–90.
173. Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. Brain. 2000;123(Pt 5):1051–61.
174. Baillieux H, De Smet HJ, Paquier PF, De Deyn PP, Marien P. Cerebellar neurocognition: insights into the bottom of the brain. Clin Neurol Neurosurg. 2008;110:763–73.
175. Lawrence AD, Hodges JR, Rosser AE, et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. Brain. 1998;121(Pt 7):1329–41.
176. Schneier FR, Barnes LF, Albert SM, Louis ED. Characteristics of social phobia among persons with essential tremor. J Clin Psychiatry. 2001;62: 367–72.
177. Miller KM, Okun MS, Fernandez HF, Jacobson CEt, Rodriguez RL, Bowers D. Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor. Mov Disord. 2007;22:666–672.
178. Walker FO. Huntington's disease. Lancet. 2007;369:218–28.
179. Kieburtz K, MacDonald M, Shih C, et al. Trinucleotide repeat length and progression of illness in Huntington's disease. J Med Genet. 1994;31:872–4.
180. Kokmen E, Ozekmekci FS, Beard CM, O'Brien PC, Kurland LT. Incidence and prevalence of Huntington's disease in Olmsted County, Minnesota (1950 through 1989). Arch Neurol. 1994;51:696–8.
181. Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet. 1993;4:398–403.
182. Snowden JS. The neuropsychology of huntington's disease. Arch Neuropsychol, in press.
183. Foroud T, Gray J, Ivashina J, Conneally PM. Differences in duration of Huntington's disease based on age at onset. J Neurol Neurosurg Psychiatry. 1999;66:52–6.
184. Ferrante RJ, Kowall NW, Richardson EP Jr. Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28 k immunocytochemistry. J Neurosci. 1991;11:3877–87.
185. Ruocco HH, Bonilha L, Li LM, Lopes-Cendes I, Cendes F. Longitudinal analysis of regional grey matter loss in Huntington disease: effects of the length of the expanded CAG repeat. J Neurol Neurosurg Psychiatry. 2008;79:130–5.

186. Hasselbalch SG, Oberg G, Sorensen SA, et al. Reduced regional cerebral blood flow in Huntington's disease studied by SPECT. J Neurol Neurosurg Psychiatry. 1992;55:1018–23.
187. Georgiou-Karistianis N, Sritharan A, Farrow M, et al. Increased cortical recruitment in Huntington's disease using a Simon task. Neuropsychologia. 2007;45:1791–800.
188. Cummings JL, Benson DF. Psychological dysfunction accompanying subcortical dementias. Annu Rev Med. 1988;39:53–61.
189. Stout JC, Weaver M, Solomon AC, et al. Are cognitive changes progressive in prediagnostic HD? Cogn Behav Neurol. 2007;20:212–8.
190. Ho AK, Sahakian BJ, Brown RG, et al. Profile of cognitive progression in early Huntington's disease. Neurology. 2003;61:1702–6.
191. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation—a longitudinal follow-up study. J Neurol. 2004;251:935–42.
192. Calder AJ, Keane J, Young AW, et al. The relation between anger and different forms of disgust: implications for emotion recognition impairments in Huntington's disease. Neuropsychologia. 2010;48:2719–29.
193. Sprengelmeyer R, Lange H, Homberg V. The pattern of attentional deficits in Huntington's disease. Brain. 1995;118(Pt 1):145–52.
194. Hanes KR, Andrewes DG, Pantelis C. Cognitive flexibility and complex integration in Parkinson's disease, Huntington's disease, and schizophrenia. J Int Neuropsychol Soc. 1995;1:545–53.
195. Watkins LH, Rogers RD, Lawrence AD, Sahakian BJ, Rosser AE, Robbins TW. Impaired planning but intact decision making in early Huntington's disease: implications for specific fronto-striatal pathology. Neuropsychologia. 2000;38:1112–25.
196. Zakzanis KK. The subcortical dementia of Huntington's disease. J Clin Exp Neuropsychol. 1998;20:565–78.
197. Peinemann A, Schuller S, Pohl C, Jahn T, Weindl A, Kassubek J. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci. 2005;239:11–9.
198. Stout JC, Rodawalt WC, Siemers ER. Risky decision making in Huntington's disease. J Int Neuropsychol Soc. 2001;7:92–101.
199. Hinton SC, Paulsen JS, Hoffmann RG, Reynolds NC, Zimbelman JL, Rao SM. Motor timing variability increases in preclinical Huntington's disease patients as estimated onset of motor symptoms approaches. J Int Neuropsychol Soc. 2007;13:539–43.
200. Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. J Clin Exp Neuropsychol. 2002;24:133–45.
201. Murray LL, Lenz LP. Productive syntax abilities in Huntington's and Parkinson's diseases. Brain Cogn. 2001;46:213–9.
202. Hodges JR, Salmon DP, Butters N. The nature of the naming deficit in Alzheimer's and Huntington's disease. Brain. 1991;114:1547–58.
203. Henry JD, Crawford JR, Phillips LH. A meta-analytic review of verbal fluency deficits in Huntington's disease. Neuropsychology. 2005;19:243–52.
204. Rich JB, Troyer AK, Bylsma FW, Brandt J. Longitudinal analysis of phonemic clustering and switching during word-list generation in Huntington's disease. Neuropsychology. 1999;13:525–31.
205. Montoya A, Pelletier M, Menear M, Duplessis E, Richer F, Lepage M. Episodic memory impairment in Huntington's disease: a meta-analysis. Neuropsychologia. 2006;44:1984–94.
206. Fine EM, Delis DC, Wetter SR, et al. Identifying the "source" of recognition memory deficits in patients with Huntington's disease or Alzheimer's disease: evidence from the CVLT-II. J Clin Exp Neuropsychol. 2008;30:463–70.
207. Delis DC, Wetter SR, Jacobson MW, et al. Recall discriminability: utility of a new CVLT-II measure in the differential diagnosis of dementia. J Int Neuropsychol Soc. 2005;11:708–15.
208. Beatty WW, Salmon DP, Butters N, Heindel WC, Granholm EL. Retrograde amnesia in patients with Alzheimer's disease or Huntington's disease. Neurobiol Aging. 1988;9:181–6.
209. Brandt J. Huntington's disease. In: Grant I, Adams KM, editors. Neuropsychological assessment of neuropsychiatric and neuromedical disorders. 3rd ed. New York: Oxford University Press; 2009. p. 223–40.
210. Blekher T, Johnson SA, Marshall J, et al. Saccades in presymptomatic and early stages of Huntington disease. Neurology. 2006;67:394–9.
211. Bylsma FW, Brandt J, Strauss ME. Personal and extrapersonal orientation in Huntington's disease patients and those at risk. Cortex. 1992;28:113–22.
212. Lineweaver TT, Salmon DP, Bondi MW, Corey-Bloom J. Differential effects of Alzheimer's disease and Huntington's disease on the performance of mental rotation. J Int Neuropsychol Soc. 2005;11:30–9.
213. Couette M, Bachoud-Levi AC, Brugieres P, Sieroff E, Bartolomeo P. Orienting of spatial attention in Huntington's Disease. Neuropsychologia. 2008;46:1391–400.
214. Nehl C, Paulsen JS. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. J Nerv Ment Dis. 2004;192:72–4.

215. Paulsen JS, Mikos A. Huntington's disease. In: Morgan JE, Ricker JH, editors. Textbook of clinical neuropsychology. New York: Psychology Press; 2008. p. 616–35.
216. Paulsen JS, Nehl C, Hoth KF, et al. Depression and stages of Huntington's disease. J Neuropsychiatry Clin Neurosci. 2005;17:496–502.
217. Farrer LA. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. Am J Med Genet. 1986;24:305–11.
218. Almqvist EW, Bloch M, Brinkman R, Craufurd D, Hayden MR. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. Am J Hum Genet. 1999;64:1293–304.
219. van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007;19:441–8.
220. Trinkler I, Devignevielle S, Achaibou A, et al. Embodied emotion impairment in huntington's disease. Cortex. 2017;92:44–56.
221. Eddy CM, Rickards HE. Interaction without intent: the shape of the social world in Huntington's disease. Soc Cogn Affect Neurosci. 2015;10:1228–35.
222. Woolley SC, Rush BK. Considerations for clinical neuropsychological evaluation in amyotrophic lateral sclerosis. Arch Clin Neuropsychol, in press.
223. Woolley SC, Katz JS. Cognitive and behavioral impairment in amyotrophic lateral sclerosis. Phys Med Rehabil Clin N Am. 2008;19:607–17, xi.
224. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol. 2007;6:994–1003.
225. Lakerveld J, Kotchoubey B, Kubler A. Cognitive function in patients with late stage amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2008;79:25–9.
226. Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008;79:6–11.
227. Hardiman O, Greenway M. The complex genetics of amyotrophic lateral sclerosis. Lancet Neurol. 2007;6:291–2.
228. Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an underrecognised association? J Neurol Neurosurg Psychiatry. 1998;65:881–9.
229. Neary D, Snowden JS, Mann DM. Cognitive change in motor neurone disease/amyotrophic lateral sclerosis (MND/ALS). J Neurol Sci. 2000;180:15–20.
230. Moretti R, Torre P, Antonello RM, Carraro N, Cazzato G, Bava A. Complex cognitive disruption in motor neuron disease. Dement Geriatr Cogn Disord. 2002;14:141–50.
231. Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS: a prospective study. Neurology. 2005;64:1222–6.
232. Kew JJ, Goldstein LH, Leigh PN, et al. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis: a neuropsychological and positron emission tomography study. Brain. 1993;116(Pt 6):1399–423.
233. Ludolph AC, Langen KJ, Regard M, et al. Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychologic and positron emission tomography study. Acta Neurol Scand. 1992;85:81–9.
234. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. Neurology. 2005;65:586–90.
235. David AS, Gillham RA. Neuropsychological study of motor neuron disease. Psychosomatics. 1986;27:441–5.
236. Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 1996;61:450–5.
237. Neary D, Snowden JS, Mann DM, Northen B, Goulding PJ, Macdermott N. Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry. 1990;53:23–32.
238. Schreiber H, Gaigalat T, Wiedemuth-Catrinescu U, et al. Cognitive function in bulbar- and spinal-onset amyotrophic lateral sclerosis: a longitudinal study in 52 patients. J Neurol. 2005;252:772–81.
239. Abrahams S, Goldstein LH, Suckling J, et al. Frontotemporal white matter changes in amyotrophic lateral sclerosis. J Neurol. 2005;252:321–31.
240. Chang JL, Lomen-Hoerth C, Murphy J, et al. A voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD. Neurology. 2005;65:75–80.
241. Murphy JM, Henry RG, Langmore S, Kramer JH, Miller BL, Lomen-Hoerth C. Continuum of frontal lobe impairment in amyotrophic lateral sclerosis. Arch Neurol. 2007;64:530–4.
242. Abe K, Fujimura H, Toyooka K, Sakoda S, Yorifuji S, Yanagihara T. Cognitive function in amyotrophic lateral sclerosis. J Neurol Sci. 1997;148:95–100.
243. Mase G, Ros S, Gemma A, et al. ALS with variable phenotypes in a six-generation family caused by leu144phe mutation in the SOD1 gene. J Neurol Sci. 2001;191:11–8.
244. Wicks P, Abrahams S, Papps B, et al. SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. J Neurol. 2009;256:234–41.
245. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative

frontotemporal dementia linked to chromosome 17. Nature. 2006;442:916–9.
246. Raaphorst J, De Visser M, Linssen WH, De Haan RJ, Schmand B. The cognitive profile of amyotrophic lateral sclerosis: a meta-analysis. Amyotroph Lateral Scler. 2009:1–13.
247. Abrahams S, Goldstein LH, Al-Chalabi A, et al. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 1997;62:464–72.
248. Rippon GA, Scarmeas N, Gordon PH, et al. An observational study of cognitive impairment in amyotrophic lateral sclerosis. Arch Neurol. 2006;63:345–52.
249. Abrahams S, Goldstein LH, Simmons A, et al. Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. Brain. 2004;127:1507–17.
250. Bak TH, Hodges JR. Motor neurone disease, dementia and aphasia: coincidence, co-occurrence or continuum? J Neurol. 2001;248:260–70.
251. Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges JR. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. Brain. 2001;124:103–20.
252. Grossman AB, Woolley-Levine S, Bradley WG, Miller RG. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2007;8:56–61.
253. Mantovan MC, Baggio L, Dalla Barba G, et al. Memory deficits and retrieval processes in ALS. Eur J Neurol. 2003;10:221–7.
254. Strong MJ, Grace GM, Orange JB, Leeper HA, Menon RS, Aere C. A prospective study of cognitive impairment in ALS. Neurology. 1999;53:1665–70.
255. Averill AJ, Kasarskis EJ, Segerstrom SC. Psychological health in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2007;8:243–54.

Part V
Immune-Mediated Disease

Chapter 20

Cognitive and Affective Neuroscience Theories of Cognition and Depression in Multiple Sclerosis and Guillain–Barré Syndrome

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The most commonly seen and studied demyelinating disorder in medical neuropsychology is multiple sclerosis (MS). As such, most of this chapter will focus on MS. Because Guillain–Barré syndrome is the most common demyelinating disorder of the peripheral nervous system, the limited neuropsychological data on this disorder will be reviewed in a brief section at the end.

Clinical neuropsychologists in medical settings play a central role in the assessment and treatment of MS patients. Prior to the advent of sensitive neuropsychological tests, cognitive difficulties were thought to affect less than 5% of patients [1]. Prevalence estimates with use of neuropsychological tests now range from 40 to 60% [2]. Because cognitive deficits in MS are associated with real-world functioning [3], neuropsychologists can first evaluate the extent to which tested difficulties displayed by patients may map onto real-world problems, then help patients make modifications to daily routines that allow them to circumvent cognitive difficulties they display. Neuropsychologists can also provide vital help toward identifying and treating depression and other psychological disturbances that are common, but often overlooked, in MS patients.

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Multiple Sclerosis

Pathophysiology, Clinical Presentation, and Course

MS is a demyelinating disease of the central nervous system thought to be caused by an autoimmune process, a slow-acting virus, or a delayed reaction to a common virus. A number of observations suggest that MS may be a series of syndromes, rather than a uniform disorder with a singular etiology and disease process [4]. Various pathophysiological processes may be involved in disease progression and there is considerable variability among patients in structural and immunologic disease features.

Demyelinated plaques are the defining pathological feature of the disease. Such plaques result in lesions characterized by loss of myelin, relative preservation of axons, and the presence of astrocytic scars. Multiple discrete plaques that are found at demyelinated sites are formed, in part, by proliferating astrocytes. Myelin sheaths within plaques are either destroyed or swollen and fragmented. Remission of symptoms is attributed to a reduction of inflammatory edema and partial remyelination. As the disease progresses, however, irreversible axonal injury may occur.

The size of plaques varies from about 1.0 mm to several centimeters. Resulting symptoms typically reflect functions associated with affected areas. Plaques can occur in the brain or spinal

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cord. A majority of plaques (about 75%) are observed in the white matter, but some occur in gray matter and in the juncture between gray and white matter. Some remyelination occurs with acute MS plaques.

MS is likely acquired before puberty, but actual disease onset occurs in most (about two-thirds) patients between ages 20 and 40. Late onset after age 40 is commonly characterized by quicker progression and greater morbidity. Average life expectancy following onset is estimated at 30+ years, but variability is great.

An environmental contribution to MS is suggested by generally higher prevalence in temperate zones away from the equator with decreasing prevalence near the equatorial tropics. The highest prevalence rates (greater than 30 in 100,000) are in northern Europe, southern Australia, and the middle latitude zones of North America. There is a 30–40% concordance in identical twins, but only 1–13% in fraternal, suggesting a genetic contribution, as well. Risk in first-degree offspring of MS patients is only 5% but is 20–40 times greater than in the general population [4].

Common symptoms include muscle weakness, urinary disturbance, and visual anomalies like diplopia, loss of visual acuity, blurry vision, and visual field defects. Fatigue, problems with balance, and paresthesias (usually numbness and tingling in the limbs, trunk, or face) are also common. The most common symptoms at MS onset are muscle weakness, paresthesias, visual disturbances, and gait/balance problems. About 50% of patients require assistance walking within 15 years of disease onset [4].

The diagnosis of MS is clinical and laboratory based. The latest criteria involve various combinations of clinical- and laboratory-based evidence [5, 6], including MRI. Patients can get an MS diagnosis from either discrete episodes or insidious progression. Attacks, relapses, or exacerbations that imply new disease activity are common. Separation of symptoms in time should be evident, as reflected by the onset of new MRI lesions or increased level of disability over the course of at least 1 year.

Several course types have been identified [7]:

(1) Relapsing–remitting (RR) – Most common type and characterized by clearly defined disease relapses. Recovery can be full or with sequelae and residual deficit. About 80% of MS patients have this type or secondary-progressive type. RR and secondary-progressive types are more common in females than males by about a 2:1 ratio.
(2) Secondary-progressive (SP) – This is the next most common course type and is first characterized by a RR course then progression. Relapses and remissions may or may not occur. Approximately 70% of RR patients convert to SP.
(3) Primary-progressive (PP) – Next most common type. There is unremitting disease progression from onset for most patients, but occasional stabilization and even improvement in functioning for others. No clear relapses. PP has equivalent prevalence in males and females.
(4) Progressive-relapsing – Least common type. Disease progression occurs from onset and acute relapses also occur from which patients may or may not fully recover. The term "chronic-progressive" formerly encompassed all progressive types.

Several factors predict poor outcome including frequent relapses within the first 2 years of onset, early motor and cerebellar findings, and male sex. Predictors of better outcome include female sex, predominantly sensory symptoms, and optic neuritis.

Cognitive Neuroscience Theories

In this section we will describehow cognitive and affective neuroscience theory has clarified, is currently clarifying, and can in the future clarify the nature of cognitive problems and the source of affective disturbances in MS. In this section, we will illustrate the following: (1) How

neurocognitive theory has helped to clarify the nature of cognitive problems seen in MS, particularly in the realm of memory. (2) How cognitive neuroscience theory is helping to clarify the brain's adaptive potential following injury due to MS. and (3) How cognitive and affective neuroscience theory may inform understanding of affective disturbances in MS.

The nature of memory deficits. The nature of the cognitive difficulties commonly experienced by individuals with MS is not well understood. It is known that 40–60% of MS patients have cognitive deficits, and around 80% of individuals with MS have at least mild cognitive deficits, e.g., [8]. It is also known that the most commonly affected domains in MS are memory, speeded information processing, executive functioning, attention, and visuospatial skills. However, the exact nature of cognitive problems in MS is debated. Memory is the most widely researched aspect of cognitive dysfunction [9]. Whether individuals with MS experience memory impairment due to difficulties in processing information and thus encoding/learning information or whether the primary deficit lies in retrieval has been debated. Many initial studies on memory in MS revealed that MS participants performed more poorly on tests of free recall compared to recognition. Such findings were interpreted as suggesting that retrieval deficits were the primary memory difficulty in MS [10]. However, DeLuca and colleagues have performed and replicated research [9, 11] providing evidence against a primary retrieval deficit in MS. Noting that past studies had not controlled for the amount of initial information acquired during learning, they allowed patients to train up to criterion of recalling all words on a list learning task. When controlling for the initial amount of information learned, MS participants showed no deficits on recognition or recall, though they required significantly more trials to reach criterion. These authors suggested that their results reflected a memory deficit in the acquisition of information, rather than retrieval. A meta-analysis of the MS memory literature [12] also failed to support a retrieval-based memory deficit, but this review mostly involved clinically based tasks that were not necessarily originally designed to separate acquisition from retrieval problems.

Although the dichotomy between acquisition and encoding vs. retrieval problems underlying long-term memory difficulties in MS has been commonly envoked, basic memory research in the cognitive neuroscience field has long suggested that this may be a false dichotomy. Also, there are well-conducted studies in the MS literature that show convincing evidence of retrieval deficits, as well as encoding anomalies, involved in long-term memory problems. In a study designed to explore the basis of long-term memory deficits in MS, Armstrong and colleagues employed a modification of Rey's Auditory Verbal Learning Test [13]. In addition to the usual five learning trials, interference trial, short- and long-delay trials, these investigators included a complex recognition task that was presented after the short-delay free recall task. Besides the initial target words, this recognition list included words that were semantically and phonologically related to the target words, words from the distracter list, and high-frequency associates of the same semantic categories as the target words. First examining serial position effects, these investigators found that MS patients performed significantly worse than controls only on their recall of the middle portion of the list during the learning trials.

Further analyses by Armstrong and colleagues showed that MS patients retained a similar proportion of words at long-delay recall compared with controls, suggesting that the MS patients were just as able to transfer information into long-term store as controls. They found that this phenomenon was true even of MS patients who initially performed poorly during the learning trials. At the short-delay recall trial following the interference list, temporal order effects were also found, but this time, MS patients performed especially worse compared with controls on the last third of the list, a phenomenon referred to as a negative recency retrieval effect. For the recognition test, no serial position effects were evident, with MS patients displaying normal recognition even for the middle portion of the list that they initially had the most difficulty learning.

Based on their findings of normal recognition combined with temporal order effects during learning and later recall, Armstrong and colleagues concluded that dysfunctional encoding processes during the learning process, as well as disruption of retrieval processes, were responsible for MS patients' long-term memory deficits.

Taken as a whole, it appears that there is evidence that acquisition problems contribute to memory deficits in MS, particularly among mildly and moderately impaired patients. Whether acquisition problems are influenced by reduced attentional and processing speed ability is still debated. Armstrong and colleagues' study also suggests that retrieval processes are likely disrupted.

Compensation, neural reorganization, or effort? Two somewhat similar theoretical concepts have been used extensively within the neuropsychological literature to describe the brain's adaptive potential following insult: compensation and neural reorganization. Both theories seek to explain how cognitive performance can be spared despite evidence of significant brain damage, and both rely on the assumption of the brain's potential for either structural or functional plasticity. A clear difference between these two terms has not yet emerged, although Hillary [14] has suggested that neural reorganization may be distinguished from compensation by the greater degree of permanence implied. Nonetheless, compensation has been used to describe changes in task-specific neural activity after injury to areas typically used to support the task. The theory suggests that parts of the brain not typically used for the task in healthy individuals are compensatorily engaged following brain injury in order to maintain or facilitate task performance. Neural reorganization, sometimes described as the mechanism through which compensation occurs, is a proposed permanent rewiring of the neural network supporting certain types of cognition [15]. Again, this rewiring is theorized to maintain task performance.

Several studies with MS samples have been conducted, focused particularly on compensation or neural reorganization in working memory capacity, a domain commonly affected in MS patients (for review, see Hillary [14]). These studies have provided similar results, demonstrating increased metabolic activity, particularly in the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, and a more distributed neural network among MS participants compared to healthy controls. When performance among MS and healthy control groups is equal, researchers have inferred that the increased activation, or more distributed neural network, represents compensation or neural reorganization (e.g., [16–18]). More specifically, following brain damage due to MS disease process, it is thought that the brain functionally recruits areas not typically involved in working memory, or that white matter changes occur, helping to aid functional reorganization.

Hillary [14, 19] has argued compellingly against the compensation and reorganization hypotheses, noting several limitations in the studies examining working memory in MS. First, equivalent accuracy on working memory tasks among MS and healthy controls has been assumed to imply equivalent performance. However, more subtle impairments in performance may be present, for instance, decrements in reaction time among MS patients. Second, increased activation in the PFC and a more distributed network among MS groups are described as compensation when task performance is equal to healthy controls but as neural inefficiencies when the MS group performs more poorly [20, 21]. Thus, greater and more widespread neural activation, rather than being a marker of task facilitation, is seen as a marker of greater neural effort on a task. Greater neural effort is interpreted as something like cognitive control, a native support mechanism deployed by all individuals when task demands increase. This interpretation is supported by several studies that have found greater PFC activation as working memory load increases and performance decreases (e.g., [22, 23]).

Thus, MS patients may not compensate on working memory tasks as previously defined. Instead, they may maintain performance on easier tasks due to native support mechanisms (although subtle deficits may still be apparent). However, if task demands increase, MS patients

may demonstrate earlier and more marked impairment compared to healthy controls. This alternate explanation does not rule out the possibility of "compensation" or "reorganization" following brain injury in MS, but it does suggest that the nature of the neural plasticity that occurs may be more complex than previously assumed.

Possible Causes of Cognitive Deficits

Primary causes. Primary causes of cognitive deficits are a direct consequence of the location and extent of neuropathology. Thus, cognitive problems caused by primary influences are generally not reversible. There is clear evidence that overall cognitive impairment is associated with total lesion damage in the brain [24], gray matter hypointensities [25], and especially gray matter atrophy [26]. There is some evidence that frontal lobe lesions are associated with deficits on executive tasks like Wisconsin Card Sorting Test (WCST) [27]. The association of lesions in other brain areas and specific cognitive deficits is less clear.

Secondary causes. Secondary causes of cognitive impairment are a consequence of MS sequelae such as depression, anxiety, or fatigue. Cognitive problems caused by these secondary influences are potentially reversible if the secondary influence is successfully treated. Less attention has been paid in the MS literature to secondary as compared to primary causes of cognitive dysfunction. Recent work shows that depression is associated with impairments in speeded attentional functioning, working memory, and executive functions, but this link is still controversial [28, 29]. A recent review from our group suggests that the mixed relationship between cognitive impairment and depression in MS in the literature may be due to lack of attention to potential moderating variables [30]. Specifically, we suggest that cognitive dysfunction in MS may lead to depression when patients use maladaptive coping strategies, have poor social support, or are characterized by negative cognitive schema. Although there is some empirical support for maladaptive coping as a moderator [31], the others remain theoretical.

There is little evidence that self-reported fatigue or anxiety is significantly associated with cognitive deficits in MS, but these associations have been examined infrequently to date. However, one study suggests that MS patients show greater decline in performance on cognitively demanding tasks over the course of an evaluation with other demanding cognitive tasks. This suggests the possibility that greater susceptibility to cognitive fatigue may emerge over long periods of testing in MS [32], something that should be taken into consideration when ordering tests in a battery.

Neuropsychological Assessment Tools

Self-report approaches to assessing cognitive dysfunction. Neuropsychological assessment strategies in MS vary. They range from relatively short self- and other-report questionnaires to comprehensive batteries that can take several hours to administer. Between these two poles are relatively brief batteries that take approximately 30 min and minimal batteries that are closer to 90 min. Regarding questionnaires, Benedict and colleagues [33] have developed analogous self and significant other neuropsychological screening questionnaires, known as the MS Neuropsychological Screening Questionnaire (MSNQ), for cognitive impairment in MS. Each takes 5 min to administer. Significant other reports were significantly correlated with objective measures of cognitive functioning, and a cutoff score of 27 showed good sensitivity and specificity in classifying patients based on objective test results. In contrast, self-reports were significantly associated with depression but not objective neuropsychological test results. These results suggest that the use of significant other reports of patients' neuropsychological functioning can provide an effective screening for cognitive problems in MS.

It is important to note, however, that not all studies have agreed with the results of Benedict and colleagues [33]. In another study using a

different measure of everyday cognitive functioning, Randolph and colleagues [34] found that *patient* reported cognitive functioning was more highly correlated with objective neuropsychological test performance than significant other reports. Whereas Benedict and colleagues' validation study of the MSNQ included a clinic-referred MS sample, Randolph and colleagues used a community-based sample. It may be that patients in the latter sample, on average, were less impaired cognitively than patients in typical clinic samples and thus were better able to monitor and rate their own level of cognitive difficulty. Taken together, such results suggest that both patient and significant other reports of cognitive functioning should be used in screening, keeping in mind that the accuracy of the reports may vary as a function of the patient's depression status, the specific measure used, and the nature of the patient population. The best approach, based on available data, is to administer both self and significant other forms of the MSNQ, as well as self-report measures of depression (such as the BDI or BDI-Fast Screen), and then make a determination, considering the patients' potential for insight into cognitive difficulties, whether to proceed with objective neuropsychological testing.

Objective approaches to assessing cognitive dysfunction. Rao's Brief Repeatable Battery (BRB) [35] has been the most widely used brief assessment battery and takes approximately 30 min to administer. It is most applicable in situations where a brief screening evaluation is needed to determine whether further testing is warranted. Because MS patients impaired in one domain of cognitive functioning are not necessarily impaired in others [36], performance on a test in one domain provides little information about the likelihood of deficits in other domains. Thus, neuropsychological assessments that evaluate major areas of cognitive functioning typically impaired in MS are critical. The BRB consists of tests most sensitive to cognitive impairments typically seen in MS, most of which include 15 alternate forms to facilitate repeat testing. The battery measures memory with the 10/36 Spatial Recall and the six-trial version of the Verbal Selective Reminding Test, processing speed and attention with the oral Symbol Digit Modalities Test and the 2s and 3s Paced Auditory Serial Addition Test (PASAT), and verbal fluency with Word List Generation. Comprehensive norms for the BRB can be found in Boringa et al. [37]. The BRB is designed to have broad applicability for use in research, clinically to track cognitive changes over time, or for the purpose of tracking treatment effects.

A more extensive neuropsychological battery that falls short of a truly comprehensive assessment is useful in many situations where a brief battery is not sufficient to fully characterize a patient's cognitive profile. The Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS) was developed for this purpose by group consensus among experts on neuropsychological functioning in MS [38]. This battery takes 90 min to administer and consists of five cognitive domains (tests measuring those domains listed in parentheses): processing speed/working memory (oral Symbol Digit Modalities Test, 2s and 3s PASAT) , learning and memory (*California Verbal Learning Test – 2nd Edition* (CVLT-II) and Brief Visuospatial Memory Test – Revised (BVMT-R)), executive function (D-KEFS Sorting Test), visual–spatial processing (Judgment of Line Orientation), and word retrieval (Controlled Oral Word Association Test (COWAT)). Nearly 60% of MS patients were found to be impaired on at least two of these subtests in a validation study of this battery [39]. Like the BRB, the MACFIMS is designed to have broad applicability for use in research, tracking of cognitive changes clinically, or for examining treatment effects.

For more comprehensive neuropsychological batteries, a number of tests can be added to the core MACFIMS battery, as necessary. A measure of current *intellectual functioning* that estimates WAIS-III Full-Scale IQ (FSIQ) can be derived using the Wechsler Abbreviated Scale of Intelligence (WASI) [40]. This consists of four subtests based on the WAIS-III (Vocabulary, Similarities, Matrix Reasoning, and Block Design). Use of the WASI can be helpful in situations where it is desirable to derive an estimate

of decline from premorbid intellectual level. This can be accomplished by subtracting the WAIS-III FSIQ estimate derived from the Wechsler Test of Adult Reading (WTAR; see below) [41] from the estimate obtained using the WASI.

Using the four subtests, WASI can be problematic, however, because it includes Block Design, a subtest that has significant motor manipulation and visual demands. As a result, some patient scores may be artificially lowered by poor performance on this subtest. One solution to this problem involves the measurement of more rudimentary motor and visual skills, as described in the section below. Alternatively, the two-subtest version of the WASI (Vocabulary and Matrix Reasoning subtests only) can be administered, and a WAIS-III FSIQ estimate derived from that. Because of the visual demands of Matrix Reasoning, however, the contribution of significant primary visual disturbances must still be considered. The four-subtest version of the WASI takes about 30 min to administer and the two-subtest version takes about 15 min.

It is not typically necessary to measure *academic skills* as part of the neuropsychological assessment of MS patients. However, when a psychosocial interview reveals the possibility of a developmental learning disability that might contribute to the overall test results and confound interpretation of deficits as specific to MS, core academic skills can be screened using the fourth edition of the Wide Range Achievement Test (WRAT-4) [42]. This battery takes approximately 30–45 min to administer and assesses reading, writing, and arithmetic skills.

Given that *memory* is most commonly impaired in MS, it is sometimes useful to supplement the memory testing from the MACFIMS with additional measures. The Logical Memory subtests (I and II) from the Wechsler Memory Scale (WMS-III or WMS-IV) [43, 44] examine thematic memory, a type of verbal memory that may not be impaired even when impairments on tests such as the CVLT-II are found. Such information can be useful, especially in light of attempts to devise compensatory memory strategies for patients. The 10/36 Spatial Recall can be a useful measure of visual memory, as many patients have significant motor–writing difficulties and the 10/36 requires no drawing component. Although the contribution of motor drawing impairments to BVMT-R performance can be evaluated using the copy trial of this test, the 10/36 offers a more direct way of measuring visual memory without having to factor in possible motor drawing impairments to the process. Remote memory can be screened using the Information subtest from the WAIS-III [45] or WAIS-IV [46], and orientation can be evaluated with the Information and Orientation subtest from WMS-III.

Both the PASAT and the oral Symbol Digit, which are part of the MACFIMS, are recommended for assessing *attention*, *working memory*, and *processing speed*. To break down contributors to impairments on such tests, measures such as Digit Span – Forward and Spatial Span – Forward from WMS-III are sometimes useful as measures of simple attention span. Letter–Number Sequencing, Spatial Span – Backward, and Digit Span – Backward subtests from the WMS-III can be used as measures of working memory that are relatively independent of speed.

Although complaints of primary problems with language are less common than complaints of problems in other cognitive domains, they do occur. Patients presenting with significant linguistic complaints can be screened with the *Boston Naming Test, 2nd Edition* [47]. The use of the COWAT for screening verbal fluency problems can be supplemented with screening measures of semantic fluency (such as animal naming). Significantly better animal naming than letter–word fluency can suggest that letter–word fluency problems are, in part, a function of memory retrieval difficulties. Additionally, comprehensive review has suggested that semantic fluency is just as sensitive as letter–word fluency to verbal fluency problems in MS [48] and is more easily interpretable in non-English speakers.

When executive problems are salient, it can be useful to include measures of executive functioning in addition to the Sorting Test from the D-KEFS suggested by the MACFIMS. This may be especially important given the multi-faceted

nature of executive functioning. As MS patients have consistently been shown to display deficits in planning [49, 50] and verbal abstraction [36], the inclusion of the Tower Test from D-KEFS can be used for measuring planning ability and the Similarities subtest from WAIS-III or WAIS-IV for measuring verbal abstraction.

Addressing possible confounds in the assessment process. There are several factors that should be routinely addressed when neuropsychological deficits are found in MS, most of which were suggested as part of the MACFIMS process described above. First, premorbid ability needs to be considered. A culturally appropriate measure of premorbid ability is recommended when a patient is first assessed to provide a context for interpreting specific neuropsychological tests. The North American Adult Reading Test (NAART) can be used, as can the Wechsler Test of Adult Reading (WTAR) [51], which provides an estimate of premorbid Full-Scale WAIS-III IQ.

Second, depression should be addressed. The CMDI, a 42-item depression measure that includes mood, evaluative, and vegetative scales, is preferred for screening depression because of the overlap between MS disease symptoms and vegetative depression symptoms (e.g., fatigue, sleep disturbance, concentration difficulties, sexual dysfunction). The CMDI allows clinicians to evaluate whether total depression scores are artificially elevated due to the differential contribution of vegetative symptoms [52]. Nyenhuis et al.'s [53] validation study of the CMDI suggests a cutoff *t*-score of 65 or more for determining the clinical significance of total and subscale scores. The Beck Depression Inventory-Fast Screen (BDI-FS) [54] can also be used. It consists of only seven items and does not include any vegetative symptoms, thus circumventing the potential vegetative depression symptom/MS disease symptom confound. Raw scores greater than 3 suggest that further evaluation of depression is needed [55].

The possibility of primary problems with vision contributing to poor performance on visually based tests is a third issue that should be addressed. Performance on any neuropsychological test requiring some visual acuity for good performance (e.g., BVMT-R, JLO, Symbol Digit) can be compromised by visual problems. A measure like the Rosenbaum Pocket Vision Screener can be used to assess such problems. A 20/50–70 threshold at 14 in. from the corrected eye is recommended because it is similar to the small print characters presented during neuropsychological testing. It is important to keep in mind, however, that some research has shown that even patients with visual acuity at or below this threshold show variability in performance on some neuropsychological tasks as a function of variability in their visual acuity [56].

Fourth, the impact of primary motor problems and fine motor writing deficits needs to be addressed with neuropsychological tests that involve such skills (e.g., BVMT-R). The copy portion of the BVMT-R administration, as well as the 9-Hole Peg Test, can be used, as suggested by the MACFIMS consensus group [38]. Deficits in rudimentary oral motor speed can also impact performance on neuropsychological tests requiring a rapid spoken response (e.g., oral Symbol Digit, PASAT, verbal fluency tasks). The Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC) [57] requires examinees to repeat the phonemes "pa," "ta," or "ka" as quickly as possible in one good breath lasting at least 6 s. A fourth trial requiring the repetition of the "pa–ta–ka" sequence is also administered. Number of syllables per second is the main scoring index. Given the frequency of dysarthria in MS, slowed speech might impair patients' performance on such tasks.

A recent study examining this test in MS and controls found that MS patients performed significantly more slowly on the task [58]. These authors also found that consideration of the MRRSMC task before comparing group differences on several standard neuropsychological tasks requiring a rapid spoken response (e.g., COWAT, Animal Naming, oral Symbol Digit, and PASAT) significantly reduced group differences with controls. Thus, the data suggested that a significant proportion of the variance in group differences between MS patients and controls on these standard neuropsychological tasks was due

to the relatively slower speech of MS patients. Comparable results were reported in another study that simply used interviewer ratings of dysarthria [59].

A fifth potential influence on cognitive performance in MS is fatigue. Although the literature on the influence of fatigue on cognitive functioning in MS is mixed [32, 60], fatigue may influence performance in some MS patients as well as domains related to quality of life. Fatigue can be screened quickly using the Fatigue Severity Scale (FSS) [61]. This nine-item measure takes less than 5 min to administer. A more detailed screening of fatigue, and its impact on different life domains (social, cognitive, physical), can be accomplished by administering the Fatigue Impact Scale (FIS) [62]. This consists of 40 items and measures the impact of fatigue on social, cognitive, and physical functioning. A cutoff score of 75 for the total score has been recommended to identify those with significant functional limitations relating to fatigue [38]. Providing breaks throughout the testing day may help to minimize the possible impact of fatigue on test performance.

Relationship Between Cognitive Deficits and Illness Variables

Kurtzke's Expanded Disability Status Scale (EDSS) [63] has been the most commonly used measure of disability in MS. Occasional studies have reported a relationship between EDSS scores and cognitive impairment, but the majority of studies have found no such relationship. Because of problems with the EDSS as a measure of disability, particularly its overemphasis of ambulation, a new measure of disability has been developed, the Multiple Sclerosis Functional Composite (MSFC) [64]. This assesses three clinical dimensions including leg function/ambulation, arm/hand function, and cognitive function. The MSFC is now recommended for use in standard clinical evaluations.

Recent longitudinal work on cognitive decline in MS paints a variable picture. Most studies show relative stability over about a 3–4-year period [65]. However, patients identified as cognitively impaired are more likely to show cognitive decline [66], even over a relatively short period of time (e.g., 3 years). The most extensive longitudinal study to date (10 years) has shown that nearly 50% of MS patients who are unimpaired initially remain so 10 years later [67]. These investigators also found, however, that whereas 26% of patients were mild/moderately impaired at baseline, 56% were similarly impaired at the 10-year follow-up. Visual and verbal recall memory, verbal fluency, visuospatial function, processing speed, and verbal intelligence appear to be the most susceptible to decline over an 8–10-year period [68–70]. Compared with relapsing–remitting patients, progressive patients show greater cognitive dysfunction; one study estimated that secondary-progressive patients had seven times greater risk of cognitive impairment than relapsing–remitting patients [71]. Nonetheless, relapsing–remitting patients have been shown to have greater cognitive deficits relative to healthy matched controls even when they are in remission.

Neurocognitive Theories of Depression

Problematic for any comprehensive theory of depression in MS is that both MS and depression are characterized by heterogeneity. MS is associated with demyelination that is somewhat unsystematic. Although plaques and scarring are primarily detected in the periventricular regions, optic nerves, juxtacortical areas, corpus callosum, cerebellum, and brain stem, they can be found anywhere throughout the central nervous system [72]. Likewise, it is generally believed that depression is a heterogeneous psychiatric disorder, an endpoint arrived at via highly variable pathways that may include neural, psychosocial, personality, and other factors, e.g., [73–75]. Additionally, the presentation of depression is highly variable, at times characterized by affective flattening and relative indifference, at times characterized by agitation and distress, e.g., [76].

We recently proposed a model that attempts to explain how depression evolves in MS [30]. This

model reflects the highly variable influences on depression in MS, including immunological and neurophysiological anomalies, lesions and brain atrophy, and common MS sequelae, such as fatigue, physical disability, cognitive dysfunction, and pain. Important to the model is the reciprocal nature of these factors and depression. For instance, lesions and brain atrophy may underlie cognitive dysfunction in MS, which may primarily or secondarily lead to depression. However, increased depression may affect immunological anomalies, which may put an individual at greater risk for disease exacerbation. Many similar scenarios can be gleaned from the model.

Another important feature of the model involves several moderators which are either supported or speculated to protect against or exacerbate depression. These moderators include social support, coping, conceptions of the self and illness, and stress. In one study supporting the influence of such moderators involved, we found that coping moderated the relationship between cognitive dysfunction and depression [31]. We recently replicated this finding longitudinally [77]. Our data from these studies suggested that, although high levels of cognitive dysfunction are associated with depression, effective coping can prevent depression, even among those with considerable cognitive difficulties. Indirectly, this study also suggests that brain injury related to depression may be compensated for by psychological strategies or social relationships. Overall, the model reflects the burgeoning data on biological, psychosocial, neuropsychological, and environmental factors that impact mood in MS.

Our proposed model of depression has a number of practical implications. Specifically, it suggests that a number of factors can buffer various sequelae of MS. Take cognitive dysfunction. Our model suggests that this may lead to depression in MS, but that a number of factors (e.g., good social support, adaptive coping, and more positive cognitive schema) can moderate (i.e., reduce) the likelihood of it leading to depression. In the model we theorize that MS patients with cognitive difficulties will be less likely to be depressed if they have better social support, use better coping strategies, and develop more positive cognitive schema. Given that this is a relatively new model of depression in MS with many elements still in need of empirical evaluation, it would be premature to suggest that improving social support, cognitive schema, and coping strategies will actually provide a buffer against the impact of cognitive dysfunction on depression in MS. However, because there is already ample support that each of the proposed moderators is associated with depression in MS, it is reasonable to suggest that using therapeutic approaches that improve social support, coping, and cognitive schema will result in reduced depression in MS. The mechanism by which such factors might reduce depression is what remains unclear. In our model, the conceptualization outlined here for cognitive dysfunction can equally apply to other common sequelae of MS including physical disability, fatigue, and pain.

As far as testing our model of depression, much more work needs to be done to evaluate different elements of it. This can be done by examining small elements of the model, or through more comprehensive work. Regarding the former, for example, one could conduct a study to evaluate whether social support moderates the relationship between cognitive dysfunction and depression in MS. More comprehensive approaches could involve the examination of several MS sequelae and several moderators within the context of one study.

Numerous neurocognitive theories of depression and related findings have been discussed in the general depression literature that are relevant to MS. Though these theories do not account for all of the factors influencing depression or other affective problems in MS, they provide potentially important insights into the neurobiological risk for depression initiated by MS. Findings related to two prominent theories will be discussed, focusing on hemispheric dominance related to depression (e.g., [78–80]) and on a cortico-limbic system model of depression [81]. The assumption of this discussion is that damage to certain brain regions confers risk for depression. Brain areas associated with depression in the neuroscience literature are often found to be

abnormal in MS samples. The increased prevalence of depression among those with MS may thus reflect the impact of MS disease processes on the neurobiological substrates of depression.

Many studies, using a variety of research methodologies, have revealed that the left and right frontal cortices are involved in different emotional or motivational processes (for review, see [82]). Researchers have suggested that greater left frontal activity is associated with processing positive affect and greater right frontal activity is associated with processing negative affect (e.g., [83]). An alternate account suggests that greater left frontal activity is related to approach, or appetitive, motivation, whereas greater right frontal activity is related to increased withdrawal, or avoidance, motivation (e.g., [84]). Within the depression literature, research on hemispheric specialization has yielded several hemispheric models of depression, including a right hemisphere model [85], balance or asymmetry models (e.g., [86]), a circumplex model [80], and approach–avoidance models [87]. A consistent finding in electroencephalographic (EEG) studies is that depressed or dysphoric individuals demonstrate a reduced left frontal relative to right frontal activation (for review, see [79]), implying that depressed individuals preferentially process negative emotion and/or experience heightened trait withdrawal motivation.

These models provide a gross organization for the possible neural substrates of different types of depressive symptoms and may be applicable to MS, particularly because the frontal lobes are often affected by atrophy [88]. Based on previous lesion and EEG studies [89–91], individuals with left frontal lobe lesions due to MS may be most likely to evince a melancholic depression [76], because this area is associated with positive emotions and approach-related behaviors. Decreased left frontal activation has been linked to human sadness, fewer approach-related behaviors, and attenuated response to reward [92], and patients with left frontal regions are found to be more severely depressed than patients with lesions in other brain areas [93]. The anterior region of the right hemisphere is associated with avoidance, withdrawal, and negative affect (e.g., [76, 92]). Increased activation in this area may be associated with increased negative affect and avoidance.

Some researchers have suggested (e.g., [86]) that deactivation of the anterior region of one hemisphere may lead to the relative activation of the other, resulting in the increased expression of that brain area's primary emotional and motivational pattern. Thus, MS patients with lesions in the left frontal cortex may demonstrate affective problems related to decreased left frontal and increased right frontal function, meaning decreased positive affect and approach behaviors, and increased negative affect and withdrawal behaviors, consistent with depression. Interestingly, despite robust findings of the relationship between left anterior damage and depression in non-MS lesion studies, to our knowledge, only one study has found such a relationship in the MS literature [94] (though other studies have found a relationship between depression and frontal lobe atrophy or superior frontal lesions, e.g., [95]). The absence of such a finding may be due to the moderators described above attenuating depression or perhaps to resolution of depression symptoms due to neural plasticity restoring emotional processes over time. Further, to our knowledge, no functional imaging studies have examined the relationship between left anterior frontal cortex and depression in MS. Such studies may be important for detecting functional changes due to more subtle MS-related changes. Few studies have actually assessed brain–depression relationships in MS, and most have suffered from small sample sizes and methodological problems (for review, see [96, 97]).

As reviewed by Shenel and colleagues [75], individuals with right brain lesions present with different affective symptoms, though it is not clear that these symptoms resemble depression as currently characterized. Lesions in the right anterior region have been associated with problems in emotion regulation, lability for crying, and hostility [98, 99]. Interestingly, researchers have found greater hostility among MS patients with depression compared to non-MS individuals with depression (e.g., [100]). This may be due partly to right anterior damage and resultant relative left anterior dominance. Importantly, greater relative

left anterior activation, although commonly associated with positive affect, has also been related to hostility [101]. Surprisingly, more researchers have found a relationship between right prefrontal damage and depression in MS [102–104]. Such findings may be congruent with reports of a more hostile depression in MS, characterized by more affective disinhibition.

Although the prefrontal regions and the cerebral cortex, in general, are thought to be particularly important to depression and emotion regulation, others have suggested a depression-related cortico-limbic neural network, most prominently involving the frontal lobe, rostral anterior cingulate cortex (ACC), hippocampus, and amygdala [79, 81]. Mayberg [105] has presented a model of depression which involves a widely distributed, functionally integrative network along cortico-limbic and cortico-striatal pathways. The model consists of a dorsal compartment (neocortical and midline limbic elements) thought to be involved in apathy, psychomotor slowing, and cognitive impairments of depression, and a ventral compartment (paralimbic cortical, subcortical, and brainstem regions) thought to be associated with vegetative and somatic features of depression. In Mayberg's model the rostral anterior cingulate, isolated from these other compartments, plays a critical role in the functioning of the system, serving a regulatory function by initiating interaction between the dorsal and ventral compartment. Depression is proposed to be a dysfunction of the coordinated actions of this system.

This model of depression seems particularly applicable in MS given the frequency of reported anterior cingulate abnormalities [106–110] and paralimbic lesions related to depression (for review, see Siegert and Abernathy [106]), as well as the frontal findings already noted. The model is also conceptually compelling, because a widespread network of depression would mirror the widespread nature of brain injury characteristic of MS. Rather than suggesting that specific brain areas may be related to specific depressive symptoms, the model suggests that complex relationships within the system may have effects on mood, cognition, and somatic symptoms. Thus, lesions within the system and disconnection between parts of this system may interrupt the regulation of mood by disrupting the coordinated functioning of these brain areas.

In summary, we have described two prominent neurobiological models of depression and suggested their applicability toward understanding depression in individuals with MS. Prominent in each of these models is the prefrontal cortex. Within the PFC, hemispheric differences may account for different affective symptoms. Additionally, the rostral ACC and limbic structures may also be involved in depression. Studies have implicated all of these brain regions in the neuro-circuitry of depression and have also suggested that they are affected by the diffuse nature of axonal damage in MS, indicating their potential importance for understanding the high rates of depression associated with MS.

Given these neurobiological and neuropathological implications, the apparent ability of some individuals with MS to effectively adapt to these neural challenges – demonstrating lower rates of depression as the disease progresses, and based on available psychotherapy studies, prompt resolution of depressive symptoms with treatment [111, 112] – is somewhat surprising. These data suggest, as proposed in Arnett and colleagues' [30] model, that while neurobiological factors appear to confer risk for depression, numerous psychological, relational, and cognitive control strategies confer possibilities for effectively regulating affect. Although we have not provided an exhaustive discussion of brain areas commonly affected in MS that may predispose an individual to depression (e.g., the hippocampus), we hope to have demonstrated how neurobiological theories may help guide understanding and future research of the neurobiology of depression in MS.

Family and Social Issues

Several studies have examined some aspect of social support in MS, and all have found that low levels of social support are associated with depression. In a study of 120 MS patients mostly affected in the spinal cord, McIvor and colleagues

[113] found that perceived lack of or low social support from family and friends was the best predictor of depression: combined with disability severity, age, and course of illness; it predicted 65% of the variance in BDI scores. Individually, family-based social support accounted for 36% of the variance in depression and friend-based social support accounted for 50%. Similarly, in a study of 130 individuals with MS, Ritvo and colleagues [114] found that fatigue, perceived social support, disease duration, and response to stressful life events predicted almost 50% of the variance in Mental Health Inventory scores. Other studies have found similar associations between social support and depression [115–117] and suicidality in individuals with MS [118].

Additionally, certain characteristics of MS patients are associated with increased difficulty for caregivers. Figved and colleagues [119] found that dementia and higher levels of neuropsychiatric symptoms in MS patients were associated with poorer quality of life in caregivers. Additionally, higher levels of life stress in caregivers were significantly associated with greater neuropsychiatric symptoms, physical disability, dementia, and cognitive dysfunction in patients. Furthermore, higher levels of personal distress and negative feelings in caregivers were significantly associated with higher levels of neuropsychiatric symptoms, physical disability, and dementia in the MS patients. Caregivers' most frequent neuropsychiatric symptoms were depression, irritability, apathy, and fatigue. Finally, caregiver distress was greatest when the patients displayed symptoms of delusions, followed by disinhibition, agitation, and anxiety.

Guillain–Barré Syndrome

Pathophysiology, Clinical Presentation, and Course

Whereas MS is the most common demyelinating disorder of the CNS, Guillain–Barré syndrome (GBS) is the most common demyelinating disorder of the peripheral nervous system. GBS is an acute, immune-mediated disorder of the peripheral nervous system whose clinical features were described as early as 1859. Incidence rates are 1–2 persons per 100,000 each year in Europe and between 1 and 4 cases per 100,000 persons worldwide. The risk of GBS is 1.5 times greater for men than for women. In Europe and North America, the incidence of GBS increases gradually with age, whereas in China, the incidence is about the same in children and adults [120].

GBS often follows 1–6 weeks after a prior viral or bacterial infection, most commonly a flu-like illness but also gastroenteritis. Although definitive evidence has yet to emerge, implicated organisms include the influenza virus, cytomegalovirus, Epstein–Barr virus, *Mycloplasma pneumoniae*, and *Campylobacter jejuni*. Epitopes on the surface of these infectious organisms are similar to epitopes on the surface of peripheral nerves, causing the immune system to attack the infectious agents as well as peripheral nerve myelin proteins and axonal gangliosides. There is marginal or no evidence for increased risk of GBS as a result of routine immunization, except for rabies vaccines that contain brain material [120, 121].

The most common form of GBS is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP), involving demyelination of peripheral nerves, spinal roots and, less often, cranial nerves. It occurs more frequently among European and North American adults. During recent decades, other variants have been identified in which immune-mediated axonal loss rather than demyelination is primary. These variants include acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN). They appear more frequently in China, Japan, and South America. Other variants include Miller Fisher syndrome and Bickerstaff's brainstem encephalitis [120, 121].

Initial GBS symptoms usually begin abruptly and progress rapidly, peaking in 2–4 weeks, although in subacute and chronic inflammatory demyelinating polyradiculoneuropathy, the onset phase may last up to 8 weeks or more. Pain, numbness, and paraesthesias are followed by

symmetrical and ascending limb weakness. Loss of tendon reflexes is common, and most patients become unable to walk for some period during the illness. More severe cases can involve temporary quadriplegia and/or loss of all brainstem reflexes. In 20–30% of patients, respiratory failure due to neuromuscular weakness necessitates mechanical ventilation. Life-threatening autonomic dysfunction, including disturbances in cardiac rhythm, blood pressure regulation, and bowel and bladder function, develops in over half of GBS patients [120, 121].

The mortality rate for GBS is from 4 to 15%, and prognosis is worse in elderly patients or those with severe GBS. Recovery from GBS is slow and can continue for months or years after the onset of illness. Persistent disability occurs in 20–30% of adult GBS patients, especially those who have a rapid onset and who become non-ambulatory or require mechanical ventilation during the illness. Residual symptoms that fall short of severe disability are common in the remaining 70–80% of patients. Children tend to recover more rapidly and completely, and disability or death is less frequent [120, 121].

During the past two decades, evidence has accumulated for the efficacy of plasma exchange (PE) and intravenous immunoglobulin infusion (IVIg) in treating most GBS variants. However, these therapies must be given within 2–4 weeks of disease onset for greatest benefit. Because IVIg is more convenient to administer, has fewer associated risks, and is equally efficacious as PE, it has now become the preferred treatment for severe GBS. However, best practice guidelines continue to evolve. Corticosteroid treatment has shown benefit in treating chronic inflammatory demyelinating polyradiculoneuropathy, but it has proven ineffective in treating acute subtypes of GBS for reasons that remain unclear [120].

Other procedures are often used to confirm GBS diagnosis and classify GBS subtype including (1) analysis of cerebral spinal fluid for elevated protein concentration; (2) electrodiagnostic testing to reveal nerve conduction abnormalities associated with demyelination; and (3) magnetic resonance imaging (MRI) of the spine or brain to rule out alternative diagnoses [121].

Neuropsychological Factors

Neuropsychological testing is rarely used to aid in the diagnosis of GBS. This is primarily due to the fact that there seems to be little evidence for changes in cognitive functioning in those patients experiencing milder GBS symptoms. The common assumption among clinicians is that GBS, even at its most severe, affects only the peripheral rather than the central nervous system.

Administering neuropsychological measures to patients with more severe GBS symptoms, including patients who experience partial or complete paralysis or coma, is difficult to impossible. When GBS patients are "locked in" by paralysis and coma, electrophysiological testing or observation of primitive behavioral responses can be used to assess simpler cognitive functions, but the conclusions that can be drawn from such methods are indirect and limited. For example, Neppe [122] described the assessment of higher cortical functioning in a persistently vegetative GBS patient. Simple verbal instructions were given by familiar and unfamiliar individuals, and differential behavioral responses were observed in the patient. The most that could be concluded, however, was that the patient was in a minimally conscious, rather than persistently vegetative, state. Without neuropsychological testing, the integrity of the patient's higher cognitive functions could not be investigated, nor could those higher cognitive functions be linked to explicit behaviors.

Similarly, Ragazzone and colleagues [123] described a study in which repeated electrophysiological testing was conducted with two GBS patients experiencing a locked-in state due to exceptionally severe GBS. The authors found abnormal event-related potentials (ERPs) in the two patients, despite no evidence of brain damage on neuroimaging scans and no toxic or metabolic perturbations. They interpreted these results, along with the clinical observation that one patient reported no memory of events during this period, to indicate that the patients' cognitive functioning had been partially disturbed. Again, the conclusions which can be drawn from such

testing are indirect and limited. EEG criteria are able to document alertness and arousal, but they are only non-specifically related to cognition. Even ERPs, which reflect more directly cognitive activities, cannot demonstrate the integrity of higher cognitive functioning or link that functioning to behavior. At most, electrophysiological testing can sometimes help to reveal simple cognitive deficits [124].

When CNS involvement occurs secondary to GBS and without paralysis or loss of consciousness, more extensive neuropsychological testing can be utilized. For example, Lui and colleagues [125] presented a single case study of normal pressure hydrocephalus associated with GBS diagnosis in which neuropsychological assessment using the MMSE proved helpful in diagnosing the problem, determining the degree of cognitive impairment, and assessing the extent of cognitive recovery. However, such cases occur infrequently. It is important to note that the common assumption that GBS affects only peripheral rather than central nervous system functioning remains untested. For most GBS cases, the incidence or extent of any associated cognitive impairment remains unclear, and the use of neuropsychological assessment to characterize the capacity for cognition in GBS patients remains difficult.

Summary and Conclusions

We have reviewed cognitive features of MS and GBS, disorders converging in terms of both being autoimmune, demyelinating disorders and diverging in terms of proposed area affected (central vs. peripheral nervous system), and perhaps cognitive and physical functions affected. Important neuropsychological findings for MS are that diverse cognitive domains are affected, though most commonly memory, processing speed, attention, and executive function. Although the specific nature of cognitive impairment is not well understood, accumulating evidence suggests that memory impairments in MS involve dysfunction in both encoding and retrieval mechanisms and may be influenced by impairments in processing speed. Numerous options are available for neuropsychological assessment with MS, from screening measures to comprehensive batteries, though more intensive assessment is typically recommended to provide a detailed cognitive profile. Depression is highly prevalent among those with MS and has been found to affect the same areas of cognition most frequently affected by the disorder, making assessment of depression essential to any neuropsychological evaluation of MS. Thought to be a disorder of the peripheral nervous system, few studies have examined the effects on cognition due to GBS and findings are often limited by barriers to testing individuals with the disorder.

In the disciplines of affective and cognitive neuroscience, the boundary between emotion and cognition is often blurred. Impaired cognition – attention, for instance – is often linked to reduced ability to modulate affect, while emotional disturbance, such as depression, appears to affect cognition. We reviewed neurobiological theories of depression both to attempt to demonstrate the possible relevance of these theories to emotional disturbance in MS, as well as to illuminate the often blurred boundaries between emotion and cognition. Given that both emotional and cognitive processes rely on the brain, this blurring is not surprising. However, as described, numerous psychological and relational factors are highly important to cognition and particularly emotion and well-being. As described by our model, such factors may moderate emotional disturbance and, because they are associated, cognitive difficulties. Continued understanding of the interrelationships between emotional, cognitive, psychological, and relational domains, we propose, is essential to informed neuropsychological assessment, informing increasingly effective psychotherapeutic and pharmacological treatments and maximizing the effects of cognitive rehabilitation in MS and other neurological disorders.

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References

1. Rao SM. Neuropsychology of multiple sclerosis: a critical review. J Clin Exp Neuropsychol. 1986; 8:503–42.
2. Tröster AI, Arnett PA. Assessment of movement and demyelinating disorders. In: Snyder PJ, Nussbaum PD, Robins DL, editors. Clinical neuropsychology: a pocket handbook for assessment. 2nd ed. Washington, DC: The American Psychological Association; 2006. pp. 243–93.
3. Arnett PA, Smith MM. Cognitive functioning and everyday tasks in multiple sclerosis. In: Grant I, Marcotte T, editors. The neuropsychology of everyday functioning. New York, NY: Guilford Press; 2010. pp. 357–88.
4. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Eng. J Med. 2000;343:938–52.
5. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50: 121–7.
6. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58:840–6.
7. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology. 1996;46:907–11.
8. Rao SM, Leo GJ, Ellington L, et al. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology. 1991; 41:692–6.
9. DeLuca J, Gaudino EA, Diamond BJ, et al. Acquisition and storage deficits in multiple sclerosis. J Clin Exp Neuropsychol. 1998;20:376–90.
10. Grafman J, Rao SM, Litvan I. Disorders of memory. In: Rao SM, editor. Neurobehavioral aspects of multiple sclerosis. New York, NY: Oxford University Press; 1990. pp. 102–17.
11. DeLuca J, Barbieri-Berger S, Johnson SK. The nature of memory impairments in multiple sclerosis: aquisition versus retrieval. J Clin Exp Neuropsychol. 1994;16:183–9.
12. Thornton AE, Raz N. Memory impairment in multiple sclerosis: a quantitative review. Neuropsychology. 1997;11:356–7.
13. Rey A. L'examen Clinique en Psvchologie. Paris: Presses Universitaires de France; 1964.
14. Hillary FG. Neuroimaging of working memory dysfunction and the dilemna with brain reorganization hypotheses. J Int Neuropsychol Soc. 2008;14:526–34.
15. Forn C, Barros-Loscertales A, Escudero J. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. Neuroimage. 2006;31:686–91.
16. Penner I-K, Rausch M, Kappos L, et al. Analysis of impairment related functional architecture in MS patients during performance of different attention tasks. J Neurol. 2003;250:461–72.
17. Forn C, Barros-Loscertales A, Escudero J, et al. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. Neuroimage. 2006;31:686–91.
18. Forn C, Barros-Loscertales A, Escudero J, et al. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. Hum Brain Mapp. 2007; 28:424–30.
19. Hillary FG, Genova HM, Chiaravalloti ND, DeLuca J. Prefrontal modulation of working memory performance in brain injury and disease. Hum Brain Mapp. 2006;27:837–47.
20. Chiaravalloti ND, Hillary FG, Ricker JH, et al. Cerebral activation patterns during working memory performance in multiple sclerosis using fMRI. J Clin Exp Neuropsychol. 2005;27:33–54.
21. Hillary FG, Chiaravalloti ND, Ricker JH, et al. An investigation of working memory rehearsal in multiple sclerosis using fMRI. J Clin Exp Neuropsychol. 2003;25:965–78.
22. Braver TS, Cohen JD, Nystrom LE, et al. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage. 1997;5:49–62.
23. D'Esposito M, Aguirre GK, Zarahan E, et al. Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res. 1998;7:1–13.
24. Rao SM, Leo GJ, Haughton VM, et al. Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology. 1989;39:161–6.
25. Brass SD, Benedict RHB, Weinstock-Guttman B, et al. Cognitive impairment is associated with subcortical magnetic resonance imaging grey matter T2 hypointensity in multiple sclerosis. Mult Scler. 2006;12:437–44.
26. Benedict RHB, Bruce JM, Dwyer MG, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. Arch Neurol. 2006;63:1301–6.
27. Arnett PA, Rao SM, Bernardin L, et al. Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. Neurology. 1994;44:420–5.
28. Arnett PA. Longitudinal consistency of the relationship between depression symptoms and cognitive functioning in multiple sclerosis. CNS Spectrums Int J Neuropsychiatr Med. 2005;10: 372–82.
29. Landro NI, Celius EG, Sletvold H. Depressive symptoms account for deficient information processing speed but not for impaired working memory in early phase multiple sclerosis (MS). J Neurol Sci. 2004;217:211–6.

30. Arnett PA, Barwick FH, Beeney JE. Depression in multiple sclerosis: review and theoretical proposal. J. Int. Neuropsychol Soc. 2008;14:691–724.
31. Arnett PA, Higginson CI, Voss WD, et al. Relationship between coping, depression, and cognitive dysfunction in multiple sclerosis. Clin Neuropsychol. 2002;16:341–55.
32. Krupp LB, Elkins LE. Fatigue and declines in cognitive functioning in multiple sclerosis. Neurology. 2000;55:934–9.
33. Benedict RHB, Munschauer FE, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Mult Scler. 2003;9:95–101.
34. Randolph JJ, Arnett PA, Higginson CI. Metamemory and tested cognitive functioning in multiple sclerosis. Clin Neuropsychol. 2001;15:357–68.
35. Rao SM, and the Cognitive Function Study Group of the National Multiple Sclerosis Society. Manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis. New York, NY: National Multiple Sclerosis Society; 1990.
36. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. 1. Frequency, patterns, and prediction. Neurology. 1991;41:685–91.
37. Boringa JB, Lazeron RHC, Reuling IEW, et al. The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. Mult Scler. 2001; 7:263–7.
38. Benedict RHB, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. Clin Neuropsychol. 2002;16:381–97.
39. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Int Neuropsychol Soc. 2006;12:549–58.
40. The Psychological Corporation. WASI (wechsler abbreviated scale of intelligence) manual. San Antonio, TX: The Psychological Corporation; 1999.
41. The Psychological Corporation. Wechsler test of adult reading – manual. San Antonio, TX: The Psychological Corporation; 2001.
42. Wilkinson GS, Robertson GJ. Wide range achievement test – 4, professional manual. Lutz, FL: Psychological Assessment Resources Inc; 2006.
43. Wechsler D. Wechsler memory scale. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.
44. Wechsler D. Wechsler memory scale. 4th ed. San Antonio, TX: The Psychological Corporation; 2009.
45. Wechsler D. Wechsler adult intelligence scale. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997.
46. Wechsler D. Wechsler adult intelligence scale. 4th ed. San Antonio, TX: The Psychological Corporation; 2008.
47. Kaplan E, Goodglass H, Weintraub S. Boston naming test. 2nd ed. Austin, TX: Pro-Ed; 2001.
48. Henry JD, Beatty WW. Verbal fluency deficits in multiple sclerosis. Neuropsychologia. 2006;44: 1166–74.
49. Arnett PA, Rao SM, Grafman J, et al. Executive functions in multiple sclerosis: an analysis of temporal ordering, semantic encoding, and planning abilities. Neuropsychology. 1997;11:535–44.
50. Foong J, Rozewicz L, Davie CA, et al. Correlates of executive function in multiple sclerosis: the use of magnetic resonance spectroscopy as an index of focal pathology. J Neuropsychiatry Clin Neurosci. 1999;11:45–50.
51. The Psychological Corporation. The Wechsler test of adult reading (WTAR): test manual. San Antonio, TX: The Psychological Corporation; 2001.
52. Randolph JJ, Arnett PA, Higginson CI, Voss WD. Neurovegetative symptoms in multiple sclerosis: relationship to depressed mood, fatigue, and physical disability. Arch Clin Neuropsychol. 2000; 15:387–98.
53. Nyenhuis DL, Rao SM, Zajecka J, et al. Mood disturbance versus other symptoms of depression in multiple sclerosis. J Int Neuropsychol Soc. 1995; 1:291–6.
54. Beck AT, Steer RA, Brown GK. BDI-Fast screen for medical patients manual. San Antonio, TX: The Psychological Corporation; 2000.
55. Benedict RHB, Fishman I, McClellan MM, et al. Validity of the beck depression inventory-fast screen in multiple sclerosis. Mult Scler. 2003;9:393–6.
56. Bruce JM, Bruce AS, Arnett PA. Mild visual acuity disturbances are associated with performance on tests of complex visual attention in MS. J Clin Exp Neuropsychol. 2007;13:544–8.
57. Kent RD, Kent JF, Rosenbek JC. Maximum performance tests of speech production. J Speech Hear Disord. 1987;52:367–87.
58. Arnett PA, Smith MM, Barwick FH, et al. Oral motor slowing in multiple sclerosis: relationship to neuropsychological tasks requiring an oral response. J Int Neuropsychol Soc. 2008;14:454–62.
59. Smith MM, Arnett PA. Dysarthria predicts poorer performance on cognitive tasks requiring a speeded oral response in an MS population. J Clin Exp Neuropsychol. 2007;29:804–12.
60. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult Scler. 2002;8:523–6.
61. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46:1121–3.
62. Fisk JD, Pontefract A, Ritvo PG, et al. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci. 1994;21:9–14.

63. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–52.
64. Fischer JS, Rudick RA, Cutter GA, Reingold SC. The multiple sclerosis functional composite (MSFC): an integrated approach to MS clinical outcome assessment. Mult Scler. 1999;3:244–50.
65. Longley WA. Multiple sclerosis-related dementia: relatively rare and often misunderstood. Clin Pract Curr Opin. 2007;8:154–67.
66. Kujala P, Portin R, Ruutiainen J. The progress of cognitive decline in multiple sclerosis: a controlled 3-year follow-up. Brain. 1997;120:289–97.
67. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol. 2001;58:1602–6.
68. Bobholz J, Rao S. Cognitive dysfunction in multiple sclerosis: a review of recent developments. Curr Opin Neurol. 2003;16:283–8.
69. Achiron A, Polliack M, Rao SM, et al. Cognitive patterns and progression in multiple sclerosis: construction and validation of percentile curves. J Neurol Neurosurg Psychiatry. 2005;76:744–9.
70. Piras MR, Magnano I, Canu EDG, et al. Longitudinal study of cognitive dysfunction in multiple sclerosis: neuropsychological, neuroradiological, and neurophysiological findings. J Neurol Neurosurg Psychiatry. 2003;74:878–85.
71. Chelune GJ, Feisthamel K, Stone L. Assessing the prevalence and relative risk of cognitive dysfunction in patients with multiple sclerosis. Brain Impair. 2004;5(Suppl):77.
72. Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician. 2004;70:1935–44.
73. Mayberg HS. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clin N Am. 2003;13:805–15.
74. Parker G. Classifying depression: should paradigms lost be regained? Am J Psychiatry. 2000;157:1195–203.
75. Shenal BV, Harrison DW, Demaree HA. The neuropsychology of depression: a literature review and preliminary model. Neuropsychol Rev. 2003;13:33–42.
76. Heller W, Nitschke JB, Miller GA. Lateralization in emotion and emotional disorders. Curr Dir Psychol Sci. 1998;7:26–32.
77. Rabinowitz AR, Arnett PA. A longitudinal analysis of cognitive dysfunction, coping, and depression in multiple sclerosis. Neuropsychology. 2009;23:581–91.
78. Davidson RJ. Anterior brain asymmetry and the nature of emotion. Brain Cogn. 1992;20:125–51.
79. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. Ann Rev Psychol. 2002;53:545–74.
80. Heller W. Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. Neuropsychology. 1993;7:476–89.
81. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry. 1997;9:471–81.
82. Coan JA, Allen JJ. Frontal EEG asymmetry as a moderator and mediator of emotion. Biol Psychol. 2004;67:7–49.
83. Heller W, editor. The neuropsychology of emotion: developmental patterns and implications of psychopathology. Hillsdale, NJ: Erlbaum; 1990.
84. Sutton SK, Davidson RJ. Prefrontal brain asymmetry: a biological substrate of the behavioral approach and inhibition systems. Psychol Sci. 1997;8:204–10.
85. Borod JC, Koff E, Lorch MP, Nicholas M. The expression and perception of facial emotion in brain damaged patients. Neuropsychologia. 1986;30:827–44.
86. Tucker DM, Frederick SL, editors. Emotion and brain lateralization. New York, NY: Wiley; 1989.
87. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. Trends Cogn Sci. 1999;3:11–21.
88. Sperling RA, Guttmann CR, Hohol MJ, et al. Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. Arch Neurol. 2001;58:115–21.
89. Debener S, Beaudecel A, Nessler D, et al. Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. Neuropsychobiology. 2000;41:31–7.
90. Fleminger S. Left-sided Parkinson's disease is associated with greater anxiety and depression. Psychol Med. 1991;21:629–8.
91. Robinson RG, Kubos KL, Starr LB, et al. Mood disorders in stroke patients: importance of location of lesion. Brain. 1984;107:81–93.
92. Davidson RJ. Cerebral asymmetry, emotion, and affective style. In: Davidson RJ, Hugdahl K, editors. Brain asymmetry. Cambridge, MA: MIT Press; 1995. pp. 361–87.
93. Robinson RG, Starr LB, Lipsy JR, et al. A two-year longitudinal study of poststroke mood disorders. In-hospital prognostic factors associated with six-month outcome. J Nerv Ment Disord. 1985;173:221–6.
94. Feinstein A, Roy P, Lobaugh N, et al. Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology. 2004;62:586–90.
95. Bakshi R, Czarnecki D, Shaikh ZA, et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. Neuroreport. 2000;11:1153–8.
96. Arnett PA, Barwick FH, Beeney JE. Depression in multiple sclerosis: review and theoretical proposal. J Int Neuropsychol Soc. 2008;14:691–724.

97. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. J Neurosurg Psychiatry. 2005;76:469–75.
98. Heilman KM, Bowers D, Valenstein. E. Emotional disorders associated with neurological diseases. In: Heilman KM, Valenstein E, editors. Emotional disorders associated with neurological diseases. New York, NY: Oxford University Press; 1993. pp. 461–98.
99. Robinson RG, Parikh RM, Lipsy JR, Starkstein SE. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry. 1993;150:286–93.
100. Minden SL, Schiffer RB. Depression and mood disorders in multiple sclerosis. Neuropsychiatry Neuropsychol Behav Neurol. 1991;4:62–77.
101. Harmon-Jones E. Contributions from research on anger and cognitive dissonance to understanding the motivational functions of asymmetrical frontal brain activity. Biol Psychol. 2004;67:51–76.
102. Benesova Y, Niedermayerova I, Mechl M, Havlikova P. The relation between brain MRI lesions and depressive symptoms in multiple sclerosis. Bratislavské lekárske listy. 2003;104:174–6.
103. Berg D, Supprian T, Thomae J, et al. Lesion pattern in patients with multiple sclerosis and depression. Mult Scler. 2000;6:156–62.
104. Zorzon M, de Masi R, Nasuelli D, et al. Depression and anxiety in multiple sclerosis: a clinical and MRI study in 95 subjects. J Neurol. 2001;248:416–21.
105. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport Int J Rapid Commun Res Neurosci. 1997;8:1057–61.
106. Santa Maria MP, Benedict RH, Bakshi R, et al. Functional imaging during covert auditory attention in multiple sclerosis. J Neurol Sci. 2004;218:9–15.
107. Au Duong MV, Boulanouar K, Audoin B, et al. Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. Neuroimage. 2005; 24:533–8.
108. Morgen K, Sammer G, Courtney SM, et al. Distinct mechanisms of altered brain activation in patients with multiple sclerosis. Neuroimage. 2007;37: 937–46.
109. Charil A, Dagher A, Lerch JP, et al. Focal cortical atrophy in multiple sclerosis: relation to lesion load and disability. Neuroimage. 2007;34:509–17.
110. Cader S, Cifelli A, Abu-Omar Y, et al. Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. Brain. 2006;129:527–37.
111. Mohr DC, Boudewyn AC, Goodkin DE, et al. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. J Consult Clin Psychol. 2001;69:1–8.
112. Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: review and meta-analysis. Clin Psychol Sci Pract. 1999;6:1–9.
113. McIvor GP, Riklan M, Reznikoff M. Depression in multiple sclerosis as a function of length and severity of illness, age, remissions, and perceived social support. J Clin Psychol. 1984;40:1028–33.
114. Ritvo PG, Fisk JD, Archibald CJ, et al. Psychosocial and neurological predictors of mental health in multiple sclerosis patients. J Clin Epidemiol. 1996;49:467–72.
115. McCabe MP, McKern S, McDonald E. Coping and psychological adjustment among people with multiple sclerosis. J Psychosom Res. 2004;56:355–61.
116. Schwartz L, Kraft GH. The role of spouse responses to disability and family environment in multiple sclerosis. Am J Phys Med Rehabil. 1999;78: 525–32.
117. King KE, Arnett PA. Predictors of dyadic adjustment in multiple sclerosis. Mult Scler. 2005;11:700–7.
118. Feinstein A. An examination of suicidal intent in patients with multiple sclerosis. Neurology. 2002;59:674–8.
119. Figved N, Myhr K-M, Larsen J-P, Aarsland D. Caregiver burden in multiple sclerosis: the impact of neuropsychiatric symptoms. J Neurol Neurosurg Psychiatry. 2007;78:1097–102.
120. Hughes RC, Cornblath DR. Guillain-Barré syndrome. The Lancet. 2005;366:1653–66.
121. Burns TM. Guillain-Barré syndrome. Semin Neurol. 2008;28:152–67.
122. Neppe VM. Differential cerebral cortical responsiveness examination in minimally conscious versus persistent vegetative states: a new role for neuropsychiatry and behavioral neurology. J Neuropsychiatry Clin Neurosci. 2007;19:478–9.
123. Ragazzoni A, Grippo A, Tozzi F, Zaccara G. Event-related potentials in patients with total locked-in state due to fulminant Guillain-Barré syndrome. Int J Psychophysiol. 2000;37:99–109.
124. Kotchoubey B, Lang S, Bostanov V, Birbaumer N. Cortical processing in Guillain-Barré syndrome after years of total immobility. J Neurol. 2003;250:1121–3.
125. Liu CY, Kao CD, Chen JT, et al. Hydrocephalus associated with Guillain-Barré Syndrome. J Clin Neurosci Case Rep. 2006;13:866–9.

Chapter 21

Neurocognitive Function in Systemic Autoimmune and Rheumatic Diseases

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Introduction

An autoimmune disease is a disorder in which the body's immune system attacks itself. The dysregulation of the immune system associated with systemic autoimmune diseases can affect various organs systems, including the brain. This chapter will review the neuropsychological involvement and the resulting cognitive changes associated with three systemic autoimmune or rheumatic diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and primary Sjögren's syndrome (SS). Diagnosis, neuropsychological assessment, and treatment planning are challenging since most of the disease manifestations are nonspecific. Due to the abundant literature on cognitive dysfunction in SLE as compared to the other two diseases, the discussion of cognition is focused mainly in SLE.

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Systemic Lupus Erythematosus

Definitions and Epidemiology

SLE is an autoimmune disease with predominance among women of child-bearing age. In the United States, SLE is more prevalent among African-Americans, Hispanics, and Asians compared to non-Hispanic Caucasians [1]. This autoimmune disease is characterized by chronic tissue/organ inflammation mediated through autoantibodies, immune complexes, and complement activation that results in multiorgan involvement. Chronic vascular inflammation is a hallmark of SLE. Although the molecular and cellular mechanisms responsible for this condition are largely unknown, the complement system participates in virtually all inflammatory and immune-mediated processes and may also contribute to vascular pathology in SLE.

Neuropsychiatric SLE (NPSLE) is arguably the least understood yet perhaps the most prevalent manifestation of lupus. It occurs in 14 to over 80% of patients with SLE and is associated with increased morbidity and mortality [2–6]. The clinical spectrum of NPSLE is broad and includes severe and acute symptoms such as psychosis, cerebrovascular accident, and myelopathy, in addition to more chronic symptoms such as headache and cognitive dysfunction.

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Classification of Neuropsychiatric SLE

The manifestations of NPSLE can be diverse and can occur in the absence of SLE activity or serologic markers. The American College of Rheumatology (ACR) research committee established case definitions for 19 neuropsychiatric syndromes involving the central and peripheral nervous systems as shown in Table 21.1 [7]. Seizure and psychosis, however, are the only two NPSLE manifestations that comprise the neurologic component of the ACR classification criteria for SLE [8, 9]. Cognitive dysfunction is one of the case definitions for NPSLE. Some studies may include subjects with NPSLE based on the ACR case definitions, whereas other studies may have subjects with SLE who do not have overt symptoms of NPSLE or are termed as "non-NPSLE" but may actually have underlying cognitive dysfunction upon neuropsychological testing during the study. Currently, there is no case definition for neuropsychiatric syndromes in other autoimmune diseases such as RA and SS.

Pathophysiology of Cognitive Dysfunction Is Elusive

Among the protean manifestations of NPSLE, cognitive dysfunction may be the most difficult to comprehend due to the varying definitions and complexity of its pathophysiology. The prevalence of cognitive dysfunction ranges from 21 to over 80% of patients with SLE, depending on how the condition is defined [2–5]. Indeed, cognitive impairment can occur without signs of overt structural brain abnormalities. However, in order to treat the varied presentations of NPSLE, one needs to understand the mechanisms of cognitive dysfunction in hopes of identifying therapeutic targets. Using murine models, Diamond and colleagues have demonstrated that both a leaky blood–brain barrier and the presence of DNA antibodies that cross-react with NR2 subunits of the *N*-methyl-D-aspartate (NMDA) receptors are required to cause neuronal death in the hippocampus with resulting cognitive impairment [10]. The neuronal death was non-inflammatory by histopathologic examination and could be

Table 21.1 Neuropsychiatric syndromes of systemic lupuserythematosus [7]

Central nervous system
Aseptic meningitis
Cerebrovascular disease
Cognitive dysfunction
Headache
Movement disorder (chorea)
Seizures
Acute confusional state
Anxiety disorder
Mood disorder
Psychosis
Demyelinating syndrome
Myelopathy (transverse myelitis)
Peripheral nervous system
Autonomic disorder
Mononeuropathy
Cranial neuropathy
Plexopathy
Polyneuropathy
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
Myasthenia gravis

prevented by the administration of memantine, an NMDA receptor antagonist. Similarly, epinephrine, a catecholamine, also breached the blood–brain barrier and caused selective neuronal loss in the lateral amygdala, leading to emotional disorder in the murine model [11]. This study implies that agents such as epinephrine can determine the region of brain that is made vulnerable to neurotoxic autoantibodies. However, clinical findings have been less consistent than this animal model. A recent cross-sectional study of 60 SLE patients demonstrated the association of serum anti-NR2 antibodies with depressive mood but not with cognitive dysfunction [12]. In another study of 93 SLE patients, no association was found between serum anti-NR2 antibodies and cognitive dysfunction, depressive symptoms, or anxiety [13]. Similarly, in a study of 65 SLE female patients by Hanly and colleagues it was found that the prevalence of anti-NR2 antibodies was 35% and the presence of this antibody was not associated with cognitive dysfunction or change in cognitive function over time [14]. The negative findings in these clinical studies, all of which included well-recognized neuropsychological assessments, may be due to the small sample size and the lack of assessment of the breach in blood–brain barrier in these patients.

There have been several other notable studies to support a potential mechanism for central nervous system (CNS) changes associated with NPSLE that involve antiphospholipid (aPL) antibodies, platelets, complement activation, and thrombosis. First, a longitudinal study that followed 123 SLE patients for at least 3 years identified the presence of aPL antibodies as a predictor of cognitive dysfunction [15]. Furthermore, in this study, aspirin, an anti-platelet agent, appeared to be protective in the older age group of 42–69 years. A cross-sectional study showed that the presence of aPL antibodies along with hypertension, cumulative organ damage due to SLE, and brain lesions identified by magnetic resonance imaging (MRI) was independently associated with severity of cognitive impairment in SLE [16]. Second, cognitive dysfunction was frequently found in patients with aPL syndrome, independent of history of CNS involvement [17]. Third, studies have demonstrated aPL-mediated direct neuronal injury in the absence of ischemia [18–21]. Fourth, the presence of aPL antibodies have been associated with vascular occlusive events, particularly stroke in non-lupus patients [22, 23]. Finally, the capacity of aPL to bind to platelets provides further evidence that aPL, platelets, and complement activation may participate in a pathogenic thrombotic and/or vasculopathic mechanism in SLE.

Risk Factors for Cognitive Dysfunction

The risk factors for patients having CNS involvement are poorly defined. Various risk factors have been proposed but are difficult to delineate. For instance, while there does seem to be a role for aPL antibodies in cognitive dysfunction, most studies have failed to show an association between neuroradiologic findings and cognitive deficits or a clear correlation between aPL positivity and specific neuroradiologic lesions [16]. It is also unclear whether cardiovascular risk factors or Raynaud's phenomenon via cerebral vasospasm contribute to the risk of CNS disease. Tomietto and colleagues studied 52 consecutive SLE patients to determine the presence and severity of cognitive impairment, in addition to the assessment of risk factors associated with neuropsychological deficits and cardiovascular disease [16]. They also studied patients with RA as controls since they were likely to have a similar background of prolonged disease and chronic corticosteroid use. Study subjects had a variety of testing including neuropsychological assessment, psychiatric evaluation, serologic tests including aPL antibodies, neuroradiographic testing, as well as historical evidence regarding presence of Raynaud's phenomenon and cardiovascular risk factors. Several risk factors including hypertension, obesity, and age all played a substantial role in patients with SLE as compared to patients with RA. In addition to these risk factors, both Raynaud's phenomenon and aPL antibodies are also independent risk factors for cognitive dysfunction. Raynaud's phenomenon is

vasospasm of small vessels causing tricolor changes in the hands and feet that is frequently seen in SLE and sometimes RA. Antiphospholipid antibodies, also seen frequently in SLE, are often associated with a predisposition for hypercoagulability and patients may manifest with venous and/or arterial thrombosis. The association of Raynaud's phenomenon may be related to cerebral vasospasm. Ferraccioli and colleagues note that cerebral vasospasm is more frequent in individuals with both SLE and peripheral Raynaud's compared to those without SLE [24]. In addition, cerebral vasospasm is related to more frequent headaches.

Due to the multiple confounding factors including disease state and morbidity associated with therapeutic medications used to treat these conditions including prednisone (i.e., glucocorticoid) – often at high doses, it is difficult to clearly define the risk factors that contribute to cognitive dysfunction seen in autoimmune disease. SLE disease activity has not been associated with cognitive dysfunction in cross-sectional and longitudinal studies [25, 26]. Furthermore, cognitive impairment appears to be a stable symptom of NPSLE. Carlomagno and colleagues conducted a longitudinal study of SLE patients (10 with NPSLE and 5 non-NPSLE) with cognitive impairment based on the Mental Deterioration Battery and the Mini-Mental State Examination, cognitive deficits persisted in all patients except for one non-NPSLE patient at mean follow-up of 21.5 months [27]. The Mental Deterioration Battery [28] evaluates for verbal abilities (Verbal Fluency and Phrase Construction tests), short- and long-term verbal memory (Rey Auditory Verbal Learning Test), immediate visual–spatial memory, visual–spatial reasoning (Raven Colored Progressive Matrices), and visuoconstructive abilities (Simple Copy and Copy with Landmarks tests).

Glucocorticoids are commonly used to treat SLE, RA, and SS. These patients, especially SLE patients, may be exposed to acute or short-term high dosages of glucocorticoids and then long-term lower maintenance dosages. Long-term glucocorticoid exposure may cause cognitive impairment from cumulative and long-lasting influences on hippocampal function and volume [29–31]. Acute effects of glucocorticoids can also impair memory retrieval [31, 32]. However, most studies did not find a relationship between glucocorticoid use and cognitive impairment [33–37].

Patients with cognitive impairment may also have co-existing mood disorder (i.e., depression) and fatigue that can further exacerbate the impairment [38–40]. In fact, depression has been reported to be present frequently in SLE patients with and without overt neuropsychiatric manifestations. In a study of 52 SLE patients without neuropsychiatric manifestations (non-NPSLE), 23 NPSLE patients and 27 healthy controls, Monastero and colleagues showed that depression levels significantly and independently predicted cognitive performance in SLE patients [41]. Both SLE groups demonstrated significant impairment compared with controls on tasks that assess verbal and non-verbal long-term memory and visuoconstructional abilities. Interestingly, NPSLE patients were more likely to be anxious and depressed compared to the other two groups. In a recent study of 67 non-NPSLE patients and 29 healthy controls by Kozora and colleagues, patients without overt NPSLE or neurologic dysfunction defined by standardized neurologic examination (the Scripps Neurologic Rating Scale) showed greater depressive symptoms on the Beck Depression Inventory-II and perceived cognitive difficulties compared with controls [42]. Furthermore, another study by Kozora and colleagues on 13 depressed SLE patients, 10 depressed control subjects, and 25 healthy controls showed a moderate agreement (86.4%) between the comprehensive neuropsychological battery and the American College of Rheumatology (ACR)-SLE battery of cognitive impairment in the depressed SLE patients [43]. In addition, depressed SLE patients performed worse than the depressed controls and healthy controls on the cognitive impairment index, a global score of cognitive functioning generated from the ACR-SLE battery. However, cognitive impairment in depressed SLE patients was not explained by depression alone. Other investigators have found that daily stress, but not depression or

anxiety, was associated with impairments in visual memory, fluency, and attention in patients with SLE [44].

Risk factors for development of cognitive dysfunction are numerous, which can be related to the autoimmune disease, its treatment, and the associated comorbidities including cardiovascular disease, depression, and daily stress. However, SLE disease activity has not been associated with cognitive dysfunction. Furthermore, cognitive dysfunction persists and appears to be stable in a small longitudinal study of SLE patients.

The Role of Neuropsychological Testing in the Diagnosis of Cognitive Dysfunction in SLE

There is no single laboratory test that can confirm either the diagnosis of NPSLE or the associated cognitive impairment. Autoantibodies to ribosomal P protein are highly specific for SLE in serum and cerebral spinal fluid and have been found to be associated with psychosis and/or depression in some studies [45, 46]. In a larger series of 149 SLE patients using the ACR nomenclature for NPSLE, there was no association between anti-ribosomal P antibodies and cognitive dysfunction [47]. Table 21.2 provides descriptions and neuropsychological domains assessed for SLE studies that we were able to identify from the current literature. In general, most studies found neuropsychological impairments to be more prevalent in the SLE group than in healthy controls. Some, but not all, investigations report higher prevalence or severity of impairment in SLE compared to RA. Several studies discussed below have linked neuropsychological results to neuroimaging findings and/or hormonal and autoantibody status. In SLE, domains of impairment varied across studies, with deficits found in verbal fluency, visuospatial skills, memory, attention, and executive function. The myriad of cognitive changes associated with NPSLE have led to attempts to develop relatively brief neuropsychological test batteries that would be sensitive to the types of cognitive deficits associated with SLE.

ACR Neuropsychological Test Battery. The ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature defined cognitive dysfunction as documented impairment in any or all of the following cognitive domains: simple or complex attention, reasoning or problem solving, executive skills (e.g., planning, organizing, and sequencing), memory (e.g., learning and recall), visual–spatial processing, language (e.g., verbal fluency), and psychomotor speed. This research committee also proposed a standard 1-h battery of neuropsychological tests for use in patients with SLE as outlined in Table 21.3. Kozora and colleagues found that the validity and reliability of this ACR battery to be acceptable in a study of 31 patients with history of NPSLE, 22 non-NPSLE patients, and 25 healthy controls [48]. Findings for this study also indicate that the 1-h ACR battery for SLE patients has good sensitivity and specificity as compared to a 4-h comprehensive battery in patients without NPSLE as compared to controls. However, a problem with the brief battery becomes apparent in patients with NPSLE. Due to the wide variety of presentations seen in these patients, overall agreement between the 1- and 4-h battery decreases. The 1-h battery may be adequate to detect global impairment; however, a comprehensive traditional neuropsychological evaluation is recommended to identify specific deficits in NPSLE.

Automated Neuropsychological Assessment Metrics (ANAM) Testing. ANAM is a repeatable computerized cognitive battery that was initially developed by the United States military to monitor performance changes in healthy individuals undergoing environmental challenges [49, 50]. It is used to assess the effects of chemical agents, extreme environments, and fatigue on cognitive function and includes complex attention, cognitive processing speed, and cognitive efficiency. Since its development, this test has been used for measurement in various disease states including multiple sclerosis and SLE. ANAM tests typically used in SLE studies include Simple Reaction Time, Continuous Performance, Code Substitution, Immediate and Delayed Memory, Simultaneous Spatial Processing, Sternberg Task (i.e., sustained attention/working memory), Digit Span, and

Table 21.2 Domains of cognitive dysfunction in systemic lupus erythematosus in recent studies

Authors	Subjects	Design/assessments	NP domains	Outcomes
Denburg et al. [98]	• 118 SLE women • 35 HC women	• aPL status (LA) • History of neuropsychiatric events • Traditional NP testing	• General intelligence • Attention/mental flexibility • Visuospatial skills • Psychomotor speed/manual dexterity • Learning and memory	• Cognitive impairment in SLE was associated with positive LA status in the entire SLE group and in the subset of SLE without history of neuropsychiatric events. • Verbal learning and psychomotor speed worse in LA positive compared with LA negative • LA positive worse than control on all domains, regardless of neuropsychiatric history
Hanly et al. [14]	• 65 SLE women	Prospective study • Traditional NP testing • Anti-dsDNA • Anti-NR2	• Delayed recognition memory • Attention–concentration • Verbal abstraction • Visual construction • Psychomotor speed • Global memory • Immediate and delayed recall	• 23% of SLE cognitively impaired at enrollment, 13% impaired at follow-up • Visual construction impaired in 37% • Retrieval memory impaired in 39% • No association between cognitive impairment and anti- NR2 or anti-dsDNA antibodies
Harrison et al. [13]	• 93 SLE women	• ACR NP battery (1-h) • Psychological assessment • SLE disease activity and cumulative organ damage • Anti-NR2a	• Executive function • Simple and complex attention • Visuospatial processing • Psychomotor speed • Verbal and non-verbal memory	• 31% of patients with cognitive impairment had positive anti-NR2a antibodies compared to 20% of those without cognitive impairment (p = 0.24) • Anti-NR2 was not associated with cognitive dysfunction, depressive symptoms, or anxiety
Kozora et al. [37]	• 51 non-CNS SLE • 29 RA • 27 HC	• Traditional NP testing • Psychological assessment • SLE disease activity • Anti-ribosomal P protein	• Intelligence • Attention • Reasoning • Learning • Recall • Fluency • Language • Perceptual–motor	• Intelligence, attention, and fluency lower in SLE and RA than HC • 29% of SLE, 31% of RA, and 11% of HC were cognitively impaired (t-score <40 on >1 domain) • Anti-ribosomal P protein antibodies not associated with cognitive or psychological deficits

(continued)

Table 21.2 (continued)

Authors	Subjects	Design/assessments	NP domains	Outcomes
Kozora et al. [76]	• 15 non-CNS SLE • 15 RA • 15 HC	• Traditional NP testing • DHEA and DHEA-S • IL-6 • Cortisol • Depression	• Intelligence • Attention • Reasoning • Learning • Recall • Fluency • Language • Perceptual–motor	• Learning lower in SLE than RA and HC • Attention lower in SLE than HC • Depression higher in SLE • DHEA-S level lower in SLE than RA and HC • IL-6 and somatic symptoms of depression contributed to the variance in learning in hierarchical regression analysis
Kozora et al. [42]	• 67 non-NPSLE • 29 HC	Cross-sectional study • ACR NP Battery • Neurologic exam • Cognitive failures questionnaires • Depression assessment	• Executive function • Simple and complex attention • Psychomotor speed • Language • Visuospatial processing • Memory • Reasoning/problem solving	• 20.9% of SLE patients and 13.8% of controls were impaired based on the ACR-SLE cognitive impairment index using a cutoff of 4 of 12 scores • WAIS-III number-letter sequencing subtest was more impaired in SLE patients • No difference in the cognitive impairment index between SLE and controls • Memory impaired in 28.4% of SLE • Sustained visual attention impaired in 19.4% of SLE • SLE patients had greater levels of self-reported depression using Beck Depression Inventory compared to controls
McLaurin et al. [99]	• 123 SLE	Prospective study • Three yearly NP (ANAM), rheumatology, and autoantibody evaluations	• Sustained attention • Visual learning • Visuospatial perception • Non-verbal memory • Working memory	Variables predicting declining ANAM total score over time: • Anti-β2GP1 antibodies • aPL antibodies • Prednisone use • Diabetes • Higher depression scores • Lower education level

(continued)

Table 21.2 (continued)

Authors	Subjects	Design/assessments	NP domains	Outcomes
Lapteva et al. [12]	• 60 SLE	Cross-sectional study • Traditional NP testing • Rheumatologic and autoantibody evaluations (including anti-NR2) • ^{1}H-MR spectroscopy	• Executive function • Attention • Visuospatial processing • Motor function • Psychomotor speed • Memory	• Patients with moderate or severe cognitive dysfunction had higher choline:creatine ratio in the dorsolateral prefrontal cortex and the white matter, compared to those with mild or absent cognitive dysfunction • Serum anti-NR2 antibodies were associated with depressive symptoms by Beck Depression Inventory-II
Petri et al. [51]	• 111 SLE diagnosed within 9 months • 79 healthy controls	Cross-sectional study • ANAM battery • SLE disease activity and damage	• Simple and complex attention • Visuospatial processing • Psychomotor speed • Memory	• Newly diagnosed SLE patients scored lower in four ANAM subtests compared to controls (code substitution immediate recall, continuous performance, matching to sample, and Sternberg test) after adjusting for age, sex, race, and education • Higher scores on damage scale was associated with worse performance on the continuous performance test • Higher erythrocyte sedimentation rate was associated with worse performance on matching to sample
Tektonidou et al. [17]	• 39 primary APS • 21 SLE-related APS • 25 disease controls: 15 SLE and 10 RA without APS • 60 HC	Cross-sectional study • Traditional NP testing • MRI	• Learning • Complex attention • Visuospatial perception • Verbal fluency • Mental flexibility • Visuospatial construction and memory • Verbal memory	• 42% of APS, 18% of HC, and 16% of disease control (all SLE) had cognitive deficits • Significant association between WMLs and cognitive deficits • Cognitive deficits were in the domains of verbal fluency and complex attention • Cognitive deficits were independent of history of CNS involvement

(continued)

Table 21.2 (continued)

Authors	Subjects	Design/assessments	NP domains	Outcomes
Tomietto et al. [16]	• 52 SLE • 20 RA	• Traditional NP testing • MRI • SLE disease activity • aPL antibodies	• Executive function • Simple and complex attention • Psychomotor speed • Language • Visuospatial processing • Reasoning/problem solving • Memory	• 59.6% of SLE and 25% of RA were impaired on ≥ 1 domain, with all impaired RA in "mild" range • Memory impaired in 50% of SLE • Complex attention impaired in 42.3% of SLE • Executive function impaired in 26.9% of SLE • Executive function and complex attention more frequently impaired in aPL positive than negative SLE • Brain areas suggested to be damaged based on NP results corresponded with MRI findings in 71% of SLE

Abbreviations: Anti-β2 GP1, anti-β2 glycoprotein 1; ANAM, automated neuropsychological assessment metrics; aPL, antiphospholipid; APS, antiphospholipid syndrome; CFS, chronic fatigue syndrome; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; dsDNA, double-stranded DNA; FM, fibromyalgia; HC, healthy control; IL-6, interleukin-6; LA, lupus anticoagulant; MSK, musculoskeletal pain; MRI, magnetic resonance imaging; NR2, *N*-methyl-D-aspartate receptor 2; NP, neuropsychological; RA, rheumatoid arthritis; SJRA, systemic juvenile rheumatoid arthritis; SLE, systemic lupus erythematosus; SPECT, single photon emission computed tomography; SS, Sjögren's syndrome; WMH, white matter hyperintensities; WML, white matter lesions.

Table 21.3 Proposed 1-h neuropsychological battery for SLE recommended by the ACR ad hoc committee

North American Adult Reading Test (to estimate IQ)
Digit Symbol Substitution Test
Trail Making Test (Parts A and B)
Stroop Color–Word Test [94]
California Verbal Learning Test [95]
Rey–Osterrieth Complex Figure Test (with delayed recall) [96]
WAIS-III Letter–Number Sequencing [97]
Controlled Oral Word Association Test
Animal Naming
Finger-Tapping Test

Matching to Sample and Mathematical Processing [51]. Various studies have attempted to evaluate the validity of ANAM testing in SLE [52, 53]. A 5-year longitudinal study of neuropsychiatric disease in SLE conducted by Holliday and colleagues in the San Antonio Study of Lupus Neuropsychiatric Disease (SALUD) compared both the traditional neuropsychological battery and the ANAM [52]. Sixty-seven patients with SLE and predominantly Hispanic/Latino (54%) completed the ANAM and the battery of traditional neuropsychological tests. ANAM testing was able to replicate the high prevalence (80%) of cognitive deficits in SLE and may be useful for assessment of cognitive impairment in the mixed-ethnic population with Hispanic patients. ANAM testing was also found to moderately correlate with the traditional neuropsychological test battery. The Hispanic SLE patients were younger, had less education, and had more current SLE disease activity. Hispanic and younger patients were found to be more impaired on the traditional tests, whereas ANAM test was not affected by Hispanic ethnicity or education. It appears that ANAM testing may less likely be influenced by confounding factors including effects of education, English language proficiency, and ethnic differences as compared to a traditional neuropsychological battery. Furthermore, Roebuck-Spencer and colleagues showed that ANAM is an efficient tool for screening and monitoring of cognitive functioning and emotional distress in SLE [53]. Sixty patients with SLE and without NPSLE were administered a 2-h battery of traditional neuropsychological tests and the Beck Depression Inventory-II. ANAM cognitive subtests were significantly correlated with many traditional neuropsychological tests (i.e., psychomotor processing speed and executive functioning using WAIS-III Digit Symbol and Part B of the Trail Making Test). After controlling for premorbid levels of cognitive ability, ANAM cognitive subtests also predicted SLE patients who had probable cognitive impairment versus no impairment with sensitivity of 76.2% and specificity of 82.8%.

A multicenter study by Petri and colleagues assessed 111 patients with recently diagnosed SLE (within 9 months of enrollment) and 79 healthy controls [51]. The SLE patients were more likely to be female, African-American, and Asian-American compared to the control group. After adjusting for age, sex, ethnicity, and education, the SLE patients performed significantly worse than normal controls on four of the nine ANAM cognitive subtests that require sustained attention/vigilance (continuous performance subtest) and sustained attention/working memory (Sternberg subtest), visual–spatial perception/working memory (matching to sample subtest), and non-verbal memory (code substitution immediate recall subtest). In the SLE patients, those with greater cumulative organ damage related to SLE or its treatment had worse performance on the spatial recognition test and the continuous performance test. The SLE patients with higher Calgary depression scale scores also had worse performance in the spatial recognition test. SLE medications and laboratory measures that include autoantibodies were not significantly associated with cognitive dysfunction.

Neuroimaging Modalities in Studies of Cognitive Dysfunction

Neuroimaging provides noninvasive assessment of brain pathology in NPSLE. Magnetic resonance imaging (MRI) is commonly used to review anatomical lesions in the brain tissue of patients with NPSLE; however, these lesions can be nonspecific and not reflective of the activity of NPSLE. Other neuroimaging modalities that have been used to study NPSLE include proton magnetic resonance spectroscopy (^{1}HMRS), functional MRI (fMRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). The majority of these studies are pilot investigations using small sample sizes.

MRI. Conventional MRI of the brain evaluates volume and findings varying from ischemic lesions to nonspecific small hyperintense deep white matter lesions. Lesions detected by MRI have been shown to correlate with cognitive impairment measured by neuropsychological testing in 72% of SLE patients (Kappa statistics for agreement = 0.42, p = 0.005) [16]. MRI abnormalities, such as T1- and T2-weighted lesions and cerebral atrophy, are more commonly detected in patients with SLE related to NPSLE compared to sex- and age-matched controls from the general population [54]. In SLE patients, cerebral atrophy was associated with cognitive dysfunction, seizures, and cerebrovascular disease, whereas T1- and T2-weighted lesions were more specifically associated with seizures and cognitive dysfunction, respectively.

^{1}H-MRS. ^{1}H-MRS has identified abnormal levels of neurometabolites as markers of neuronal function in areas that appear normal on anatomical MRI in SLE patients with cognitive dysfunction or active disease [12, 55, 56]. *N*-Acetylaspartate (NAA), choline (Cho), and creatine (Cr) are the neurometabolites most frequently measured in patients with SLE. NAA is a marker of neuronal and axonal integrity, and Cho appears to reflect cell membrane metabolism. A decrease in NAA peak in MR spectrum may represent neuronal or axonal dysfunction or loss and an increased in Cho peak may represent a heightened state of cell membrane turnover seen in demyelination, remyelination, or inflammation [57]. In SLE patients, progressive increase in Cho/Cr has been associated with an increased number of T2-weighted white matter hyperintense lesions in the ^{1}H-MRS region of interest during follow-up [58]. SLE patients with moderate or severe cognitive dysfunction also had significantly higher Cho/Cr than those with mild or no cognitive dysfunction [12]. SLE patients with active disease, independent of CNS manifestations, had decreased NAA/Cr that returned to normal range after disease remission [56]. Conversely, patients who had active SLE during follow-up developed significant reduction in NAA/Cr. These findings suggest evidence of reversible neuronal dysfunction during periods of inactive SLE.

SPECT and PET. SPECT with technetium-99m hexamethylpropylene amine oxime has been used to assess regional cerebral blood flow. PET scan using glucose metabolism with fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG-PET) can identify changes in regional cerebral metabolism in patients with NPSLE even without obvious structural lesions on conventional MRI. However, due to its expense and availability, PET is not suitable for routine clinical use. Abnormal FDG-PET can be found in SLE patients without obvious NPSLE or with normal MRI findings [59, 60]. Several studies have showed reduced cerebral blood flow in SPECT but intact glucose metabolism in PET in patients with NPSLE, suggesting a cerebrovascular disorder rather than a neuronal tissue disorder [59, 61]. Furthermore, in SLE patients with normal conventional MRI, glucose hypometabolism by PET along with decrease in cerebral blood flow by SPECT is associated with major NPSLE presentation such as confusion, and psychosis, whereas normal PET with decreases in cerebral blood flow by SPECT may be found in patients with or without NPSLE [60].

fMRI. fMRI is a promising functional neuroimaging technique, currently used in research applications, that evaluates brain activation patterns associated with specific cognitive tasks and

may elucidate mechanisms involved in the development of cognitive dysfunction in SLE. Deoxyhemoglobin acts as an endogenous contrast agent to identify areas of increased perfusion in blood oxygen level-dependent fMRI or BOLD-fMRI. Contrast between images obtained during active and control task periods of paradigms reflects changes in regional brain activity. One fMRI study of 14 right-handed NPSLE patients and 14 sex- and age-matched right-handed healthy controls has shown an altered brain pattern of cortical activation in NPSLE patients when compared to healthy controls during simple motor task performance using the maximum finger-tapping frequency rate and the nine-hole peg test [62]. There were no neuropsychological testings performed in this study. Strong correlations were found between activation of sensorimotor areas and the extent and severity of brain lesions detected by conventional MRI. The findings suggest that cortical reorganization may contribute to the maintenance of normal function capacities in patients with NPSLE. Similarly, another fMRI study of nine NPSLE patients, nine RA patients, and nine healthy controls showed a greater frontoparietal activation during a working memory task (i.e., *N*-Back task) in NPSLE patients compared to RA patients and controls [63] but no between-group differences on the activation task. According to the SLE Disease Activity Index (SLEDAI) [64], none of the patients had neuropsychiatric symptoms at the time of fMRI scan. The CNS manifestations of the NPSLE patients varied and included cognitive deficits, seizure, brain stem lesions, mood disorder, psychosis, and stroke. This study suggests a need to recruit extra-cortical pathways as a compensatory mechanism in patients with NPSLE to achieve the same level of function as controls. In a small study of 10 female patients with childhood-onset SLE (i.e., age of onset <16 years) and 10 healthy controls, fMRI findings reveal widespread differences and imbalances of brain activation in the SLE patients compared with healthy controls [65]. They underwent formal neuropsychological testing and fMRI using three paradigms: a continuous performance task to evaluate attention, an *N*-Back task to assess working memory, and verbal generation to evaluate language processing. Composite Z maps were generated to summarize the brain activation patterns for each fMRI paradigm in the SLE patients and compared the patterns in the healthy controls. Cognitive dysfunction was found in 6 of the 10 SLE patients using the formal neuropsychological testing. None of these SLE patients had any active CNS manifestations as defined by the SLEDAI [64] or damage in the neuropsychological category of the Systemic Lupus International Collaborating Clinics Damage Index [66]. In the absence of an active stimulus, the SLE patients showed more baseline activity in the cingulate gyrus, an inhibitory brain region, during times of paradigm control tasks. These findings implied damage or malfunction of the underlying neural network connectivity in these SLE patients. In other words, more effort is needed to perform a task in SLE patients, whereas less effort is applied to inhibit task action during control periods.

These studies illustrate the importance of not only using a well-defined sample in studies of SLE patients but also the need to carefully consider the activation task used during fMRI procedures. For example, some tests may not be sensitive enough to activate brain regions of interest and others may lack validity with respect to the construct in question. Recent advances in computerized testing using paradigms, such as *N*-Back test as described above and the touch screen Cambridge Neuropsychological Test Automated Battery (CANTAB) [67–69] which has been used along with fMRI in non-SLE studies, developed by cognitive neuroscientists hold promise for use during imaging procedures.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that manifests primarily as symmetric inflammation of multiple joints with the development of joint deformities from joint erosion and destruction over the course of many years. Presenting symptoms usually include morning stiffness as well as joint pain and swelling. However, RA can involve extra-articular organs and can be

the underlying cause of interstitial lung disease, pericarditis, and premature atherosclerotic cardiovascular disease. Although not as well defined as in SLE, neuropsychiatric manifestations have been described in RA, including difficulties in memory, attention, and executive function [4].

Bartolini and colleagues investigated the hypothesis that CNS alterations in RA could directly affect behavior in 30 inpatients (27 females) with RA in Italy [70]. The mean age of the patients was 55.6 years with average disease duration of 11.8 years. Importantly, RA patients with motor impairment due to joint deformities were excluded from the sample, as were patients with current depression and previous psychiatric or neurological history. The patients received cerebral MRI scans, SPECT, and a 2-h neuropsychological battery that included attention, memory, visual–spatial, and executive function tests. Only two patients performed in the normal range on all tasks. Visuospatial planning ability (Block Design) was impaired in 71% of patients, and visual memory (Rey Complex Figure) was impaired in 50%. Forty-seven percent were impaired on the Wisconsin Card Sort Test, a measure of novel problem solving and higher order reasoning abilities. Phonemic verbal fluency was impaired in 44% but semantic verbal fluency (e.g., animal naming) was impaired in only 6%, suggesting more prominent left frontal involvement. Verbal memory (Rey Auditory Verbal Learning Test) was impaired in 35%. The authors correlated the NP results with the results of clinical evaluations, including swollen joint count, Ritchie articular index, morning stiffness in minutes, erythrocyte sedimentation rate, C-reactive protein, and overall disease severity using the Lee functional index. For the most part, impairment on specific tests was not correlated with the clinical parameters. However, impairment on Block Design was associated with swollen joint count, the articular index, and Lee functional impairment. This finding is not unexpected because this test requires the manual manipulation of blocks under strict time constraints. Mental flexibility on Trails B and WCST was also associated with the Lee scale. In multivariable regression analysis using cognitive scores as dependent variables and age, education, disease duration, and the disease severity indices as independent variables, there was an effect of age on WCST, and an effect of Ritchie and Lee severity indices on executive function overall (Block Design, Phonemic Verbal Fluency, and WCST). On MRI, 35% of patients (11 of 30) showed white matter hyperintensities, and each of these patients had low scores on attentional, executive function, and visuospatial tests. On SPECT, hypoperfusion was evident in the frontal lobes in 85% of patients, and in the parietal lobes in 40% of patients. The authors postulated that motor impairment could be, in part, due to microangiopathy in subcortical and parietal–frontal areas and that joint pain and stiffness could lead to sensory changes that affect motor planning processes. Although the study is notable for its attention to parameters such as depression and hand deformities that might confound NP testing in RA, there were several methodological limitations. These included subjective interpretation of MRI and SPECT images, lack of control group, and unavailability of Italian norms for some neuropsychological tests.

An investigation of cognitive function in systemic-onset juvenile idiopathic arthritis (SJIA) [71] contrasts with the Bartolini study. The 31 children and adolescents with SJIA and a healthy age-matched control group all scored within normal limits on Verbal, Performance, and Full-Scale IQ scores on the WISCR and WAIS-R. No memory deficits were seen on the Auditory Verbal Learning Test in either group, and no deficits were seen on a computerized fine motor performance task. The children and adolescents, who had average disease duration of 6 years and 2 months, also showed no difficulties in social and emotional adjustment on Achenbach's child behavior checklist.

Dick and colleagues compared attentional abilities in adults with and without chronic pain: 20 RA patients, 20 fibromyalgia syndrome patients, 20 musculoskeletal pain patients, and 20 pain-free community controls age-matched to the RA patients [72]. Those with a history of neurologic disorder or psychiatric illness were excluded. The participants completed the Test of Everyday Attention (TEA), a standardized

neuropsychological battery with ecological validity. The TEA provides a composite score as well as age-referenced domains scores for selective attention, sustained attention, attention switching, and auditory–verbal working memory. RA patients had lower scores compared to the pain-free controls on TEA composite as well as on three of the four test domains: selective attention, sustained attention, and working memory. The between-group differences using analysis of variance remained significant after controlling for age, depressive symptoms, anxiety, and pain catastrophizing. Scores on attention switching did not differ among the four groups, and there were no significant differences between the three different pain groups on the attention tasks. This study may not have included a large enough sample size to detect differences among the pain groups. The authors did not report the numbers of patients in each diagnostic group who scored in the clinically impaired range. However, they did report that 60% of patients scored in the clinically impaired range on at least one TEA subtest, compared to 20% of healthy controls. Moreover, 38% of patients and 5% of healthy controls had more than one subtest in the clinically impaired range. The study suggests that having a history of chronic pain, whether due to RA, fibromyalgia, or other musculoskeletal origin, is associated with greater attentional difficulties on everyday tasks relative to pain-free controls.

In a controlled study by DeLuca and colleagues [73] designed to investigate working memory and speed of information processing in chronic fatigue syndrome (CFS) patients, 18 RA patients were included as a medically ill control group. The RA patients were without history of psychiatric or neurologic disorder. A series of computerized tasks adapted from the Paced Auditory Serial Addition Test (PASAT) were administered to assess speed of information processing and working memory. A set of simple auditory and visual reaction time tasks and choice auditory and visual reaction time tasks were also administered. CFS participants who were without comorbid psychiatric disorder (CFS-no-psych) had slower choice auditory reaction time and simple visual reaction time than RA patients. The RA patients did not differ significantly from a healthy control group of 29 individuals on any of the tasks of information processing speed or memory. This finding contrasts with the study by Dick and colleagues [72], in which RA performed more poorly compared to the pain-free controls in the areas of working memory and attention. The inconsistency in results could be attributed to differences in task, sample selection, and demographics. For example, in the study by Dick and colleagues, 75% of RA patients in the pain group were hospitalized and predominantly female, whereas the majority of pain-free controls were male. In the DeLuca study, the RA patients were recruited from rheumatology outpatient offices.

Brown and colleagues [74] highlight the importance of pain and depression as possible contributors to cognitive problems in autoimmune disease. These authors used structural equation modeling to determine whether depression mediates the association between pain and cognitive function. The participants consisted of 100 women and 21 men with RA from a larger medication adherence study. The average RA disease duration was 3.8 years (range 34–84 years). The majority of the patients (80%) rated their RA disease as moderate or severe. In a single study visit, participant completed the Arthritis Impact Measurement Scales-2 Pain scale and another pain scale devised for the adherence study, the Depressive Affect subscale of the Center for Epidemiologic Studies Depression Scale, and the Depression subscale of the Multiple Affect Adjective Checklist – Revised. Participants completed assessments of processing speed, inductive reasoning, working memory, and long-term episodic memory. However, the specific tests were not those typically used by clinical neuropsychologists, limiting a comparison of results with those of other studies. Pain and depression were associated with worse performance on the set of cognitive measures. Depression was a mediator of the pain–cognitive function relationship, in that the effect of pain on cognition was no longer significant after controlling for depression. These authors also found that

older age had a negative effect on cognitive functioning that was largely independent of pain and depression, not a surprising finding considering recent work regarding mild cognitive impairment [75]. The cross-sectional design is a limitation of the study, as are the lack of control group and use of relatively infrequently used cognitive tasks. No conclusions can be drawn regarding the prevalence and severity of cognitive dysfunction in RA based on this study. However, it suggests that treatment addressing pain and depression may have positive effects on cognitive performance in RA.

Overall, there are few studies of cognitive function in RA, and fewer still that include healthy comparison groups or imaging studies. Although the different methodologies and tests used in the RA investigations make cross-study comparisons problematic, several studies found greater cognitive impairment in RA than healthy controls [37, 72] and less cognitive impairment in RA than SLE [16, 17, 76]. This latter finding suggests that disease mechanisms specific to SLE may contribute to the more prevalent cognitive dysfunction in that disorder as compared to RA, another autoimmune disease with involvement of inflammation and pain. Joint pain, joint stiffness, and RA-related factors may impact cognition function in RA.

Sjögren's Syndrome

Another rheumatic disease that can manifest as neurologic dysfunction is Sjögren's syndrome (SS). Primary SS is a chronic autoimmune disorder that targets exocrine glands resulting in dry eyes and dry mouth as the main symptoms. However, there may also be extra-glandular manifestations, including CNS symptoms, and patients with SS may have memory disorders and impaired intellectual performance. Other neurologic manifestations have been reported in patients with SS, including central nervous system (e.g., transverse myelitis), cranial neuropathies (e.g., optic neuritis), myopathy, and peripheral neuropathies. Secondary SS can be commonly associated with the presence of other systemic autoimmune diseases, such as SLE, RA, and systemic sclerosis. This overlap makes it difficult to attribute CNS manifestations to SS alone.

In primary SS, there is evidence that cerebral anti-muscarinic acetylcholine receptor (mAChR) autoantibodies may have a pathogenic role in immune-mediated neuroinflammation and on cognitive dysfunction. In a study of 15 women with primary SS who had frontal lobe syndrome-related disorder (defined as slowness, shifting capacity disorder, incapacity to resist cognitive conflict, programming capacity disorder, and decrease verbal fluency) and 15 age-matched controls, the circulating antibodies from the primary SS patients interacted with rat cerebral frontal cortex by activating the mAChR [77, 78]. These antibodies also have agonistic activity that promotes proinflammatory/cytotoxic prostaglandin E_2 production and nitric oxide synthase (NOS) activity. The proposed downstream effect is the progressive loss of cerebral muscarinic receptor expression and activity, leading to cognitive dysfunction that involves synaptic plasticity and memory.

Few studies have systematically evaluated cognitive function using neuropsychological testing in SS patients; and none included large sample sizes. An investigation by Belin and colleagues [79] provides support for prevalent CNS involvement in SS. This study included 14 women with SS who were under 60 years old and not being treated with pain or antidepressant medications. They completed neurological examination, brain MRI, brain HMPAO-SPECT, and a battery of neuropsychological tests. Half of the patients had primary SS, and the other half had SS secondary to diseases that are not known to involve thrombosis or brain vasculitis (RA, progressive systemic scleroderma, and chronic hepatitis). Specific neuropsychological tests included are as follows: Rey Complex Figure Test with 5 min delay, semantic and phonemic verbal fluency, object and face recognition tasks, Trail Making Test, Stroop Color–Word Test, Wisconsin Card Sorting Test, digit span forward and backward, a block tapping task to assess immediate recall, and Wechsler Memory Scale. Only one patient had signs of CNS

involvement on neurological exam. MRI revealed multiple areas of hyperintensity in half of the patients, six of whom were without any neurological history. All patients had abnormality on SPECT, with mild or moderate hypoperfusion in the periventricular white matter and/or subcortical rim. Likewise, abnormalities on neuropsychological testing were seen in all patients. Executive function was mildly or moderately impaired in all patients, compared to age and gender norms. Memory was impaired in 10/14 patients, primarily on the delayed memory task from the Rey Complex Figure. The authors concluded that cognitive evaluation using neuropsychological tests is the most sensitive method to diagnose CNS involvement in SS.

In a German descriptive study [78], 16/20 patients with primary SS were administered a vocabulary test to estimate Full-Scale IQ, the Benton Visual Memory Test, and the Zahlen-Verbindungs-Test, a test of perceptual speed similar to Trails A. Only 1 patient had an estimated IQ that was below average, but 4 patients (25%) showed below average visual memory; and 11 (70%) had deficits in perceptual speed. In contrast to the high rate of cognitive impairment on neuropsychological testing, only 4 of 20 patients showed cortical atrophy on head CT.

In a sample of 40 patients with SS, Malinow and colleagues [80] administered the Wechsler Memory Scale and an abbreviated Wechsler Adult Intelligence Scale – Revised to 16 patients with suspected cognitive impairments. The authors found 7/16 (46.6%) had mild to moderate memory and concentration difficulties. Unfortunately, comprehensive neuropsychological testing and neurologic evaluations were not performed in all patients, so the study is not informative regarding overall prevalence of cognitive dysfunction in SS. Other investigations report up to 25% prevalence of clinical manifestations of CNS involvement in SS, but without systematic neuropsychological evaluation [81]. A recent population study of 68 SLE patients and 72 primary SS patients by Harboe and colleagues showed common and comparable frequency of cognitive dysfunction, headache, and mood disorders in these diseases [82]. However, cerebrovascular disease was more prevalent in SLE, whereas peripheral neuropathies were more common in SS. The few SS studies that included neuropsychological testing indicate that cognitive dysfunction is prevalent in SS, particularly in areas of memory and executive function, even in the absence of neurological signs or MRI abnormalities.

Family and Social Issues

Neurocognitive changes increase the psychosocial burden of SLE, RA, and SS for both the patients and their families. SLE is typically characterized by flare-ups or fluctuations in tissue and organ inflammation that may last for weeks or months and are often associated with cognitive changes. The unpredictable flares so often associated with SLE disrupt family caregiving roles, and the disease is associated with work disability in 15–48% of patients [83–86]. When the flare involves the CNS, the associated acute cognitive disturbance may further compromise social, work, and family roles. In a survey of 829 SLE patients, reports of CNS involvement, cognitive difficulties, greater fatigue, and higher rating of SLE activity were associated with disability in valued life activities in a multivariable model [85]. Over 91% of patients reported disability in at least one valued life activity. Problems with family care were reported by over 50% of patients, and social activities were affected in 39–48% of patients. A study of work disability in 143 SLE patients revealed that 42.7% reported formal work disability due to their SLE. Cumulative damage due to SLE, severity of fatigue, African-American race, and global pain score was associated with formal work disability in a multivariable logistic regression model [87]. The same research team also reported on presence of neuropsychiatric dysfunction by neuropsychological testing in 50 work-disabled and non-disabled SLE patients [87]. Visual memory (Rey Complex Figure Test), processing speed and attention (Trail Making Test, Stroop Color–Word Test, and Symbol Digit Modalities Test) differed significantly between the 16 patients reporting formal work disability and 26 non-disabled

patients. Verbal memory, verbal fluency, and motor speed did not differ between these groups. In a multivariable logistic regression model examining the effects of demographic and clinical variables on disability status, only cognitive impairment and cumulative organ damage due to SLE remained independently predictive of work disability. A recent survey study of 741 SLE patients found that severe memory impairment on the Hopkins Verbal Learning Test – Revised was associated with self-reported work disability in SLE [88]. Although these studies found somewhat different cognitive domains to be associated with work dysfunction in SLE, the role of cognitive impairment as an independent predictor of work role changes is noteworthy. In addition to flares, the majority of SLE patients experienced fluctuations in pain and fatigue. These symptoms, and associated depressive symptoms, can have a profound impact on the patient's ability to plan and carry out activities and can also contribute to poorer cognitive performance in domains such as attention and memory [15, 89].

Fluctuations in pain and fatigue level are also a hallmark of RA and other rheumatic diseases. These symptoms can have similar effects on family roles and social and work functioning. In a cohort of 210 employed patients with recently diagnosed RA and other inflammatory conditions, 75% of sick leave periods were due to their joint conditions [90]. In multivariable analyses, high levels of pain, poorer physical function, and passive behavioral coping with pain were independently associated with increased sick leave. A telephone survey study of subclinical disability in 508 RA patients' valued life activities revealed that over 75% reported disability in at least one valued life activity [91]. Difficulty with and need for accommodations in child care was reported by 39.5% of respondents, whereas difficulty with preparation of meals was experienced in 44.7%. Leisure activities, such as socializing, were problematic in approximately a third of patients. Patients who reported disabilities at baseline were more likely to report greater functional limitations at follow-up 2 years later (OR 1.14, 95% CI 10.6–1.23). No studies have directly evaluated the effects of cognitive difficulties on social functioning and family roles in patients with RA or SS. Nonetheless, the musculoskeletal pain, general fatigue, psychological distress, and cognitive difficulties are likely contributors of psychosocial burden in these autoimmune diseases.

Treatment

The recognition and treatment of cognitive dysfunction in patients with SLE, RA, or primary SS continue to be a major diagnostic and therapeutic challenge. Treating the underlying rheumatic disease may not be effective in the management of cognitive deficits since several studies, specifically in SLE, have not demonstrated the relationship between disease activity and cognitive dysfunction [27, 92]. However, the regular use of aspirin in older SLE patients with diabetes especially is associated with improved cognitive function in the SALUD study [15]. On the other hand, consistent glucocorticoid use, which may be a surrogate of more active or severe disease, is associated with decline in cognitive function.

Cognitive rehabilitation programs may teach patients the ways to adapt to their cognitive impairment and improve the ability to perform daily activities. A pilot study of 8-week psychoeducational group intervention for 17 female SLE patients with reported cognitive dysfunction showed improvement of metamemory and memory self-efficacy after participation [93]. The heterogeneity of the neuropsychological manifestations and the affected cognitive domains has led to a paucity of controlled clinical trials for cognitive rehabilitation of SLE patients. Thus, the current therapeutic approach is empirical and based on clinical experience and small clinical studies.

Summary and Conclusions

Cognitive dysfunction can occur in SLE patients with or without overt neuropsychological manifestations with varying prevalence depending on the definitions. In SLE, cognitive impairment

commonly appears in attention and information processing, learning, memory, and executive/reasoning skills. However, there is no specific pattern of cognitive deficits. Although not as extensively studied as in SLE, patients with other autoimmune diseases such as RA and SS can also exhibit cognitive changes, particularly in the areas of attention, memory, and executive function. Since the batteries of NP tests and definition of cognitive dysfunction have varied in different studies, some recent studies began to use the brief ACR Neuropsychological Test Battery with established validity and reliability. While studies have attempted to identify the potential risk factors and mechanisms of cognitive dysfunction that would shed light on this challenging area, neuroimaging modalities, particularly fMRI, coupled with highly specialized, computer-administered tests based on experimental paradigms adopted from cognitive neuroscience hold the most promise to improve our understanding of the biological involvement in the brain of patients with autoimmune diseases. Thus, a multidisciplinary approach is needed to improve our understanding of the mechanisms of CNS involvement in autoimmune disease and to identify and treat these patients with cognitive deficits.

The widespread scientific interest in applying neuropsychological assessment and neuroimaging to evaluate neuropsychiatric involvement in systemic autoimmune and rheumatic diseases is a relatively recent phenomenon. Understandably, the field has been subject to certain growing pains. For example, small cross-sectional studies using diverse test batteries and case definition have been conducted in the past, leading to conflicting or inconclusive results. In order to have a better understanding of cognitive dysfunction, including possible mechanisms and risk factors, it is crucial to conduct multicenter longitudinal studies with a large sample size using the same definition of cognitive dysfunction and methodology in neuropsychological assessment and other data collection. The growing acceptance of the 1-h ACR Neuropsychological Test Battery and ANAM computerized testing battery along with ever improving neuroimaging methods should lead to advances in detection and classification of cognitive dysfunction in SLE. As the field advances, treatment to reduce the suffering of patients with neurocognitive dysfunction can also be addressed systematically.

References

1. Danchenko N, Satia J, Anthony M. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006;15(5):308–18.
2. Ainiala H, Loukkola J, Peltola J, et al. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology. 2001;57:496–99.
3. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology. 2002;58(8):1214–20.
4. Hanly J, Fisk J, McCurdy G, et al. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol. 2005;32(8):1459–1456.
5. Hanly JG, Urowitz MB, Sanchez-Guerrero J, et al. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum. 2007;56(1):265–73.
6. Kovacs J, Urowitz MB, Gladman D. Dilemmas in neuropsychiatric lupus. Rheum Dis Clin North Am. 1993;19:795–819.
7. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42:599–608.
8. Tan E, Cohen A, Fries J. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–77.
9. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725.
10. Kowal C, DeGiorgio LA, Nakaoka T, et al. Cognition and immunity: antibody impairs memory. Immunity. 2004;21(2):179–88.
11. Huerta PT, Kowal C, DeGiorgio LA, et al. Immunity and behavior: antibodies alter emotion. Proc Natl Acad Sci USA. 2006;103(3):678–83.
12. Lapteva L, Nowak M, Yarboro CH, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2505–14.
13. Harrison MJ, Ravdin LD, Lockshin MD. Relationship between serum NR2a antibodies and cognitive dysfunction in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2515–22.

14. Hanly J, Robichaud J, Fisk J. Anti-NR2 glutamate receptor antibodies and cognitive function in systemic lupus erythematosus. J Rheumatol. 2006;33 (8):1553–8.
15. McLaurin EY, Holliday SL, Williams P, et al. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology. 2005;64 (2):297–303.
16. Tomietto P, Annese V, D'agostini S, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 2007;57(8):1461–72.
17. Tektonidou MG, Varsou N, Kotoulas G, et al. Cognitive deficits in patients with antiphospholipid syndrome: association with clinical, laboratory, and brain magnetic resonance imaging findings. Arch Intern Med. 2006;166(20):2278–84.
18. Kent M, Alvarez F, Vogt E, et al. Monoclonal antiphosphatidylserine antibodies react directly with feline and murine central nervous system. J Rheumatol. 1997;24(9):1725–33.
19. Shoenfeld Y, Nahum A, Korczyn A, et al. Neuronal-binding antibodies from patients with antiphospholipid syndrome induce cognitive deficits following intrathecal passive transfer. Lupus. 2003;12(6):436–42.
20. Caronti B, Pittoni V, Palladini G, et al. Anti-beta 2-glycoprotein I antibodies bind to central nervous system. J Neuro Sci. 1998;156(2):211–19.
21. Caronti B, Calderaro C, Alessandri C, et al. Serum anti-beta2-glycoprotein I antibodies from patients with antiphospholipid antibody syndrome bind central nervous system cells. J Autoimmun. 1998;11 (5):425–29.
22. Terashi H, Uchiyama S, Hashimoto S, et al. Clinical characteristics of stroke patients with antiphospholipid antibodies. Cerebrovasc Dis. 2005;19(6): 384–90.
23. Nencini P, Baruffi M, Abbate R, et al. Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia. Stroke. 1992;23 (2):189–93.
24. Ferraccioli G, Poi ED, Gregorio FD, et al. Changes in regional cerebral blood flow after a cold hand test in systemic lupus erythematosus patients with Raynaud's syndrome. Lancet. 1999;354(9196):2135–2136.
25. Carbotte R, Denburg S, Denburg J. Cognitive dysfunction in systemic lupus erythematosus is independent of active disease. J Rheumatol. 1995;22 (5):863–67.
26. Hanly J, Fisk J, Sherwood G, et al. Clinical course of cognitive dysfunction in systemic lupus erythematosus. J Rheumatol. 1994;21(10):1825–31.
27. Carlomagno S, Migliaresi S, Ambrosone L, et al. Cognitive impairment in systemic lupus erythematosus: a follow-up study. J Neurol. 2000;247:273–79.
28. Caltagirone C, Gainotti G, Masullo C, et al. Validity of some neuropsychological tests in the assessment of mental deterioration. Acta Psychiatr Scand. 1979;60(1):50–56.
29. de Quervain DJF, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature. 1998;394(6695):787–90.
30. Keenan PA, Jacobson MW, Soleymani RM, et al. The effect on memory of chronic prednisone treatment in patients with systemic disease. Neurology. 1996;47(6):1396–402.
31. Coluccia D, Wolf OT, Kollias S, et al. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. J Neurosci. 2008;28(13):3474–78.
32. de Quervain DJF, Roozendaal B, Nitsch RM, et al. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci. 2000;3(4):313–314.
33. Holliday SL, Navarete G, Escalante A, et al. Demographic, symptomatic, and serologic predictors of cognitive function in systemic lupus erythematosus: preliminary results from SALUD. Abstract. J Int Neuropsychol Soc. 2000;6:231–232.
34. Gladman DD, Urowitz MB, Slonim D, et al. Evaluation of predictive factors for neurocognitive dysfunction in patients with inactive systemic lupus erythematosus. J Rheumatol. 2000;27:2367–71.
35. Glanz BI, Slonim D, Urowitz MB, et al. Pattern of neuropsychologic dysfunction in inactive systemic lupus erythematosus. Neuropsychiatry Neuropsychol Behav Neurol. 1997;10:232–38.
36. Hay EM, Black D, Huddy A, et al. Psychiatric disorder and cognitive impairment in systemic lupus erythematosus. Arthritis Rheum. 1992;35:411–16.
37. Kozora E, Thompson LL, West SG, et al. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 1996;39 (12):2035–45.
38. Kozora E, Ellison MC, West S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): relationship to the American College of Rheumatology SLE neuropsychological battery. Arthritis Rheum. 2006;55:628–35.
39. Carbotte RM, Denburg SD, Denburg JA. Prevalence of cognitive impairment in systemic lupus erythematosus. J Nerv Ment Dis. 1986;174:357–64.
40. Wekking EM, Nossent JC, van Dam AP, et al. Cognitive and emotional disturbances in systemic lupus erythematosus. Psychother Psychosom. 1991; 55:126–31.
41. Monastero R, Bettini P, Del Zotto E, et al. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J Neurol Sci. 2001;184(1):33–39.
42. Kozora E, Arciniegas DB, Filley CM, et al. Cognitive and neurologic status in patients with systemic lupus erythematosus without major neuropsychiatric syndromes. Arthritis Rheum. 2008;59(11):1639–46.

43. Kozora E, Arciniegas D, Zhang L, et al. Neuropsychological patterns in systemic lupus erythematosus patients with depression. Arthritis Res Ther. 2007;9(3):R48.
44. Peralta-Ramirez MI, Coin-Mejias MA, Jimenez-Alonso J, et al. Stress as a predictor of cognitive functioning in lupus. Lupus. 2006;15(12):858–64.
45. Isshi K, Hirohata S. Differential roles of the anti-ribosomal P antibody and antineuronal antibody in the pathogenesis of central nervous system involvement in systemic lupus erythematosus. Arthritis Rheum. 1998;41(10):1819–27.
46. Abdel-Nasser A, Ghaleb R, Mahmoud J, et al. Association of anti-ribosomal P protein antibodies with neuropsychiatric and other manifestations of systemic lupus erythematosus. Clin Rheumatol. 2008;27(11):1377–85.
47. Gerli R, Caponi L, Tincani A, et al. Clinical and serological associations of ribosomal P autoantibodies in systemic lupus erythematosus: prospective evaluation in a large cohort of Italian patients. Rheumatology. 2002;41(12):1357–66.
48. Kozora E, Ellison MC, West S. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis Rheum. 2004;51(5):810–8.
49. Reeves D, Bleiberg J, Spector J. Validation of the ANAM battery in multi-center head injury studies [abstract]. Arch Clin Neuropsychol. 1993;8:356.
50. Reeves D, Kane R, Winter K. Automated neuropsychological assessment metrics (ANAM V3.11a/96). User's manual: clinical and neurotoxicology subset. San Diego, CA: National Cognitive Foundation; 1996.
51. Petri M, Naqibuddin M, Carson K, et al. Cognitive function in a systemic lupus erythematosus inception cohort. J Rheumatol. 2008;35(9):1776–81.
52. Holliday S, Navarrete M, Hermosillo-Romo D, et al. Validating a computerized neuropsychological test battery for mixed ethnic lupus patients. Lupus. 2003;12(9):697–703.
53. Roebuck-Spencer TM, Yarboro C, Nowak M, et al. Use of computerized assessment to predict neuropsychological functioning and emotional distress in patients with systemic lupus erythematosus. Arthritis Rheum. 2006;55(3):434–41.
54. Ainiala H, Dastidar P, Loukkola J, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study. Scand J Rheumatol. 2005;34(5):376–82.
55. Kozora E, Arciniegas DB, Filley CM, et al. Cognition, MRS neurometabolites, and MRI volumetrics in non-neuropsychiatric systemic lupus erythematosus: preliminary data. Cogn Behav Neurol. 2005;18(3):159–62.
56. Appenzeller S, Li LM, Costallat LTL, et al. Evidence of reversible axonal dysfunction in systemic lupus erythematosus: a proton MRS study. Brain. 2005;128(12):2933–40.
57. Narayana P. Magnetic resonance spectroscopy in the monitoring of multiple sclerosis. J Neuroimaging. 2005;15(4 Suppl):46S–57S.
58. Appenzeller S, Li LM, Costallat LTL, et al. Neurometabolic changes in normal white matter may predict appearance of hyperintense lesions in systemic lupus erythematosus. Lupus. 2007;16(12):963–71.
59. Kao C-H, Lan J-L, ChangLai S-P, et al. The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus. Eur J Nucl Med Mol Imaging. 1999;26(2):129–34.
60. Kao C-H, Ho Y-J, Lan J-L, et al. Discrepancy between regional cerebral blood flow and glucose metabolism of the brain in systemic lupus erythematosus patients with normal brain magnetic resonance imaging findings. Arthritis Rheum. 1999;42(1):61–68.
61. Grunwald F, Schomburg A, Badali A, et al. 18FDG PET and acetazolamide-enhanced 99mTc-HMPAO SPET in systemic lupus erythematosus. Eur J Nucl Med. 1995;22:1073–77.
62. Rocca MA, Agosta F, Mezzapesa DM, et al. An fMRI study of the motor system in patients with neuropsychiatric systemic lupus erythematosus. NeuroImage. 2006;30(2):478–84.
63. Fitzgibbon BM, Fairhall SL, Kirk IJ, et al. Functional MRI in NPSLE patients reveals increased parietal and frontal brain activation during a working memory task compared with controls. Rheumatology. 2008;47(1):50–53.
64. Bombardier C, Gladman D, Urowitz M, et al. Derivation of the SLEDAI: a disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992;35(6):630–40.
65. DiFrancesco MW, Holland SK, Ris MD, et al. Functional magnetic resonance imaging assessment of cognitive function in childhood-onset systemic lupus erythematosus: a pilot study. Arthritis Rheum. 2007;56(12):4151–63.
66. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the systemic lupus international collaborating clinics/American college of rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996;39(3):363–69.
67. Robbins T, James M, Owen A, et al. Cambridge neuropsychological test automated battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia. 1994;5(5):266–81.
68. Robbins T, James M, Owen A, et al. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J Int Neuropsychol Soc. 1998;4(5):474–90.

69. Chase HW, Clark L, Sahakian BJ, et al. Dissociable roles of prefrontal subregions in self-ordered working memory performance. Neuropsychologia. 2008;46 (11):2650–61.
70. Bartolini M, Candela M, Brugni M, et al. Are behaviour and motor performances of rheumatoid arthritis patients influenced by subclinical cognitive impairments? A clinical and neuroimaging study. Clin Exp Rheumatol. 2002;20(4):491–97.
71. Feldmann R, Weglage J, Roth J, et al. Systemic juvenile rheumatoid arthritis: cognitive function and social adjustment. Ann Neurol. 2005;58(4):605–09.
72. Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum. 2002;47(6):639–44.
73. DeLuca J, Christodoulou C, Diamond B, et al. Working memory deficits in chronic fatigue syndrome: differentiating between speed and accuracy of information processing. J Int Neuropsychol Soc. 2004;10(1):101–09.
74. Brown SC, Glass JM, Park DC. The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Pain. 2002;96(3):279–84.
75. Smith G. Bondi MNormal aging, mild cognitive impairment, and Alzheimer's disease. In: Morgan J, Ricker J, editors. Textbook of clinical neuropsychology. New York, NY: Taylor & Francis; 2008. pp. 762–80.
76. Kozora E, Laudenslager M, Lemieux A, et al. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J Int Neuropsychol Soc. 2001;7(6):745–54.
77. Orman B, Sterin-Borda L, De Couto Pita A, Reina S, Borda E. Anti-brain cholinergic auto antibodies from primary Sjögren syndrome sera modify simultaneously cerebral nitric oxide and prostaglandin biosynthesis. Int Immunopharmacol. 2007;7(12):1535–43.
78. Mauch E, Volk C, Kratzsch G, et al. Neurological and neuropsychiatric dysfunction in primary Sjogren's syndrome. Acta Neurol Scand. 1994;89(1):31–35.
79. Belin C, Moroni C, Caillat-Vigneron N, et al. Central nervous system involvement in Sjogren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. Ann Med Interne. 1999;150 (8):598–604.
80. Malinow KL, Molina R, Gordon B, et al. Neuropsychiatric dysfunction in primary Sjogren's syndrome. Ann Intern Med. 1985;103(3):344–50.
81. Alexander EL. Neurologic disease in Sjogren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update of immunopathogenesis. Rheum Dis Clin North Am. 1993;19 (4):869–908.
82. Harboe E, Tjensvoll AB, Maroni S, et al. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjogren's syndrome – A comparative population-based study. Ann Rheum Dis. 2008; ard.2008.098301.
83. Bertoli A, Fernandez M, Alarcon G, et al. Systemic lupus erythematosus in a multiethnic US cohort LUMINA (XLI): factors predictive of self-reported work disability. Ann Rheum Dis. 2007;66(1):12–7.
84. Utset TO, Chohan S, Booth SA, et al. Correlates of formal work disability in an urban university systemic lupus erythematosus practice. J Rheumatol. 2008;35:1046–52.
85. Scofield L, Reinlib L, Alarcon GS, et al. Employment and disability issues in systemic lupus erythematosus: a review. Arthritis Rheum. 2008;59(10): 1475–79.
86. Katz P, Morris A, Trupin L, et al. Disability in valued life activities among individuals with systemic lupus erythematosus. Arthritis Rheum. 2008;59(4):465–73.
87. Utset TO, Fink J, Doninger NA. Prevalence of neurocognitive dysfunction and other clinical manifestations in disabled patients with systemic lupus erythematosus. J Rheumatol. 2006;33(3):531–38.
88. Panopalis P, Julian L, Yazdany J, et al. Impact of memory impairment on employment status in persons with systemic lupus erythematosus. Arthritis Rheum. 2007;57(8):1453–60.
89. Kozora E, West SG, Forrest S, et al. Attention and depression in systemic lupus erythematosus. *59th Annual Meeting of American Psychosomatic Society: 2001 March 7–10* 2001.
90. Geuskens GA, Hazes JMW, Barendregt PJ, et al. Work and sick leave among patients with early inflammatory joint conditions. Arthritis Rheum. 2008;59(10):1458–66.
91. Katz P, Morris A, Yelin E. Subclinical disability in valued life activities among individuals with rheumatoid arthritis. Arthritis Rheum. 2008;59(10):1416–23.
92. Kozora E, Thompson LL, West SG, et al. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum. 1996;39 (12):2035–45.
93. Harrison MJ, Morris KA, Horton R, et al. Results of intervention for lupus patients with self-perceived cognitive difficulties. Neurology. 2005;65(8): 1325–27.
94. Stroop J. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643–62.
95. Delis D, Kramer J, Kaplan E, et al. California verbal learning test. 2nd ed. San Antonio, TX: Psychological Corporation; 2000.
96. Le Osterrieth P. test de copie d'une figure complex. Arch Psychol. 1944;30:286–356.
97. Wechsler D. Wechsler adult intelligence scale. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
98. Denburg S, Carbotte R, Ginsberg J, et al. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J Int Neuropsychol. 1997;3:377–86.
99. McLaurin EY, Holliday SL, Williams P, et al. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology. 2005;64(2): 297–303.

Chapter 22

HIV–AIDS: The Neurologic and Cognitive Consequences of HIV-1 Infection

David F. Tate, Robert H. Paul, Kinga Kertesz, Jared Conley, and Troy Russell

Relatively speaking, the human immunodeficiency virus (HIV) is a recent epidemic and was only first identified in the mid 1980s. Since this time, it has become clear that HIV is an efficient negative moderator of host immune function with deadly consequences. In fact, it is estimated that nearly 60 million people have died from the consequences of the virus since the mid 1980s. Despite our current efforts at education and prevention, we continue to see increases in the number of new infections (2.5 million) each year with an estimated 33 million people throughout the world currently infected. Sub-Saharan Africa bears the brunt of the pandemic with more than half the world's infections occurring within the region ($\sim$25 million). With infections occurring across the globe, HIV truly is a global pandemic with significant economic, political, and social ramifications.

Concurrently with the identification of the virus, there were reports of patients experiencing significant cognitive dysfunction, even dementia. Early research findings have consistently agreed with later findings of significant neurologic complications from HIV infection. Previous to the introduction of highly active antiretroviral therapies (HAART), as many as 50% of HIV-infected patients would experience frank dementia during the course of their infection with dementia symptoms being associated with increased risk of mortality. Since the introduction of HAART, the natural progression of HIV infection has been altered, resulting in a reduction in the number of patients experiencing frank dementia. However, with the decline in the number of patients experiencing dementia, there has been an increase in the number of patients experiencing mild to moderate amounts of cognitive dysfunction that negatively impact quality of life and participation in activities of daily living (ADLs).

The focus of this chapter will be on the current cognitive findings associated with HIV infection. We will begin the chapter by discussing neurologic consequences of HIV infection including a brief discussion of the pathological consequences, common mechanisms of injury, and possible cognitive consequences associated with these changes. We will discuss recent diagnostic

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categories and the updated cognitive nosology recently proposed. We will then describe the current state of the literature regarding cognitive dysfunction associated with HIV infection. We will offer a brief discussion of common tools to examine HIV-associated cognitive decline, as well as describe the growing literature regarding potential cognitive confounds that are commonly identified in HIV cohorts. Finally, we will discuss potential directions for future research.

Neuropathological Consequences of HIV Infection

The human immunodeficiency virus has many pathological consequences in the central nervous system (CNS). In the first few years surrounding the discovery of HIV (1984), clinicians and researchers focused their efforts primarily on clarifying the more apparent and deadly CNS pathology of infected patients. This pathology was not the direct consequence of HIV virions in the brain, but rather the result of a weakened immune system that allowed for the pathogenic influx of a variety of opportunistic organisms into the CNS. These opportunistic organisms included cytomegalovirus, cryptococcus, toxoplasma gondii, herpes simplex virus, Epstein Barr virus, and the reactivation of JC virus and often caused various serious complications – most notably lesions, encephalitis, and cognitive/behavioral dysfunction. Weakened immune status (due to HIV infection) also often led to the development of several uncommon or even unknown tumors in HIV-infected patients, such as non-Hodgkin lymphomas and Kaposi's sarcoma. These pathogenic occurrences disrupted normal cognitive function and often resulted in death.

Since these initial findings of opportunistic infections and tumors, much has been elucidated from further research and investigation. As the HIV pandemic increased in the late 1980s and early 1990s, studies identified both the means of HIV entry into the brain and many of the specific effects of the virus in the CNS pathology independent of weakened immune status. HIV was observed to enter the brain shortly after initial infection, most likely via a "Trojan horse" mechanism using infected microglial cells and macrophages to cross the blood–brain barrier (BBB). Once inside the CNS, the virus was suggested to habit most regions of the brain, but seemed to have a predilection for frontal, subcortical regions, particularly the basal ganglia [1]. Pathogenic effects of localized virus in the CNS included the fusion of infected macrophages (multi-nucleated giant cells), widespread axonal, dendritic and synaptic damage, myelin pallor, microglial activation, and neuronal loss via apoptosis.

Over time, it became apparent that HIV exerts its effects on the brain via two distinct mechanisms of action, non-inflammatory and inflammatory processes [2] – illustrated in Fig. 22.1. Each process is driven primarily by the presence of the HIV proteins gp120 and Tat.

In the non-inflammatory process, these two proteins directly affect astrocytes and neurons, causing inhibition of growth factor production and decreased glutamate uptake in astrocytes and stress/dysfunction in neurons. Glutamate reuptake inhibition and the resulting increase in glutamate in the synaptic cleft lead to the glutamate-mediated excitotoxicity response, resulting in pathological influxes of calcium and eventual cell death. In the inflammatory cascade, gp120, Tat, and HIV virions cause monocytes and macrophages to release various cytokines and chemokines, which result in further neuronal stress and apoptosis. Such factors include nitric oxide, TNF-alpha, IL-1, IL-6, and MCP-1. Other HIV proteins (gp41 and nef) and glial cell-derived proteins (prostaglandins, proteases, arachidonic acid, and quinolinic acid metabolites) may also contribute to neuronal damage [3].

Since 1995–1996 and the advent of highly active antiretroviral therapy (HAART), the pathognomonic features of HIV infection in the CNS appear to be changing. Treatment drugs have improved the ability of the host to maintain a more healthy number of CD4+ T lymphocytes in the body and, as a result, many of the readily observed pre-HAART opportunistic infections and tumors in the brain of HIV-infected patients have been reduced significantly. Yet, while HAART was

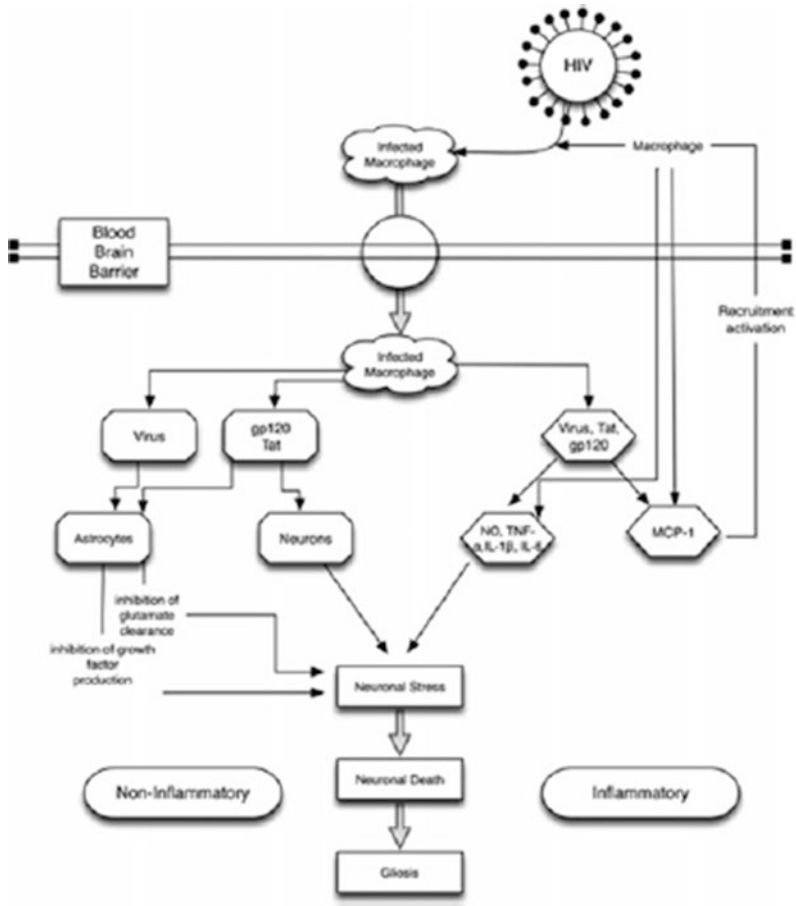

Fig. 22.1 This illustration depicts two common pathways of pathological injury. Adapted from Avison, Nath, and Berger [2]

seen to improve the CNS pathological consequences of a weakened immune system, the literature suggests a different course for the direct effects of HIV on the brain. Initially, it was hoped that antiretroviral therapy would diminish and perhaps eradicate the presence of HIV virions in the brain, in addition to the plasma. However, as plasma viral levels in treated patients often remain negligible, antiretro- viral drugs appear to have variable penetration into the CNS compartment due to the BBB. Due to limited immune surveillance and long-lived HIV-infected microglial cells, the brain has become one of the potential latent and active reservoirs for the virus in HAART-treated patients [4].

As a result of the continued presence of HIV in the brain, the common pathological findings of neuroinflammation in pre-HAART HIV-infected patients continue to be seen in the era of HAART. Surprisingly, the level of inflammation, in the form of microglial/macrophage activation, remains essentially the same in treated patients [4]. Recent pathological studies have found evidence of a previously unobserved shift in the location of HIV-related inflammation and damage in treated patients that may result in new or additional cognitive dysfunction among HIV-infected patients. These findings suggest that the main site of inflammation has moved from the sub-cortical structures of the basal ganglia to the hippocampus and surrounding entorhinal and temporal cortex [3–5]. This finding is still being examined and validated via in vivo and cognitive testing models. In addition to this apparent shift in pathology,

studies of HAART-treated patients have shown elevated levels of both hyperphosphorylated paired helical filament (PHF) Tau and beta amyloid, proteins normally associated with Alzheimer's disease, in the hippocampus and other structures [5–7]. Such findings were not seen in the era of pre-HAART and may indicate accelerated neuroaging in treated patients [4, 8].

The ongoing and shifting neuroinflammation of treated HIV-infected patients, compounded with the potential accelerated neuroaging rates, could have significant consequences on CNS-related outcomes in the era of HAART. In fact, as will be shown hereafter, though the overall rates of dementia have been reduced in the treated HIV-infected patient population, the absolute rates of mild to moderate cognitive dysfunction appear to be increasing. These two significant changes in the pathology of treated patients will need to be further investigated through neuropsychological examination which may further elucidate the subtle changes in disease evolution and progression.

Common HIV Staging Criterion

Resulting from these direct effects of HIV on the brain, infected patients can and do experience impairments across a wide range of cognitive domains. Cognitive deficits can range from severe and debilitating, as in the case of HIV-associated dementia, to more mild forms of pathology, as in the case of minor cognitive motor disorder. In earlier stages of the HIV pandemic, dementia was frequent, and motor deficits were considered the hallmark of the disease. With the advent of HAART there have been significant shifts in the cognitive pathology of the disease. As patients survive longer and experience a more cognitive course of the disease, cases of dementia have made way for milder forms of cognitive pathology and impairments in the domains of executive function, attention, and learning have emerged as the domains most affected by HIV [9].

In an effort to systematically define and categorize the progression of HIV infection in the CNS, various organizations developed several independent staging systems often used in cognitive studies. To best understand the current literature describing various cognitive consequences associated with HIV infection, it is important to understand the various staging systems often employed to discriminate between clinical subgroups of patients infected with HIV. These systems are based on both medical and cognitive criteria though the earlier systems tended to emphasize medical variables. The most commonly used clinically based systems include the US Center for Disease Control (CDC) staging

Table 22.1 Center for Disease Control HIV disease severity staging system summary

CD4 categories	CDC A	CDC B	CDC C
Category 1 $\geq$ 500 cells/μL Category 2 200–499 cells/μL Category 3 < 200 cells/μL	Asymptomatic, acute HIV or persistent generalized lymphadenopathy	Symptomatic conditions and not A or C (bacillary angiomatosis, oral candidiasis, pelvic inflammatory disease, cervical dysplasia, hairy leukoplakia, fever, diarrhea lasting >1 month, peripheral neuropathy, herpes zoster $\geq$2 episodes	AIDS-indicating conditions (bacterial pneumonia, bronchial/trachea/lung candidiasis, esophageal candidiasis, cervical carcinoma, cryptococcosis, cryptosporididosis, cytomegalovirus, encephalopathy, herpes simplex, Kaposi's sarcoma, lymphoma, tuberculosis, progressive multifocal leukoencephalopathy, toxoplasmosis of brain

Table 22.2 World Health Organization HIV disease severity staging system summary

WHO stage	Description
Clinical stage 1	Asymptomatic
	Persistent generalized lymphadenopathy
Clinical stage 2	Moderate unexplained weight loss (<10% of measured body weight)
	Recurrent respiratory infections
	Herpes zoster
	Minor mucocutaneous manifestations
Clinical stage 3	Severe weight loss (>10% of measured body weight)
	Unexplained chronic diarrhea (>1 month)
	Unexplained persistent fever (>1 month)
	Oral candidiasis (thrush)
	Oral hairy leukoplakia
	Pulmonary tuberculosis within the last 2 years
	Severe presumed bacterial infections
	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontis
	Unexplained anemia
	Neutropenia
	Thrombocytopenia
Clinical stage 4	HIV wasting syndrome
	Pneumocystis jiroveci pneumonia
	Recurrent severe bacterial pneumonia
	Chronic herpes simplex infection
	Esophogeal candidiasis
	Extrapulmonary tuberculosis
	Kaposi's sarcoma
	CNS toxoplasmosis
	HIV encephalopathy
	Cryptococcosis
	Progressive multifocal leukoencephalopathy
	Candida of the trachea, bronchi, or lungs
	Cryptosporidiosis
	Isosporiasis
	Visceral herpes simplex infection
	Any disseminated mycosis
	Lymphoma
	Invasive cervical carcinoma
	Visceral leishmaniasis

criterion, the World Health Organization (WHO) classification system, and the AIDS Dementia Complex staging. These staging systems are summarized in Tables 22.1, 22.2, 22.3, and 22.4 as well as described briefly below.

The CDC staging is broken into three basic clinical categories simply named CDC A, B, and C and further divided into sub-categories based on CD4 cell counts. Distinction between the broad clinical categories is based on specific clinical criterion with CDC A patients being asymptomatic, CDC B patients experiencing symptomatic symptoms, and CDC C patients experiencing AIDS-type indicators. Typical, as one might expect, with advancing disease and worsening immunologic function, cognitive dysfunction is typically exacerbated. For example, when using this staging criterion to examine cognitive deficits, there was a significant increase in the number of patients experiencing cognitive difficulties in the more advanced CDC stages. The overall rate of dementia did not increase across the stages though the number of patients

Table 22.3 AIDS dementia HIV disease severity staging system summary

ADC stage	Description
Stage 0: normal	Normal mental function
	Normal motor function
Stage 0.5: equivocal or subclinical	Minimal or equivocal cognitive symptoms
	Minimal or equivocal motor symptoms
	Mild neurologic signs (snout response, slowed extremity response)
	Gait and strength are normal
	No impairment at work or with capacity to perform ADLs
Stage 1: mild	Unequivocal cognitive symptoms
	Unequivocal motor symptoms
	Can walk with assistance
	Able to perform all but more demanding aspects of work or ADLs
Stage 2: moderate	Unequivocal cognitive symptoms
	Unequivocal motor symptoms
	Ambulatory but may require single prop
	Cannot work or maintain more demanding aspects of daily life
	Can perform basic activities of self-care
Stage 3: severe	Major intellectual incapacity (cannot follow news or personal events, sustain complex conversation, considerable slowing of output)
	Major motor disability (cannot walk unassisted, requires walker or personal support, slowing and clumsiness of arms as well)
	Cannot work or maintain basic ADLs without assistance
Stage 4: end stage	Nearly vegetative
	Intellectual and social comprehension and response at rudimentary level
	Nearly or absolutely mute
	Paraparetic or paraplegic
	Double incontinence

Table 22.4 American Academy of Neurology disease severity staging system summary

AAN stages	Cognitive/behavioral symptoms	Motor symptoms	ADLs
Asymptomatic	No significant dysfunction noted	No significant dysfunction noted	No impairment of work or ADL function
Mild cognitive motor disorder (MCMD)	History of impaired cognitive or behavioral function	History of motor dysfunction	Minimal impairment of work or ADL function
HIV-associated dementia (HAD)	Acquired abnormality in at least two cognitive domains (non-motor)	Acquired abnormality of motor function	Impaired ability to maintain employment
	Acquired abnormality for neuropsychiatric or psychosocial function (motivation, emotional control, social behavior)		Impaired basic and complex activities of daily living (medication adherence, bill paying, cooking, cleaning, driving, etc.)

experiencing mild to moderate degrees of cognitive deficits did demonstrate a significant increase (CDC staging study).

The WHO Clinical Staging of HIV/AIDS was developed for implementation in "resource-constrained" settings and was developed in 1990 and then later revised in 2005 [10, 11]. This system is based on clinical symptom presentation and does not require a CD4 cell count. Stages are categorized into two asymptomatic stages (primary HIV infection, clinical stage 1) and three symptomatic clinical categories that require the presence of specific clinical conditions. With the advent of rapid testing and improved laboratory methods specifically designed for resource-limited areas of the world, WHO staging criteria is being used less frequently. Additionally, the lack of the cognitive tests and normative data available for non-English speaking populations makes the assessment of HIV-infected patients in developing countries more difficult due to cognitive symptoms being evaluated more subjectively by physicians though studies examining the relationship between WHO staging and cognitive performance typically demonstrate worse cognitive symptoms in the more advanced WHO stages. However, there is still much to be learned with regard to HIV cognitive deficits among non-English speaking populations.

The AIDS Dementia Complex (ADC) staging system is also widely used and includes an asymptomatic stage and three additional symptomatic stages [12]. This system is based on neurologic and/or cognitive signs and symptoms. Stage 0 represents a patient state with no abnormal manifestations of mental or motor function. Stage 0.5 is used to implicate a subclinical stage of minimal or equivocal symptoms of cognitive or motor dysfunction that does not result in impairment of daily activities. Stage 1 characterizes a mild stage in which equivocal symptoms of cognitive (i.e., neuropsychological testing) or motor dysfunction impairs more demanding aspects of work. Stage 2, or moderate stage, includes cognitive and motor (i.e., ambulatory but may require single prop) symptoms that impair all but basic self-care activities of daily living. Stage 3 (severe) comprises major cognitive (i.e., difficulty following news, relating personal events, engaging in conversation, slow output) and motor (i.e., cannot walk unassisted, slow and clumsy) symptoms affecting all aspects of daily living. Patients in stage 4 (end stage) are nearly vegetative with only rudimentary comprehension of self.

In addition to these staging systems, researchers and clinicians have outlined more specific diagnostic criteria for several HIV-associated cognitive disorders. Initially, these disorders only included three basic diagnostic categories: asymptomatic, mild cognitive, and motor disorder (MCMD), and HIV-associated dementia (HAD) . In 1991, the American Academy of Neurology defined HIV-associated neurological deficits under two main categories, minor cognitive motor disorder (MCMD) and HIV-associated dementia (HAD). HAD is a multi-system disorder, characterized by cognitive, motor, and behavioral deficits [13] that impact activities of daily living. MCMD is a milder form of dementia that affects day-to-day activities like medication adherence and driving [14]. The annual incidence of HAD has dropped significantly after the introduction of HAART, but evidence indicates that incidence rates are once again rising with age of patients becoming an additional neurologic risk for dementia in patients infected with HIV. In fact, in a large multicenter study of cognitive dysfunction in HIV-infected patients, HAD and MCMD were shown to be very high, totaling 37% for individuals who are in the advanced stages of HIV/AIDS. In another recent study [14], at least 30% of symptomatic HIV+ adults were shown to have symptoms consistent with MCMD. These studies illustrate the need for further investigation of HIV-associated cognitive changes.

For this reason, a recent US National Institutes of Mental Health panel suggested changes of the classification of cognitive disorders for HIV-infected patients [15] due to the evolution of cognitive changes in the era of HAART. This new system is briefly summarized in Table 22.5. Rather than using earlier terms such as HIV-associated dementia, the panel suggests using HIV-associated neurocognitive disorder (HAND) to reflect the broad spectrum of neurologic disease and variability of behavioral/ cognitive presentation

Table 22.5 The NIMH HIV-associated neurocognitive disorder staging system summary

HAND stages	Cognitive symptoms	Activities of daily living	Other criterion
Asymptomatic neurocognitive impairment (ANI)	Acquire impairment of cognitive function involving at least two cognitive domains (>1 standard deviation below mean)	No impairment of ADL	Not the result of delirium
		No employment dysfunction	Cognitive change not result of another preexisting or comorbid condition
Minor neurocognitive disorder (MND)	Same as ANI	Mild or equivocal impairment of ADLs	Same as ANI
		Mild or equivocal employment dysfunction	
HIV-associated dementia (HAD)	Same as ANI	Marked impairment of ADLs	Same as ANI
		Marked employment dysfunction	

associated with HIV infection. Furthermore, this cognitive staging system delineates between three subtypes of cognitive dysfunction among HIV-infected patients, arguing that there are important differences in terms of the presence or absence of motor and/or psychosocial symptoms from patient to patient. The categories progress from asymptomatic neurologic impairment (ANI) to minor neurocognitive disorder (MND) to frank dementia. The ANI category captures the subset of patients experiencing impairment on tests of cognitive function without any problems in activities of daily functioning or employment. Patients diagnosed with ANI perform at least 1 standard deviation below the mean of normative scores in at least two of the following cognitive areas: attention–information processing, language, abstraction–executive, complex perceptual motor skills, memory, simple motor skills or sensory perceptual abilities. The MND category is similar to the American Academy of Neurology MCMD category described above. It differs from the ANI category in that patients must experience mild impairment of everyday functioning. A diagnosis of HIV-associated dementia is reserved for those patients who experience marked decline or dysfunction in their activities of daily living or employment. The cognitive changes associated with each category in this classification system must not occur solely as part of a delirium or be better explained by another comorbid disorder. The refinement of this criterion improves the specificity of research efforts aimed at understanding the progression of cognitive disorders associated with HIV infection.

Cognitive Domains Affected

HIV has a wide range of deleterious effects on cognition. Impairments in attention, memory and retrieval, verbal abilities, psychomotor speed, executive functions, and visuospatial abilities occur in patients affected by this disease. To simplify the discussion of these common deficits, it is helpful to describe the effects of HIV on each cognitive domain.

Attention

To best examine the cognitive affects of HIV infection for the attentional domain, it is more straightforward to discuss the findings in terms of simple and complex attention tasks [16, 17]. Simple attention involves basic processing ability with relatively few cognitive demands and is characteristic of tests such as digit vigilance, continuous performance, digit span, and cancellation tasks [17]. Research has demonstrated that simple attention as measured by these tasks is relatively spared in asymptomatic and symptomatic HIV-infected patients. However, with increasing disease severity, impairments in simple attention worsen or become more evident [18, 19]. In contrast, complex attention tasks measuring more complicated processing such as the divided or selective attention [20, 21] and covert-orientating tasks [22, 23] display significant changes in impairment even in asymptomatic patients. These deficits are present even in the era of HAART and appear to be one of the more consistent findings in HIV-infected cohorts [16]. Performances for the Paced Auditory Serial Addition Test [18, 24, 25], the Digit Symbol Test [26–29], and fMRI attention challenging tests give further evidence to HIV disruption of complex attention. Interestingly, fMRI in HIV-seropositive patients demonstrated recruitment of additional neural processes in the post-parietal cortex, left prefrontal cortex, and supplementary motor area to perform equally with control subjects on complex attention tasks suggesting impairment or disorganization in brain circuitry [30].

Post-HAART studies have detected no neuroprotective or restorative effects for HAART on attention impairments (see Table 22.6 for additional summary of longitudinal studies). For example, performance on the WAIS-R Digit Span tasks demonstrated that 62.8% of long-term HAART patients have persistent attention

Table 22.6 Test batteries commonly used in HIV assessment

Domain	HIV MRS consortium	CHARTER study
Attention/speed of processing	Trail making part A, WAIS-digit symbol	Trail making part A, WAIS-digit symbol
Executive function	Trail making part B, paced auditory serial addition task-50 item version	Trail making part B, Wisconsin Card Sort Test-64 card version, Paced Auditory Serial Addition Task-50 item version
Working memory	WAIS-letter-number sequencing	WAIS-letter-number sequencing
Language	Control oral word association test, category fluency – action, category fluency – animals	Control oral word association test, category fluency – animals
Motor	Grooved Pegboard	Grooved Pegboard
Visuospatial processing	WAIS-symbol search	WAIS-symbol search
Learning and memory	Hopkins verbal learning test – revised	Hopkins verbal learning test – revised
	Brief visuospatial memory test – revised	Brief visuospatial memory test – revised
		Story memory test
		Figure memory test
Academic	WRAT3-reading subtest	WRAT3-reading subtest
Behavioral	Frontal systems behavioral scale – FrsBe	Substance use history
Activities of daily living	Activities of daily living questionnaire	Activities of daily living questionnaire, employment questionnaire, medication management task, Valpar vocational assessment
Mood	CES depression scale	Beck depression inventory – II
Misc.	Patient's assessment of own functioning, MOS HIV Health Survey	Patient's assessment of own functioning

deficits even after 5 years of treatment [31]. In an effort to predict the evolution and progression of attention deficits in HAART-treated patients, traditional clinical and laboratory markers such as CD4 cell count and plasma viral load at baseline, HIV disease stage, age, CDC stage, and risk category have been employed but no consistent statistically significant clinical correlation has been found [32]. Some studies have discovered relevant clinical indicators to be accurate predictors of NP impairment while others have not. For these reasons, some researchers doubt the clinical reliability of attention testing to define disease stages in HIV-infected patient populations. The prevalence of psychiatric disorders associated with the progression of HIV infection also casts some doubt on the clinical application of attention tasks [33]. In an 8-year longitudinal study, one-third of HIV+ participants experienced a major depressive episode with symptoms correlating with diminished performance on measures of attention. Poor performance was linked to the intensity of depressive symptoms resulting in less general concentration dedicated to attention as well as other cognition tasks [31]. However, more recent cross-sectional studies [34] have shown cognitive impairment in attention and major depression should be considered as independent processes and not as a systematic association [35].

Memory

Typical assessment of memory in HIV-infected patients often includes examining several functional related sub-domains of memory including visual and verbal learning, working memory, short and long delay free/cued recall, explicit and implicit memory. As noted in the pathology section of this chapter, there is a new interest in examining changes in memory function due to the more medial temporal lobe involvement. For example, it has long been known that during the progression of HIV infection many of the manifested memory impairments mimic symptoms found in multiple sclerosis (MS), Parkinson's disease (PD), and/or Alzheimer's disease (AD) [36, 37] though the underlying pathology for these symptoms has not been fully appreciated in HIV infection. However, recent pathological results seem to indicate that the overlap in memory symptoms across these disorders may be attributable to increased hippocampal inflammation and hyperphosphorylation of Tau proteins [4, 5] resulting in short-term memory disturbances while implicit and remote explicit memories remain functionally intact [18, 36]. However, the direct relationship between pathological change in the temporal lobe and memory deficits needs to be examined.

The ability to recall learned and/or stored information has been shown to be impaired in HIV-infected patients. For example, pre-HAART studies measuring logical learning deficits by utilizing story tasks, such as Wechsler Memory Scales [24, 38] and the Expanded Halstead–Reitan Battery [18, 39], detected changes in memory function early in the disease process. More current post-HAART longitudinal studies have yielded equivocal results with some studies demonstrating modest improvements [32, 40], others demonstrating no change [41], and yet others demonstrating decline [42] though differences in patient populations and study duration make it more difficult to interpret these findings. Importantly, it appears that memory impairment progression was strongly associated with a composite global cognitive baseline score (see Table 22.6 for a summary of other longitudinal memory studies). Additionally, in this study the variability of baseline and current memory performance was also significantly associated with education level and hepatitis C virus co-infection status (see discussion of cognitive confounds below). For example, asymptomatic and symptomatic patients with less education demonstrated persistent memory deficits [32]. This finding validates an early study that demonstrated that the initial discrepancies found for the Rey Auditory Verbal Learning Task (RAVLT) and California Verbal Learning Test (CVLT) were accounted for by differences in the patient's education level [43] suggesting the need

to take education level into account when examining memory in HIV-infected patients.

As pointed out earlier, the importance of memory and learning in HIV-infected patients may be underestimated at this time. With the recent findings of increased inflammatory markers of disease action in the medial temporal lobe among treated patients, one could reasonably expect memory and learning deficits to increase in this population. However, this needs to be examined directly among HIV-infected patients.

Language

Verbal and language abilities are considered one of the expressive functions, such as speaking, writing, and physical gestures, that together make up all observable behavior. Verbal deficits come in many forms, most of which are not characteristic of HIV infection. HIV rarely causes aphasic symptoms, which are defects of symbol formation that can manifest in many ways including semantic deficits, abnormal repetition, and other difficulties with expression [17]. When verbal deficits occur in HIV, they usually emerge as problems with verbal fluency, which are most often assessed with letter and category fluency tests [9]. Impairments in letter fluency, which involve the generation of as many words beginning with a certain letter as possible in a given time, are associated with executive functions and frontal systems. Problems in verbal fluency are reported in earlier studies [18, 44], with worsening performance among patients with more advanced disease.

Research conducted post-HAART demonstrates less consistent findings with regard to verbal fluency. Some studies report no difference between seronegative controls and HIV+ patients [7, 45], whereas others find impairments [46], though once again the most significant differences appear in more advanced disease states [46]. A meta-analysis conducted by Iudicello et al. [47] found small deficits in both letter and category fluency across 37 studies conducted between 1985 and 2005 [47]. In conclusion, although fluency deficits commonly occur in HIV, they are typically not severe and may be relegated to a subgroup of patients in more advanced stages of the disease.

Psychomotor Abilities

Psychomotor deficits are common in HIV+ populations and were documented in the early years of HIV discovery [48]. These symptoms were once considered to be the hallmark of HIV-related neuropsychological impairment, but research in recent years has shown that other cognitive deficits are much more characteristic of HIV [9]. Psychomotor deficits are typically measured as slowed performance on motor task tests such as the Finger Tapping Test, Grooved Pegboard Test, Trail Making Test (A and B), and the Symbol Digit Modalities. Psychomotor impairments were typically found on the Grooved Pegboard Test [18, 49–51] and the Purdue Pegboard Test [52].

Several studies have been conducted post-HAART that measure psychomotor ability in HIV+ individuals. These studies tend to have variable findings, but they generally show that HIV-infected patients continue to suffer from psychomotor deficits, especially in more advanced stages of disease. Suarez et al. [40] found an improvement in motor function (assessed by the Purdue Pegboard tests) for patients using HAART, while Sacktor et al. [14] did not [14, 40]. Research on clinically asymptomatic patients failed to detect deficits in psychomotor processing [53]; such deficits appear to be manifested more during the later symptomatic and AIDS stages of the disease [54]. However, when using more sophisticated electrophysiology measures of motor abilities, Von Giesen et al. demonstrated minor motor deficits in HIV-infected patients in asymptomatic patients [55]. Tremor peak frequency (TPF), the frequency of the most rapid alternating index finger (MRAM), simple reaction time (RT), and

contraction time were recorded (CT). HIV-infected patients performed significantly worse than controls on MRAMs for both hands, reaction time for the right hand, and contraction time for both hands.

Deficits involving psychomotor slowing are consistent with pathological evidence of myelin changes commonly observed in HIV-infected patients as white matter integrity has long been known to mediate speed of process functions. As the majority of pathological changes occur in white matter even in the era of HAART, it is expected that psychomotor slowing will continue to be a predominant feature of HIV infection and should be assessed routinely in this patient population.

Executive Functions

Executive functions refer to the ability of an individual to engage in independent, purposeful, self-serving behavior [17]. HIV-infected individuals have significant impairments in this domain when assessed by commonly administered measures of executive function (Stroop Color and Word Test, Trailmaking Test Part B, Wisconsin Card Sorting Test, and the Halstead Category Test). Using the Halstead Category Test, Grant et al. demonstrated impairments in abstraction for patients with clinically asymptomatic HIV that worsened with more advanced stages of disease [38]. Impairments were also commonly observed in measures of set shifting (Trails B) [18] and for response inhibition (Stroop) [56, 57].

Tests conducted post-HAART continue to demonstrate deficits in measures of executive function, (e.g., Stroop Test [58]; Trail Making Test B [54, 59]; Wisconsin Card Sorting Test [60]). Recent studies also report impairments in decision making as assessed by the Iowa gambling task [61, 62]. After attention, executive function is the cognitive domain affected most by HIV despite improved treatment.

Visuospatial Deficits

Tasks designed to assess visuospatial processing often demonstrate minor deficits in HIV-infected patients. For example, using a perceptional span task where a target letter must be discriminated from a display of nontarget letters, Hardy [63] demonstrated a significant reduction in the accuracy of performance for HIV-infected patients when compared to controls [63]. This difference can become exaggerated in more demanding perceptual conditions and as such is interpreted as a demonstration of impairment in early-stage visual perception processing. This finding is similar to working memory tasks [9, 21] and divided attention [16, 20–22] where more complex, difficult tasks are increasingly affected. It is also interesting to note that there was no significant main effect or interaction for either experimental group (HIV infected versus healthy controls) with respect to gender or alcohol/chemical substance abuse [63]. Some have attributed the changes in perception span to be in reality an associated symptom of other upper-level impairments due to pre-frontal–subcortical dysfunction found in HIV infection [1, 64]. For example, performance for the Tactual Performance Test from the Halstead–Reitan Battery provides evidence to an associative motor component of visuospatial impairments through assessments of motor performance speed, tactile perception, and spatial problem solving [18, 24, 65, 66] all of which demonstrate HIV-associated changes. Patients with significant visual defects as assessed via objective cognitive testing were found to be more likely to be diagnosed with HIV-associated dementia or minor cognitive/motor disorder displaying further correlation [63].

Table 22.7 Cognitive sequelae as observed in longitudinal retrospective/prospective studies

Domain	Publication, year	Study duration	Results
Psychomotor	Cole et al., 2007 [53]	5 years, 40 visits	Function preserved in asymptomatic HAART patients
	Tozzi et al., 2007 [32]	8 years, 8	Maintained level of function at HAART initiation
	Baldewicz et al., 2004 [31]	8 years, 16	Function declined from asymptomatic to AIDS stage for HAART patients
	Ferrando, 2003	6 months, 3	Slight to moderate improvements in function as a result of HAART potency
	Cohen et al., 2001 [41]	1–2 years, variable	Function improved in women on HAART
	Sacktor et al., 1999 [70]	2 years, 4 visits	Function improved in patients on combination antiretroviral therapy
Learning and memory	Tozzi et al., 2007 [32]	8 years, 8	Impairments remained even after HAART initiation
	Suarez et al., 2001 [40]	4 years, 1–6	Modest improvements and eventual plateau in HAART patients
	Cohen et al., 2001 [41]	1–2 years, variable	No improvements found in women on HAART
	Basso et al., 2000 [42]	6 months, 2	Significant decline in function especially in the AIDS stage
Attention	Tozzi et al., 2007 [32]	8 years, 8	Decline in function in HAART patients
	Baldewicz et al., 2004 [31]	8 years, 16	Found no significant decline in function
	Reger et al., 2002 [54]	~6 years, variable	Small to moderate decline in symptomatic and AIDS patients
Verbal ability	Dolan et al., 2003 [69]	2–3 years, variable	Improvement in fluency for women on HAART for 18 months+
	Reger et al., 2002 [54]	~6 years, variable	Small deficits in HAART patients
	Cohen et al., 2001 [41]	1–2 years, variable	Improvements in women on HAART
	Basso et al., 2000 [42]	6 months, 2	Progressive decline through stages of disease and plateau in AIDS stage
Executive function	Tozzi et al., 2007 [32]	8 years, 8	<50% patients retain function, >50% decline, baseline severity predicts progression
	Dolan et al., 2003 [69]	2–3 years, variable	Improvements in function for women on HAART for 18 months+
	Reger et al., 2002 [54]	~6 years, variable	Moderate function decline in symptomatic stage; large function decline in AIDS
	Suarez et al., 2001 [40]	4 years, 1–6	Function improvements in HAART patients
Visuospatial	Tozzi et al., 2007 [32]	8 years, 8	Persistent decline in function despite HAART
	Dolan et al., 2003 [69]	2–3 years, variable	Decline in function in HAART patients
	Knippels, 2002	3 years, variable	Decline in function in HAART patients

Cognitive Sequelae

7Cognitive sequelae among HIV-infected patients can be described in two general ways. In cross-sectional research studies, HIV-infected patients typically experience a decline in cognitive functioning that is associated with disease stage or symptom severity with asymptomatic HIV+ patients experiencing the least amount of cognitive change while symptomatic HIV-infected and AIDS patients experiencing the most cognitive deterioration. Importantly, however, on cognitive tests even asymptomatic patients – those with minimal clinical and/or cognitive symptoms and who do not experience difficulties in daily functioning – perform more poorly than seronegative controls on many standardized neuropsychological tests. In their meta-analysis paper, Reger et al. [54] used Cohen-defined parameters for small (0.00–0.35), moderate (0.36–0.75), and large effect sizes (0.76–1.00) finding small effect sizes (0.05–0.21) for asymptomatic patients for a wide range of cognitive deficits [54, 67]. The greatest differences at this stage were observed in the area of language, specifically naming. These authors found small to

moderate differences in patients with symptomatic HIV (0.18–0.65) with the greatest differences occurring in areas of motor functioning followed by problem solving and executive functions, information processing speed, and language. There were relatively moderate to large effect sizes (0.42–0.82) for patients with clinical AIDS. These patients experienced the greatest decline in motor and executive functioning followed by slower information processing speed and a decrease in immediate visual memory. Moderate differences were observed for language and visual construction while small differences were seen for attention and concentration. Evidence for HIV impairments is found in the wide range of neurocognitive domains with severity varying in a dose-dependent way according to clinical staging.

In prospective studies of cognitive symptom progression, HIV-infected patients can manifest different trends. In the recent report by Mariana Cherner on the CHARTER HIV cohort [68], 15% of the patients examined demonstrated improvements in function, 4% demonstrated declines in function, and 22% demonstrated variability in cognitive domains impaired. In the era of HAART, the course of cognitive dysfunction appears to be independent of CD4 cell counts and viral loads making it difficult for researchers and clinicians to understand cognitive changes in this population. This finding underscores the importance of prospective studies and/or repeated clinic visits to fully appreciate the evolution and progression of symptoms in HIV-infected patients. Examination of treatment effects on cognitive performance across samples produces equivocal results with some studies demonstrating improvement on cognitive function for effectively reconstituted or treated patients [40, 41, 53, 69, 70] while others demonstrate either minimal or no improvement with treatment [31, 32, 41, 42, 54]. Improvement is likely the best among patients treated early before significant reduction in CD4 cell counts occurs. In fact, there are many studies that demonstrate a significant association between the nadir CD4 cell count (lowest clinical CD4 cell count) and cognitive performance with those patients having the lowest nadir CD4 cell counts having the worst cognitive outcome or limited recovery of cognitive function after treatment (Table 22.7).

Cognitive Batteries Used to Assess HIV-Associated Cognitive Dysfunction

Early in the pandemic, the emphasis in patient care was on survival and cognitive testing only played a minor role and typically included a small number of tests that focused primarily on motor functioning and speed of processing. As the patient's life expectancy has been prolonged with improved treatment options, there has been a growing interest in understanding the nature, extent, and severity of cognitive change in HIV-infected patients.

Currently, there are no specific tests or test batteries recommended for this population, though the general idea is to use a broad battery of tests that cover most of the cognitive domains typically assessed by neuropsychologist. This improves the ability of clinical neuropsychologist to examine more subtle forms of cognitive impairment that typify most patients infected with HIV in the era of HAART. Tests from two large studies (HIV Magnetic Resonance Spectroscopy (MRS) Consortium Study and CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Study) of cognitive dysfunction in HIV-infected patients are listed in Table 22.6 as examples of possible test batteries to use in this population. Differences in the batteries are highlighted as well.

Cognitive Confounds

The biological complexity of HIV as a pathogen has proven a true challenge in terms of under-

standing the impact of the disease on the brain and central nervous system. At present the field is just beginning to identify key properties of the virus (envelope proteins, clade variants, etc.) that determine overall impact on the brain, though much more work is needed before a complete neuropathogenic model can be developed. Yet, despite the complexity of the viral factors noted above, it is clear that key host factors also determine the integrity of CNS function in this population. Factors such as alcohol and illicit drug abuse and comorbid infections (e.g., hepatitis C) are common population characteristics embedded within the epidemic and each of these are well known to impact brain function independent of HIV. Further, issues associated with treatment of HIV with antiretroviral compounds such as efavirenz and the impact of advanced age on cognitive function have both emerged as areas of research and clinical focus now that treatment, but not eradication, of HIV has changed the natural history and demographic climate of the disease.

Somewhat frightening is the very real possibility that many of these host factors already work synergistically to complicate the outcomes associated with the disease and the likelihood that such interactions will increase in frequency in the absence of a cure. That is, the longer the people survive and continue to age, the greater the possibility that any one of these host factors will interact with advanced age and impact clinical outcomes. In addition, evidence that cognitive function is intimately linked to adherence to medications [71], employment opportunities [25, 72, 73], and quality of life [74] underscores the need to review the impact of these host factors on cognitive function. For several of these factors (alcohol and drugs, co-infections, and treatment with efavirenz) clinical decisions can be made to minimize their overall impact, again emphasizing the importance of careful attention to these factors.

It should be noted that recent review papers have addressed these specific topics, including excellent reviews by Gonzalez and Cherner [75] and Tyor and Middaugh [76]. The reader is referred to these review papers for more detail regarding the mechanisms by which HIV and alcohol/illicit drug use, co-infection status, and aging may interact with HIV to negatively impact brain function. Here we present a brief synopsis of this literature and offer some unique insights into the points of interest.

Alcohol and Drug Abuse Issues

The relationship between alcohol and illicit drug abuse and the HIV epidemic is painfully obvious. Injection drug use is the primary vehicle of infection in the USA and Europe [77], and risky sexual behavior conducted in the context of alcohol/drug intoxication represents a secondary pathway by which individuals become infected (or infect others). However, alcohol and illicit drug use are also recognized as factors that directly impact brain function, raising the question as to whether or not seropositive patients with current or recent histories of alcohol or illicit drug abuse exhibit more impaired brain function than individuals without similar histories. The answer to the question seems almost intuitively obvious given that both factors have independently been associated with impaired brain function, yet the outcomes of behavioral studies have not been nearly as clear as one might expect, with some studies demonstrating significant effects of alcohol and/or illicit drugs [78–80] and other studies demonstrating no significant impact of comorbid histories on cognitive function [81].

As noted by Gonzales and Cherner, one potential explanation for the lack of consistent effects is related to the complexity of studying variance attributed to both HIV and alcohol/substance abuse [75]. HIV has recently been described as exhibiting fluctuating symptoms over time [82] and in the era of HAART this variability may be increasing as there is now a clear disconnect between cognitive status and CD4 count. Further, many substance abusers do not abuse a single drug and different illicit drugs do not involve or impact the same neurotransmitter systems, resulting in notable biologic heterogeneity. Further, as members of our group

have previously described [83], efforts to classify drug abusers using clinical criteria do not necessarily provide optimum information regarding the degree of exposure of these substances to the brain because there can be substantial range of alcohol and drug use within a given clinical classification. Quantitative ratings of alcohol or drug use help to circumvent this issue but even relying on these methods do not necessarily identify robust relationships between use and cognitive status among HIV-infected patients [81].

With these limitations noted, there have been several interesting mechanisms proposed to account for possible synergistic or additive effects of alcohol and/or illicit substance abuse and HIV on brain function (see Gonzalez and Cherner [75] for review). For example, alcohol and illicit substance abuse have been implicated in immune suppression [84, 85], altered cytokine production in the CNS [86, 87], and disruption of the blood–brain barrier [88, 89]. Each of these factors have the potential to alter the natural history of HIV, as all three systems are intimately involved in the initial trafficking and regulation of the virus within the brain. Further, stimulants such as cocaine have been shown to increase the risk of cerebrovascular disease, creating a possible greater vascular burden among infected patients. Among younger patients this may not have a substantial impact but for older infected patients, who are already at risk for vascular disease as a function of age-related vascular decompensation, the combined effects of age, HIV, and stimulant abuse may have greater impact [90, 91].

A further variable that has yet to receive significant attention in the literature is the impact of both substance abuse and HIV on dopamine as regulated by brain-derived neurotropic factor (BDNF). HIV directly down-regulates BDNF [92] and this neurotropic factor is itself important in the regulation of dopamine in the mesolimbic dopamine system [93]. Substance abuse is well known to alter the dopamine system directly and there is potential that individuals with HIV and substance abuse exhibit greater disruption in this critical neurotransmitter system than individuals with either condition alone. If true, this could have significant implications for the expression of depression and apathy that is so common among infected patients. However, at this point the impact of HIV and alcohol/substance abuse on BDNF or the other biological systems noted above represents little more than interesting models since limited work directly addressing these factors has been completed at a behavioral or brain systems level.

Some of the most exciting recent work in brain systems has utilized neuroimaging methods to gain a better understanding of the potential interactions between HIV and alcohol/substance abuse. The outcomes of these studies are important because studies utilizing structural neuroimaging (e.g., MRI) have reported opposing effects of HIV and substance abuse. For example, Jernigan et al. [94] reported that individuals with histories of methamphetamine dependence without HIV exhibited increased volumes of the basal ganglia (and parietal cortex), whereas individuals with HIV but without methamphetamine-dependence exhibited significantly smaller volumes of striatal structures [94]. These findings suggest that while both conditions may influence similar brain systems, the direction of the influence may not be consistent. This may be further modified by HIV disease stage or other viral factors, as Castelo et al. [95] have reported hypertrophy of the putamen among nondemented HIV-infected patients with cognitive compromise, and these findings were independent of substance abuse [95].

More consistent findings have been reported utilizing diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). For example, two studies demonstrated that individuals with HIV exhibited significantly reduced integrity of white matter fiber in the corpus callosum and this impact was further enhanced substantially within the genu of the corpus callosum among individuals with histories of alcoholism [80, 96]. Behaviorally, these alterations in the integrity of the white matter covaried with reduced performance on tests of motor function [96].

Additional studies have demonstrated greater abnormalities in brain function among

HIV-infected alcohol and methamphetamine users using MRS. For example, Taylor et al. examined four groups of participants that differed according to HIV serostatus and methamphetamine abuse history and reported that HIV-positive individuals who abused methamphetamine exhibited strong relationships between plasma HIV viral load and both *N*-acetylaspartate (NAA) reductions in the frontal white matter and increased myoinositol (MI) in both frontal white and frontal gray matter compared to HIV-infected patients without amphetamine abuse histories [97]. These findings suggest an interaction between HIV disease burden factors and metabolite markers of mature neurons and glosis, respectively. Similarly, Chang et al. [78] reported significant changes in NAA in the basal ganglia, frontal white matter, and frontal gray matter among HIV-positive individuals with chronic methamphetamine abuse compared to HIV-infected patients without such histories [78].

As described from the studies above, it is clear that individuals with histories of substance abuse exhibit alterations in brain integrity that are more pronounced than patients without such histories. While few behavioral studies have clearly defined the functional nature of these effects, the sensitivities of MRS and DTI have allowed investigators to begin to address the impact of alcohol and substance abuse on the brain in this population. Additional studies that integrate behavioral testing, neuroimaging, along with quantified substance abuse measures will be important to define these relationships with greater certainty. Ultimately this work will be critical in building the most accurate neuropathogenic model of HIV and the brain.

Co-infection with Hepatitis C

HCV, like alcohol and substance abuse, is intimately tied into the basic HIV epidemic because the majority of injection drug users infected with HIV are also infected with HCV [75]. Transmitted through blood contact, injection drug users are at high risk for infection with both viruses. In addition, like substance abuse, HCV mono-infection is known to impact cognitive function independent of HIV (for reviews see Forton et al. [98]). Only recently has the research community devoted attention and resources to defining the neuropsychological impact of HIV–HCV co-infection and interestingly the results of these studies have revealed consistent deleterious effects of HCV co-infection on brain function.

The literature has recently been reviewed by members of our group [83] and these studies point to a common deficit in cognitive processing speed that is more apparent among co-infected patients than individuals who are mono-infected with HIV. Von Giesen et al. was among the first group to address this issue and they reported slower reaction times among co-infected patients compared to HIV mono-infected patients [55]. Similarly, Martin et al. reported poorer performance on a computerized Stroop task among co-infected patients compared to mono-infected patients [58] with similar findings being reported elsewhere [99–101].

As such, the question is not whether or not HCV coinfection is an important contributor to cognitive outcome in HIV, but rather, what is/are the mechanism(s) by which co-infection status disrupts the brain. A number of factors have been proposed including greater depression and substance abuse histories among coinfected patients compared to mono-infected patients. Indeed, Clifford et al. [99] and Richardson et al. [101] reported significantly higher rates of depression and substance abuse histories among co-infected patients. Given the discussion in the previous section that substance abuse status is itself associated with cognitive impairment independent of HIV, it seems parsimonious that the greater cognitive impairment among this population is associated with the more severe substance abuse histories. However, the connection between these two is not very clear and in fact we have reported that the two factors are not statistically correlated [102]. As such, while depression and substance abuse histories are more severe in the co-infected populations, it is not clear that the greater cognitive impairment reported in this population is related to these patient factors.

An alternative hypothesis is that processing speed deficits associated with co-infection are associated with direct impact of the HCV virus on the brain. There is evidence that HCV is present in the central compartment, suggesting the possibility that HCV presence in the brain initiates an inflammatory response not very different from the model widely accepted for HIV neuropathogenesis. MRS studies of HCV mono-infection indeed demonstrate abnormalities in the white matter of infected patients [98] consistent with the idea that viral presence in the brain may result in a proinflammatory cascade targeting the white matter. However, it is not clear at the present time that sufficient viral load exists in the central compartment to fully account for these effects and no studies of co-infected patients have examined CSF viral loads of HCV to map the direct relationships between viral presence within the brain and associated abnormalities in brain structure and function.

A second hypothesis that has been proposed is related to liver damage associated with HCV, and the possibility that brain dysfunction among co-infected patients reflects secondary processes due to liver damage. Indeed patients with liver disease independent of HCV exhibit cognitive deficits that are related to the extent of liver damage as defined by liver fibrosis stage. This mediational model is interesting because several studies of co-infected patients have found relationships between liver fibrosis stage and the extent of processing speed deficits [100]. However, not all studies have found similar effects suggesting this model may be incomplete, and Morgello et al. [103] identified an interesting differentiation between MRS brain metabolite changes associated with HCV and metabolite changes associated with liver encephalopathy. Specifically, individuals with HCV mono-infection exhibit increased choline/creatine ratios on MRS that are not evident among individuals with hepatic damage unrelated to HCV.

Of course the suggestions that among co-infected patients the brain is affected by the direct presence of the virus in the central compartment and through secondary processes associated with liver disease are not mutually exclusive or competing models. In fact the most complete model may include both processes. Unfortunately this issue will not be more clear until comprehensive studies of cognition in co-infected populations examine liver variables, viral factors (both HIV and HCV), brain function, and brain structure in the same cohort but there is little doubt if this work is important toward understanding the impact of host factors on clinical outcome in HIV.

Advanced Age, HIV, and the Brain

A third host factor that has gained traction in the research literature is advanced age. The average age of a patient infected with HIV has increased significantly since the beginning of the epidemic in the USA, where several young adults with opportunistic infections and severely compromised immune systems were described in the clinical literature. At least two factors have contributed to this shift in the age curve, including longer survival time associated with antiretroviral therapy and a later age of initial infection for a smaller percentage of patients. In fact there has been a 10-fold increase in the number of HIV-infected cases over the age of 65 in the past decade [104] and recent estimates suggest that by 2015 approximately 50% of the prevalent US AIDS cases will be classified as older patients [105].

Concern regarding the impact of advanced age on cognitive outcome associated with HIV is generally based on the observation that the immune system undergoes aging processes in the absence of HIV and as such there is a possibility that the older immune system is less capable of responding to the viral impact of HIV [106, 107]. However, on a positive note direct evidence of poorer general disease outcome of older HIV-infected patients is not common and as members of our group have previously noted [105] this may in part be influenced by the generally better adherence to HAART medications among older patients compared to younger patients (thus resulting in improved viremic control).

The second pathway by which older age may influence cognitive outcome in this population is through additive effects of general age-related cognitive decline. Cognitive function tends to decrease across most cognitive domains after the age of approximately 45 [108] and the declines appear most prominent in areas of motor speed and information processing. This change in cognitive integrity may relate to underlying neuronal integrity in frontal brain systems and related white matter pathways that breakdown due to age (or age-related cerebrovascular disease [109]). Of interest is that these cognitive domains that decline among older seronegative individuals overlap significantly with the cognitive domains and brain regions typically involved in HIV. These findings suggest that both older age and HIV may independently impact brain function resulting in additive effects on cognitive compromise within this population.

A third possibility is that older age and HIV may interact synergistically to lower the threshold for the development of degenerative CNS diseases. For example, there has been some concern that older HIV-infected patients may be at risk for Alzheimer's disease at a younger age than noninfected patients. In fact, PET imaging with PIB has revealed significantly greater amyloid deposition in the brain among infected patients [110, 111]. The deposition has been described as reflecting a near 10-year shift in the age profile of patients. These findings are interesting and potentially very clinically relevant but it is worth noting that amyloid plaque deposition (via PIB binding) is not a perfect biomarker of Alzheimer's disease and may reflect general injury in the brain. In fact there is no information at the present time that the cognitive profile of older infected patients has shifted from the classic "subcortical" pattern of HIV to a mixed subcortical/cortical pattern with amnestic memory impairment that is characteristic of Alzheimer's disease.

This is not to say that HIV-infected patients are not at greater risk for developing Alzheimer's disease at a later period in the adult lifespan. That is, the risk may be whether or not they exhibit symptoms during the lifespan, rather than the time point at which they exhibit symptoms characteristic of the disease. This is supported by the fact that many conditions (head injury, stroke, etc.) that lower the overall integrity of the brain tend to increase the risk of developing Alzheimer's disease later in life (for a review see van den Heuvel [112]); certainly HIV infection of the brain represents a condition that could lower cognitive reserve and increase the risk of dementia at a later date.

Studies that have directly measured cognitive function among older individuals compared to younger individuals have revealed some conflicting results. When cognitive status has been defined clinically as demented versus not demented, the results tend to be more consistent with older patients exhibiting an increased risk for dementia associated with HIV compared to younger patients [8, 26, 113–115]. However, when raw scores on neuropsychological tests are included in analyses rather than a clinical diagnosis of dementia, the differences between older and younger age status and HIV infection are less clear. For example, Kissel et al. [116] recently failed to identify significant differences according to age breakdown among HIV-positive individuals relative to seronegative counterparts. The discrepancy between the two sets of findings may reflect the relative subtlety of effects of age in the younger age "old" cohort and/or the importance of considering functional scores of activities of daily living in identifying the impact of age on cognition in this population. Future studies that incorporate both clinical and raw scores might help define these relationships with greater certainty.

Additional Host Risk Factors

Along with substance abuse, comorbid infections, and age there are several other host risk factors that have been identified among HIV-infected patients that worth mentioning briefly. The likelihood of major psychiatric illness, cognitive effects from HAART, and facing difficult social issues must be discussed to adequately address the entirety of the HIV-infected patient experience.

Psychiatric Illness

The issue of psychiatric illness in HIV-infected patients is also an important potential cognitive confound in this population. In fact, relative to the general population, prevalence rates for psychiatric disorders among HIV-infected patients are typically two to six times higher (depending on the disorder) with the most common psychiatric disorder being major depression. If combined with other related disorders (i.e., dysthymia), depressive mood disorders account for about 50–60% of all the psychiatric disorders in HIV-infected patients. Though there are other disorders observed in this population that exist either comorbidly or in isolation (anxiety, mania, psychosis, delirium, sleep disorders, and substance abuse), we focus on depression in our discussion as it has been shown to relate to disease progression and cognitive dysfunction.

Prevalence rates of current major depression among HIV-infected patients range from 4 to 36% depending on the setting and risk groups studied [117–121]. Typically rates of depression are higher in men who have sex with men (MSM) and substance abusers. However, regardless of the HIV subpopulation studied, the lifetime rates of major depression are as high as 50% [122] in HIV -infected patients though those with symptomatic HIV infection are more likely to experience a major depression episode when compared to asymptomatic patients. With extended survival afforded by improved treatments, HIV-infected patients may thus experience more episodes of depression over a greater span of time [123]. Thus, recognizing, diagnosing, and treating depressive symptoms in HIV-infected patients become more important.

Beyond the prevalence rates, there are other reasons for an increased interest in depression in the context of HIV infection. First, chronic depressive symptoms are associated with higher mortality rates among HIV-infected patient populations. The HIV Epidemiology Research Study (a large multicenter study of HIV-infected women) found that the rate of death in patients experiencing chronic depressive symptoms was approximately double that of patients experiencing limited or no depressive symptoms. Second, the presence of chronic depressive symptoms is associated with a more rapid decline in CD4 cell counts heralding a decline in host immunological health [124]. Some studies even suggest that presence of baseline depressive symptoms (symptoms previous to or at the time of initial infection) may predict a more rapid immunological decline when compared to patients without depressive symptoms [125]. Third, depressive symptoms are negatively associated with rates of medication adherence while the successful treatment of these symptoms improves adherence to medication regimens [126–128]. Poor adherence is recognized as a critical factor in increases of resistance and shorter survival periods. Fourth, chronic or intermittent depressive symptoms can negatively impact or worsen cognitive function in HIV-infected patients.

Disentangling the effects of HIV on cognitive dysfunctions is complicated and has yielded equivocal results though a recent study by Castellon et al. demonstrated that the equivocal findings may be related to the multidimensional aspects of depression [129]. Typical examination of depression in research and clinical settings often includes instruments that yield a single summary score though depressive symptoms are known to range from somatic, affective, cognitive, and motivational components. In fact, findings from their study demonstrated that when examining these components separately, mood and motivation symptoms of depression were most related to cognitive performance across several domains. These findings suggest that certain items for a given depression rating scale may be more indicative of CNS involvement and that there may be disease-specific mechanisms underlying specific depression symptoms and cognitive dysfunction. For these reason, careful examination of depressive symptoms in HIV-infected patients continues to be an important component of any clinical assessment.

Treatment of depressive symptoms using pharmacological, psychotherapy, or a combination of both typically demonstrate an improvement in depressive symptoms. This is encouraging and as noted above has led to improved immunological function in HIV-infected patients. On a cautionary note, antidepressant medications and medications used to treat HIV infection share similar metabolic pathways and care must be taken in choosing medications when treating depressive symptoms in HIV-infected patients as there may be potential interaction between the medications that can worsen depressive and/or clinical symptoms (for a review see Ferrando and Freyberg [123]). Regular evaluation of the HIV-infected patients for psychiatric types of disorders will provide the optimal care for patients, providing evaluation for health-care providers with the information that they need for optimal care and the greatest chances of improved immunological recovery and virologic response thereby improving quality of life and diminishing morbidity and mortality.

Effects of HIV Treatment on Brain Function

As been discussed before, HAART typically improves HAND specifically reducing the amount of severe cognitive dysfunction. Yet, despite the improvements in cognition, patients do not appear to return to baseline function with the prevalence of mild to moderate cognitive impairment increasing. Indeed autopsy data indicate that some degree of encephalopathy is nearly twice as common in the post-ART era despite a near total elimination of CNS opportunistic infections [130]. These findings have led to speculation that factors associated with treatment itself may lead to some degree of neurotoxicity that damages the brain in the long term. While much speculation has been raised regarding this issue, there is very limited real data at the behavioral level and when present it is often confounded by disease duration, age, nadir CD4.

Additional concern has been raised about specific treatment regimens as conferring some degree of additional cognitive risk. Of the available interventions, efavirenz has received the most attention. Efavirenz is a non-nucleoside reverse transcriptase inhibitor that has been used with notable success as part of an antiretroviral approach to HIV. However, patients have often described a number of neuropsychiatric symptoms associated with use of the drug including LSD-like psychosis, nightmares, and mental "fogginess" [131]. At present there have been no controlled human studies regarding these effects specifically, however, an interesting study in rats randomized to efavirenz revealed significant deficits in spatial memory on the Morris Water Maze. Rats treated with efavirenz also demonstrated a greater susceptibility to stress that could be ameliorated with the antidepressant medication paroxetine reference.

While the results of the animal study described above are certainly of interest, it is not clear to what extent the findings can be extrapolated to patients, particularly in the context of disease-associated cognitive compromise. Further, there is a general clinical lore that patients on efavirenz experience improvement in these symptoms following several weeks of continuous therapy. In our own analyses of a large cohort of patients taking efavirenz, we have found no differences in cognitive function among patients on this drug versus patients not taking this medication (Paul, unpublished data). Nevertheless, the possibility of acute effects from this medication is real and important for patients to expect at least in the short term.

Relevant Family or Social Issues

There are many family and social issues that should also be considered when examining HIV-infected patients. Diminished capacity to participate in activities of daily living also constitutes another important aspect of HIV-associated cognitive dysfunction and often has deleterious effects for the patient as well as their immediate social network. Individual environment variations and other contextual factors create difficult challenges for health-care

professionals to accurately determine and predict the everyday impairments in work, personality, and social situations [132–134]. However, evidence provided from cognitive tests and patient self-assessments supplement and validate patient expressions of impairments in their day-to-day activities, personality and social communication, employment, and feelings of self-worth. In a study by Heaton et al. [135] 267 HIV+ participants were given the standard neuropsychological test battery and also laboratory-based tests of shopping, cooking, financial management, medication management, and vocational abilities. Results suggest that individuals defined as impaired by NP testing performed worse on all measures of daily living by associated large effect sizes [135]. Another study used a self-reported assessment of 504 patients to suggest that 86% of HIV-infected patients despite HAART have increasing worry, while 85% had sensations of fatigue, sadness in 82%, and 72.5% experiencing symptoms of depression [133]. Some have attributed the symptoms of fatigue to many HIV patients' lack of exercise, poor dieting, and depressive mood [134, 136] though this hypothesis should be examined more closely.

Depressive symptoms and shifts in behavior and personality caused by emotional state changes are implicated as possible causes for the increases in social isolation. Loss of social networks coupled with public misconceptions of HIV-infected patients has led to discrimination in employment, housing, health care, and public assistance [134, 136]. Physical impairments such as stiff or painful joints in 78.9% of patients, aching muscles in 77.1%, and diarrhea in 72.5% complicate employment tasks and driving believed to cause high patient unemployment and difficulty in personal transportation [137]. Increasing physical and cognitive disability in HIV-infected patients has lead to an increase in rehabilitation and in-home health-care services as well as difficulties in routine upper level cognitive functions [136].

It is important in the HIV-infected patients to account for these typical confounds when conducting a neuropsychological assessment. Though our discussion is limited to the depression, substance abuse, treatment affects, and age this should not be considered an exhaustive discussion of potential confounds. Thorough evaluation of patient including a good clinical interview should be considered essential. This type of evaluation will improve our understanding of the evolution and progression of cognitive dysfunction in HIV-infected patients as well as improve access and thoroughness of treatment provided.

Future Directions

Though there have been advancements in the study and clinical treatment of HIV-infected patients, many unanswered questions remain with regard to behavioral and cognitive consequences of the disease. Research of the deleterious pathological effects on the CNS and its resulting changes in cognitive performance have been important in understanding a clinical pattern of CNS involvement and possible future developments especially in the context of new treatments.

Researchers and clinicians agree that there are several ways that clinical assessment and treatment of HIV-infected patients might be improved. First, the combination of cognitive test findings with direct examination of the CNS using neuroimaging techniques will improve our understanding of CNS involvement in HIV infection. A large number of studies to date have examined these relationships and have provided direction in how to uncover further associations of the CNS and HIV infection. For example, several metabolite changes in the brain (i.e., inflammatory and neuronal) are shown to occur early in the disease process while structural or volumetric changes occur later in the disease. Importantly, both these processes are often found to be associated with cognitive performance. However, the connection between these processes (metabolic and structural change) is not completely understood and warrants further investigation. This type of research will be vastly improved with the development of advanced imaging sequences and/or multi-modal imaging techniques as these are likely to improve the

pathological specificity with which we can examine the brain.

The assessment of cognitive dysfunction in HIV patients is also hampered by the lack of repeatable test batteries. This is particularly problematic when attempting to examine the evolution and progression of cognitive dysfunction in this population. As described previously, research investigating the change over time across multiple cognitive domains in patients infected with HIV has produced inconsistent outcomes with some patients experiencing improvement, others a decline, and a third group with variable course. Subjective observations of treating physicians often relate a variable pattern of cognitive dysfunction that may occur more rapidly than we are currently able to measure with our current testing procedures. More frequent test administration or equivalent standards of testing may improve our ability to discern subtypes of patients who might be experiencing different cognitive progression.

Given the global nature of the HIV pandemic, there is a need to develop additional assessment tools capable of examining non-English speaking populations. Developing language-specific assessments sensitive to cultural differences would provide more reliable normalization of international data. This is a critical component in examining the full impact of HIV infection on the CNS by controlling for cultural-dependent behaviors that are believed to complicate current research models (i.e., substance abuse, comorbid infections). Significant portions of our current knowledge with respect to HIV infection and the CNS were obtained in subjects found in developed nations where many previously mentioned confounds are introduced. Reliable interpretation of global data through the use of better tool sets may provide new perspective into disease progression predominately seen from the lens of the developed world's patient populations.

Another related potentially confounding factor in the examination of cognitive dysfunction among the world's HIV-infected populations is the regional differences in the virus type. In fact, the genetic variation in the virus strains (referred to as Clade) is thought to result in subtle genetic variations that might spare cognitive function. Even though preliminary studies of these differences have yielded little evidence to support this fact [138, 139], variations may exist in the way cognitive dysfunction evolves and/or progresses. Insight into these viral differences will reveal additional insights into the CNS affects of HIV infection.

As a neurologic disease, HIV is a relatively new disorder and though our understanding of its pathological and cognitive consequences has matured nicely, there is still a great deal yet to be discovered. Future development of models for cognitive dysfunction in HIV will necessarily need to account for differences in host and viral factors. Neuropsychological measures for intents and purposes remain a valid and reliable indicator of HIV-associated CNS dysfunction. As such, neuropsychological assessment should remain an essential part of any effective treatment management strategy in patients with HIV infection.

References

1. Melrose RJ, Tinaz S, Castelo JM, et al. Compromised fronto-striatal functioning in HIV: an fMRI investigation of semantic event sequencing. Behav Brain Res. 2008;188:337–47.
2. Avison MJ, Nath A, Berger JR. Understanding pathogenesis and treatment of HIV dementia: a role for magnetic resonance? Trends Neurosci. 2002;25:468–73.
3. Scaravilli F, Bazille C, Gray F. Neuropathologic contributions to understanding AIDS and the central nervous system. Brain Pathol. 2007;17:197–208.
4. Anthony IC, Bell JE. The neuropathology of HIV/AIDS. Int Rev Psychiatry. 2008;20:15–24.
5. Anthony IC, Ramage SN, Carnie FW, et al. Accelerated Tau deposition in the brains of individuals infected with human immunodeficiency virus-1 before and after the advent of highly active anti-retroviral therapy. Acta Neuropathol. 2006;111:529–38.
6. Brew BJ, Pemberton L, Blennow K, et al. CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. Neurology. 2005;65:1490–2.
7. Green JE, Saveanu RV, Bornstein RA. The effect of previous alcohol abuse on cognitive function in HIV infection. Am J Psychiatry. 2004;161:249–54.
8. Valcour V, Shikuma C, Shiramizu B, et al. Age, apolipoprotein E4, and the risk of HIV dementia: the Hawaii Aging with HIV Cohort. J Neuroimmunol. 2004;157:197–202.

9. Grant I. Neurocognitive disturbances in HIV. Int Rev Psychiatry. 2008;20:33–47.
10. World Health Organization. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. Geneva: World Health Organization; 2005.
11. Hare C. WHO staging system for HIV infection and disease in adolescents and adults, table 3; clinical overview of HIV disease. In: Peiperl L, Coffey S, Volberding PA, editors. HIV insite knowledge base. San Francisco, CA: UCSF Center for HIV Information; 2006.
12. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. Ann Neurol. 1986;19:517–24.
13. Ghafouri M, Amini S, Khalili K, Sawaya BE. HIV-1 associated dementia: symptoms and causes. Retrovirology. 2006;3:28.
14. Sacktor N, McDermott MP, Marder K, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol. 2002;8:136–42.
15. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789–99.
16. Hardy DJ, Hinkin CH. Reaction time performance in adults with HIV/AIDS. J Clin Exp Neuropsychol. 2002;24:912–29.
17. Lezak MD, Howieson DB, Loring DW. Orientation and attention. 4th ed. New York, NY: Oxford University Press; 2004.
18. Heaton RK, Grant I, Butters N, et al. The HNRC 500 – neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc. 1995;1:231–51.
19. Hinkin CH, Castellon SA, van Gorp WG, Satz P. Neuropsychological features of HIV disease. New York, NY: Guilford Press; 1998.
20. Hinkin CH, Castellon SA, Hardy DJ. Dual task performance in HIV-1 infection. J Clin Exp Neuropsychol. 2000;22:16–24.
21. Martin EM, Pitrak DL, Robertson LC, Novak RM, Mullane KM, Pursell KJ. Global-local analysis in HIV-1 infection. Neuropsychology. 1995;9:102–09.
22. Maruff P, Malone V, McArthur-Jackson C, et al. Abnormalities of visual spatial attention in HIV infection and the HIV-associated dementia complex. J Neuropsychiatry Clin Neurosci. 1995;7:325–33.
23. Sorenson DJ, Martin EM, Robertson LC. Visual attention in HIV infection. Neuropsychology. 1994;8:424–32.
24. Grant I, Heaton RK, Atkinson JH, et al. HIV-1 associated neurocognitive disorder. The HNRC Group. Clin Neuropharmacol. 1992;15(Suppl 1 Pt A):364A–5A.
25. Marcotte TD, Heaton RK, Wolfson T, et al. The impact of HIV-related neuropsychological dysfunction on driving behaviour. The HNRC Group. J Int Neuropsychol Soc. 1999;5:579–92.
26. Becker JT, Sanchez J, Dew MA, et al. Neuropsychological abnormalities among HIV-infected individuals in a community-based sample. Neuropsychology. 1997;11:592–601.
27. Ferrando S, van Gorp W, McElhiney M, et al. Highly active antiretroviral treatment in HIV infection: benefits for neuropsychological function. AIDS. 1998;12:F65–70.
28. Manly JJ, Patterson TL, Heaton RK, Semple SJ, White DA, Velin RA. The relationship between neuropsychological functioning and coping activity among HIV-positive men. AIDS Behav. 1997;1:81–91.
29. Stern Y, Liu X, Marder K, et al. Neuropsychological changes in a prospectively followed cohort of homosexual and bisexual men with and without HIV infection. Neurology. 1995;45:467–72.
30. Ernst T, Chang L, Jovicich J, et al. Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. Neurology. 2002;59:1343–9.
31. Baldewicz TT, Leserman J, Silva SG, et al. Changes in neuropsychological functioning with progression of HIV-1 infection: results of an 8-year longitudinal investigation. AIDS Behav. 2004;8:345–55.
32. Tozzi V, Balestra P, Bellagamba R, et al. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. J Acquir Immune Defic Syndr. 2007;45:174–82.
33. Evans DL, Bauer R, Lesermans J, Mason KI, Petitto J. Neuropsychiatric manifestations of HIV-1 infection and AIDS. New York, NY: Raven Press; 2002.
34. Woods SP, Rippeth JD, Frol AB, et al. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. J Clin Exp Neuropsychol. 2004;26:759–78.
35. Cysique LA, Deutsch R, Atkinson JH, et al. Incident major depression does not affect neuropsychological functioning in HIV-infected men. J Int Neuropsychol Soc. 2007;13:1–11.
36. Delis DC, Peavy G, Heaton R, Butters N, et al. Do patients with HIV-associated minor cognitive/motor disorder exhibit a 'subcortical' memory profile? Evidence using the California Verbal Learning Test. Assessment. 1995;2:151–65.
37. Peavy G, Jacobs D, Salmon DP, et al. Verbal memory performance of patients with human immunodeficiency virus infection: evidence of subcortical dysfunction. The HNRC Group. J Clin Exp Neuropsychol. 1994;16:508–23.
38. Grant I, Atkinson JH, Hesselink JR, et al. Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuropsychologic testing and magnetic resonance imaging. Ann Intern Med. 1987;107:828–36.

39. Heaton RK, Grant I, Matthews CG. Comprehensive norms for an expanded Halstead-Retian battery. Lutz, FL: Psychological Assessment Resources; 1991.
40. Suarez S, Baril L, Stankoff B, et al. Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. AIDS. 2001;15:195–200.
41. Cohen RA, Boland R, Paul R, et al. Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. AIDS. 2001;15:341–5.
42. Basso MR, Bornstein RA. Effects of immunosuppression and disease severity upon neuropsychological function in HIV infection. J Clin Exp Neuropsychol. 2000;22:104–14.
43. Luo X, Carlson KA, Wojna V, et al. Macrophage proteomic fingerprinting predicts HIV-1-associated cognitive impairment. Neurology. 2003;60:1931–7.
44. Stern RA, Silva SG, Chaisson N, Evans DL. Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus-1 infection. Arch Neurol. 1996;53:148–53.
45. Blanchette N, Smith ML, King S, et al. Cognitive development in school-age children with vertically transmitted HIV infection. Dev Neuropsychol. 2002;21:223–41.
46. Woods SP, Carey CL, Troster AI, Grant I. Action (verb) generation in HIV-1 infection. Neuropsychologia. 2005;43:1144–51.
47. Iudicello JE, Woods SP, Parsons TD, et al. Verbal fluency in HIV infection: a meta-analytic review. J Int Neuropsychol Soc. 2007;13:183–9.
48. Navia BA, Price RW. The acquired immunodeficiency syndrome dementia complex as the presenting or sole manifestation of human immunodeficiency virus infection. Arch Neurol. 1987;44:65–9.
49. Llorente AM, Miller EN, D'Elia LF, et al. Slowed information processing in HIV-1 disease. The Multicenter AIDS Cohort Study (MACS). J Clin Exp Neuropsychol. 1998;20:60–72.
50. Miller EN, Selnes OA, McArthur JC, et al. Neuropsychological performance in HIV-1-infected homosexual men: the Multicenter AIDS Cohort Study (MACS). Neurology. 1990;40:197–203.
51. Selnes OA, Galai N, McArthur JC, et al. HIV infection and cognition in intravenous drug users: long-term follow-up. Neurology. 1997;48:223–30.
52. Desi DC, Peavy G, Heaton R, Butters N, et al. Cognitive impairment in HIV infection: validation of a brief battery for neuropsychological assessment. Encephale. 1995;21:5.
53. Cole MA, Margolick JB, Cox C, et al. Longitudinally preserved psychomotor performance in long-term asymptomatic HIV-infected individuals. Neurology. 2007;69:2213–20.
54. Reger M, Welsh R, Razani J, et al. A meta-analysis of the neuropsychological sequelae of HIV infection. J Int Neuropsychol Soc. 2002;8:410–24.
55. von Giesen HJ, Heintges T, Abbasi-Boroudjeni N, et al. Psychomotor slowing in hepatitis C and HIV infection. J Acquir Immune Defic Syndr. 2004;35:131–7.
56. Hinkin CH, Castellon SA, Hardy DJ, et al. Computerized and traditional Stroop task dysfunction in HIV-1 infection. Neuropsychology. 1999;13:306–16.
57. Tozzi V, Balestra P, Galgani S, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. AIDS. 1999;13:1889–97.
58. Martin EM, Novak RM, Fendrich M, et al. Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. J Int Neuropsychol Soc. 2004a;10:298–300.
59. Basso MR, Bornstein RA. Effects of past noninjection drug abuse upon executive function and working memory in HIV infection. J Clin Exp Neuropsychol. 2003;25:893–903.
60. Carter SL, Rourke SB, Murji S, et al. Cognitive complaints, depression, medical symptoms, and their association with neuropsychological functioning in HIV infection: a structural equation model analysis. Neuropsychology. 2003;17:410–9.
61. Hardy DJ, Hinkin CH, Levine AJ, et al. Risky decision making assessed with the gambling task in adults with HIV. Neuropsychology. 2006;20:355–60.
62. Martin EM, Pitrak DL, Weddington W, et al. Cognitive impulsivity and HIV serostatus in substance dependent males. J Int Neuropsychol Soc. 2004b;10:931–8.
63. Hardy J. The genetic causes of neurodegenerative diseases. J Alzheimers Dis. 2001;3:109–16.
64. Martin A. Clinically significant cognitive dysfunction in medically asymptomatic human immunodeficiency virus-infected (HIV+) individuals? Psychosom Med. 1994;56:18–19.
65. Butters N, Grant I, Haxby J, et al. Assessment of AIDS-related cognitive changes: recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches. J Clin Exp Neuropsychol. 1990;12:963–78.
66. Cherner M, Masliah E, Ellis RJ, et al. Neurocognitive dysfunction predicts postmortem findings of HIV encephalitis. Neurology. 2002;59:1563–7.
67. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.
68. Cherner M. Comorbid risk factor of HIV international neuropsychological society. HI: Waikoloa; 2008.
69. Dolan S, Montagno A, Wilkie S, et al. Neurocognitive function in HIV-infected patients with low weight and weight loss. J Acquir Immune Defic Syndr. 2003;34:155–64.

70. Sacktor NC, Lyles RH, Skolasky RL, et al. Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. Multicenter AIDS Cohort Study (MACS). Neurology. 1999;52:1640–7.
71. Hinkin CH, Hardy DJ, Mason KI, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. AIDS. 2004;18(Suppl 1):S19–25.
72. Marcotte DE, Wilcox-Gok V. Estimating the employment and earnings costs of mental illness: recent developments in the United States. Soc Sci Med. 2001;53:21–7.
73. Marcotte TD, Lazzaretto D, Scott JC, et al. Visual attention deficits are associated with driving accidents in cognitively-impaired HIV-infected individuals. J Clin Exp Neuropsychol. 2006;28:13–28.
74. Osowiecki DM, Cohen RA, Morrow KM, et al. Neurocognitive and psychological contributions to quality of life in HIV-1-infected women. AIDS. 2000;14:1327–32.
75. Gonzalez R, Cherner M. Co-factors in HIV neurobehavioural disturbances: substance abuse, hepatitis C and aging. Int Rev Psychiatry. 2008;20:49–60.
76. Tyor WR, Middaugh LD. Do alcohol and cocaine abuse alter the course of HIV-associated dementia complex? J Leukoc Biol. 1999;65:475–81.
77. World Health Organization. The world health report 2006: working together for health. World Health Report. Geneva: World Health Organization, 2006.
78. Chang L, Ernst T, Speck O, Grob CS. Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. Am J Psychiatry. 2005;162:361–9.
79. Pfefferbaum A, Rosenbloom M, Sullivan EV. Alcoholism AIDS magnetic resonance imaging approaches for detecting interactive neuropathology. Alcohol Clin Exp Res. 2002;26:1031–46.
80. <aug>Pfefferbaum A, Rosenbloom MJ, Rohlfing T, et al. Contribution of alcoholism to brain dysmorphology in HIV infection: effects on the ventricles and corpus callosum. Neuroimage. 2006;33:239–51.
81. Bornstein RA, Fama R, Rosenberger P, et al. Drug and alcohol use and neuropsychological performance in asymptomatic HIV infection. J Neuropsychiatry Clin Neurosci. 1993;5:254–9.
82. McArthur JC, Haughey N, Gartner S, et al. Human immunodeficiency virus-associated dementia: an evolving disease. J Neurovirol. 2003;9:205–21.
83. Paul RH, Grieve SM, Niaura R, et al. Chronic cigarette smoking and the microstructural integrity of white matter in healthy adults: a diffusion tensor imaging study. Nicotine Tob Res. 2008;10:137–47.
84. Quang-Cantagrel ND, Wallace MS, Ashar N, Mathews C. Long-term methadone treatment: effect on CD4+ lymphocyte counts and HIV-1 plasma RNA level in patients with HIV infection. Eur J Pain. 2001;5:415–20.
85. Wang X, Tan N, Douglas SD, et al. Morphine inhibits CD8+ T cell-mediated, noncytolytic, anti-HIV activity in latently infected immune cells. J Leukoc Biol. 2005;78:772–6.
86. Donahoe RM, Vlahov D. Opiates as potential cofactors in progression of HIV-1 infections to AIDS. J Neuroimmunol. 1998;83:77–87.
87. Vallejo R, de Leon-Casasola O, Benyamin R. Opioid therapy and immunosuppression: a review. Am J Ther. 2004;11:354–65.
88. Fiala M, Eshleman AJ, Cashman J, et al. Cocaine increases human immunodeficiency virus type 1 neuroinvasion through remodeling brain microvascular endothelial cells. J Neurovirol. 2005;11:281–91.
89. Zhang L, Looney D, Taub D, et al. Cocaine opens the blood-brain barrier to HIV-1 invasion. J Neurovirol. 1998;4:619–26.
90. McMurtray A, Nakamoto B, Shikuma C, Valcour V. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. J Stroke Cerebrovasc Dis. 2008;17:212–7.
91. Valcour V, Haman A, Cornes S, et al. A case of enteroviral meningoencephalitis presenting as rapidly progressive dementia. Nat Clin Pract Neurol. 2008;4:399–403.
92. Nosheny RL, Bachis A, Acquas E, Mocchetti I. Human immunodeficiency virus type 1 glycoprotein gp120 reduces the levels of brain-derived neurotrophic factor in vivo: potential implication for neuronal cell death. Eur J Neurosci. 2004;20:2857–64.
93. Corominas M, Roncero C, Ribases M, et al. Brain-derived neurotrophic factor and its intracellular signaling pathways in cocaine addiction. Neuropsychobiology. 2007;55:2–13.
94. Jernigan TL, Gamst AC, Archibald SL, et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am J Psychiatry. 2005;162:1461–72.
95. Castelo JM, Courtney MG, Melrose RJ, Stern CE. Putamen hypertrophy in nondemented patients with human immunodeficiency virus infection and cognitive compromise. Arch Neurol. 2007;64:1275–80.
96. Pfefferbaum A, Rosenbloom MJ, Adalsteinsson E, Sullivan EV. Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. Brain. 2007;130:48–64.
97. Taylor MJ, Schweinsburg BC, Alhassoon OM, et al. Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. J Neurovirol. 2007;13:150–9.
98. Forton DM, Allsop JM, Cox IJ, et al. A review of cognitive impairment and cerebral metabolite abnormalities in patients with hepatitis C infection. AIDS. 2005;19(Suppl 3):S53–63.
99. Clifford DB, Yang Y, Evans S. Neurologic consequences of hepatitis C and human immunodeficiency

virus coin-fection. J Neurovirol. 2005;11(Suppl 3):67–71.
100. Perry W, Carlson MD, Barakat F, et al. Neuropsy chological test performance in patients co-infected with hepatitis C virus and HIV. AIDS. 2005;19 (Suppl 3):S79–84.
101. Richardson JL, Nowicki M, Danley K, et al. Neuropsychological functioning in a cohort of HIV – and hepatitis C virus-infected women. AIDS. 2005;19:1659–67.
102. Paul R, Taylor L, Tate D, et al. Cognitive dysfunction in patients HIV-HCV. Co-infection is not mediated by severity of drug use. Proceedings of the 13th conference on retroviruses and opportunistic infections. Denver, CO, 2006.
103. Morgello S, Estanislao L, Ryan E, et al. Effects of hepatic function and hepatitis C virus on the nervous system assessment of advanced-stage HIV-infected individuals. AIDS. 2005;19(Suppl 3):S116–22.
104. Stoff DM, Khalsa JH, Monjan A, Portegies P. Introduction: HIV/AIDS and Aging. AIDS. 2004;18 (Suppl 1):S1–2.
105. Valcour V, Paul R. HIV infection and dementia in older adults. Clin Infect Dis. 2006;42:1449–54.
106. Goodkin K, Wilkie FL, Concha M, et al. Aging and neuro-AIDS conditions and the changing spectrum of HIV-1-associated morbidity and mortality. J Clin Epidemiol. 2001;54(Suppl 1):S35–43.
107. Murasko DM, Weiner P, Kaye D. Decline in mitogen induced proliferation of lymphocytes with increasing age. Clin. Exp. Immunol. 1987;70:440–8.
108. Clark CR, Paul RH, Williams LM, et al. Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. Arch Clin Neuropsychol. 2006;21:449–67.
109. Paul RH, Haque O, Gunstad J, et al. Subcortical hyperintensities impact cognitive function among a select subset of healthy elderly. Arch Clin Neuropsychol. 2005;20:697–704.
110. Esiri MM, Biddolph SC, Morris CS. Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry. 1998;65:29–33.
111. Green DA, Masliah E, Vinters HV, et al. Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS. 2005;19:407–11.
112. Van Den Heuvel C, Thornton E, Vink R. Traumatic brain injury and Alzheimer's disease: a review. Prog Brain Res. 2007;161:303–16.
113. Chiesi A, Vella S, Dally LG, et al. Epidemiology of AIDS dementia complex in Europe. AIDS in Europe Study Group. J Acquir Immune Defic Syndr Hum Retrovirol. 1996;11:39–44.
114. Janssen RS. Epidemiology of human immunodeficiency virus infection and the neurologic complications of the infection. Semin Neurol. 1992;12:10–7.
115. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology. 1993;43:2245–52.
116. Kissel EC, Pukay-Martin ND, Bornstein RA. The relationship between age and cognitive function in HIV-infected men. J Neuropsychiatry Clin Neurosci. 2005;17:180–4.
117. Batki SL. Drug abuse, psychiatric disorders, and AIDS. Dual and triple diagnosis. West J Med. 1990;152:547–52.
118. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry. 2001;58:721–8.
119. Burnam MA, Bing EG, Morton SC, et al. Use of mental health and substance abuse treatment services among adults with HIV in the United States. Arch Gen Psychiatry. 2001;58:729–36.
120. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:617–27.
121. Rabkin JG, Ferrando SJ, Jacobsberg LB, Fishman B. Prevalence of axis I disorders in an AIDS cohort: a cross-sectional, controlled study. Compr Psychiatry. 1997;38:146–54.
122. Acuff C, Archambeault J, Greenberg B. Mental health care for people living with or affected by HIV/AIDS: a practical guide. Research Triangle Park, NC: Research Triangle Institute; 1999.
123. Ferrando SJ, Freyberg Z. Treatment of depression in HIV positive individuals: a critical review. Int Rev Psychiatry. 2008;20:61–71.
124. Ickovics J, Chesney M. Issues regarding antiretroviral treatment for patients with HIV-1 infection. JAMA. 1997;278:1233–4; author reply 1235.
125. Cruess DG, Evans DL, Repetto MJ, et al. Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. Biol Psychiatry. 2003;54:307–16.
126. Avants SK, Margolin A, Warburton LA, et al. Predictors of nonadherence to HIV-related medication regimens during methadone stabilization. Am J Addict. 2001;10:69–78.
127. Reynolds NR, Testa MA, Marc LG, et al. Factors influencing medication adherence beliefs and self-efficacy in persons naive to antiretroviral therapy: a multicenter, cross-sectional study. AIDS Behav. 2004;8:141–50.
128. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Am J Med. 2003;114:573–80.
129. Castellon SA, Hardy DJ, Hinkin CH, et al. Components of depression in HIV-1 infection: their differential relationship to neurocognitive performance. J Clin Exp Neuropsychol. 2006;28:420–37.
130. Neuenburg JK, Brodt HR, Herndier BG, et al. HIV-related neuropathology, 1985 to 1999: rising

prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2002;31:171–7.
131. Arendt G, de Nocker D, von Giesen HJ, Nolting T. Neuropsychiatric side effects of efavirenz therapy. Expert Opin Drug Saf. 2007;6:147–54.
132. Holzemer WL. HIV and AIDS: the symptom experience. What cell counts and viral loads won't tell you. Am J Nurs. 2002;102:48–52.
133. Holzemer WL, Hudson A, Kirksey KM, et al. The revised Sign and Symptom Check-List for HIV (SSC-HIVrev). J Assoc Nurses AIDS Care. 2001;12:60–70.
134. Huang GDaMF. ADA litigation and Musculoskeletal-related impairments: implications for work re-entry. J Occup Rehabil. 1998;8:91–102.
135. Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc. 2004;10:317–31.
136. Fish GaDL R. The potential role of OT in acute care with clients with HIV/AIDS. Occup Thera Int. 1998;5:1–6.
137. Johnson MO, Stallworth T, Neilands TB. The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. AIDS Behav. 2003;7:109–17.
138. Gupta JD, Satishchandra P, Gopukumar K, et al. Neuropsychological deficits in human immunodeficiency virus type 1 clade C-seropositive adults from South India. J Neurovirol. 2007;13:195–202.
139. Yepthomi T, Paul R, Vallabhaneni S, et al. Neurocognitive consequences of HIV in southern India: a preliminary study of clade C virus. J Int Neuropsychol Soc. 2006;12:424–30.

Chapter 23

Rheumatologic Conditions: Sjögren's Syndrome, Fibromyalgia, and Chronic Fatigue Syndrome

Jennifer M. Glass

Rheumatologists are trained to diagnose diseases of joints and connective tissue, and treat patients with the goal of alleviating pain and slowing or stopping degenerative processes. However, many patients who are seen in a rheumatology practice will also present with complaints of cognitive dysfunction, and it is known that chronic pain is associated with neuropsychological impairment [1]. In this chapter, I will summarize the current findings on cognitive function in fibromyalgia (FM) and chronic fatigue syndrome (CFS), two syndromes that are frequently treated by rheumatologists and where cognitive dysfunction is prevalent [2–5].

Fibromyalgia

FM is a disorder characterized by widespread musculoskeletal pain and the presence of at least 11 of 18 well-defined tender points with no clinical markers of pathology [6]. FM patients often report memory and concentration problems, and have even coined a term for these cognitive symptoms: Fibrofog. In the past decade a small, but growing body of research has demonstrated the existence of cognitive problems in FM (Table 23.1). For example, Zachrisson et al. reported a 95% incidence rate for "concentration difficulties" and a 93% incidence rate for "failing memory" on their FibroFatigue scale [7]. FM patients report more cognitive problems and dissociative states than do other rheumatology patients [8, 9]. In a large Internet survey of FM patients, forgetfulness and problems with concentration were the 5th and 6th most prevalent symptoms, with stiffness, fatigue, nonrestorative sleep, and pain at the top of the list [10]. Glass et al. found that FM patients reported lower memory capacity, more memory deterioration, less self-efficacy over memory performance, more anxiety about memory, and higher use of strategies to support memory than do age- and education-matched controls [11].

In addition to self-report of cognitive problems, there are now a number of studies demonstrating impairment on objective tests of cognitive function. The pattern of results emerging from these studies points to impairment of memory and of attention. In general, consistent impairment has been found across studies on tasks that measure three types of memory function: working memory, episodic memory, and verbal fluency. Each of these is described below.

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Table 23.1 Measures and results of neuropsychological and cognitive testing in fibromyalgia patients

Authors	Date	Title	Measures	Results
Sletvold et al. [12]	1995	Information processing in primary FM	Digit Symbol Test	FM < HC
			Trail Making Tests A and B	FM = HC
			PASAT	FM < HC
			Reaction time (left hand)	FM > HC
			Reaction time (right hand)	FM = HC
			Reaction time, inhibition (left hand)	FM > HC
			Reaction time, inhibition (right hand)	FM = HC
Pincus et al. [74]	1996 (abstract)	A self-report cognitive symptoms inventory to assess patients with rheumatic diseases	Pincus cognitive symptoms inventory	FM > HC
Landro et al. [20]	1997	Memory function in primary FM	Digit span	FM = HC
			Randt Memory Test	FM < HC
			Code Memory Test	FM < HC
			FAS fluency	FM < HC
			Kimura Recurring Recognition Figures	FM = HC
			Incidental Memory Test (Randt)	FM = HC
			IQ (similarities, block design)	FM = HC
Cote and Moldofsky [75]	1997	Sleep, daytime symptoms, and cognitive performance in FM	Computerized battery of cognitive performance (grammatical reasoning, serial addition/subtraction, simulated multi-task office procedure)	FM slower than HC
Grace et al. [13]	1999	Concentration and memory deficits in FM	Wechsler Memory Scale-R	FM < HC
			General memory	FM < HC
			Verbal memory	FM < HC (trend)
			Visual memory	FM = HC
			Attention/concentration	FM < HC
			Delayed recall	FM = HC
			RAVLT	FM < HC
			PASAT	FM < HC (trend)
			SDMT	FM < HC

(continued)

Table 23.1 (continued)

Authors	Date	Title	Measures	Results
			Memory observation questionnaire	
Park et al. [16]	2001	Cognitive Fxn in FM	Pincus cognitive symptoms inventory	FM > HC
			Letter, number, pattern comparison	FM = HC
			Reading, computation span	FM < HC
			Word list free recall	FM < HC
			Word list recognition	FM < HC
			FAS verbal fluency	FM < HC (trend)
			Vocabulary	FM < HC
Dick et al. [18]	2002	Attentional Fxn in FM, RA, and musculoskeletal pain	Test of everyday attention	Results FM < HC
			Selective attention	FM = HC
			Sustained attention	FM = HC
			Attention switching	FM < HC
			Working memory	
Grisart et al. [76]	2002	Controlled processes and automaticity in memory fxn in FM: emotional distress and hypervigilance	Process dissociation procedure	FM < HC
			Controlled processes	FM = HC
			Automatic processes	
Zachrisson et al. [7]	2002	A rating scale for fibromyalgia and cfs (FibroFatigue scale)	FibroFatigue scale (uses items from CPRS)	95% incidence
			Concentration difficulties	93% incidence
			Failing memory	
Leavitt et al. [9]	2003	Cognitive and dissociative manifestations in FM	Cognitive complaints	FM > other rheum pts
Suhr [77]	2003	Neuropsych imp in FM	Metamemory Q (effort subscale)	FM > HC
			IQ (Block design and information)	FM = HC
			Wisconsin Card Sorting TestStroop interference	FM = HC
			Auditory Verb Learning Test	FM = HC
			Effort testing with AVLT	5 FM pts excluded, 0HC
			Complex figure test delayed recall	FM = HC
			Digit span	FM = HC

(continued)

Table 23.1 (continued)

Authors	Date	Title	Measures	Results
			Letter–number sequencing	FM = HC
			PASAT	FM = HC
			Digit symbol	FM = HC
			Symbol search	FM = HC
			Controlled oral word assoc. test	FM = HC
			Trail Making Tests A and B	FM = HC
Sephton et al. [78]	2003	Biological and psychological factors associated with memory function in fibromyalgia syndrome	Wechsler memory scale	Lower salivary cortisol levels correlated with visual memory
			Visual reproduction, imm	
			Visual reproduction, delayed	
			Logical memory, imm	Depression was negatively correlated with logical memory
			Logical memory, delayed	
Glass et al. [21]	2004 (abstract)	Memory performance with divided attention in fibromyalgia (FM) patients	Word list recall with and without a secondary task during list learning and list recall	FM < HC overall
				FM < HC especially with maximum distraction
Katz et al. [8]	2004	The prevalence and clinical impact of reported cognitive difficulties in RD with and w/o FM	Memory decline	FM > nonFM
			Mental confusion	FM > nonFM
Bennett et al. [10]	2007	An Internet survey of 2,596 people with FM	Forgetfulness	5.9 (fifth highest sx)
			Concentration	5.9 (fifth highest sx)
Glass et al. [11]	2005	Memory beliefs and function in FM	Metamemory in adulthood quest	FM > HC
			Strategy	FM = HC
			Knowledge	FM < HC
			Capacity	FM < HC
			Stability	FM > HC
			Anxiety	FM > HC
			Achievement	FM < HC

(continued)

Table 23.1 (continued)

Authors	Date	Title	Measures	Results
			Self-efficacy	
Glass et al. [79]	2006 (abstract)	Fibromyalgia patients show reduced executive/cognitive control in a task-switching test	Card sorting test, alternating between sorting rules. Rules could be simple or complex	FM < HC overall FM < HC especially for complex sorting rules
Leavitt and Katz [14]	2006	Distraction ... imp memory in FM	WMS logical memory	–0.77 sd of norm
			WMS paired associates	–0.37 sd of norm
			IQ (vocabulary)	+0.07 sd of norm
			Digit span	–1.6 sd of norm
			Paced auditory serial add. task	–0.93 sd of norm
			Letter–number sequencing	–2.5 sd of norm
			Auditory consonant trigram	
Walitt et al. [80]	2007	Automated neuropsychiatric measurements of information processing in fibromyalgia	ANAM	FM = HC
			Visual short-term memory	FM = HC
			Visual scanning and learning	FM = HC
			Spatial processing	FM = HC
			Short-term memory	FM = HC
			Arithmetic processing	FM = HC
			Sustained attention	FM = HC
			Simple RT	FM = HC
			Trail Making Tests A and B	FM = HC
			Stroop word and color	FM > HC
			Stroop color–word	
Glass et al. [81]	2007 (abstract)	Working memory in fibromyalgia patients: impaired function caused by distracting information, not rapid decay of stored information	Brown–Peterson paradigm	FM < HC recall
			Consonant trigrams held in STM for variable duration (0–6 s)	FM = HC rate of decay

PASAT, Paced Auditory Serial Attention Test; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; WMS, Wechsler Memory Scale; RT, reaction time; ANAM, Automated Neuropsychological Assessment Metrics.

Working Memory

Working memory can be thought of as the amount of mental power or online cognitive resource an individual has available in any given situation. Working memory is critical to accurate performance in demanding cognitive situations. A good example of a job that has extremely high working memory demands is that of an air traffic controller who is simultaneously trying to remember the location of many airplanes (storage) and make decisions about how to get them on and off the ground (processing). In the laboratory, we measure working memory by determining how well people can both store and process information. A quick laboratory index of working memory function is how many digits an individual can listen to and then repeat in backward order. Other tasks involve keeping track of a past event while performing a mental operation on a new event. There are now several studies that have reported impairment in this important cognitive function in FM patients, using several different tests of working memory. Sletvold et al. [12], Grace et al. [13], and Leavitt and Katz [14] all used the Paced Auditory Serial Attention Test (PASAT) [15]. Although commonly called a test of attention, the PASAT is also a challenging working memory test. Participants listen to a series of digits. The task is to add together the most recent two digits and state the answer out loud. Thus, if the auditory digits were 2, 7, 3, 4, ..., the correct answers would be "nine," "ten," "seven." All three studies using the PASAT found that FM patients performed more poorly on this task. Leavitt and Katz also used the Auditory Consonant Trigram (ACT) test. This is a test of short-term or immediate memory where a list of three consonants is presented for a short period. The consonants are replaced by a delay period (9, 18, or 36 s), during which the participant counts backward by 3s (to prevent rehearsal of the trigram) from a randomly chosen number. After the delay period, the participant recalls the trigram. There are five trials for each length of the delay period. FM patients recalled fewer of the trigrams correctly, and nearly 83% performed in the impaired range compared with 20% of the control participants. Park et al. [16] used two tests of working memory that had identical structure, but used different content: reading span and computational span [17]. During the reading span task, participants hear factual sentences and are asked multiple choice questions about the sentences immediately after hearing the sentence. At the same time, they also tried to remember the last word in the sentence. After a certain number of sentences (between 1 and 6), participants recalled the words from the sentence in order. The score is the number of words that could be successfully recalled while correctly answering the questions. Computational span is similar, except that participants hear simple equations (e.g., 8 + 1) and choose the correct answer from multiple choice. Participants must also remember the last digit from each equation. These span tasks have been used extensively to study working memory performance in healthy older adults. Fibromyalgia patients performed more poorly than age-matched controls and at a level that was not different from controls who were 20 years older. Dick et al. [18] used the Test of Everyday Attention (TEA) [19], a standardized test designed to have high ecological validity. All components of this test take place within the context of a sightseeing trip. The working memory tests involve keeping track of which floor an elevator occupied by counting the tones, with and without distraction. The results showed that FM patients had lower scores on the working memory component of the TEA.

The wide variety of working memory tests that demonstrate lower performance in FM is striking and this suggests that this deficit is quite robust. This is a crucial finding since working memory is a basic cognitive mechanism that underlies successful performance on many other cognitive tasks. Therefore, deficits in working memory ability have repercussive effects on other aspects of cognition, and a small deficit in working memory may have a large impact on performance on complex tasks. Future research will be necessary to understand the effects of FM on working memory in more detail. For example, is short-term storage to blame or difficulty managing competing information (central

executive), or both? To this end, it is interesting to note that Landro et al. [20] did not find performance differences between FM and controls using simple short-term storage tests (digit span forward and backward). This suggests that processes that control and manage the contents of working memory are more likely disrupted in FM than storage mechanisms.

Episodic Memory

Episodic memory refers to the ability to remember specific events or episodes (e.g., the memory of when you received your first bicycle or, in a laboratory setting, your ability to remember a list of words). Episodic memory is different from semantic memory which involves facts and information that are not tied to a specific event (such as the meanings of words or the fact that George Washington was the first president). When we tested fibromyalgia patients on an episodic task we found deficits relative to age-matched controls [16], as did Sletvold et al. [12, 20] and Grace et al. [13]. In the Park et al. study, episodic memory was tested in two ways, with a recall task and a recognition memory task. During the recall task, participants studied a list of 16 words. The list was presented one word at a time, for 5 s per word. At the end of the list, participants were prompted to recall as many words as they could by writing them on an answer sheet. Items could be recalled in any order. FM patients recalled about 1.5 fewer items than age-matched controls. During the recognition task, participants studied a list of 32 words, as in the recall task. A 32-word recognition list was shown that contained half old words and half new words. Performance was scored by d', a measure of the ability to discriminate old from new words. The higher the d' score, the better the ability to discriminate; FM patients had significantly lower d' scores than age-matched controls.

Grace et al. [13] used the Wechsler Memory Scale – Revised (WMS-R) and the Rey Auditory Verbal Learning Test (RAVLT) to examine memory function in FM patients. They found that FM patients performed more poorly on the general memory, verbal memory, and delayed recall components of the WMS-R, but not on the visual memory or attention/concentration components. They also did not find significant differences with the RAVLT. Significant correlations were found between pain severity and WMS-R general memory and between anxiety and WMS-R general memory and delayed recall.

Landro et al. [20] tested a group of FM patients and compared their performance on several standardized memory tests with a group of patients with major depressive disorder and with healthy controls. Their test battery included the Randt Memory Test, the Code Memory Test, and the Kimura Recurring Recognition Figures Test. FM patients (and major depressive disorder patients) scored lower on the Randt Memory Test and the Code Memory Test, but not on the Kimura Recurring Figures Recognition Test. The authors also split the FM group into those who had experienced a depressive episode during the lifetime and those who had not. The group without a history of depression was not significantly different from the healthy controls. Although Landro et al. interpreted this as evidence that memory dysfunction in FM may be due to comorbid depression, it is just as likely that the lack of significant effects was due to the smaller group (N = 14), particularly since the non-depressed FM group means were similar to the entire FM group. It should also be noted that Park et al. and Grace et al. did not find significant correlations between depressive symptoms and memory performance.

As in the research on working memory, our research shows that fibromyalgia patients recalled episodic memories at a level that is frequently below the recall of healthy controls, across a variety of tests. This consistency in findings across studies makes it clear that fibromyalgia patients do in fact have memory problems, as they often report.

Verbal Fluency

Verbal fluency is a measure of how quickly and efficiently a person can access stored knowledge about words. Typically, it is measured by having

participants write down (or say out loud) as many words as they can that start with a given letter, as in the FAS verbal fluency tests. Our data indicate that fibromyalgia patients perform significantly more poorly on these tests than age-matched controls [16], and this is consistent with the report of Landro et al. [20]. Thus, fibromyalgia patients appear to have a deficit in accessing stored knowledge or semantic memory. This deficit can make it difficult for patients to think quickly and to come up with the right word for a given situation and indeed, several patients have told us that they have just this kind of difficulty.

In addition to verbal fluency deficits, we have also found that fibromyalgia patients perform more poorly than education-matched controls on tests of vocabulary. This is consistent with the verbal fluency deficit since it suggests a deficit in semantic memory. Further research is necessary to fully understand the semantic memory problems.

Attention and Concentration

Leavitt and Katz [14] suggest that the typical setting for testing neuropsychological function that minimizes distractions may not be the most sensitive way to find cognitive problems in FM patients. They found the most impairment on tasks where distraction from a competing source of information was prominent (PASAT, Letter–Number Sequencing, ACT) in contrast to tasks without distraction (digit span, Logical Memory, Paired Associate). Other findings demonstrate that memory in FM patients is more disrupted than healthy controls during conditions of maximal distraction where attention was divided while learning a word list and while recalling the word list [21]. These findings show that FM patients may have difficulty controlling attention, perhaps due to the attention-capturing properties of pain itself [22].

A painful sensation automatically garners attention from many levels of the cognitive system, including attention networks that are not typically under conscious control. Many have speculated that chronic pain states may therefore interfere with attention in everyday settings. For example, FM patients, rheumatoid arthritis patients, and musculoskeletal pain patients all exhibited lower function in a test of everyday attention [18]. Self-reported level of pain is correlated with cognitive performance among FM patients [16, 23]. These results suggest that pain may disrupt the normal function of the attention system. Recently, this idea has been tested directly by using techniques from cognitive psychology that help separate the contributions of controlled processing (i.e., conscious attention) from automatic processing. For example, in a memory recognition test, controlled processing would be involved in the explicit knowledge that a word had been presented earlier; this is the phenomenon of knowing that you know. On the other hand, automatic processes are more involved when you cannot explicitly remember a word as having been presented before, but it nonetheless seems familiar. Grisart et al. found that the contribution of controlled processing to performance on a memory test was reduced in FM patients, but contributions of automatic processing to performance was not [24]. This result is consistent with the hypothesis that chronic pain interferes with or reduces limited attention resources.

In a similar vein, others have hypothesized that the abnormal sensory pain processing present in FM and other chronic pain syndromes may extend into other aspects of cognitive function. One common way to assess this is with the modified Stroop task. In the original Stroop interference task, participants are shown words that spell color names (i.e., blue, red, green) printed in colored ink. The interference task is to name the color of the ink, while ignoring the actual word. People are much slower at this than naming the color of the ink when it is presented as a non-word, showing that there is interference from the word itself. There is some evidence that chronic pain patients are impaired (i.e., have more interference) on the original Stroop task. Grisart and Plaghki [25] reported that chronic pain patients (mostly low back pain) demonstrated small but significant impairments on the non-interfering word reading and color naming portions of the test. In contrast, much larger impairments were seen on the interference portion of the test. A modified version of

the Stroop paradigm is sometimes used to assess cognitive effects that are specifically pain related. In this version, pain-related words are used instead of color words, for example, the word "aching" written in colored ink where the patient's task is to name the color of the ink. Slower responses for the pain words among chronic pain patients compared to healthy controls is an indication of greater interference because the pain word is presumed to be more salient to the pain patient and therefore harder to inhibit. In a meta-analysis of five modified stroop tests with chronic pain patients (including FM patients), Roelofs et al. report that chronic pain patients show evidence of greater interference from both sensory and affective pain words, indicating a tendency among patients to selectively attend to pain words [26]. Other cognitive methods have been tested in chronic pain syndromes with the overall conclusion that pain interferes with attention and that chronic pain patients show an attentional bias to pain-related information [27–29]. These studies frequently test a mix of chronic pain patients (sometimes including FM patients), so we cannot know how specific the findings would be for FM; nonetheless, the results are intriguing enough to warrant further study exclusively with FM patients. Such studies would be informative not only about FM but about the neurocognitive aspects of pain processing as well [22, 30].

Neuroimaging and Brain Activity

Montoya and colleagues used evoked response potentials (ERP), a method of measuring electrical activity in the brain in response to stimulation, to study attention and cognitive processing of pain-related words in FM patients. Both patients and controls showed enhanced p300 amplitudes to the pain-related words than to neutral words [31]. The p300 is a large positive evoked potential that occurs about 300 ms after the presentation of a stimulus that is either unexpected or is important for task performance. The p300 is thought to be an index of attention to or appraisal of the stimulus. In contrast, controls but not patients showed enhanced late potential complex (LPC; occurring 500–800 ms after presentation) amplitudes in response to pain-related words. Increased LPC amplitudes are common in ERP studies of emotional stimuli, thought to reflect ongoing processing of emotionally arousing material. Thus, the finding that LPC was not influenced by the emotional content of the words in FM patients is counter-intuitive, but it could indicate an adaptive mechanism to reduce engagement in emotional stimuli. FM patients may avoid further processing of the unpleasant pain words because of their experience of chronic pain. Further research will be necessary to understand the implication of these ERP findings, but they do illustrate differences between FM patients and controls in the cognitive processing of pain-related information. In another study, Montoya and colleagues measured ERPs while FM patients and controls received non-painful tactile stimulation [32]. During the tactile stimulation, participants viewed pictures from the International Affective Picture System (IAPS) with either pleasant or unpleasant contents. For FM patients, viewing unpleasant pictures significantly increased the early tactile ERP components, demonstrating increased sensitivity to the tactile stimuli. The authors suggest this may mean that FM patients have an abnormal vulnerability to the negative emotional context in which pain occurs. Although further studies are necessary, these results demonstrate the complex interaction between sensory processing, attention, cognition, and emotion that can occur in FM [22, 28, 30].

Some studies with FM patients have found reduced regional cerebral blood flow using single photon emission computed tomography (SPECT) in the thalamus [33, 34], an area typically thought of as the gateway for sensory stimulation. A recent study using Diffusion Tensor Imaging to detect cerebral abnormalities in FM also found lower fractional anisotropy between FM and healthy controls in the right thalamus [35], consistent with the earlier SPECT studies. These findings lend support to the hypothesis that FM is due to dysfunction in central neural mechanisms of pain perception.

The studies mentioned above tell about differences in cerebral blood flow during resting states, but not during evoked pain. Other studies used functional magnetic resonance imaging (fMRI) during painful stimulation and showed augmented activation in FM patients in pain-processing areas of the brain. For example, Gracely [36, 37] and colleagues used fMRI in conjunction with pressure pain testing on the base of the thumb nail. In this groundbreaking study, they found that when pain levels were equal between FM and controls (lower pressure for FM patients), both FM patients and controls activated similar brain areas that are normally associated with pain perception (primary and secondary sensory cortex, putamen, inferior parietal lobule, superior temporal gyrus, and cerebellum). In contrast, when the pressure levels were equal (mild pain for controls and moderate pain for FM), the FM patients evidenced an enhanced response to the pressure testing in primary cortex, secondary cortex, inferior parietal lobule, insula, and posterior cingulate cortex. Similar results were reported using heat as the pain stimulus [38]. The findings supporting augmented central pain processing are informative for cognitive function since painful stimulation activates some areas of the brain that are also involved in attention demanding cognitive tasks, in particular the anterior cingulate cortex, areas of the posterior parietal lobe, and the dorsolateral prefrontal cortex [30, 39–42]. This overlap in neural activation is not too surprising if one thinks of the attention system as "attention to action." In other words, the role of the attention system is to select salient stimuli from the environment in order to guide subsequent action. A painful stimulus is one that in most cases should elicit immediate action to avoid harm or further harm. To date, no functional imaging studies have been published with FM patients performing cognitive tasks, but there is preliminary evidence that patients activate more cortical areas (bilateral middle frontal gyrus and right superior parietal lobule) during a working memory task [43].

Chronic Fatigue Syndrome

CFS is a syndrome defined by long-standing (greater than 6 months) fatigue that is not resolved with rest, and the presence of four or more other symptoms, that can include self-reported cognitive impairment [44]. Perhaps because cognitive impairment plays a role in the definition of CFS, there have been substantially more studies of cognitive function in CFS than in FM.

Summary of Neuropsychological Findings

Several reviews were published between the years 1996 and 2001 [3, 4, 45], the reader is referred to these for a comprehensive review of the early literature. Table 23.2 shows a summary of Michiels and Cluydts 2001 review [3]. The most consistent finding in studies of cognitive function in CFS is that information processing speed and efficiency are impaired [3, 4, 45]. Thus, CFS patients do more poorly on tasks that require rapid manipulation of information, as is the case for complex tasks, and tasks that are time limited. Learning and encoding new memory is impaired, as is working memory. Interestingly, the processing speed and working memory results mirror what is frequently found in studies of cognitive aging, where slowed information processing speed has played an important role in theories of cognitive aging [46]. If speed of information processing is slowed, then it will be difficult to rapidly and efficiently encode new information, leading to problems with learning and memory. Likewise, working memory performance will be adversely affected by slow information processing since items stored in working memory buffers may be lost by the time they are needed for further processing. Thus, it would be interesting to test this information processing speed hypothesis in future work with CFS patients [47].

Table 23.2 Summary of findings from Michiels and Cluydts [3] review of neuropsychological function in chronic fatigue syndrome

Neuropsychological function	Description and tests most often used	Evidence for dysfunction in CFS
Attention		
Alertness	Rapid change in arousal in response to stimuli	No
Focused and sustained attention	Ability to maintain focus, cancellation tasks, digit symbol substitution, continuous performance test	Mixed: dysfunction shown in cancellation and digit symbol substitution, but not continuous performance
Visual–spatial selective attention	Ability to selectively attend to a location in space, Posner covert attention test	No
Executive control and flexibility	Ability to change focus of attention, Wisconsin Card Sorting Test, Tower of Hanoi	No
Interference	Ability to suppress interfering information, Stroop Color–Word Test	Yes
Processing speed		
Motor processing speed	Ability to make fast fine motor movements, finger tapping	No
Cognitive processing speed	Speed of processing that does not include motor movement, reaction time tests, comparison tests	Yes
Memory		
Short-term memory span	Ability to store small amount of information for short duration (seconds), digit span forward	No
Working memory	Combines short-term storage with processing and management of interfering information, reading span, PASAT	Yes
Verbal learning	Ability to learn verbal information and store for longer duration, word list learning tasks, Wechsler memory scale	Mixed, 8 out of 13 studies report dysfunction
Non-verbal learning	Complex Figure Test, Benton Visual Retention Test, visual reproduction from WMS	Mixed, 5 out of 12 studies report dysfunction
Interference	Previously learned information can interfere with new learning, and new learning can interfere with recall of old information	No, but limited evidence
Incidental learning	Ability to acquire information without deliberate effort	Yes, but only one study

More recent work examining neuropsychological function in CFS has both confirmed and extended the pattern of slow processing speed, impaired working memory, and impaired learning. Busichio and colleagues [48] conducted a large study (141 CFS patients) using a comprehensive battery of neuropsychological tests. The battery included the California Verbal Learning Test (CVLT), the Paced Auditory Serial Attention Task (PASAT), the Rey–Osterrieth Complex Figure Test, the Continuous Performance Test (CPT), simple reaction time, the Category Test, the Grooved Pegboard Test, Trail Making Tests A and B, Digit Span and Digit Symbol tests, and the Test of Memory Malingering. The results indicated a variety of impairments across the neuropsychological domains. The domains where CFS patients showed the most deficits were concentration (digit span total and digit symbol), speed of processing, and motor speed. It is important to note that these authors included PASAT in the speed of processing category, thus their results are consistent with WM deficits. CFS patients were not more likely than healthy controls to have low scores on the memory (verbal and non-verbal learning and digit span forward) or executive function (Category Test, Trails B, digit span backward).

The study described above is notable for the large number of CFS patients who participated. In another approach, Claypoole and colleagues

[49] used a cotwin control method. Twenty-two twins, one with CFS, and one without CFS were tested with a large neuropsychological battery. Although the overall number of participants is lower, the matching between each CFS-positive twin and CFS-negative twin is a very powerful design advantage. The results show that CFS-positive twins had similar intellectual function and visual memory compared to their CFS-negative twins. On the other hand, the CFS-positive twins had impaired scores for motor functioning (finger tapping, grooved pegboard, and simple reaction time), speed of processing (Stroop Color–Word Test – word and color subtests, PASAT), verbal memory (Wechsler Memory Scale, Rey Auditory Verbal Learning Test), and executive functioning (Stroop Color–Word interference subtest, Trail Making Tests A and B, verbal fluency, and Wisconsin Card Sorting Test). Note that PASAT was again included in speed of processing and this is again consistent with WM impairments in CFS. This twin-control study also found differences in verbal memory and in executive functioning in contrast to Busichio et al. The verbal memory tests used here may be more sensitive to differences associated with CFS than the California Verbal Learning Test, or perhaps the twin-control study is more sensitive to memory differences. The disparate findings regarding executive function may be explained by the various tests used by the two separate research groups. Claypoole et al. used the Stroop interference condition and the Wisconsin Card Sorting Test, and both of these have been found to be sensitive to CFS by other researchers (see Table 23.2).

Neuroimaging and Brain Activity

In CFS, abnormalities in white matter have been reported [50, 51], as well as reduced global gray matter volume [52]. Reduced cerebral blood flow has also been reported globally [53] and in the frontal and occipital lobes [54], although the findings may depend on the choice of control group. For example, monozygotic twins discordant for CFS do not show differences in cerebral blood flow [55]. Changes in cerebral metabolism, as measured by proton magnetic resonance spectroscopy (^{1}H-MRS), have also been reported [56, 57]. The abnormalities in structure, cerebral blood flow, and metabolism are all consistent with cognitive dysfunction. More direct evidence comes from studies that link brain activity with cognitive function. For example, Schmalling et al. [58] used single photon emission computerized tomography (SPECT) to compare brain activity during a resting state to activity while performing the PASAT, a demanding working memory task. They found that CFS patients had widespread, diffuse activity in the frontal lobes, temporal lobes, and thalamus compared to controls. Similarly, Lange et al. [59] used functional magnetic resonance imagery (fMRI) to study brain activations during a modified version of the PASAT. In this modified version, participants do not verbalize the sum of the preceding two digits, instead they press a button whenever the sum of two digits equals 10. This modification reduces head movement artifacts in the fMRI data. They found no behavioral performance differences between CFS patients and controls, but did note more activity in the verbal working memory system in the patients, specifically in bilateral supplementary motor and premotor cortices as well as the left superior parietal lobe. A third fMRI study of working memory in CFS patients used the *n*-back task [60]. In this task, a series of letters is shown. Participants press a button whenever the letter presented matched the letter shown *n* trials (1, 2, or 3 trials) previously. The *n*-back task has been used extensively to study working memory. In this study, the CFS patients performed as well as the healthy controls in terms of accuracy. However, there were differences in brain activation between the two groups. During 1-back, the CFS patients showed greater activation in the medial prefrontal cortex, including the anterior cingulate. During 2- and 3-back CFS patients showed reduced activation (compared to controls) in dorsolateral prefrontal cortex and parietal cortex: two areas that are normally active during working memory tasks. In contrast, CFS patients had greater activations in right

inferior/medial temporal lobe during the two 2- and 3-back. The authors interpreted these findings as evidence that during high task demands, the CFS patients do not recruit the normal working memory system and may instead rely on a compensatory strategy. These three studies corroborate patient's experiences of greater mental effort even when performance levels do not differ from controls. In another fMRI study, CFS patients evidenced increased activation compared to controls in visual processing areas of the brain (occipital cortex) during a motor imagery task [61]. Cook and colleagues [62] used fMRI to study the effects of mental fatigue on neural activation in both CFS patients and healthy controls. They found relationships between self-reported mental fatigue and activation during a difficult cognitive task (PASAT) but not during a simple motor task (finger-tapping) or simple cognitive task (number recognition). The CFS patients had greater activity during the fatiguing task in a number of brain areas as compared to healthy controls in left cerebellum and vermis, bilateral hippocampus, bilateral superior temporal cortices, right inferior frontal cortex, and left thalamus. Furthermore, this pattern of increased activation became more pronounced in the last block of testing when participants were the most fatigued. Thus, the functional imaging studies seem to be converging on a pattern of increased brain activity compared to control subjects even when performance levels are equivalent, although the work with the *n*-back task suggests that the pattern may be more complex than this as the level of task difficulty increases.

Other Rheumatologic Conditions

Sjögren's Syndrome and Cognitive Function

Sjögren's syndrome is a systemic autoimmune disease that affects the moisture-producing glands. It can occur as a primary disease or in association with other connective tissue diseases like systemic lupus erythematous, progressive systemic scleroderma, or rheumatoid arthritis [63, 64]. The most prominent symptoms are dry eyes and mouth; however, it can affect the central nervous system (CNS) and neurological symptoms in primary Sjögren's syndrome occur in about 20% of cases [64, 65]. Given the potential for CNS involvement with Sjögren's syndrome, it is perhaps not surprising that cognitive deficits are also part of the range of symptoms. The deficits described in the literature range from mild memory and attention impairments [66] to severe impairment indistinguishable from Alzheimer's disease [67, 68]. Although it is clear from the literature that cognitive dysfunction is present in some patients, many of the studies do not provide details on the cognitive tests used or the exact nature of the cognitive impairments. In an early neuroimaging study, Belin et al. [63] used single photon emission computed tomography (SPECT) and neuropsychological tests to investigate CNS involvement in Sjögren's. They found that all of their patients had impairment on a frontal lobe composite measure (verbal fluency, Trail Making Test, Stroop Test, Wisconsin Card Sorting Test), and many patients had incidental learning impairment, verbal working memory impairment, or face naming impairment. These authors also found an association between neuropsychological performance and hypoperfusion in the frontal lobes. In a later study using magnetic resonance imaging (MRI) to examine brain structure, Mataro et al. [69] found cognitive dysfunction in 47% of their Sjögren's syndrome patients, mostly in memory and frontal lobe tests. Ventricular volume (a measure that indexes loss of brain volume) was correlated with the continuous performance test, a test of attention/vigilance. The pathogenesis of CNS involvement in this disorder is not yet known, although there is a suspicion of immune-mediated inflammation [63, 67, 69].

Chronic Pain and Cognitive Function

As mentioned in the section on FM, chronic pain of any kind is distracting [22] and therefore may interfere with cognitive performance. Chronic pain is a common symptom in the rheumatology

clinic, and patients with chronic pain problems other than FM or CFS may also have some cognitive dysfunction, although cognitive complaints are much more common among FM patients than other rheumatology patients [8]. Hart et al. provide an excellent review of many studies of different chronic pain populations [1]. Included in their review are studies of FM, whiplash, TMD, myofascial pain, rheumatism, and several groups of unspecified chronic pain syndromes. They found that impairments were found especially on tests of attentional capacity, processing speed, and psychomotor speed, mirroring the findings for FM and CFS. More recent studies have confirmed the relationship between chronic pain and neuropsychological performance [70, 71], and have provided more details on the exact attention mechanisms that are affected by chronic and acute pain. For example, work by Dick and colleagues [40] suggests that chronic pain disrupts working memory storage. Work by Veldhuijzen and colleagues [72] suggests that processes of attention allocation are disrupted; Van Damme and colleagues [27, 29, 73] have further evidence that this is specifically due to diminished ability to disengage attention from a painful stimulus. Although the mechanisms by which chronic pain is associated with cognitive dysfunction are not yet fully elucidated, it is clinically very important to observe that cognitive dysfunction, even if subtle, often accompanies chronic pain because chronic pain is so common.

Summary

Although it is not normally considered part of a rheumatologist's bailiwick, many patients seen by rheumatologists may have cognitive dysfunction. Patients who complain of substantial cognitive problems may need referral to a neuropsychologist for testing. Unfortunately, research in this field is fairly new and there are no specific interventions for cognitive dysfunction that have been tested in FM, CFS, Sjögren's syndrome, or chronic pain. It is expected that in many cases, ameliorating primary symptoms (e.g., pain, fatigue) will also improve cognitive function, although this remains to be tested.

References

1. Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. Neuropsychol Rev. 2000 Sept;10(3):131–49.
2. Glass JM, Park DC. Cognitive dysfunction in fibromyalgia. Curr Rheumatol Rep. 2001 Apr;3(2):123–7.
3. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand. 2001 Feb;103(2):84–93.
4. Tiersky LA, Johnson SK, Lange G, Natelson BH, Deluca J. Neuropsychology of chronic fatigue syndrome: a critical review. J Clin Exp Neuropsychol. 1997 Aug;19(4):560–86.
5. Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions. Curr Rheumatol Rep. 2006 Dec;8(6):425–9.
6. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American college of rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum. 1990 Feb;33(2):160–72.
7. Zachrisson O, Regland B, Jahreskog M, Kron M, Gottfries CG. A rating scale for fibromyalgia and chronic fatigue syndrome (the FibroFatigue scale). J Psychosom Res. 2002 Jun;52(6):501–9.
8. Katz RS, Heard AR, Mills M, Leavitt F. The prevalence and clinical impact of reported cognitive difficulties (fibrofog) in patients with rheumatic disease with and without fibromyalgia. J Clin Rheumatol. 2004 Apr;10(2):53–8.
9. Leavitt F, Katz RS, Mills M, Heard AR. Cognitive and dissociative manifestations in fibromyalgia. J Clin Rheumatol. 2002 Apr;8(2):77–84.
10. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord. 2007 Mar;8(27):27.
11. Glass JM, Park DC, Minear M, Crofford LJ. Memory beliefs and function in fibromyalgia patients. J Psychosom Res. 2005 Mar;58(3):263–9.
12. Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression and healthy controls. J Rheumatol. 1995 Jan;22(1):137–42.
13. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. J Clin Exp Neuropsychol. 1999;21(4):477–87.

14. Leavitt F, Katz RS. Distraction as a key determinant of impaired memory in patients with fibromyalgia. J Rheumatol. 2006;33(1):127–32.
15. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills. 1977;44(2):367–73.
16. Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. Arthritis Rheum. 2001 Sept;44(9):2125–33.
17. Salthouse TA, Babcock RL. Decomposing adult age differences in working memory. Dev Psychol. 1991;27(5):763–76.
18. Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum. 2002;47(6):639–44.
19. Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I. The structure of normal human attention: the Test of Everyday Attention. J Int Neuropsychol Soc. 1996;2(6):525–34.
20. Landro NI, Stiles TC, Sletvold H. Memory functioning in patients with primary fibromyalgia and major depression and healthy controls. J Psychosom Res. 1997;42(3):297–306.
21. Glass JM, Park DC, Crofford LJ. Memory performance with divided attention in fibromyalgia (FM) patients. Arthritis Rheum. 2004 (Abstract);50 (Supplemental Issue):S489.
22. McCabe C, Lewis J, Shenker N, Hall J, Cohen H, Blake D. Don't look now! Pain and attention. Clin Med. 2005 Sept;5(5):482–6.
23. Glass JM, Williams DA, Gracely RH, Clauw DJ. Relationship of self-reported pain, tender-point count, and evoked pressure pain sensitivity to cognitive function in fibromyalgia. J Pain. 2004 (Abstract); 5(Supplemental Issue).
24. Grisart JM, Van der LM. Conscious and automatic uses of memory in chronic pain patients. Pain. 2001;94:305–13.
25. Grisart JM, Plaghki LH. Impaired selective attention in chronic pain patients. Eur J Pain. 1999;3(4):325–33.
26. Roelofs J, Peters ML, Zeegers MP, Vlaeyen JW. The modified Stroop paradigm as a measure of selective attention towards pain-related stimuli among chronic pain patients: a meta-analysis. Eur J Pain. 2002;6 (4):273–81.
27. Crombez G, Van DS, Eccleston C. Hypervigilance to pain: an experimental and clinical analysis. Pain. 2005;116(1–2):4–7.
28. Pincus T, Morley S. Cognitive-processing bias in chronic pain: a review and integration. Psychol Bull. 2001 Sept;127(5):599–617.
29. Van DS, Crombez G, Eccleston C, Goubert L. Impaired disengagement from threatening cues of impending pain in a crossmodal cueing paradigm. Eur J Pain. 2004;8:227–36.
30. Eccleston C, Crombez G. Attention and pain: merging behavioural and neuroscience investigations. Pain. 2005;113(1–2):7–8.
31. Montoya P, Pauli P, Batra A, Wiedemann G. Altered processing of pain-related information in patients with fibromyalgia. Eur J Pain. 2005;9(3):293–303.
32. Montoya P, Sitges C, Garcia-Herrera M, Izquierdo R, Truyols M, Blay N, et al. Abnormal affective modula tion of somatosensory brain processing among patients with fibromyalgia. Psychosom Med. 2005;67(6):957–63.
33. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcon GS, Mountz JM, Deutsch G. Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. Curr Rheumatol Rep. 2000;2(2):141–8.
34. Kwiatek R, Barnden L, Tedman R, Jarrett R, Chew J, Rowe C, et al. Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthritis Rheum. 2000;43(12):2823–33.
35. Sundgren PC, Petrou M, Harris RE, Fan X, Foerster B, Mehrotra N, et al. Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. Acad Radiol. 2007;14(7):839–46.
36. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46(5):1333–43.
37. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain. 2004;127(Pt 4):835–43.
38. Cook DB, Lange G, Ciccone DS, Liu WC, Steffener J, Natelson BH. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol. 2004;31(2):364–78.
39. Wik G, Fischer H, Finer B, Bragee B, Kristianson M, Fredrikson M. Retrospenial cortical deactivation during painful stimulation of fibromyalgic patients. Int J Neurosci. 2006;116(1):1–8.
40. Dick BD, Rashiq S. Disruption of attention and working memory traces in individuals with chronic pain. Anesth Analg. 2007 May;104(5):1223–9, tables.
41. Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull. 1999;125(3):356–66.
42. Wik G, Fischer H, Bragee B, Finer B, Fredrikson M. Functional anatomy of hypnotic analgesia: a PET study of patients with fibromyalgia. Eur J Pain. 1999;3(1):7–12.
43. Bangert A, Glass JM, Welsh RC, Crofford LJ, Taylor SF, Park DC. Functional magnetic resonance imaging of working memory in fibromyalgia. Arthritis Rheum. 2003 (Abstract);48(9):S90.
44. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. Ann Intern Med. 1994 Dec 15;121(12):953–9.

45. Wearden AJ, Appleby L. Research on cognitive complaints and cognitive functioning in patients with chronic fatigue syndrome (CFS): what conclusions can we draw? J Psychosom Res. 1996 Sept;41 (3):197–211.
46. Byrne MD. Taking a computational approach to aging: the SPAN theory of working memory. Psychol Aging. 1998;13(2):309–22.
47. Deluca J, Christodoulou C, Diamond BJ, Rosenstein ED, Kramer N, Natelson BH. Working memory deficits in chronic fatigue syndrome: differentiating between speed and accuracy of information processing. J Int Neuropsychol Soc. 2004;10(1):101–9.
48. Busichio K, Tiersky LA, Deluca J, Natelson BH. Neuropsychological deficits in patients with chronic fatigue syndrome. J Int Neuropsychol Soc. 2004;10 (2):278–85.
49. Claypoole KH, Noonan C, Mahurin RK, Goldberg J, Erickson T, Buchwald D. A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. Neuropsychology. 2007;21 (4):507–13.
50. Lange G, Deluca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. J Neurol Sci. 1999;171(1):3–7.
51. Natelson BH, Cohen JM, Brassloff I, Lee HJ. A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. J Neurol Sci. 1993;120(2):213–7.
52. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage. 2005;26(3):777–81.
53. Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. Clin Physiol Funct Imaging. 2006;26(2):83–6.
54. MacHale SM, Lawrie SM, Cavanagh JT, Glabus MF, Murray CL, Goodwin GM, et al. Cerebral perfusion in chronic fatigue syndrome and depression. Br J Psychiatry. 2000;176:550–6.
55. Lewis DH, Mayberg HS, Fischer ME, Goldberg J, Ashton S, Graham MM, et al. Monozygotic twins discordant for chronic fatigue syndrome: regional cerebral blood flow SPECT. Radiology. 2001;219 (3):766–73.
56. Puri BK, Counsell SJ, Zaman R, Main J, Collins AG, Hajnal JV, et al. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. Acta Psychiatr Scand. 2002 Sept;106(3):224–6.
57. Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. Neuroreport. 2003;14(2):225–8.
58. Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. Psychosom Med. 2003;65(1):129–36.
59. Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, et al. Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. Neuroimage. 2005;26(2):513–24.
60. Caseras X, Mataix-Cols D, Giampietro V, Rimes KA, Brammer M, Zelaya F, et al. Probing the working memory system in chronic fatigue syndrome: a functional magnetic resonance imaging study using the n-back task. Psychosom Med. 2006;68(6):947–55.
61. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JW, et al. Neural correlates of the chronic fatigue syndrome–an fMRI study. Brain. 2004 Sept;127(Pt 9):1948–57.
62. Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage. 2007;36 (1):108–22.
63. Belin C, Moroni C, Caillat-Vigneron N, Debray M, Baudin M, Dumas JL, et al. Central nervous system involvement in Sjogren's syndrome: evidence from neuropsychological testing and HMPAO-SPECT. Ann Med Interne (Paris). 1999;150(8):598–604.
64. Lafitte C, Amoura Z, Cacoub P, Pradat-Diehl P, Picq C, Salachas F, et al. Neurological complications of primary Sjogren's syndrome. J Neurol. 2001;248 (7):577–84.
65. Alexander EL. Central nervous system (CNS) manifestations of primary Sjogren's syndrome: an overview. Scand J Rheumatol Suppl. 1986; 61:161–5.
66. Malinow KL, Molina R, Gordon B, Selnes OA, Provost TT, Alexander EL. Neuropsychiatric dysfunction in primary Sjogren's syndrome. Ann Intern Med. 1985 Sept;103(3):344–50.
67. Spezialetti R, Bluestein HG, Peter JB, Alexander EL. Neuropsychiatric disease in Sjogren's syndrome: antiribosomal P and anti-neuronal antibodies. Am J Med. 1993;95(2):153–60.
68. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients. Medicine (Baltimore). 2004 Sept;83 (5):280–91.
69. Mataro M, Escudero D, Ariza M, Sanchez-Ojanguren J, Latorre P, Junque C, et al. Magnetic resonance abnormalities associated with cognitive dysfunction in primary Sjogren syndrome. J Neurol. 2003 Sept;250(9): 1070–6.
70. Weiner DK, Rudy TE, Morrow L, Slaboda J, Lieber S. The relationship between pain, neuropsychological performance, and physical function in community-dwelling older adults with chronic low back pain. Pain Med. 2006;7(1):60–70.

71. Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy RE, et al. Chronic pain patients are impaired on an emotional decision-making task. Pain. 2004;108(1–2):129–36.
72. Veldhuijzen DS, Kenemans JL, de Bruin CM, Olivier B, Volkerts ER. Pain and attention: attentional disruption or distraction? J Pain. 2006;7(1):11–20.
73. Van DS, Crombez G, Eccleston C, Koster EH. Hypervigilance to learned pain signals: a componential analysis. J Pain. 2006;7(5):346–57.
74. Pincus T, Swearingen C, Callahan LF. A self-report cognitive symptoms inventory to assess patients with rheumatic diseases: results in eosinophilia-myalgia syndrome, fibromyalgia, rheumatoid arthritis, and other rheumatic diseases. Arthritis Rheum. 1996 (Abstract);39(Suppl 9): s261.
75. Cote KA, Moldofsky H. Sleep, daytime symptoms, and cognitive performance in patients with fibromyalgia. J Rheumatol. 1997;24(10):2014–23.
76. Grisart J, Van der LM, Masquelier E. Controlled processes and automaticity in memory functioning in fibromyalgia patients: relation with emotional distress and hypervigilance. J Clin Exp Neuropsychol. 2002;24(8):994–1009.
77. Suhr JA. Neuropsychological impairment in fibromyalgia: relation to depression, fatigue, and pain. J Psychosom Res. 2003;55:321–9.
78. Sephton SE, Studts JL, Hoover K, Weissbecker I, Lynch G, Ho I, et al. Biological and psychological factors associated with memory function in fibromyalgia syndrome. Health Psychol. 2003;22(6):592–7.
79. Glass JM, Park DC, Crofford LA, Fougnie D. Fibromyalgia patients show reduced executive/cognitive control in a task-switching test. Arthritis Rheum. 2006 (Abstract); 54(Supplemental issue):S610.
80. Walitt B, Roebuck-Spencer T, Bleiberg J, Foster G, Weinstein A. Automated neuropsychiatric measurements of information processing in fibromyalgia. Rheumatol Int. 2008;28(6):561–6.
81. Glass JM, Park DC, Crofford LA, Fougnie D, Clauw DJ. Working memory in fibromyalgia patients: impaired function caused by distracting information, not rapid decay of stored information. Arthritis Rheum. 2007 (Abstract);56(Special Issue):S94.

Part VI
Endocrine Disease

Chapter 24

Neuropsychological Sequelae of Type 1 and Type 2 Diabetes

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Type 1 Diabetes

Overview of Type 1 Diabetes

Type 1 diabetes (T1D) or insulin-dependent diabetes is an endocrine disorder of insulin deficiency secondary to pancreatic β-cell destruction. Exogenous insulin replacement is imperfect and results in variable blood glucose levels with risk of glucose excess or hyperglycemia, and glucose insufficiency or hypoglycemia. The American Diabetes Association reports an incidence of 17.9 million cases of diabetes diagnosed among children and adults in the United States in 2007. An additional 5.7 million cases are undiagnosed [1]. Type 1 diabetes accounts for 5–10% of all diagnosed diabetes patients [2].

An intensive regimen of self-care behaviors helps minimize blood glucose fluctuations through frequent blood glucose monitoring, insulin replacement via subcutaneous injections, or insulin pump therapy, along with diet and exercise requirements. Near-normal metabolic control, as measured by the glycosylated hemoglobin (HbA1c) assay, can significantly reduce micro- and macrovascular damage and other disease complications thought secondary to fluctuations in blood glucose concentrations. Retinopathy, neuropathy, nephropathy, and cardiac disease all are identified sequelae of T1D [2–8]. During the past 25 years, studies of cognitive dysfunction and cerebral anatomical status have increased dramatically. Accumulated data will be synthesized from experimental and large-scale longitudinal studies, as well as meta-analytic results and neuroanatomical findings of cerebral substrates [9–11].

T1D Cognitive Effects in Adults

Brands et al. [6] conducted a meta-analysis of 33 studies with over 660 adult patients to compare T1D cognitive effects across studies. A moderate negative effect of diabetes on psychomotor efficiency (d = –0.6) was found compared to controls, a deficit which appears across multiple T1D populations and various methods. Broader, mild-to-moderate impairments occur in overall cognitive scores (d = –0.7), lower fluid (d = –0.5) and crystallized (d = –0.8) intelligence, slower speed of information processing (d = –0.3), disrupted visual (d = –0.4) and sustained (d = –0.3) attention, cognitive flexibility (d = –0.5), and visual perception (d = –0.4) [6]. Standard score

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(mean of 100, SD of 15) differences range from 5 to 10 points lower than control scores. Interestingly, despite the statistical sensitivity afforded by over 600 patients, cognitive domains of learning and memory, motor speed, divided and selected attention, and language were unaffected. Slowed psychomotor efficiency and diminished mental flexibility may be core features that underlie broader cognitive dysfunction. When cognitive dysfunction is found, impairments are greater with accompanying microvascular and macrovascular complications, an indication that extended periods of chronic hyperglycemia are related to poorer cognitive outcomes.

Hypoglycemic Effects on Adult T1D Cognition

The landmark Diabetes Control and Complications Trial [3] demonstrated that near-normal metabolic control significantly reduces the progression of microvascular retinopathy and other disease complications. However, intensive treatment also relates to a threefold increase in transient severe hypoglycemia that can result in seizures or coma. Milder hypoglycemia is more common; approximately half of T1D individuals may experience mild hypoglycemia below 70 mg/dL up to 10% of the time [12]. At 50–55 mg/dL, transient cognitive slowing occurs in mental processing, attention [13], and planning which can negatively affect automobile operation and cause driving errors and accidents [14]. Decrements of up to 33% are demonstrated relative to normoglycemia (80–120 mg/dL); decrements increase to 52% of euglycemic levels during moderate hypoglycemia [15] (41.5 mg/dL), although simpler motor skills and accuracy remain intact. Acute hypoglycemia can be particularly dangerous since patients may be unaware of their diminished cognitive capacity. Neuroglycopenic effects, including slowed P300 markers of diminished attention, often precede adrenergic counterregulation, i.e., shakiness, which triggers awareness of hypoglycemia [16, 17]. Restoration of cognitive function does not occur until 45–75 min later or in the case of severe hypoglycemia up to 36 h later [18].

Insufficient glucose disrupts normal neuronal functioning and initially is related to reduced cerebral blood flow, particularly to the frontal cortex [19, 20] followed by two to four times greater cerebral hyperperfusion as a compensatory mechanism. Despite rebound hyperperfusion, glucose availability increases by only 3% in children [21]. Animal studies reveal severe hypoglycemia, characterized by an absence of all neuroelectric activity for several minutes, is necessary to produce neuronal death. Although neuronal necrosis is unlikely to result from most hypoglycemic episodes, cerebral potentiation or sensitization effects may occur in response to significant alterations in cerebral blood flow. Transient cerebral hypoperfusion may become persistent if counterregulatory mechanisms become impaired. Recurrent episodes of hypoglycemia are associated with persistent cerebral hypoperfusion to the frontal cortex and basal ganglia in youth [22], regardless of blood glucose level at the time of assessment, age, or chronic hyperglycemia, as indexed by glycosylated hemoglobin.

Some studies show lasting neuroanatomical effects of recurrent hypoglycemia on MRI, in the basal ganglia in particular [23–25], while others do not [26]. Inconsistent neuroimaging findings may occur for a variety of reasons. Hypoglycemic vascular changes may be relatively subtle. Congruently, detection of hypoglycemic effects may be secondary to the type and sensitivity of the neuroimaging technique or alternatively to the proportion of vulnerable populations included in any individual study, such as youth with earlier disease onset who may be uniquely vulnerable to hypoglycemic insult. Recurrent hypoglycemia appears associated with reduced gray matter density, thought to presage later cognitive difficulties, in brain regions associated with language and limbic memory structures and in the cerebellum associated with executive skills of attention and planning [25]. This pattern is consistent with transient hypoglycemic effects of slowed information processing and executive

functioning [6, 26]. Better description of the isolated effects of severe hypoglycemia will be possible with consideration of these study design issues, particularly subject sampling.

The long-term effects of recurrent severe hypoglycemia were examined in the DCCT 18-year follow-up, the Epidemiology of Diabetes Interventions and Complications [4]. Recurrent hypoglycemic seizures or coma were unrelated to decline in any of eight cognitive domains studied. Meta-analysis also fails to document cognitive differences between groups of patients with and without recurrent severe hypoglycemia [6]. The damaging effects of hypoglycemia appear limited to their immediate acute cognitive effects with no discernible lasting performance complications in most individuals, despite much speculation and concern in the earlier neurocognitive literature. However, debate still exists as to possible enduring hypoglycemic effects in youth with disease onset before the age of 7.

Hyperglycemic Effects on T1D Cognition

The acute and chronic cognitive sequelae of hyperglycemia are strikingly similar to those of hypoglycemia. An early study found acute hyperglycemia at 300 mg/dL caused reduced speed of information processing [27] along with a trend toward reduced verbal fluency, an executive functioning skill [28]. These effects were transient, subtle and not as pronounced in magnitude as those that occurred during mild hypoglycemia. Cox et al. [15] found similar results in a naturalistic study. Subjects were generally unaware of hyperglycemic impairments, similar to the effects of mild hypoglycemia. Interestingly, an optimal glucose range for cognitive functioning was found between 70 and 180 mg/dL; cognitive deterioration of up to 30% begins at either end of the glucose continuum, with a steeper decline during hypo- than hyperglycemia. Undetermined was the level of hyperglycemia necessary to produce impairments comparable in magnitude to those of hypoglycemia [29, 30].

The 18-year EDIC follow-up found that poorer metabolic control, benchmarked by chronic hyperglycemia, with glycosolated hemoglobin levels greater than 8.8%, relates to moderate decline in psychomotor efficiency and motor speed over time. Deterioration of up to 9% of baseline levels occurs and chronic hyperglycemia is the sole predictor of slower functioning. Neither recurrent severe hypoglycemia nor treatment regimen related to performance. The possibility is raised that better metabolic control might reduce mild cognitive decline much as it forestalls micro- and macrovascular complications. Beyond glycohemoglobin indices of chronic hyperglycemia, others have found the presence of retinopathic and neuropathic complications, a proxy marker of chronic hyperglycemia, relates to increasingly slower psychomotor efficiency over time [6, 31, 32]. Chronic hyperglycemia appears to exert a lasting detrimental cognitive effect, whether indexed by glycohemoglobin assay or microvascular disease complications.

Like hypoglycemia, acute hyperglycemia appears associated with disruption of cerebral vascular status. Animal models show initial hypoperfusion of approximately 25% after glucose injection is followed by an increase in cerebral blood flow that is two to four times greater than baseline, thought secondary to increased plasma osmolality [31]. Fractional brain tissue volume, relative to total intracranial volume, on structural MRI shows significantly smaller white matter volume is associated with advanced retinopathy and slower speed of information processing [33], similar to other illnesses of white matter atrophy, like multiple sclerosis [34]. Reduced white matter volume in T1D also relates to slowed attention and executive functioning [33]. Differences in gray matter density, measured by voxel-based morphometry, also are associated with advanced diabetic retinopathy [32]. Trends of reduced gray matter volume in the left middle frontal gyrus, right inferior frontal gyrus, right occipital lobe, and cerebellum are found in patients with proliferative retinopathy but not those without. Reductions in white and gray matter occur near

"water-shed" areas of the medial cerebral artery and posterior cerebral artery, and suggest relative hypoperfusion as an instigating factor [35]. Patients with T1D experience generalized reduction in white and gray matter volume, and ultimately whole brain volume, with white matter differences more reliably detected and related to slowed psychomotor functioning, diminished attention, and speed of information processing.

Cognitive Effects of Pediatric T1D

Children and adolescents (<18 years) with type 1 diabetes also experience mild cognitive dysfunction. Meta-analysis of 27 studies with over 2,000 children shows mildly lower general cognitive ability across most domains (d = –0.13), except memory and learning which are unaffected, consistent with the adult literature [6, 37]. With an average disease duration under 6 years, pediatric effects are generally small, by Cohen's criteria < 0.3, while adult effects are moderate in magnitude and related to longer disease duration and disease complications. Pediatric fluid (d = –0.18) and crystallized (d = –0.15) intelligence is lower than controls as well as other cognitive skills of psychomotor efficiency (d = –0.10), motor speed (d = –0.16), attention and executive function (d = –0.10), academic achievement (d = –0.13), and visual motor integration (d = –0.18) [36]. However, the small effect sizes translate into only 1–3 point differences in standard scores. With an average disease duration of 5 years across studies, most children with T1D appear to function similarly to their peers although some groups of youth may be more adversely impacted. Signs of pediatric psychomotor slowing [36, 38] are generally mild and do not appear until longer disease duration of 5–8 years [39]. Similar studies of newly diagnosed adults have not been conducted to conclusively establish the length of disease duration necessary to detect psychomotor slowing.

One longitudinal study of newly diagnosed youth found lower verbal and performance IQ scores 12 years post-diagnosis. IQ scores were 4 points lower than control scores, consistent with and slightly more pronounced than those of pediatric meta-analytic findings [36, 38]. Older age predicted brain volume loss and change to the basal ganglia [23], consistent with an "accelerated aging" hypothesis of diabetes [40], even in youth. Despite the smaller magnitude of neurocognitive effects, the pervasiveness of cognitive difficulties [36, 38] along with glucose and attentional fluctuations that may occur in the classroom could nevertheless exert a significant impact on learning and achievement. Indeed, only 68% of young adults at follow-up completed compulsory 12-year education versus 85% of controls [23].

Hypoglycemia in T1D Youth

Acute hypoglycemia is related to transient dysfunction in children's attention, executive skills, and speed of responding [41, 42], findings notably comparable to transient effects found in adults with T1D. Although reversible, effects may linger for up to 45 min after resumption of normoglycemia, an extended period of diminished capability that could impact complex skills required in a classroom, much like effects on adult driving skills [14]. Young preschoolers may be uniquely affected by mild recurrent hypoglycemia; a lasting impact on visual spatial abilities may be found following cumulative mild hypoglycemic episodes [43]. Interestingly, profound nocturnal hypoglycemia in older youth [44] appears to impact mood the following morning but not cognitive status (d's = 0.06 to –0.14) [36, 38], consistent with findings from the DCCT/EDIC studies.

Age of disease onset appears to be a crucial factor in youth [45] as described later. Earlier age of disease onset (<7 years) is repeatedly shown to be a risk factor for greater cognitive impairment relative to later onset. Nevertheless, youth with later disease onset still show small but broad neurocognitive sequelae that mirror the effects reported in overall pediatric samples, including spared memory and learning skills [36].

Hyperglycemia in T1D Youth

Gonder-Frederick et al. [42] found that naturally occurring acute hyperglycemia (400 mg/dL) in pediatric patients slowed mental processing up to 20% compared to normoglycemia, a pattern and magnitude of effect that was similar to that of transient, naturally occurring hypoglycemia (55 mg/dL) in the same study. Davis et al. [46] found slower responses on timed performance IQ subtests resulted in lower PIQ scores during hyperglycemia (360–540 mg/dL) compared to normoglycemia (90–180 mg/dL) in counterbalanced assessments 6 months apart.

Compared to these transient effects of hyperglycemia, chronic hyperglycemic effects are less well documented in children. Poorer metabolic control is related to reduced visuospatial and math performance, disrupted attention, and memory and executive deficits [39]. At 12 years post-diagnosis, youth with diabetes have reduced gray matter volume in the insular cortex and frontal precentral regions on MRI scans, with a reduction in mean white matter volume in the mesial temporal areas [23]. These changes are related to hyperglycemia. Disrupted white matter integrity on diffusion tensor imaging and lower verbal IQs [47] are also related to hyperglycemia.

Early Onset T1D (EOD) and the Developing Brain

The rapid development of the young brain under the age of 7 may provide a background vulnerability to the effects of recurrent hypoglycemia and chronic hyperglycemia [45], as this group is uniquely vulnerable to memory and learning deficits. Early onset of diabetes (EOD) is associated with lower overall cognition across eight domains compared to later disease onset (d = –0.20) [36]. Lower skills are found in verbal (d = –0.28) and visual (d = –0.25) memory and learning, poorer attention and executive function (d = –0.27), lower academic achievement (d = –0.19), and lower crystallized intelligence (d = –0.15) [36]. Effect sizes increase when compared to nondiabetic controls, a comparison that typically occurs in classrooms. Visual (d = –0.49) and verbal (d = –0.44) memory and learning are moderately impaired with standard score differences of approximately 6.5–7 points. Differences of this magnitude could be clinically detectable. Early disruption of memory and learning skills, if maintained across time could help explain the persistent and pervasive effects of EOD throughout the life span [5].

Moderately impaired memory and learning suggests the developing limbic system may be particularly vulnerable to metabolic insult. Neuroimaging studies reveal 14% of EOD (<7 years) young adults have small point white matter lesions in the hippocampus [7]. EOD young adults show lateral ventricle volume increased by 36% compared to later onset young adults along with a corresponding reduction in whole brain volume that relates to reduced attention/executive function and slower information processing [7]. In another study, 29% of EOD school-age children showed CNS structural abnormalities on MRI, and 16% showed mesial temporal sclerosis (MTS) consistent with hippocampal damage. All children had EOD; so it is possible to evaluate the timing of severe hypoglycemic seizures and diabetic ketoacidosis on brain imaging results. Youth with early seizures (<6 years) had reduced white matter volume compared to those with late seizures (d = –0.58). Timing of seizures did not influence gray matter differences although youth with seizures had reduced gray matter compared to those without (d = –0.502). In contrast, extreme hyperglycemia, represented by diabetic ketoacidosis, was not related to neuroimaging differences [48], although neuropsychological differences are reported by others [49] in relation to the timing of both hyper- and hypoglycemic EOD events. Perantie et al. [49] found reduced spatial intelligence and delayed recall with repeated hypoglycemia before the age of 5 years. Northam et al. [23] found congruent lower visual spatial functioning in performance IQs associated with earlier disease onset. In contrast, Wu et al. [47] reported reduced verbal intelligence with increased exposure to hyperglycemia and disrupted white matter integrity in the right superior

occipital area. To date, EOD effects have not been evaluated in those with earliest onset during infancy; a group that may be at greatest risk for neurocognitive disruption.

Cerebral Microvascular Effects in T1D

A consistent pattern of slowed psychomotor efficiency, slowed information processing, and diminished attention is found in response to acute hypo- and hyperglycemia in both adults and children with T1D. These acute neuropsychological effects are consistent with persistent effects that become detectable approximately 5 years after disease diagnosis. Disruptions in cerebral blood flow are characteristic of both acute hypoglycemia and hyperglycemia as well as diabetes of longer duration. Functional MRI studies indicate that cerebrovascular responsiveness is important during normal cognition as reflected by discrete changes in regional flow that occur in response to different cognitive tasks [26]. Repeated decreases in cerebral blood flow during glucose fluctuations could contribute to the inability of cerebral vessels to adequately vasodilate and result in cerebral ischemia [35]. Although the lasting neuropsychological effects of recurrent hypoglycemia appear negligible in adult and most child populations, pending further study of children with earlier disease onset, its vascular consequences may set the stage for later hyperglycemic insult. Hyperglycemia and resultant cerebral ischemia appear to exert enduring neuroanatomical and neuropsychological effects. Hyperglycemia produces lactate release which may be particularly damaging to the brain via cellular acidosis. Glutamate is also released during hyperglycemia, an excitatory amino acid neurotransmitter, which can cause neuronal damage [50]. These are but a few of the biochemical effects of hyperglycemia that may provide a mechanism by which transient cerebral vascular changes, and their associated cognitive patterns, may be transformed into persistent vascular and neuropsychological characteristics. Loss of both gray and white brain volume occurs, with some evidence that white matter loss in particular [33, 35] may relate to the characteristic diabetes cognitive pattern of reduced psychomotor efficiency. Diminished psychomotor efficiency also is found with general cerebral vascular disease, particularly subcortical ischemic vascular disease. Mild cerebral vascular disease is associated with early impairment of attention and executive function, slowed motor performance, and information processing while memory is relatively spared [51]. White matter lesions, when found in general cerebral vascular disease, are associated with depression.

Depression and Cardiovascular Disease in T1D

Both depression and hypertension co-occur frequently with T1D and each condition relates to declines in cognitive function in its own right, similar to that seen with T1D. Depression, in particular, is characterized by slowed mental processing. Comorbidity between depression and diabetes is 29.1% based on self-report questionnaires versus 13.6% with more stringent clinical interview of over 21,000 patients with T1D and T2D [52]. Brand et al.'s [6] meta-analysis found that T1D patients with and without comorbid depression experience similar levels of cognitive dysfunction, suggesting a negligible additive effect of depression to T1D cognitive status. Interestingly, cortisol hyper-secretion may partially mediate cognitive disruption in both T1D and depression as well as other clinical conditions of chronic stress, aging, and Alzheimer's disease [53] and provides a provocative avenue for further study. The role of depression in type 2 (T2D), non-insulin-dependent diabetes, is better substantiated and researched than in T1D.

Patients with T1D also are at a slightly increased risk for hypertension, found in 3.9% of patients, secondary to nephropathy. Hypertension is a concern given the evidence of microvascular and cerebral vascular disease, although hypertension is much more prevalent in T2D. Although a synergistic interaction of

hypertension may occur in T1D along with other disease complications, hypertension itself is sufficiently infrequent and unstudied such that it is not likely to have a major influence in T1D cognitive dysfunction [6].

T1D Conclusions and Implications

Individuals with T1D are exposed to a lifetime of blood glucose fluctuations. Chronic exposure to hyperglycemia in adulthood is linked to the development of significant micro- and macrovascular complications which in turn relate to reduced psychomotor efficiency that progresses in severity with chronic hyperglycemia. Interestingly, memory and learning is spared as is the hippocampal region when diabetes diagnosis occurs after the age of 7. Before the age of 7, bilateral hippocampal damage and impaired memory and learning predominate. Neuroimaging T1D studies suggest decreased gray and white matter consistent with disease complications. Better metabolic control appears to slow cognitive decline. Future neurocognitive and neuroimaging studies could sharpen study findings with clear delineation of samples by age of disease onset before and after the age of 7.

Mildly slowed psychomotor efficiency also occurs in pediatric patients between the ages 8 and 18, along with an array of generally mild neuropsychological dysfunction. However, memory and learning is spared, consistent with adult findings. In contrast, disease onset before the age of 7 relates to moderate cognitive difficulties, notably in memory and learning. Neuroanatomical abnormalities, particularly in the hippocampal region, are present in one-third of early onset patients. EOD cognitive dysfunction is detectable in young adults and neuroimaging results, suggesting an organic basis to the pattern of results.

Cognitive dysfunction and decline related to T1D is generally mild and possibly preventable with better metabolic control. Mild cerebral microvascular changes that predict cognitive dysfunction occur with chronic hyperglycemia. Accumulated data suggest that mild cognitive dysfunction is sufficiently pervasive such that it should be considered an early complication of type 1 diabetes much like retinopathy and neuropathy.

Type 2 Diabetes

Overview of Type 2 Diabetes

Type 2 diabetes (T2D) is a metabolic disorder characterized by elevated blood glucose levels that result from insulin resistance and relative insulin insufficiency [54]. Previously known as noninsulindependent diabetes mellitus (NIDDM), T2D accounts for 90–95% of all diabetes diagnoses [55]. T2D affects 7.8% of the population in North America, with prevalence rates as high as 15–20% among the elderly [56, 57]. The worldwide prevalence of T2D is estimated to double by 2030, particularly among minority and younger populations [1, 58].

Like T1D, the American Diabetes Association (ADA) identifies a plethora of vascular and metabolic complications of T2D, including cardiovascular disease, retinopathy, neuropathy, and nephropathy [54]. Also similar to T1D, despite a growing literature in this field, the ADA has yet to include cognitive dysfunction among reported disease complications [59].

Cognitive Function in T2D

Individuals with T2D experience mild cognitive dysfunction and accelerated cognitive decline. Studies show a relatively consistent pattern of disrupted psychomotor efficiency in middle-aged adults, with additional memory and learning impairments that begin around the age of 60 [60]. Mild neurocognitive impairments are found in verbal memory [61–65], processing speed [59, 61, 65–67], executive function [57, 67, 68], and

psychomotor speed [60]. Other researchers have broadened the scope of investigation and note cognitive atypicalities in perceptual speed [69], semantic memory [69], and attention [66, 68, 70].

Brief cognitive screening measures, like the Mini-Mental Status Exam (MMSE), are often administered particularly in elderly populations over 65. Although these measures are criticized as too broad to detect meaningful cognitive dysfunction [61], several studies find poorer performance [67, 71–74]. Mild cognitive impairments detected with the MMSE relate to decreased involvement in self-care and diminished capacity to complete activities of daily living, in addition to more frequent hospitalizations [72].

Cognitive Decline in T2D

A 1.5-fold greater risk of accelerated cognitive decline in those 60 years and older on brief screening indices like the Mini-Mental Status Exam (MMSE) and Digit Symbol Substitution test (DSS) is found in meta-analysis [75]. Over the age of 60, declines in memory, psychomotor speed, and attention can occur after only 3 or 4 years of follow-up [76]. However, longitudinal outcomes may underestimate the rate of cognitive decline due to focus on medically uncomplicated patients [76]. For example, decline is often relatively mild, such as lower scores on some psychomotor and verbal memory measures at follow-up [77]. Although performance may lower with time, it is often still within the normal range of functioning for most. Nevertheless, mild declines often "spread" across cognitive domains over time and become more pervasive. Psychomotor speed and speed of executive functioning are slowed initially, the hallmark atypicalities of T2D [57]. With time, these difficulties are sustained and additional problems may emerge over relatively brief intervals in executive function tasks that are untimed and simpler tasks of reaction time [57]. Beyond this typical course, a smaller percentage of those with T2D experience a 2:1 higher incidence of dementia. Since diabetes occurs in 15–20% of those aged 65 and older, a surge in dementia may accompany the increasing rate of T2D.

Effects of Age and Disease Duration on T2D Cognitive Status

Literature implicates age as an important factor in T2 neurocognitive status. Current studies target late adulthood, 60–85 years, and the very old population, those older than 85, for assessment. To date, middle age appears relatively spared of cognitive sequelae of T2D; no difficulties are reported in any neuropsychological domain [5, 60]. In contrast, late adulthood is a critical period during which individuals with T2D are highly susceptible to normal age-related mild neurocognitive dysfunction and decline [5]. The very old elderly experience an increased likelihood of normative cerebral vascular deterioration and Alzheimer's disease (AD), either of which can exacerbate acquired cognitive dysfunction from T2D [61].

Studies of the very old are less conclusive and intriguing. Some investigations report poorer cognitive performance in the very old over 85 years, but no difference in rate of cognitive decline after 5 years. Alternately, other researchers find no significant relation between cognitive function and T2D in the very old [5]. Perhaps the "modifying effects of age" may account for these differences. Multiple medical conditions co-occur frequently in elderly populations that can result in cognitive impairments and brain structure abnormalities; these background effects may overshadow any independent cognitive effect attributable to T2D [5, 68]. Alternatively, superthresholds may exist for relatively intact cognitive function in individuals who live to such late ages [5], in essence, a "survivor" effect.

Although T2D is emerging as a growing health concern in pediatric patients, only one preliminary investigation of cognitive effects is available. A small sample of T2D adolescents had significantly lower IQ and verbal memory scores than obese non-insulin-resistant controls

[78]. Although there were no group differences on MRI, more subtle diffusion tensor imaging revealed slight white and gray matter pathology in the T2D adolescents but none in controls.

Disease duration appears to affect cognitive function in T2D above and beyond the effect of age [67, 79–81]. Duration effects are detected as early as 3 years after diagnosis [73] and duration greater than 15 years reliably relates to mild cognitive dysfunction in processing speed and executive function [59].

Hyperglycemic Effects in T2D

Hyperglycemia, defined as elevated blood glucose levels >270 mg/dL, poses a similar cognitive threat in T2 diabetes as in T1D [75, 82]. Transient cognitive disruption is noted during naturally occurring fluctuations of hyperglycemia [83] as well as during experimental manipulation of glucose levels [84, 85]. Slowed psychomotor speed and increased subtraction and addition errors are found during hyperglycemic episodes. Risk factors for poorer performance include longer disease duration, a history of more hyperglycemic episodes, and poorer cognitive performance during normoglycemia of 70–120 mg/dL [83]. The clinical implications of math errors for miscalculation of insulin doses, and ultimately for poorer metabolic control, are apparent.

Beyond acute effects of hyperglycemia, chronic hyperglycemia, as indexed by poorer glycosylated hemoglobin (HbA1c) levels, is related to slowed information processing [68], reduced psychomotor efficiency [60, 86, 87], along with poorer declarative memory [64] and abstract reasoning [68]. A landmark recent study, the Action to Control Cardiovascular risk in Diabetes – Memory in Diabetes, ACCORD-MIND, confirmed that poorer HbA1c levels relate to poorer psychomotor speed in approximately 3,000 patients [87]. The relation between A1c and memory persisted after statistical control of numerous comorbid micro- and macro-vascular disorders. Further, each 1% increase in HbA1c related to the equivalent of 2-year deterioration in memory scores. Cognitive performance was related to HbA1c but not fasting blood glucose levels or insulin levels. While awaiting longitudinal findings from this study, initial evidence suggests that improvements in glycemic status can yield gains in memory scores [88]. Lowered fasting plasma glucose levels after 24 weeks of oral medication can result in improved working memory that is unrelated to type of medication [88]. Working memory requires complex brain function from multiple cortical systems along with an adequate glucose substrate to operate efficiently. As such, cognitive improvement may relate to greater local cerebral glucose availability [88].

T2D and Hypoglycemia

Individuals with T2D do not experience hypoglycemia as frequently as individuals with T1D. However, those who manage T2D through medication, such as metformin or insulin, are more susceptible to low blood glucose levels than those who rely solely on diet and exercise for disease management [54]. To date, there is little evidence that severe or frequent hypoglycemia is related to neurocognitive impairment in T2D [89].

Cerebral Microvascular Disease in T2D

Type 2 diabetes typically develops within a cluster of vascular and metabolic risk factors, most of which are associated with cognitive dysfunction in their own right [90]. Microvascular changes associated with T2D and cognitive dysfunction include retinopathy, neuropathy, and angiopathy [89]. Brain imaging techniques reveal a variety of cerebrovascular abnormalities in T2D populations, including white matter lesions (WML) and deep white matter lesions (DWML) [65, 68, 90], cortical and subcortical atrophy [63, 65, 68, 91–93], and the presence of infarcts [65, 68, 94].

A limited number of studies have linked structural abnormalities to mild cognitive

dysfunction. An association is found between the presence of DWMLs, infarcts, and reduced processing speed [65]. Subcortical atrophy relates to diminished attention and executive functioning. A trend between decreased hippocampal volume and poorer memory performance also is found [63]. The hippocampus is highly susceptible to the effects of severe glucose fluctuations, making it a primary target for hyperglycemia-related damage [63], although this effect may be limited to those over 60 who are undergoing normal age-related neurocognitive decline [5].

Hippocampal vascular differences also are found in association with hyperglycemia. Blood glucose, but not insulin, levels are inversely and selectively correlated with cerebral blood volume in the dentate gyrus of the hippocampus in the elderly, with and without T2 diabetes. Glycemic effects are independent of Alzheimer's disease and stroke. Further, ambient blood glucose levels are inversely related to recall on a selective naming measure sensitive to hippocampal function [95]. Transient hypoperfusion can occur throughout the vascular territory supplying the hippocampus, i.e., the basal ganglia, thalamus, internal capsule, and occipital cortex, which may explain disruption in these areas in T1 and T2 neuroimaging studies [11, 23, 49]. Data suggest that normal age-related hippocampal dysfunction begins in the fourth decade of life before the ostensible onset of many age-related diseases [95]; age-related decline appears hastened by type 2 diabetes.

Comorbid Macrovascular Disease

Macrovascular diseases, or large vessel atherosclerosis, associated with T2D include cardiovascular disease affecting the heart as well as peripheral vascular disease affecting the limbs. Hypertension is a comorbid condition of T2D and an independent risk factor of cerebral vascular disease [96]. The combination of T2D and hypertension is associated with mild cognitive impairments in reduced processing speed and memory [68]. However, comorbid hypertension and T2D in very old populations is related to pronounced cognitive decline over 6 years, although elderly participants with diabetes, with or without hypertension, started the study with lower cognitive performance on the MMSE [96]. Recent brain imaging studies detect an association between T2D, hypertension, and a higher incidence of brain structure abnormalities including WMLs, DWMLs, and a non-significant trend for greater cerebral atrophy [90].

In addition to hypertension, both obesity and smoking are vascular risk factors frequently associated with T2D. Preliminary effects of obesity on cognitive function are found for men but not for women, yet gender does not emerge as a significant predictor of cognitive function when other covariates are considered [79]. Mechanisms underlying obesity and cognitive function in men may include other male risk factors such as greater central adiposity and cardiovascular disease than found in women. In contrast, metabolic disorder which presumably underlies the association between diabetes and cognitive function may be a similar risk factor for both genders [79]. Given the high comorbidity between obesity and T2D, further exploration of the independent association of each with cognitive dysfunction and of gender differences appears warranted. Significant interactions between diabetes and current smoking also are present. T2D patients who smoke have significantly lower levels of semantic memory, working memory, and perceptual speed compared to nonsmokers with and without T2D [69]. This additional vascular risk factor is little studied to date. Given its prevalence in older populations prone to T2D, further investigation appears warranted.

The plethora of micro- and macrovascular risk factors associated with T2D may help explain inconsistencies found in cognitive dysfunction. Studies targeting uncomplicated T2D samples fail to find significant cognitive impairments, suggesting that T2D does not negatively affect cognitive function in the absence of micro- and macrovascular disease [62]. Additionally, many studies report cognitive dysfunction diminishes when statistical controls are included for

potential confounds such as micro- and macrovascular disease, hypertension, and body mass index (BMI) [69, 81, 97].

Depression and T2D

The prevalence of depression is doubled for individuals with T2D compared to the general population [98]. In older samples, 14–33% meet criteria for major depression [71, 99]. Depressed people with diabetes are at greater risk for poorer self-care and diabetes management along with poorer metabolic outcomes [71, 99–101]. The association between depression and diabetes begins early with metabolic disorder [102]. Although the relation between type 2 diabetes and depression is often considered bi-directional, this hypothesis is only recently tested. In fact, depression more often precedes diabetes than vice versa. Depression is associated with a 60% increase in the prevalence of T2D through multiple possible mechanisms of poorer lifestyle choices as well as physiological abnormalities of the hypothalamic–pituitary–adrenal axis, sympathoadrenal system, and proinflammatory cytokines, all of which can produce insulin resistance [103]. In contrast, diabetes is associated with only a modest increase in risk of depression.

Depression may affect neurocognitive processes directly, beyond the effect of T2D, as it does in the general population. Alternately, depressed individuals with T2D may experience mild cognitive impairment due to comorbid vascular disease [100]. Researchers have difficulty disentangling mild T2D cognitive impairment from co-occurring symptoms of depression or vascular disease, both of which also are independently related to poorer cognition [75]. Nevertheless, depression and T2D together appear to more negatively impact cognitive function than either one individually. Diminished attention/processing speed and executive functioning is found, although methodological variables appear crucial to interpretation. For example, individuals with both T2D and clinical depression, based on structured interviews, display disrupted executive skills (d = 0.58) and slowed psychomotor speed (d = –0.62) [100]. In contrast, those with only T2D exhibit only a trend toward disrupted executive skills (d = –0.31). However, when depression is based on self-report and varies broadly along a continuum, no additive effect is found on cognitive performance, although a primary effect of diabetes on cerebral atrophy and reduced psychomotor functioning is detectable, consistent with the literature [91]. Together, this initial evidence suggests that clinical depression has a moderate additive effect on overall T2D cognition while the impact of mild depression may be less discernible. Large-scale longitudinal studies like the ACCORD–MIND should have the power to better clarify the parameters of these interrelations.

Alzheimer's Disease

An association between T2D and Alzheimer's disease (AD) is found via multiple lines of converging evidence from longitudinal investigations, epidemiological population surveys, and brain imaging studies [89, 104]. Earlier studies have detected a higher genetic predisposition to AD in individuals with T2D compared to the general population, as measured by a higher incidence of the apolipoprotein E (APOE) genotype, and specifically the ε4 allele [105]. However, the evidence is mixed regarding the increased risk of brain structure abnormalities and cognitive dysfunction associated with the T2D carriers of the APOE genotype [104, 105].

Hippocampal atrophy and related memory dysfunction are common to both T2D and AD. However, diabetes is associated with damage to the dentate gyrus, while AD is related to damage of the entorhinal cortex as evidenced by cerebral blood flow studies [95]. The entorhinal cortex is selectively sensitive to insulin insult which provides a common anatomical site for the effects of AD, diabetes, and stroke that may explain the comorbidity among the three. T2D was thought to be associated with neurofibrillary tangles and accelerated deposition of β-amyloid plaques, "the pathological hallmark of Alzheimer's disease." However, recent autopsy studies have failed to

detect differential AD neuropathology among deceased individuals with T2D, calling into question earlier anatomical evidence [69, 104]. Until future research provides substantial evidence to support or discount this and other potential mechanisms, one can conclude only that there is a moderate co-occurrence of T2D and AD [69, 89].

Implications and Future Directions in T2D

Type 2 diabetes, like type 1, is related to a neurocognitive pattern of disrupted psychomotor efficiency and motor speed in individuals below the age of 60 who are generally in better metabolic control and without microvascular complications such as retinopathy. This cognitive pattern is strikingly similar to that found in type 1 diabetes diagnosed after the age of 7. Verbal memory also is mildly impaired in type 2 diabetes over the age of 60 as natural age-related neurocognitive decline intensifies. Although neuroimaging data are still emerging in type 2 diabetes, hemodynamic changes in reduced cerebral blood flow and cerebral atrophy occur similar to those found in type 1 diabetes. Like type 1, type 2 cerebral vascular changes relate to poorer psychomotor efficiency, suggesting a vascular etiology. Unlike T1D the period of greatest brain vulnerability in T2D appears to be in the aging brain over 60 [5]. Chronic hyperglycemia, particularly in those over age 60, may relate to selective damage to the dental gyrus region of the hippocampus with associated verbal memory disruption. Other underlying mechanisms may be present as well. Disruption of the hypothalamic–pituitary–adrenal (HPA) axis, common in T2D, can contribute to mild cognitive dysfunction in affected individuals [89]. Hippocampal damage, thought common to T2D in the elderly, may lead to impaired HPA axis feedback regulation [64]. Specifically, increased cortisol levels are associated with both HbA1c levels and mild impairment in declarative memory [64]. HbA1c also is related to dysregulation of the HPA axis among individuals with T2D, with greater dysregulation associated with higher HbA1c levels. Additional research is needed to clarify the relation between HPA axis function and mild cognitive dysfunction.

Based on available research, it is increasingly clear that individuals with T2D are likely to experience mild cognitive deficits across multiple cognitive domains, depending on age, disease progression, duration, and corresponding vascular changes. While current literature implicates multiple disease risk factors, less information is known about how to improve cognitive function other than to ameliorate underlying disease processes. Improvement in fasting plasma glucose through medication results in improved memory. Tentative evidence also suggests physical exercise may selectively improve function in the dentate gyrus of the hippocampus versus other subregions by improving blood glucose levels. The benefits of such a cost-effective and nontoxic treatment should be replicated as a measure that can be readily adopted [95]. Other treatment options to improve cognitive function logically include prevention of T2D itself or treatment of comorbid hypertension, microvascular, and macrovascular disease. Considering the growing population of individuals with T2D, and those in stages of impaired glucose tolerance or pre-diabetes, further research in this field could have broad public health implications.

T1 and T2 Diabetes: Overview and Conclusions

Initially treated as distinct diseases, increasingly, the cognitive sequelae of both T1D and T2D appear to converge across the life span [5, 15]. Chronic hyperglycemia, common to both, produces a similar neuropsychological pattern of reduced psychomotor efficiency. Underlying this cognitive profile is similar cerebral vascular insult secondary to fluctuations in cerebral blood flow and resultant microangiopathy. Acute hypoglycemia, more prevalent in T1D, shows similar cognitive characteristics and cerebral vascular substrates as hyperglycemic effects, despite different origins. Repeated episodes of acute hypoglycemia may prove to be a

synergistic factor that accelerates hyperglycemic-related vascular and cognitive decline by increasing the vascular "wear and tear" or structural alterations in the brain, although this possibility is speculative.

Acute cerebral vascular hypoperfusion and accompanying reductions in psychomotor efficiency each become enduring characteristics of both T1D and T2D after approximately 2–5 years [3, 4, 39]. Repeated episodes of cerebral hypoperfusion, whether secondary to hypo- or hyperglycemia, appear accompanied by a transient twofold to fourfold increase in cerebral *hyperperfusion*, although glucose [21] or oxygen [35] transport may remain deficient for neuronal needs and eventually microangiopathy occurs. The exact mechanisms by which cognitive sequelae and the vascular substrates of acute hypoglycemia and hyperglycemia may convert into chronic neuroanatomical and neuropsychological patterns remain to be determined.

Diabetes' effects on cognition across the life span show remarkable consistency in the pattern of cognitive sequelae that start with initial reductions in psychomotor efficiency. Despite evidence of cerebral insult, more complex memory and learning skills are generally unaffected in the majority of individuals with T1 and T2 diabetes. However, two vulnerable patient groups do not fare as well as the rest. Those with early T1D (<7 years) and those who are older with T2D (>60 years) show more pervasive cognitive deficits, especially in memory and learning skills. Supportive neuroanatomical evidence suggests selective hippocampal volume reduction in these patient groups. Individuals with T1D onset before the age of 7 experience global metabolic insult at a time of rapid brain growth and development, a time of relative neurocognitive vulnerability. At the other end of the age continuum, older individuals begin to experience more rapid age-related cognitive decline after the age of 60, neurocognitive decline which T2D appears to magnify and accelerate.

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References

1. American Diabetes Association. Total prevalence of diabetes and pre-diabetes. http://www.diabetes.org/diabetes-statistics/prevalence.jsp. Accessed Mar 1, 2009.
2. Daneman D. Type 1 diabetes. Lancet. 2006;367:847–55.
3. Research Group DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
4. DCCT/EDIC Research Group. Long-term effect of diabetes and its treatment on cognitive function. N J Med. 2007;356:1842–52.
5. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol. 2008;7:184–90.
6. Brands AMA, Biessels GJ, de Haan EHF, et al. The effects of type 1 diabetes on cognitive performance. Diabetes Care. 2005;28:726–35.
7. Ferguson SC, Blane A, Wardlow J, et al. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. Diabetes Care. 2005;28:1431–7.
8. Ryan CM. Diabetes, aging and cognitive decline. Neurobiol Aging. 2005;26S:S21–5.
9. Wessels AM, Rombouts SARB, Simsek S, et al. Microvascular disease in type 1 diabetes alters brain activation: a functional magnetic resonance imaging study. Diabetes. 2006;55:334–40.
10. Wessels AM, Simsek S, Remijnse PL, et al. Voxel-based morphometry demonstrates reduced grey matter density on brain MRI in patients with diabetic retinopathy. Diabetologia. 2006;49:2474–80.
11. Musen G. Cognition and brain imaging in type 1 diabetes. Curr Diab Rep. 2008;8:132–7.
12. Gonder-Frederick LA, Cox DJ, Driesen NR, et al. Individual differences in neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM. Diabetes. 1994;43:1407–12.
13. Holmes CS, Koepke KM, Thompson RG. Simple versus complex impairment at three blood glucose levels. Psychoneuroendocrinology. 1986;11:353–7.
14. Cox DJ, Penberthy JK, Zrebiec J, et al. Diabetes and driving mishaps: frequency and correlations from a multinational survey. Diabetes Care. 2003; 26:2329–34.
15. Cox D, Gonder-Frederick L, McCall A, et al. The effects of glucose fluctuation on cognitive function and QOL: the functional costs of hypoglycaemia and hyperglycaemia among adults with type 1 or 2 diabetes. Int J Clin Pract. 2002;129:20–6.
16. Holmes CS. Neuropsychological sequelae of acute and chronic blood glucose disruption in adults with insulin-dependent diabetes. In: Holmes CS, editor. Neuropsychological and behavioral aspects of diabetes. New York, NY: Springer; 1990. pp. 122–54.

17. Amiel SA. Cognitive function testing in studies of acute hypoglycaemia: rights and wrongs? Diabetologia. 1998;41:713–9.
18. Strachan MWJ, Ewing FME, Deary IJ, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. Diabetes Care. 2000;23:305–12.
19. Dandona P, James IM, Newbury PA, et al. Cerebral blood flow in diabetes mellitus: evidence of abnormal cerebrovascular reactivity. Br Med J. 1978;2:325–6.
20. Salem M, Barhader S, Shehata MH, et al. Hypoglycemic attacks in children with type 1 diabetes mellitus; Frequency, predisposing factors and sequelae on intellectual functions and school achievement. Egypt J Pediatr. 1999;17:345–50.
21. Jarjour IT, Ryan CM, Becker DJ. Regional cerebral blood flow during hypoglycaemia in children with IDDM. Diabetologia. 1995;38:1090–5.
22. Salem MA, Matta LF, Tantawy AA, et al. Single photon emission tomography (SPECT) study of regional cerebral blood flow in normoalbuminuric children and adolescents with type 1 diabetes. Pediatr Diabetes. 2002;3:155–62.
23. Northam EA, Rankins D, Lin A, et al. Central nervous system function in youth with type 1 diabetes 12 years after disease onset. Diabetes Care. 2009;32:445–50.
24. Perros P, Deary IJ, Sellar RJ, et al. Brain abnormalities demonstrated by magnetic resonance imaging in adult IDDM patients with and without a history of recurrent severe hypoglycemia. Diabetes Care. 1997;20:1013–8.
25. Musen G, Lyoo IK, Sparks CR, et al. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. Diabetes. 2006;55:326–33.
26. Ferguson SC, Blane A, Perros P, et al. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. Diabetes. 2003;52:149–56.
27. Holmes CS, Hayford JT, Gonzalez JL, Weydert JA. A survey of cognitive functioning at difference glucose levels in diabetic persons. Diabetes Care. 1983;6:180–5.
28. Holmes CS, Koepke KM, Thompson RG, et al. Verbal fluency and naming skills in type I diabetes at different glucose levels. Diabetes Care. 1984;7:454–9.
29. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Clarke WL. Self-treatment of hypoglycemia while driving. Diabetes Res Clin Pract. 2001;54:17–26.
30. Duckrow RB. Decreased cerebral blood flow during acute hyperglycemia. Brain Res. 1995;703:145–50.
31. Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with type 1 diabetes: effects of mircro- and macrovascular complications. Diabetologia. 2003;46:940–8.
32. Wessels AM, Simsek S, Remijnse PL, et al. Voxel-based morphometry demonstrates reduced grey matter density on brain MRI in patients with diabetic retinopathy. Diabetologia. 2006;49:2474–80.
33. Wessels AM, Rombouts SARB, Remijnse PL, et al. Cognitive performance in T1D patients associated with cerebral white matter. Diabetologia. 2007;50:1763–9.
34. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology. 2006;66:685–92.
35. Wessels AM, Scheltens P, Barkhof F, Heine RJ. Hyperglycaemia as a determinant of cognitive decline in patients with type 1 diabetes. Eur J Pharmacol. 2008;585:88–96.
36. Gaudieri PA, Greer TF, Chen R, Holmes CS. Cognitive function in children with type 1 diabetes. Diabetes Care. 2008;31:1892–7.
37. Ryan CM, Williams TM. Effects of insulin-dependent diabetes on learning and memory efficiency in adults. J Clin Exp Neuropsychol. 1993;15:685–700.
38. Naguib JM, Kulinskaya E, Lomax CL, Garralda ME. Neuro-cognitive performance in children with type 1 diabetes: a meta-analysis. J Pediatr Psychol. 2008;10:1–12.
39. Desrocher M, Rovet J. Neurocognitive correlates of type 1 diabetes mellitus in childhood. Child Neuropsychol. 2004;10:36–52.
40. Biessels GJ, Kerssen A, de Haan EHF, Kappelle LJ. Cognitive dysfunction and diabetes: implications for primary care. Prim Care Diabetes. 2007;1:187–93.
41. Ryan CM, Atchison J, Puczynski S, et al. Mild hypoglycemia associated with deterioration of mental efficiency in children with insulin-dependent diabetes mellitus. J Pediatr. 1990;117:32–8.
42. Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU, et al. Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study. Diabetes Care. 2009;32:1001–6.
43. Golden MP, Ingersoll GM, Brack CJ. Longitudinal relationship of asymptomatic hypoglycemia to cognitive function in IDDM. Diabetes Care. 1989;12:89–93.
44. Matyka KA, Wigg L, Pramming S, et al. Cognitive function and mood after profound hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes. Arch Dis Child. 1999;81:138–42.
45. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. Pediatr Diabetes. 2006;7:289–97.
46. Davis EA, Soong SA, Byrne GC, Jones TW. Acute hyperglycaemia impairs cognitive function in children with IDDM. J Pediatr Endocrinol Metab. 1996;9:455–61.
47. Wu J, Perantie DC, Sadler M, et al. Pilot diffusion tensor imaging study in youth with type 1 diabetes

mellitus reveals changes in white matter integrity associated with chronic hyperglycemia. Diabetes. 2007;56S:A477.
48. Ho MS, Weller NJ, Ives FJ, et al. Prevalence of structural central nervous system abnormalities in early-onset type 1 diabetes mellitus. J Pediatr. 2008;153:385–90.
49. Perantie DC, Lim A, Wu J, et al. Effects of prior hypoglycemia and hyperglycemia on cognition in children with type 1 diabetes mellitus. Pediatr Diabetes. 2008;10:1399–5448.
50. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. Endocr Rev. 2008;28:494–511.
51. O'Brien JT, Erkinjuntti T, Reisber B, et al. Vascular cognitive impairment. Lancet Neurol. 2003;2:89–98.
52. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes. Diabetes Care. 2001;24:1069–78.
53. Stranahan AM, Arumugam TV, Cutler RG, et al. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci. 2008;11:309–17.
54. American Diabetes Association. Standards of medical care in diabetes-2008. Diabetes Care. 2008;31: S12–54.
55. Center for Disease Control and Prevention. National diabetes fact sheet, 2007: general information and national estimates on diabetes. U.S. Department of Health and Health and Human Services, Center for Disease Control and Prevention. 2008. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed Mar 1, 2009.
56. Mokdad Ah, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:76–9.
57. Fischer Al, de Frias CM, Yeung SE, Dixon RA. Shortterm longitudinal trends in cognitive performance in older adults with type 2 diabetes. J Clin Exp Neuropsychol. 2009;31:809–22.
58. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–53.
59. Saczynski JS, Jonsdottir MK, Garcia ME, et al. Cognitive impairment: an increasingly important complication of type 2 diabetes. Am J Epidemiol. 2008;168:1132–9.
60. Ryan CM, Geckle MO. Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes. Diabetes Care. 2000;23:1486–93.
61. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol. 2004;26:1044–80.
62. Asimakopoulou KG, Hampson SE, Morrish NJ. Neuropsychological functioning in older people with type 2 diabetes: the effect of controlling for confounding factors. Diabet Med. 2002;19:311–6.
63. Gold SM, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia. 2007;50:711–9.
64. Bruehl H, Rueger M, Dziobek I, et al. Hypothalamicpituitary-adrenal axis dysregulation and memory impairments in type 2 diabetes. J Clin Endocrinol Metab. 2007;92:2439–45.
65. Manschot SM, Brands AMA, van der Grond J, et al. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes. 2006;55:1106–13.
66. van de Berg E, de Craen AJM, Biessels GJ, et al. The impact of diabetes mellitus on cognitive decline in the oldest of the old: a prospective population-based study. Diabetologia. 2006;49:2015–23.
67. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Arch Intern Med. 2000;160:174–80.
68. Manschot SM, Biessels GJ, de Valk H, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia. 2007;50:2388–97.
69. Arvanitakis Z, Wilson RS, Li Y, et al. Diabetes and function in different cognitive systems in older individuals without dementia. Diabetes Care. 2006;29:560–5.
70. Dey J, Misra A, Mahapatra AK, et al. Cognitive function in younger type II diabetes. Diabetes Care. 1997;20:32–5.
71. Bruce DG, Casey GP, Grange V, et al. Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle cognition in diabetes study. Diabetes Res Clin Pract. 2003;61:59–67.
72. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. Diabetes Res Clin Pract. 2000;50:203–12.
73. Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. Diabetes Care. 2001;24:1060–5.
74. Ebady SA, Arami MA, Shafigh MH. Investigation on the relationship between diabetes mellitus type 2 and cognitive impairment. Diabetes Res Clin Pract. 2008;82:305–09.
75. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes-systematic overview of prospective observational studies. Diabetologia. 2005;48:2460–9.
76. Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects. Diabetes Care. 2001;24:366–70.

77. Hassing LB, Grant MD, Hofer SM, et al. Type 2 diabetes mellitus contributes to cognitive decline in old age: a longitudinal population-based study. J Int Neuropsychol Soc. 2004;10:599–607.
78. Yau P, Javier D, Tsui W, et al. Structural and functional brain complications in obese adolescents with type 2 diabetes mellitus. Presentation at the 37th annual meeting of the International Neuropsychological Society, Feb 11–14, 2009, Atlanta, GA.
79. Elias MF, Elias PK, Sullivan LM, et al. Obesity, diabetes and cognitive deficit: the Framingham heart study. Neurobiol Aging. 2005;26S:S11–6.
80. Okereke OI, Kang JH, Cook NR, et al. Type 2 diabetes mellitus and cognitive decline in two large cohorts of community-dwelling older adults. J Am Geriatr Soc. 2008;56:1028–36.
81. Cosway R, Strachan MWJ, Dougall A, et al. Cognitive function and information processing in type 2 diabetes. Diabet Med. 2001;18:803–10.
82. Strachan MW, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care. 1997;20:438–45.
83. Cox DJ, Kovatchev BP, Gonder-Frederick LA, et al. Relationships between hyperglycemia and cognitive performance among adults with Type 1 and Type 2 diabetes. Diabetes Care. 2005;28:71–7.
84. Papanikolaou Y, Palmer H, Binns MA, et al. Better cognitive performance following a low-glycaemic-index compared with a high-glycaemic-index carbohydrate meal in adults with type 2 diabetes. Diabetologia. 2006;49:855–62.
85. Sommerfield AJ, Deary IJ, Frier BM. Acute hyperglycemia alters mood state and impairs cognitive performance in people with type 2 diabetes. Diabetes Care. 2004;27:2335–40.
86. Ryan CM, Geckle M. Why is learning and memory dysfunction in type 2 diabetes limited to older adults? Diabetes Metab Res Rev. 2000;16:308–15.
87. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes – memory in diabetes (ACCORD-MIND) trial. Diabetes Care. 2009;32:221–6.
88. Ryan CM, Freed MI, Rood JA, et al. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care. 2006;29:345–51.
89. Strachan MWJ, Reynolds RM, Frier BM, et al. The relationship between type 2 diabetes and dementia. Br Med Bull. 2008;88:131–46.
90. van Harten B, Oosterman JM, van Loon BJP, et al. Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. Eur Neurol. 2007;57:70–4.
91. Kumar R, Anstey KJ, Cherbuin N, et al. Association of type 2 diabetes with depression, brain atrophy, and reduced fine motor speed in a 60- to 64-year-old community sample. Am J Geriatr Psychiatry. 2008;16:989–98.
92. Schmidt R, Launer LJ, Nilsson LG, et al. Magnetic resonance imaging of the brain in diabetes: the cardiovascular determinants of dementia (CASCADE) study. Diabetes. 2004;53:687–92.
93. den Heijer T, Vermeer SE, van Dijk EJ, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologia. 2003;46:1604–10.
94. Vermeer SE, den Heijer T, Koudstaal PJ, et al. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. Stroke. 2003;34:392–6.
95. Wu W, Brickman AM, Luchsinger J, et al. The brain in the age of old: the hippocampal formation is targeted differentially by diseases of late life. Ann Neurol. 2008;64:698–706.
96. Hassing LB, Hofer SM, Nilsson SE. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. Age Ageing. 2004;33:355–61.
97. Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology. 2006;67:1960–5.
98. Egede LE, Zheng D, Simpson K. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. Diabetes Care. 2002;25:464–70.
99. Munshi M, Grande L, Hayes M, et al. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care. 2006;29:1794–9.
100. Watari K, Letamendi A, Elderkin-Thompson V, et al. Cognitive function in adults with type 2 diabetes and major depression. Arch Clin Neuropsychol. 2006;21:787–96.
101. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care. 2008;31:2398–404.
102. Dunbar JA, Reddy P, Davis-Lameloise N, et al. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes Care. 2008;31:2368–79.
103. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008;31:2383–90.
104. Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5:64–74.
105. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. Diabetes. 2002;51:1256–62.

Chapter 25

Hypothyroidism and Hashimoto's Thyroiditis: Mechanisms, Diagnosis, Neuropsychological Phenotypes, and Treatments

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Introduction

Metabolic disorders comprise a wide range of systemic medical conditions that can be both inherited and acquired. This chapter will focus on reviewing hypothyroidism and the most common autoimmune thyroid disease, Hashimoto's thyroiditis (HT). Hypothyroidism refers to thyroid hormone deficiency, which can be present at different stages of life from fetal development through adulthood, including onset during pregnancy. It occurs more frequently in females than males. It can develop as the result of treating other conditions or diseases, such as Grave's disease and thyroid cancer, as well as after thyroid surgery, radioiodine therapy, and also as a consequence of iodine deficiency. As will be discussed below, there is a wide range of physical symptoms, cognitive findings, mood disturbances, and in some cases psychotic symptoms, resulting in variable neuropsychological presentations. Similar to that of other endocrine glands, the thyroid has extensive effects on the central nervous system.

The implications of thyroid dysfunction are well documented and a review of the literature on hypothyroidism and iodine deficiency unveiled a vast body of research. While a comprehensive review of the historical timeline of hypothyroidism is beyond the scope of this chapter, it seemed necessary to point out a few authors that have made notable contributions to provide the reader with some historical references to help guide further investigation of the topic. The first is a series of three papers published in the 1960s describing the relationship between iodine deficiency, iodine metabolism, thyroid-stimulating hormone, goiter, and endemic cretinism in groups of people living in the Mulia Valley of Western New Guinea [1–3]. Next, we review a set of papers published between 1964 and 1976 documenting a series of nine studies investigating the importance of iodine and thyroid function in human pregnancy [4–12]. This chapter will review parts of these earlier investigations, as well as contemporary contributions to the literature on hypothyroidism.

The second part of this chapter will focus on Hashimoto's Thyroiditis, as it is the main cause of hypothyroidism. Previously, HT was thought of as a rare disease, however an increasing number of studies continue to demonstrate that HT is more prevalent than early estimates. These studies have

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also provided a better understanding of the pathology. Both genetic and environmental factors associated with HT will be reviewed, as well as an infrequent complication (i.e., Hashimoto's encephalopathy). Finally, we will discuss cognitive and psychiatric implications in HT, in addition to quality of life factors in hypothyroidism and HT.

Thyroid Gland Anatomy

The thyroid is one of the largest endocrine glands in an adult human, brownish-red in color, with an average weight of 20 g. It is situated at the midline in the visceral compartment of the anterior neck at the level of the fifth cervical vertebra extending downward to the first thoracic vertebra. The thyroid is divided into two lobes (right and left) bound by the isthmus crossing the midline at the second and third tracheal rings. The thyroid gland is attached to the laryngoskeleton by Berry's ligament (lateral suspensory ligament), which extends from the superior-medial aspect of each lobe to the cricoid and thyroid cartilage. In this position, the thyroid gland lies posterior to the sternothyroid and sternohyoid muscles and inferior to the laryngeal thyroid cartilage [13–16]. Microscopic analysis of the gland reveals that the tissue of the thyroid is mostly comprised of tightly packed follicles filled with colloid, a sticky fluid that fills the central cavity of the thyroid follicles. The colloid is the thyroid hormone production center, which is dependent on the mineral iodine [13, 16]. The follicles contain large stores of thyroglobulin, the primary constituent of total thyroid mass and maintain about 100 days of the average output of thyroid hormones. The stockpiling of thyroid hormone is a built-in protection system against depletion of circulating thyroid hormone, which is necessary because of the thyroid's slow rate of turnover. Without this, any event which stops or significantly slows the synthesis of thyroid hormones, even briefly, has the potential to cause havoc on a number of bodily systems [14]. Hormones are produced in the colloid of the follicles when iodine atoms combine with thyroglobulin, a glycoprotein, that is released by the follicle cells into the colloid [13].

The thyroid gland secretes hormones directly into the bloodstream, requiring it to be greatly vascularized. Relative to its size, the thyroid gland is three to four times more vascularized than the brain. Blood is supplied to the thyroid via three main arteries: The Superior Thyroid Artery (STA), the Inferior Thyroid Artery (ITA), and the Thyroidea Ima Artery of Neubauer (TIA). The paired STAs supply the superior and anterior portions of the thyroid and the paired ITAs supply the posterior-inferior divisions. The STA is a branch of the external carotid artery that emerges at the level of the superior horn of the thyroid cartilage. The ITA is a branch of the thyrocervical trunk that runs posterior to the thyroid at the level of the cricoid cartilage. The TIA is a lower thyroid artery that arises inferiorly across the anterior portion of the thyroid isthmus. Because of its location, it is liable to be cut during tracheostomy [16]. This artery is compensatory in nature and is typically present in cases when one or both of the ITAs are malformed or absent. The TIA has been estimated to normally occur in at most 10% of individuals according to a review by Bergman and colleagues [17]. In rare cases, the TIA may provide the only viable source of blood perfusion to the thyroid gland. An early study by Gruber (1845), as cited by these authors, demonstrated a number of origination sites for the TIA, with the most frequent being the right brachiocephalic artery, the carotid arteries, and the aortic arch [15–17].

The thyroid gland is mainly innervated by the autonomic nervous system, which has the primary role of influencing vasculature. Sympathetic fibers (adrenergic) begin in the inferior, middle, and superior cervical ganglia of the sympathetic trunk and parasympathetic fibers (cholinergic) are primarily from the vagus nerve [14–16]. The cervical branches of the vagus nerve that are most pertinent are the recurrent laryngeal nerve and the internal and external branches of the superior laryngeal nerve. In a small percentage of cases (less than 1%) the nonrecurrent laryngeal nerve is present, as the result of a cascade of events related to arterial irregularities occurring during embryologic development [15, 16].

Thyroid Hormones and the Hypothalamic–Pituitary–Thyroid Axis

The production of thyroid hormones is reliant on the availability of sufficient quantities of exogenous iodine mineral. Inorganic iodide ions from dietary intake, passive loss of iodide from the thyroid into the blood (iodide leak), and peripheral deiodination of thyroid hormones are the main sources of iodine used in the manufacturing of thyroid hormones. Iodide is concentrated in extracellular fluid, and stored in red blood cells and intraluminal fluids (e.g., saliva). Iodine is withdrawn during the production of thyroid hormones at approximately 1–1.5 mcg per 100 ml of serum. Iodine is metabolized mostly by the thyroid and passively by the kidney. The primary means for removal of iodine from the extracellular fluid is via the thyroid gland, containing on average 8,000 mg of iodine at any given time, which is reduced at a speed of about one percent per 24 h. Adult humans also lose about 500 mcg of iodine daily through the urine. Because of this slow rate of turnover, the thyroid has a large reserve of hormone providing extended protection against depletion of circulating thyroid hormone if there is termination of thyroid hormones synthesis [14].

The thyroid gland produces the thyroid hormones thyroxine (T4), which accounts for about 90% of hormone production, and triiodothyronine (T3) makes up the remaining 10%. T4 and T3 are the results of the stimulation of the pituitary gland's secretion of thyrotrophin, also referred to as thyroid-stimulating hormone (TSH). TSH is released from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. Over secretion of thyroid hormones triggers a decline in production of TRH from the hypothalamus and subsequently TSH from the anterior pituitary; low blood levels of T3 and T4 stimulate the release of TRH and then TSH, which stimulates the thyroid gland to secrete more T3 and T4. This negative feedback loop is termed the hypothalamic–pituitary–thyroid axis, which regulates levels of thyroid hormones (T3 and T4) in the bloodstream. Peripheral tissues convert T4 to T3 and thyroid hormones are transported in serum bound to carrier proteins, of which thyroid hormone binding globulin is the main carrier (75% of bound T4 and about all of bound T3). The remaining thyroid hormone is transported by thyroxine binding prealbumin and albumin [13, 14, 18].

Iodine Deficiency and Developmental Impacts

Iodine deficiency has a direct negative impact on thyroid hormone production, which subsequently has adverse effects during each stage of life. As a group, iodine deficiency disorders can cause different health problems and presentations depending on the age of the individual affected [19]. Some of the most common health consequences by age group are outlined in Table 25.1. Iodine deficiency disorders appear when iodine intake drops below required levels leading to insufficient production of thyroid hormones by the thyroid gland. According to the World Health Organization (WHO), the United Nations International Children's Emergency Fund (UNICEF), and the International Council for Control of Iodine Deficiency Disorder (ICCIDD) the recommended daily iodine intake by age range and specific subpopulation groups are as follows: Children 0–59 months of age (90 μg), children 6–12 years of age (120 μg), adolescents >12 years and adults (150 μg), and pregnant and lactating women (250 μg) [20, 21]. The relationship between iodine intake and thyroid disorders is U-shaped. Maintaining the required level of iodine allows for a healthy thyroid gland producing adequate levels of thyroid hormones, in the absence of other causes of thyroid dysfunction. Iodine levels below and above the recommended levels can impair thyroid function [19].

Deficient iodine intake has been demonstrated to have an ecological cause that exists throughout the world at different severities. To appreciate the role that we as humans have had on creating this health problem, we need to consider a global perspective, as discussed in the *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination, Third Edition* [21]. The chain of events begins with the reduction of vegetation due to the mass clearings of land for agricultural

Table 25.1 Consequences of iodine deficiency disorders by age group

Group	Health consequence
Fetus	Spontaneous abortion Perinatal mortality Stillbirth Congenital abnormalities
Neonate	Cretinism Mental impairments, mutism, spastic diplegia, squint, hypothyroidism, short stature
Child & Adolescent	Impairments in mental functioning Physical development delays Iodine-induced hyperthyroidism
Adults	Impairments in mental functioning Iodine-induced hyperthyroidism
All ages	Goiter Hypothyroidism Increased susceptibility to nuclear radiation

Sources [19, 21, 22]

production, use of pesticides, herbicides, and fertilizer that deplete iodine from soil used to produce food, livestock overgrazing, and the removal of trees leading to soil erosion in riverine areas, with the final result being an ever-continuing depletion of iodine in the soil. This results in foods and groundwater that lack sufficient iodine levels, which historically provided humans and other animals sufficient daily supplies of iodine [21].

Iodine is an important mineral that is required throughout the human life span, though there are critical periods when iodine insufficiency is most detrimental. Pregnancy through the third year of life requires iodine and thyroid hormones critical for neurodevelopment [21, 23, 24]. In places where iodine is deficient and thyroid hormones are not at required levels, brain development is typically delayed or impaired depending on the magnitude of the deficiency. Severe cases of iodine deficiency usually result in cretinism, a condition that is devastating for the individual and family that is characterized by severely stunted physical and mental development due to untreated congenital hypothyroidism. However, the impact of milder forms of iodine deficiency can also impact neurodevelopment, resulting in cognitive delays and deficits. It is these subtle forms of iodine deficiency that can have an overarching impact on the health and productivity of a whole community [21].

In the early 1990s, the WHO and UNICEF Joint Committee on Health Policy developed a universal salt iodization program in an attempt to combat iodine deficiency. This strategy was considered to be the most economically sustainable and safe means of increasing iodine consumption in nearly all countries. This required the development of national programs for the mass iodization of all salts used for human and livestock consumption. In areas where insufficient iodine intake and access to iodized salt is poor, other strategies have been implemented, such as direct iodine supplementation, especially for vulnerable populations (e.g., pregnant women, children 7–24 months of age) [21]. Out of 130 countries that have carried out urinary iodine national surveys, 126 were identified with an iodine deficiency (ID) public health problem in 1993. Since the implementation of universal salt iodization, 54 countries were identified as still having ID in 2004, with the number dropping to 47 in 2007. At the time of the 2007 WHO report, it was estimated that 31% of the world's population continued to have insufficient iodine intake. Countries most affected in terms of proportion of citizens included those in Europe (52%), the Eastern Mediterranean (47.2%), and Africa (41.5%). Regions with the overall most affected number of people include Southeast Asia (503.6 million) and Europe (459.7 million). The Americas have an estimated 98.6 million affected individuals, which accounts for about 11% of the overall population in these countries. Additional information regarding these statistics can be found at: http://www.who.int/vmnis.

Even with the tremendous increase in the number of iodine-sufficient countries using iodized salt (IS) programming, large populations are still iodine

deficient including countries across the spectrum of economic development (e.g., Ethiopia, Mozambique, Russia, Ukraine, Denmark, Italy, UK). Additionally, studies have also determined that several economically advantaged countries such as the USA and Australia have had overall decrease in iodine intake over the past three decades [19]. Most micronutrient deficiencies are restricted to populations with poor diets and/or access to healthy foods. However, this is not the case with iodine deficiency, as is evident in the goiter belts of Midwestern USA, the Alps and Apennines in Europe, southern Australia, and landlocked areas of the UK [19, 25]. To some extent, the cause of these decreases is due to governmental regulations and dietary changes. For example, besides iodized salt, another main source of dietary iodine is dairy products, as least in North American and Europe. Milk has fairly low native iodine, but iodine supplements given to cows increase iodine levels in their milk. However, government regulations in some countries have required the reduction in iodine supplementation. Also, due to other health reasons many individuals have decreased or eliminated the consumption of dairy products in their diets [19], which does have many health benefits [26, 27]. Iodine deficiency becomes a problem typically only when other sources of dietary iodine are not available or insufficient.

The overall increase in iodine intake due to IS programming has had positive results. Cognitive outcomes due to increased iodine intake from IS have improved according to two large-scale reviews of 89 studies. Populations who received iodized salt interventions showed a 72–76% reduction in the risk for intellectual delay/impairment (IQ < 70) and an overall increase in IQ scores of 6.9–10.5 points compared to iodine-deficient peers [28, 29].

Hypothyroidism

Hypothyroidism is defined as a significant deficiency of thyroid hormones. In adults, hypothyroidism is also referred to as Gull's disease. The term myxedema is sometimes used synonymously, but should be reserved for cases of severe hypothyroidism to emphasize notable dermatological changes and serious life-threatening complications. In adults, hypothyroidism occurs at a rate of about one-eighth that of hyperthyroidism and has a prevalence of about 2% in women and 0.2% in men [14, 30]. In women, the risk of developing hypothyroidism increases with age and during pregnancy, the postpartum period, and menopause [31]. The condition often occurs as the result of treating Grave's disease (hyperthyroidism) or due to Hashimoto's thyroiditis (HT), which is the result of damage to the thyroid gland due to chronic inflammation initiated and sustained by an autoimmune response. HT manifests as a diffuse enlargement of the thyroid gland and is often painless [14, 31]; HT will be discussed in great detail in a later section.

Hypothyroidism can also develop as the result of iodine deficiency following surgery, radioiodine therapy, and pregnancy, among other causes. One common line of intervention for hypothyroidism is Levothyroxine (L-T4). The daily therapeutic requirement is somewhat greater in males (125–150 μg/day) than females (100–125 μg/day) due to differences in fat-free mass between the sexes. This may be associated with increased cardiovascular risks in men since overtreatment of hypothyroidism in men more often can result in atrial fibrillation, whereas women are more prone to develop fractures [30]. During pregnancy, thyroid function needs to be monitored, keeping in mind lower TSH-reference ranges, in order to reduce the possibility of maternal thyroid dysfunction and subsequent harm to the fetus [30].

There are four primary categories of thyroid dysfunction, which are based on laboratory testing of T3, free thyroxine (fT4), and TSH levels. Depending on the severity and pattern of laboratory findings patients usually fit one of four categories: overt hypothyroidism (low-serum fT4 and elevated TSH), overt thyrotoxicosis (high-serum fT4 and/or T3 and suppressed TSH), subclinical hypothyroidism (elevated TSH, normal fT4), and subclinical thyrotoxicosis (suppressed TSH, normal fT4, and T3) [18, 32]. Overt hypothyroidism and subclinical hypothyroidism are classifications of deficient levels of thyroid hormones and will be discussed in great detail, as they are the focus of this chapter. Overt thyrotoxicosis (i.e., hyperthyroidism) and subclinical thyrotoxicosis are the medical classifications used when thyroid

hormone is over abundant, and is the opposite side of the thyroid disorder spectrum from hypothyroidism, and thus will not be further discussed as it goes beyond the scope of this chapter. The reader should also note the term hypothyroxinemia, which is a common term used in the literature of thyroid disorders and refers to a lack of thyroid hormone during early fetal life. Laboratory evidence of hypothyroxinemia is defined as low free T4 but normal thyroid-stimulating hormone (TSH) levels [33]. Prominent clinical signs of hypothyroidism include puffy face, marked cold intolerance, and dry skin and hair [14, 18, 32]. Euthyroidism is the term used to indicate normal thyroid hormone levels in both healthy individuals and patients receiving treatment for hypothyroidism and Hashimoto's thyroiditis whose thyroid hormone levels are in the normal range.

Cognitive, Behavioral, and Mood Findings in Adult Hypothyroidism

Different severities of hypothyroidism have been associated with cognitive impairment and dementia [34]. Hypothyroidism falls into the category of one of the potentially reversible dementias, if diagnosed and treated quickly. In overt hypothyroidism (OH), patients can present with mild to moderate deficits in a number of cognitive domains, including declines in intelligence, perceptual and visual-spatial abilities, slowed mental speed, poor attention and concentration, slowed speech, semantic fluency, visual tracking and psychomotor speed, executive functions, apathy, and most notably memory impairments [35–43], however the consistency in these findings seems to be directly associated with methodology and the interpretation of the tests used to measure cognition. In the section that follows we will present some of the cognitive findings and methodology in the literature of OH and subclinical hypothyroidism (SCH).

Correia and colleagues [41] provided evidence to suggest a specific hippocampal memory deficit in both OH and SCH patients. Baseline testing of spatial, verbal, associative, and working memory, as well as attention and response inhibition was completed prior to L-thyroxine (L-T4) replacement. Patients with OH showed impairments in spatial, associative, and verbal memory, while patients with SCH showed deficits in spatial and verbal memory at baseline. TSH levels correlated negatively with these deficits. Following treatment, verbal memory improved in both groups. However, spatial memory only improved to a normal range in the SCH group, but not the OH group. Associative memory deficits also persisted in the OH group. Performances on tests of attention and inhibition were not significantly different compared to controls. The authors posed that the lack of improvement on certain tests in the OH group in comparison to the SCH group seems to suggest a critical time period after which memory deficit might be irreversible, and thus quick intervention is crucial. This finding has also been observed in studies using animal models of congenital hypothyroidism [44]. Miller and colleagues [42] found mixed results on measures of episodic memory in individuals with untreated hypothyroidism. Specifically, hypothyroid subjects performed poorer than controls on short-delayed cued, long-delay free, and long-delay cued recall performances on the California Verbal Learning Test. However, there was no significant difference in performance between groups on immediate and delayed recall on a prose task (Logical Memory) or on a test of visual memory (Rey Complex Figure Test delayed recall). Beydoun and colleagues (2015) conducted a longitudinal study sourcing data from the Healthy Aging in Neighborhoods of Diversity Across the Lifespan study, between 2004 and 2013. The sample consisted of more than 1400 participants ranging in age from 30 to 64 years at baseline. The cognitive battery included 7 standard neuropsychological tests (CVLT, Digit Span forward and backward, Benton Visual Retention Test, Animal Fluency, Brief Test of Attention, Trail Making A and B, and the Clock-Drawing Test) and a screening measure (MMSE). Results of the study indicated a statistically significant change across time in verbal and visual memory in men and women and in both African Americans and Whites. Performance scores on the MMSE showed

improvement over time seemingly due to learning effects, which was more prominent in Whites. There were no changes on the other cognitive measures across time. Concerning the effects of TSH, total thyroxine (tT4), free thyroxine (fT4), and triiodothyronine (T3) on cognition, the researchers used multiple mixed-effects regression models. Participants with above-reference range TSH (0.4–4.5 mU/L) showed faster rates of decline on Digit Span-backward (SD-B) and declining performances on the Clock-Drawing Test (CDT). In addition, subclinical hypothyroidism, determined by the combination of TSH and fT4 (reference range: 0.8–1.8 ng/dL) was associated with a 15% decline in DS-B performance and a 7% decline on the CDT over 5 years, in comparison to a minimal change (<1%) in performance on these measures in individuals who had TSH and fT4 levels in the normal range. Additionally, in women, it was found that the higher the TSH level, the faster the rate of decline on the CDT [43]. A study by Hogervorst and colleagues (2009) documented that high TSH and high-normal range fT4 were associated with declining performance on the MMSE in an older adult (≥65 years) cohort of 1047. The authors were unclear why high-normal fT4 were independently associated with increased rates of general cognitive decline (MMSE). They suggested that thyroxine has been shown to generate oxidative stress and damage neurons. De Jong and colleagues (2006) were not able to demonstrate a relationship between thyroid function and dementia risk. They used the MMSE, Geriatric Mental State Schedule (GMSS), and additional neuropsychological testing as necessary to make a clinical diagnosis and place subjects into groups. The researchers did demonstrate a relationship between greater hippocampal and amygdalar atrophy on MRI and higher levels of fT4 and reverse triiodothyronine (rT3) [45]. A similar study by Forti and colleagues (2012) investigated the prospective relationship of serum TSH and risk of developing mild cognitive impairment (MCI), Alzheimer's disease (AD), and vascular dementia (VaD) in a sample of 660 subjects ages 65 years and older. No associations were found between baseline TSH and risk for developing any subtype of MCI or AD. However, a risk for the development of VaD was found to increase with higher TSH levels, where subjects with TSH in the highest tertile had 3× increased risk of VaD compared to the lower tertile [46]. While, Tan and colleagues (2009) report a risk for AD to be linked to high and low TSH levels, specifically in women [47].

A single case report of a 63-year-old female with hypothyroidism demonstrates the negative effects of low thyroid hormone on cognitive abilities [35]. At baseline, laboratory results indicated an elevated TSH (27.8) and a low T3 (80), and T4 (1.2) serum levels. Cholesterol (334 mg/100 ml) and triglyceride (164 mg/100 ml) levels were elevated. Venereal disease research laboratory test (VDRL), B-12 folate, electrolytes, and liver functions were all within normal reference ranges. CT of the head was also normal. A full neuropsychological evaluation was conducted at baseline (pretreatment), evidencing an FSIQ of 89 (Wechsler Adult Intelligence Test-Revised) with a 15-point difference between VIQ (SS = 96) and PIQ (SS = 81). Go-No-Go, phonemic fluency (FAS), Luria's test of graphomotor sequencing (m and ns), Paced Auditory Serial Addition Test (PASAT), Wisconsin Card Sorting Test (WCST), and all language functions were within normal limits. Performances on the Wechsler Memory Scale (WMS) and Buschke Selective Reminding Test (B-SRT) were below age-matched controls. Performance on the Rey Complex Figure Test (RCFT), Milner Facial Memory Test (MFMT), Continuous Visual Memory Test (CVMT), and the Figural Memory subtest of the WMS were impaired. Seven months following thyroid replacement therapy (Synthroid 0.05 mg daily, then increased to 0.1 mg a day 15 days later) TSH, T3, and T4 were all reported to be in the normal range and remained normal to the date of the neuropsychological post-test. Posttreatment performances on Block Design (BD) and Object Assembly (OA) from the WAIS-R were greater than what would be expected for normal test–retest findings, (BD T1 ss = 5, T2 ss = 7; OA T1 ss = 4, T2 ss = 9). Performances on Logical Memory and Figural Memory subtests of the WMS at T2 were better compared to T1, but remained below control performances. Verbal Paired Associates learning from the WMS, and scores from the

B-SRT, RCFT, CVMT, and MFMT also showed no notable improvement. The patient's performance on frontal lobe tests remained unchanged after 7 months of treatment. Finger taping showed consistent improvement over time. Grip strength did not change. Despite some mild improvements in memory scores during and following treatment with Synthroid, thyroid replacement therapy appeared to only arrest the progression of memory decline, but not return the patient's memory functioning to within the normal range compared to controls [35].

A study by Burmeister and colleagues (2001) evaluated the effects of hypothyroidism in a clinical sample of 13 patients with thyroid cancer on and off of thyroid replacement (levothyroxine) comparing them to a smaller sample of euthyroid controls. List learning immediate recall showed no effect on thyroid state. In contrast, delayed recall of the word list was significantly poorer when patients had laboratory results consistent with a hypothyroid state, even when practice effects were controlled for. Measures of inhibition (Stroop), processing speed (Digit Symbol Substitution Test from the WAIS-R), attention, and visual tracking (Trail Making Test) showed no significant differences when comparing euthyroid and hypothyroid states. Intensity of depressive symptoms measured by the Beck Depression Inventory (BDI) showed no significant difference on neuropsychological measures between more-depressed and less-depressed groups [37].

Constant et al. (2005) studied attention and executive functioning in relation to anxiety and depressive symptoms in a group of 23 patients who received thyroid hormone replacement after undergoing thyroidectomy for low-grade thyroid carcinoma. Cognitive measures included the Test Battery for Attentional Performance (TAP), a computerized version of the Stroop Test, an emotional variant of the Stroop, the Beck Depression Inventory, and the State-Trait Anxiety Inventory. They found that compared to healthy euthyroid controls, the thyroid patients had poorer attention and executive functioning and endorsed more anxiety and depressive symptoms. These cognitive problems were thought to reflect a general cognitive slowing impacting inhibition, which were more prominent in those with elevated anxiety [40].

Individuals with subclinical hypothyroidism have demonstrated mild deficits in memory and executive functioning [32, 48–51]. Nystrom et al. (1988) found that four of 17 women with SCH showed significant improvement on at least two neuropsychological measures following treatment with levothyroxine (150 μg/day) in a placebo-controlled crossover study [50]. Monzani and colleagues (1993) showed that the administration of levothyroxine (100-150 μg/day for 6 months) had beneficial effects on verbal and visual recall in 14 subjects with SCH [49]. In a study by Jenovsky et al. (2002), SCH patients also demonstrated significant improvement in verbal and visual memory after levothyroxine treatment compared to placebo [48]. Aghili and colleagues (2012) used the Wechsler Memory Scale (WMS) to evaluate temporal orientation and orientation to self, attention/concentration, and learning and memory in a sample of 60 patients with SCH. Patients were divided equally into a control and an intervention group. Pretreatment scores were reported as not statistically significant between the groups. Following treatment, TSH levels normalized in the intervention group. Post-test performances on the WMS showed a mean memory quotient score improvement of 9.9 in the intervention group and only a 2.5-point increase in the control group, which was statistically significant ($p = 0.002$). The overall memory quotient and specific subtest (viz., Mental Control, Logical Memory, Associate Learning) performances were significantly improved in the intervention group following treatment. Performance on the Information and Orientation, Digits Span (forward and backward), and Visual Reproduction subtests were not influenced by treatment [51].

In a study by Osterweil et al. (1992), a screening measure of general cognitive status (viz., MMSE) showed sensitivity to the effects of OH and differentiated OH patients from healthy controls. Approximately 28% of OH patients had scores below 24 out of 30. It should be noted that the OH group mean was above the standard threshold for impairment and 3% of euthyroid controls also performed below a score of 24 [36].

However, methodological constraints may have affected outcomes. A large study of older subjects (65 years +) found no difference in cognitive performances on the Folstein Mini-Mental State Examination (MMSE) and the Middlesex Elderly Assessment of Mental State (MEAMS) between SCH and euthyroid groups [52]. The reader should keep in mind that these measures are cognitive screenings, which often are less sensitive to subtle cognitive deficits that may be identified by a comprehensive neuropsychological evaluation. In conclusion, large-scale studies using screening measures, tend to find no relationship between SCH and cognitive impairment, while studies with smaller sample sizes that employ more labor-intensive cognitive batteries report mild cognitive impairments in SCH.

In terms of psychiatric symptoms, individuals with SCH and OH often present with increased rates of anxiety and depressive-like symptoms, and those with greater thyroid hormone deficiency have higher symptom severity. However, this is not a consistent finding across the literature in SCH. It has been hypothesized that mood alterations in individuals with SCH may develop due to the knowledge of having a medical condition rather than the direct effect of thyroid hormone levels. The largest cross-sectional studies of mood in SCH found no difference in depression and anxiety between SCH patients and euthyroid controls [52–56]. These larger studies have several strengths, including large sample sizes, a wide range of patient ages, and are population based. Randomized placebo-controlled blinded studies of L-T4 in subjects with SCH have demonstrated no improvement in psychological symptom and functioning scores [57–59]. In addition, OH patients without obvious clinical symptoms may show subtle alterations in mood, which can be elicited on objective tests and during clinical interview. Gulseren and colleagues (2006) found self-reports of anxiety and depressive symptoms to be greater in individuals with OH than controls (and greater in individuals with hyperthyroidism). On ratings of quality of life, patients with OH and SCH endorsed more problems than matched controls on the physical and mental composite scores. Following intervention, mood symptoms and quality of life scores improved [60]. In severe hypothyroidism, also known as myxedema, patients can present with symptoms of psychosis referred to as "myxedema madness." The milder presentations of depressive and anxiety symptoms may be more prevalent in SCH, but have been shown by some studies to not reliably improve with L-T4 intervention [32]. Overall, there seems to be some disagreement in the literature as to whether mood symptoms are a common presentation in individuals with hypothyroidism. From our review it seems that moderate to severe affective symptoms are unlikely to be the result of SCH, and require evaluation and treatment as a separate condition.

Critical Periods of Hypothyroidism and Hypothyroxinemia in Pregnancy and Child Development

Approximately, 2–3% of women in reproductive age, considered medically healthy, have an elevated TSH (2–2.5% subclinical hypothyroidism, 0.3–0.5% overt hypothyroidism) [30, 61]. Quite often in the second and third trimester, free thyroxine (fT4) concentrations are lower in pregnant women compared to women who are not pregnant [61]. Because of the high risk for developing hypothyroidism during pregnancy, accurate diagnosis and use of appropriate target ranges for thyroid hormones need to be considered. During pregnancy, the risk for developing hypothyroidism is high [62]. In pregnancy, overt hypothyroidism is defined as TSH > 10 mU/l and or TSH > 2.5 mU/l plus decreased fT4. It has been estimated that three percent of all healthy women of reproductive age have elevated TSH. Antibodies, such as thyrotropin-receptor-blocking antibody, are responsible for depleting maternal thyroid function, can cross the placenta, and in certain cases degrade fetal and neonatal thyroid [8, 63–67].

To provide a historical time line, over a century ago McCarrison (1917) using the terminology of the time, commented on the possibility of an association between thyroid dysfunction in

mothers and disability in many of their offspring: "It is of greatest importance to inquire into the ante-natal history of all backward children and to examine the mother for thyroid defect." ([68], pp. 27). This suggestion was grounded in a multitude of observations in areas with serious iodine deficiency, where the rate of cretinism was high. Decades passed until Choufoer and colleagues (1964) published data demonstrating the association between birth defects in children with neurologically affected cretinism, and low circulating thyroxine (T4) in their mothers during pregnancy, even when T4 levels were subclinical [2]. During the last 35 years, there has been a surge of published findings related to deficient thyroid hormone during pregnancy and the association of neurodevelopmental outcomes in these children. In 1969, a large cohort study was published showing that mild maternal hypothyroxinemia was associated with lower child scores on the COLR form of the Bayley's Scales of Mental and Motor Development [8]. Twenty years later, Matsuura and Konishi (1990) reported on the negative effects of maternal and fetal chronic autoimmune thyroiditis (hypothyroidism) on fetal brain development [69]. Similarly, Haddow and colleagues (1999) demonstrated that children born from mothers who had subclinical hypothyroidism, not treated during pregnancy, showed lower cognitive performance compared to controls. In this study, children of mothers with untreated subclinical hypothyroidism (u-SCH) and children of mothers with SCH who were treated (t-SCH) went through neuropsychological testing between 7 and 9 years of age, as were age-matched controls of euthyroid mothers. Neuropsychological test performances showed a 7-point decrement in FSIQ scores on the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) in the u-SCH group, compared to the control group. Nineteen percent of u-SCH had FSIQ scores of 85 or lower, compared to 5 percent of the controls. Comparing other WISC-III index scores, the mean u-SCH group scores were significantly lower than the control group (FDI = 97 versus 102, $p = 0.03$; VIQ = 101 versus 107, $p = 0.006$; PIQ = 99 versus 105, $p = 0.01$). Additionally, the t-SCH group's WISC-III performances were better across the board (FSIQ = 111, FDI = 103, VIQ = 111, PIQ = 109) when compared to both the u-SCH and control groups. This study demonstrated that decrease in cognitive ability can occur in children of mothers with mild hypothyroidism, which in many cases were asymptomatic. The authors concluded that treating hypothyroidism, even at subclinical levels during pregnancy is likely beneficial not only for the mothers, but for the development of the child [70].

It is known that the fetal thyroid gland becomes active at about the third month of gestation, prior to which the mother is the sole source of thyroid hormones [70]. Animal studies have also documented evidence of fetal dependence in early pregnancy on maternal fT4 concentrations [71]. Decreased neurologic development in children two years of age who were born to mothers with subclinical hypothyroidism during pregnancy have been reported [72, 73]. Maternal thyroid sufficiency seems to be quite important during the first trimester, a theory that was also supported by Pop and colleagues (1999). In their study, children born from mothers with lower serum-free thyroxine concentrations at 12 weeks of gestation had impaired psychomotor development at 10 months of age, as measured by the Dutch version of the Bayley Scales of Infant Development [74]. Psychomotor retardation has also been associated with low postnatal thyroxine concentrations in premature neonates [75–77]. Later stages of fetal brain development may also be affected possibly by insufficient thyroid hormones, as these stages involve neuronal migration and organization [78], processes that are required for higher order functions measured by many neuropsychological tests [8, 70, 74, 79–82]. In general, a number of clinical studies have documented negative impacts on brain development in fetal and neonatal thyroid hormone insufficiency due to iodine deficiency or congenital hypothyroidism [24, 73, 83–85].

Pop and colleagues (1999) reported associations with fT4 below the 10th percentile at 12 weeks of gestation and higher risk for impaired psychomotor development measured at 10 months with the Bayley Mental Development

Index (MDI) and Psychomotor Developmental Index (PDI) in a sample of 220 [74]. In a subsequent study, they evaluated maternal hypothyroxinemia at 12, 24, and 32 weeks of gestation, which showed associations between lower MDI and PDI performances with maternal thyroid levels at 12 and 24 months [79]. A year later, Vermiglio and colleagues (2004) published their findings, showing that 87.5% of the women in their study with hypothyroxinemia during 8, 13, and 20 weeks of gestation had children subsequently diagnosed with ADHD between age 8–10 years [80]. Berbel et al. (2009) showed that a 6 to 10-week delay in iodine supplementation for mothers with hypothyroxinemia (fT4 < 10.5 percentile) during 4–6 and 12–14 weeks of gestation increased the risk of overall neurobehavioral delay in children at 18 months [82]. The risk for expressive language delay at 18 months and 30 months, measured with the MacArthur–Bates Communicative Development Inventory (MCDI), the Language Development Survey (LDS), and Parent Report of Children's Abilities (PARCA) at 30 months, was found to be associated with mild (fT4 < 10th percentile) and severe (fT4 < 5th percentile) maternal hypothyroxinemia [86]. Li et al. (2010) found that children of mothers with hypothyroxinemia (<2.5th percentile of total T4) at 16–20 weeks of gestation had notably lower MDI and PDI performance on the Bayley Scales compared to controls [73]. Using the 5th percentile cutoff for free T4, Julvez and colleagues (2013) showed that a median gestational age of 13 weeks predicted lower MDI and PDI performances in toddlers at 14 months [81]. Other studies have shown deficient overall alertness, attention to visual and auditory stimuli, vision abnormalities, and behavioral changes in children with mothers who had hypothyroidism during pregnancy [87–89].

Animal studies have also documented the importance of thyroid hormones in early fetal brain development, likely due to the direct action on the T3 nuclear receptors in the cerebrum [90]. Some studies have found that OH in pregnant mothers can cause gestational hypertension, preeclampsia, and increased placental weight. Adverse fetal outcomes include low birth weight, cretinism, fetal death, spontaneous abortion, and intrauterine growth retardation [61]. Hypothyroidism in the context of autoimmune thyroiditis (i.e., Hashimoto's Disease) in pregnancy increases the risk for miscarriage and premature birth. About 50 percent of affected women experience some form of thyroid dysfunction during the postpartum period [91].

Giving the literature review thus far it seems clear that hypothyroidism in the context of pregnancy has concerning results on child development. However, the literature is somewhat conflicting, as other studies have reported no association between low maternal T4 and offspring cognitive functioning. This in part seems to be due to differences in methodology and the timeline of thyroid hormone interventions. Nonetheless, it is important to review some of the large studies with null results. Oken and colleagues (2009) reported no association between low maternal T4, below the lowest decile at 10.5 weeks of gestation and children's scores on Visual Recognition Memory (VRM) at age 6 months and Peabody Picture Vocabulary Test (PPVT) and Wide-Range Assessment of Visual Motor Abilities (WRAVMA) at 3 years [92]. Another study found no association between an increase in fT4 and subsequent performances on the Bayley MDI and PDI, as well as performances on other language, motor, and intelligence tests in children at 6, 12, 24, and 60 months [93]. Similarly, Craig and colleagues (2012) reported that hypothyroxinemia during the second trimester resulted in no delay on the cognitive, language, and motor scales of the Bayley Scales-III at 24 months [94].

A large multisite study (with an overall sample of 21,846 women) in the UK and Italy showed no significant difference in children's intelligence scores at 3 years of age between the screening group (n = 390, mothers identified as testing positive for hypothyroidism who received levothyroxine at 13 weeks of gestation) and control group (n = 404, mother's identified as testing positive for hypothyroidism who were untreated). The screening group had a mean FSIQ of 99.2 (SD 13.3) and the control group had a mean FSIQ of 100 (SD 13.3) on the

Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III). The proportion of children in each group who had FSIQ scores below 85 were also not significant (screening group 12.1%, control group 14.1%). The authors indicated that thyrotropin levels were higher in the screening group than the control group at baseline [62].

Casey and colleagues (2017) evaluated the outcomes of mothers treated for subclinical hypothyroidism and hypothyroxinemia during pregnancy, and subsequent child intelligence [95]. Thyroid hormone screenings of women (n = 97,228) with a single pregnancy were conducted before the 20th week of gestation, of those screened 1,432 were eligible and enrolled. Women were then randomly assigned to receive levothyroxine or placebo in separate trials for each of the two conditions (subclinical hypothyroidism sample n = 677; 28 of these were lost to follow-up [included in analysis: received levothyroxine n = 323, received placebo n = 326]; hypothyroxinemia sample n = 526; 19 were lost to follow-up [included in analysis: received levothyroxine n = 253, received placebo n = 253]). Subclinical hypothyroidism was defined as thyrotropine level of 4.00 mU or more per liter, and a normal free thyroxine (T4) level (0.86–1.90 ng per deciliter. Hypothyroxinemia was defined as a normal thyrotropin level (0.08–3.99 mU per liter) and a low free T4 level (<0.86 ng per deciliter). Follow-ups were conducted monthly to evaluate thyroid function, and the dosage of levothyroxine was adjusted for each participant to attain a normal thyrotropin or free T4 level. The same procedures were performed with the placebo groups using sham adjustments. Following birth, children were assessed annually for five years. Results showed no statistically significant between-group differences in children's Cognitive, Motor, or Language index performances on the Bayley Scales-III at 12 and 24 months of age in mothers with subclinical hypothyroidism treated with levothyroxine, and mothers with subclinical hypothyroidism receiving placebo. Similar results were also found at 36 and 48 months with the Differential Ability Scales-II, the Child Behavioral Checklist at 36 and 60 months, the Conners' Rating Scales-revised ADHD at 48 months, and the WPPSI-II at 60 months. Results of the trial of mothers with hypothyroxinemia treated with levothyroxine versus placebo were also null using the same outcome measures and assessment time points. On the basis of this study, there were no significantly better neurodevelopmental outcomes in children whose mothers received thyroid hormone treatment compared to placebo. One of the limitations of this study highlighted by the authors was the late timing of the randomization and subsequent treatment (~20 weeks), at which point the fetal thyroid gland has already initiated production of thyroid hormone and is less or not dependent on the mother [95].

Overall, it has been suggested in the literature that maternal hypothyroxinemia during the first half of pregnancy but not after, seems to have direct effects on the cognitive development of offspring, which is consistent with the evidence found in the animal literature [96, 97].

Congenital Hypothyroidism

The first two to three years of life are critical periods, and thyroid hormone is an essential component of normal growth and brain development. The occurrence of hypothyroidism during this time frame is a leading cause of cognitive disability that in most cases could be prevented with proper detection and treatment. Neonate screenings implemented in the 1970s have been highly successful, in some cases eliminating significant cognitive disability in many countries [98]. The majority of cases of congenital hypothyroidism result from a defective thyroid gland, termed primary hypothyroidism.

There are two main causes of primary congenital hypothyroidism, the first is dysgenesis, which is the failure of the gland to develop. Thyroid dysgenesis has an estimated incidence of 1 in 4000 neonates. It has been estimated that 2–5% of thyroid dysgenesis cases are due to genetic mutations; causes underlying

the remaining 95% are unknown. A number of genetic biomarkers have been identified as important for the development of the thyroid, including PAX8, NKX2-1, FOXE1, and NKX2-5. Mutations in GLIS3 have been associated with a multifaceted syndrome comprised of hypothyroidism, diabetes mellitus, glaucoma, hepatic fibrosis, polycystic kidney disease, and developmental delays in neonates. GLIS3 mutations have also been associated with thyroid dysgenesis and in other cases in which the thyroid tissue is found to be abnormal upon histological examination. Variants of CDCA8 have been shown to impair cell migration and adhesion in vitro. Phenotype expression in individuals with CDCA8 is broad, and can range from agenesis or ectopy of the thyroid gland to euthyroid individuals with anatomically asymmetric thyroid lobes or nodules [98]. A full list of identified genes associated with congenital hypothyroidism is presented in Fig. 25.1.

Another primary cause of congenital thyroid dysfunction is dyshormonogenesis, which is the failure of an anatomically normal thyroid to synthesize sufficient amounts of thyroid hormones [98]. Historically, the term dyshormonogenesis referred to specific breakdowns in the cellular production of thyroid hormone thought to always lead to a goitrous hypothyroidism during early childhood. Early on it was estimated that dyshormonogenesis was the cause of thyroid dysfunction in about 15% of congenital hypothyroidism diagnoses. With the advent of new and improved screening practices, the rate of occurrence ranges from 30 to 40% depending on the study [99–101], with most of these cases being children with an ectopic thyroid. Dyshormonogenesis is typically the result of a disruption of thyroid hormone synthesis due to a genetic flaw. Some of the better understood include mutations in thyroglobulin (TG), thyroperoxidase (TPO), dual oxidase 2 (DUOX2), dual oxidase accessory 2 (DUOXA2), sodium–iodide symporter (SLC5A5), pendrin (SLC26A4), iodotyrosin deiodinase (IYD), and JAG1 [98].

Central congenital hypothyroidism (CCH) is considered a rare disease and is the result of a dysfunction of the hypothalamic–pituitary–thyroid (HPT) axis leading to depleted production

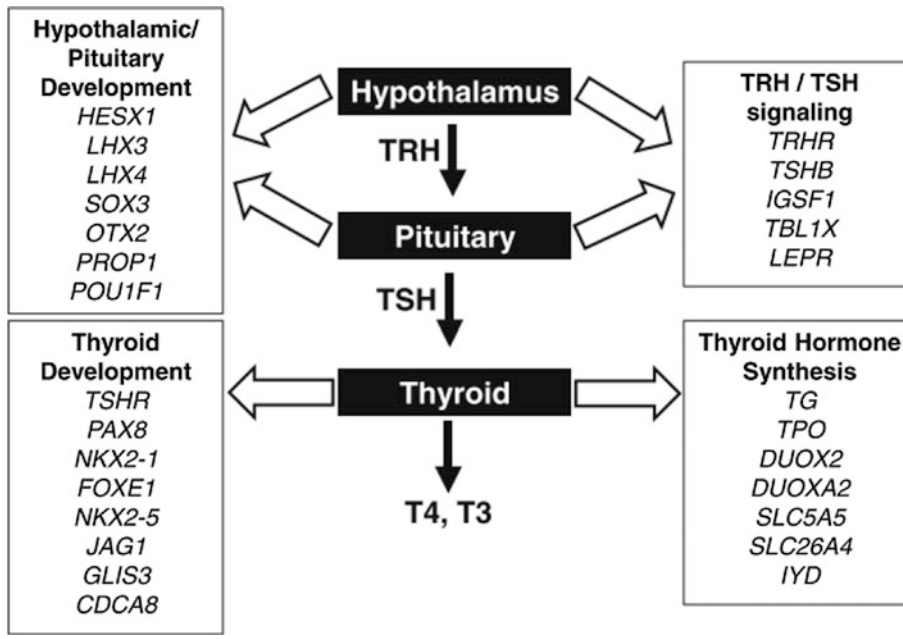

Fig. 25.1 Genes associated with congenital hypothyroidism. *Note* TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine. This figure is reproduced with permission via open access licensing [98]

and decreased activity of thyroid-stimulating hormone (TSH). The estimated incidence of CCH is notably different across studies, likely due to the populations being studied and methodology. Some authors have estimated an incidence of 1 in 16,000 [102, 103], while others have estimated rates to be 1 in 29,000–110,000 [104–106]. Central hypothyroidism is not well detected by screening methods only using TSH-based strategies, which are in many cases still the standard throughout the world. A better approach for detection has employed measures of T4 concentrations and TSH measurements at the same time or when it is found that the infant has low T4. Although, there are still reported limitations in sensitivity to these procedures and many cases of central hypothyroidism are still missed [107, 108]. Congenital defects in the HPT axis result from abnormalities in hypothalamic and/or pituitary development from genetic mutations, while other etiologies have yet to be identified. The known genetic biomarkers include mutations in HESX1, LHX3, LHX4, SOX3, and OTX2 [98]. Mutations in these genes have effects on fetal development, which result in pituitary hormone insufficiency coupled with each transcription factor's specific set of syndromic characteristics. Two outliers include the transcription factors POU1F1 and PROP1, which have been found to be expressed later in the differentiation of the anterior pituitary gland. Their disruption leads to only a shortage of pituitary hormone without other syndromic features (see Table 25.1) [98, 109]. The first genetic mutations identified to be associated causes of central developmental abnormalities in CCH were the TRH receptor (TRHR) and the TSH β–subunit (TSHB). A study by Sun and colleagues (2012) was the first to identify the now most common identifiable genetic cause of isolated CCH, the X-linked deficiency of IGSF1. This was identified in a series of investigations of 11 families with central congenital hypothyroidism [110]. Since the identification of IGSF1 deficiency as a cause of CCH, there have been other confirmatory studies published [111].

Neurodevelopmental Outcomes in Congenital Hypothyroidism

Congenital hypothyroidism (CH) is documented as one of the most frequent, but preventable etiologies of intellectual disability. Even after the implementation of early intervention, neurodevelopmental outcomes were mixed in the 1990s, where some longitudinal studies reported mild decrements in intelligence scores in CH children, while others showed good IQ outcomes consistent with healthy controls and no school problems [112–119]. Deficits in language abilities, motor skills, and reports of learning problems were also documented during this time period [115, 119–123]. However, prevention has evolved with better methods and early screenings, which has improved the overall neurodevelopmental prognosis in children with CH [119, 124].

A recent study by Lain and colleagues (2016) evaluated the associations between low thyroid-stimulating hormone (TSH) concentrations and educational and developmental outcomes in all newborns (n = 507,685) undergoing screenings in New South Wales, Australia between 1994 and 2008. Follow-up assessments of development and school performance were done longitudinally as the children aged. Results showed an association between neonatal TSH blood concentrations and outcome that are consistent with elevations in TSH reflecting failure of the thyroid: In those whose TSH concentrations rose from the 75th percentile to the 99.95th percentile, the likelihood of a typical developmental and educational trajectory worsened. In comparing neonates with a TSH concentration lower than the 75th percentile to those with TSH levels at the 75th percentile or higher, the latter group were more likely to have mothers with diabetes and aged 35 years and older, have a disadvantaged socioeconomic status at birth, be born preterm and/or of low birthweight (<2500 g), have Apgar scores of 7 or less at 5 min, and a mother born in either New Zealand,

Oceania, Middle East, North Africa, or Asia. When TSH concentrations increased higher than the 99.95th percentile (including those children with congenital hypothyroidism requiring treatment as neonates), these children had developmental and educational outcomes consistent with peers who had neonatal TSH concentration lower than the 75th percentile, highlighting the positive outcome of early intervention [125].

Hashimoto's Thyroiditis

Hashimoto's thyroiditis (HT) is one of the diseases falling under the spectrum of a broader entity denominated autoimmune thyroid disease. HT is the main cause of hypothyroidism, resulting in autoimmune damage of the thyroid gland. As multiple studies have gradually unveiled that HT is not as rare as it was once thought, there is increasing interest in this disease. A growing body of literature not only reveals new details about HT, but also provides a better understanding of autoimmune diseases in general. Thus, the remainder of this chapter will focus on reviewing the pathogenesis, clinical presentation, and current treatment of HT, including some of the techniques that have permitted a more accurate diagnosis of this multifaceted autoimmune process. Relevant genetic and environmental factors known to be linked to HT will also be described, as well as a rare complication of this disease, called Hashimoto's encephalopathy (HE). Finally, we will discuss cognitive and psychiatric implications in HT, relevant for neuropsychologists and other mental health providers.

The most common type of thyroiditis is HT, also known as Autoimmune Thyroiditis or Chronic Lymphocytic Thyroiditis. It received its name after Hakaru Hashimoto, the Japanese physician who first described its histological findings as Struma lymphomatosa in 1912 [126]. HT refers to chronic inflammation of the thyroid gland, and it remains the most common mechanism for hypothyroidism [127]. This autoimmune disease is marked by progressive multistep damage and fibrosis of the thyroid parenchyma by thyroid autoantibodies (TAb) due to lymphocytic infiltration of the thyroid gland [128]. As a result, the thyroid gland gradually loses the ability to store iodine, releases iodine-containing proteins (iodoproteins) into the plasma, and becomes inefficient in hormone production. HT is the most prevalent autoimmune disease, occurring 15–20 times more often in women during middle adulthood [129], on the order of 3.5 cases per 1,000 per year in women, and 0.8 cases per 1,000 per year in men, in the United States [130, 131]. Although its precise etiology is uncertain, HT is thought to result from a combination of genetic predisposition in conjunction with environmental factors [132].

Epidemiology

Given the variable expression of HT, it is difficult to establish its precise incidence. Some have estimated the prevalence rates in the United States to be approximately 2% among the general population [133], whereas others have suggested ranges from 0.3 to 1.2% [134]. Family and twin studies have revealed a genetic predisposition to autoimmune thyroid disease. The rate of concordance for HT was found to be 3% and 55% for dizygotic and monozygotic Danish twins, respectively [135]. Similarly, rates of 50–55% in monozygotic twins, compared to 0–2% in dizygotic twins have been reported more recently [136]. Based on information provided by the third United States National Health and Nutrition Examination Survey (NHANES III), the sibling risk ratio (λ_s) was estimated. The λ_s is the ratio of the frequency of individuals who go on to develop a particular disease when they have an affected sibling with the condition. This estimate showed increased risk for autoimmune thyroid disease (16.9%) and for HT (28.0%) in siblings, thus, confirming the considerable hereditary contribution [137]. As mentioned earlier, the presence of TAb has been associated with varying levels of hypothyroidism [138]. Data from the NHANES III showed hypothyroidism in the context of adult HT to have a prevalence of 4.3%,

with positive TAb rates extending from 4.5% for Black non-Hispanics to 12.3% for White non-Hispanics. Overall, compared to the general population, first-degree relatives of individuals with HT are reportedly nine times at greater risk for developing HT [129]. Females are more likely to show positive TAbs, TPOAbs, and TgAbs than their male counterparts, resulting in increased susceptibility to thyroid autoimmunity. This sex preference has also been observed in pediatric samples at a 2:1 ratio, and has been attributed to a possibly high number of immune-related genes in the X chromosome, as well as the immune modulating role of sex hormones [139, 140].

Etiology

Several variables, hereditary and environmental, have been implicated in the development of HT. Research showing a link between HT and other autoimmune diseases, such as type 1 diabetes and autoimmune hepatitis, has further uncovered shared genetic evidence across these disorders. Among some of the most common genetic factors considered to underlie the development of these diseases are the major histocompatibility complex (MHC), the human leukocyte antigen (HLA), and the cytotoxic T-lymphocyte antigen 4 (CTLA-4). Aberration of these genes appears to cause susceptibility for autoimmune thyroiditis [141]. Along with genetic influences, numerous external factors have been shown to affect autoimmune disease, including, but not limited to, intake of specific minerals, infections, and cytokine treatments for cancer and hepatitis, for example. These environmental variables appear to trigger the disease in individuals with a genetic predisposition [142]. We will further discuss these and other genetic and external factors in more detail below.

Genetic Factors

Like other organ-specific autoimmune diseases, HT is frequently comorbid with other autoimmune processes within the same individual and/or present among several family members. This has raised interest for decades leading to the study of shared genetic influences among first-degree relatives. Advances in genetic methods have allowed the identification of several candidate genes proposed to play a role in HT include the HLADR gene locus and non-MHC genes such as CTLA-4, PTPN22, CD40, thyroglobulin (Tg), and TSH receptor genes [142]. The MHC is a large set of genes, some better understood than others, that code proteins on the surface of cells with the main purpose of allowing the immune system recognize extraneous pathogens. These molecules are comprised of widely different forms, which are crucial for specific antigen identification [143]. The MHC region encodes the human leukocyte antigen (HLA), which was one of the initial gene loci associated with thyroid dysfunction. Although not completely understood, HLA has often been linked to autoimmune disease in general, and HT in particular [144]. For instance, while increased expression of HLA class I is involved in organ-specific autoimmune diseases, inhibited expression of this antigen has been shown to block the development of systemic lupus erythematosus in laboratory experiments, and abnormal expression of HLA class II has been shown in HT [145–147].

Another important immune-regulatory gene in thyroid disease is the CTLA-4. This is an important checkpoint supporting the body's equilibrium and negative regulation of the immune system through inhibition of T-cells. Suppression of the CTLA-4 gene, though not necessarily each of its polymorphisms, seems to increase vulnerability to immune response via inhibition of T-cell proliferation. This process is thought to denote one of the early stages in the development of HT [148, 149]. Similarly, Tg is a thyroid specific antigen sensitive to autoimmune response due to its prevalence in the circulation. Although Tg does not seem to be directly responsible for thyroid damage, Tg antibodies are found in about four-fifths of individuals with HT, and it appears to mediate cytotoxicity in T-cells [150]. PTPN22 has lately been examined for its role in autoimmunity, and has been related to thyroid disease. This gene is largely expressed

in lymphocytes, and similar to CTLA-4, which behaves as a negative regulatory molecule that activates T-cells [151].

Environmental Factors

Although cases of HT were initially thought to be infrequent, often incidentally confirmed through histopathological thyroid gland studies after thyroidectomy, the increased sensitivity of diagnostic modalities has improved diagnosis. This has created an opportunity to further evaluate the possible association of HT with other diseases, such as diabetes, rheumatoid arthritis, and multiple sclerosis. Additionally, certain environmental influences are believed to trigger HT in individuals genetically predisposed. Most commonly associated aspects include nutritional factors, certain medications, infections, exposure to some toxins, smoking, and stress [152–154]. For instance, a strong correlation between increased iodine intake and thyroid autoimmunity has been shown, such as both deficiency or excessive amounts of iodine absorption are linked to 13–25% of cases, respectively. This apparently happens as the enzyme thyroid peroxidase (TPO) iodinates Tg, which boosts its ability to provoke an immune response [152]. Also, the thyroid gland has large concentrations of selenium, which has multiple antioxidant and anti-inflammatory properties. Thus, deficiency of this mineral has been linked to hypothyroidism and other autoimmune conditions, and several studies argue for the relevance of selenium supplementation in these diseases [155].

Likewise, production of the thyroid hormones T3 and T4 has been shown to strongly depend on iron metabolism. Iron deficiency is often seen in individuals with HT, and it appears that hypothyroidism disrupts gastrointestinal iron absorption [156]. Among drugs associated with thyroid dysfunction, seemingly due to thyrotoxicosis, are interferon-α (INF-α) for treatment of hepatitis, interlukin-2 (IL-2) for treatment of cancers such as melanoma and renal carcinoma, and lithium for treatment of bipolar disorder [157–159]. In addition to the side effects of specific medications, several viruses have been shown to trigger or mediate thyroid autoimmunity. Specific to HT are Human T lymphocytic virus-1 (HTLV-1), enterovirus, mumps, herpes simplex virus (HSV), Epstein Barr virus (EBV), parvovirus, and rubella [160].

Lithium carbonate is a common pharmacological treatment for bipolar disorders. According to Lazarus [161], lithium increased the retention of radioactive iodine in the thyroid gland. In comparison, women on lithium develop hypothyroidism and goiters more than three times as often as men (41 versus 13%) [162]. In a daily dose of 600–1,000 mg, lithium blocks the release of hormones and can be given as a treatment for iodine allergy and useful for thionamide-resistant hyperthyroidism. Lithium is freely filtered and eventually excreted by the kidneys proportional to the glomerular filtration rate, which has different pharmacokinetics depending on gender [30, 163].

Radioiodine therapy with the beta emitter Iodine-131 is used to treat hyperthyroidism and is similar to surgery, as it is an ablative form of treatment, which can lead to hypothyroidism [164]. The likelihood of developing hypothyroidism following radioiodine therapy increases with time, and is often the treatment goal, such as with treating Graves' disease. Factors that increase the chance of the development of hypothyroidism include radioiodine dose, no pretreatment with thionamides, no goiter, less severe hyperthyroidism at the start of treatment, positive autoantibodies, and female gender. The use of radioiodine imaging or therapy is contraindicated during pregnancy, as the fetus is exposed to radiation from Iodine-131 circulating in the mother's blood and the pathway for excretion in the urinary and gastrointestinal tract [30]. All women should be screened within 72 h or less for possible pregnancy prior to radioiodine use [30, 165].

Pathogenesis and Clinical Presentation

As described above, the development of HT is multifaceted, involving several genetic predisposing variables and environmental activating

factors that disrupt the body's immunological processes. When the body becomes unable to recognize normal thyroid cells, it starts fabricating antibodies that attack the thyroid tissue, resulting in obliteration of the thyroid gland. The initial step in this process seems to be an inflammatory response that worsens prompted by previously mentioned external factors. HT is characterized by enlargement of the thyroid gland, with or without a goiter, which often functions normally although hypothyroidism can progress over time. While the etiology of this disease is not completely understood, it can be classified into primary or secondary [166].

Primary Hashimoto's Thyroiditis

Primary HS refers to cases where the exact cause is unknown or has not yet been identified. Based on their clinical and pathological characteristics, this classification includes at least the six following forms: **Classic, fibrous, IgG4-related, Hashitoxicosis, juvenile, and painless**. They typically present with lymphocytic infiltration of the thyroid gland, goiter, and hypothyroidism may develop though not always, and other comorbid autoimmune disorders may be present as well [167–170].

Classic form: The classic form is pathologically characterized by the interstitial permeation of hematopoietic mononuclear cells largely made up of small white blood cells called lymphocytes. These organize into lymphoid follicles and interact with follicular cells in the thyroid gland responsible for secreting thyroid hormones T3 and T4. This interaction is thought to cause thyrocyte destruction, and these lesions differ in degree within various areas of the thyroid gland, resulting in a distinct appearance. This variant is by far more common in females after the age of 40, who present clinically with an enlarged and hard thyroid gland, but often do not show elevated TSH [171].

Fibrous form: Like the classic form of HT, the fibrous variant is marked by interstitial fibrosis. However, the dense bands of fibrosis in the fibrous variant are much more prominent, which give the thyroid a nodular appearance without extending into adjacent structures. This variant is less common, occurring in approximately 10% of cases, mostly women in their 60s, who often require thyroid hormone replacement. The fibrous form can be difficult to distinguish from other fibro-inflammatory conditions such as Riedel disease, and require careful clinical and histological evaluation [172].

IgG4 form: On the other hand, immunoglobulin G4-related diseases include multiple systemic inflammatory conditions characterized by elevated IgG4-secreting plasma cells. Unsurprisingly, the IgG4-related form of HT features thyroid inflammation and fibrosis, as well as IgG4-positive plasma cell infiltration, and interestingly, it has been more often reported in males although it also occurs in women. This variant usually develops faster and more aggressively, often resulting in elevated TAb's and subclinical hypothyroidism despite sustained treatment [173].

Hashitoxicosis, Juvenile, and Painless forms: There is little written about the Hashitoxicosis, juvenile, and painless variants of HT, except that they are histologically comparable, and commonly show interstitial lymphocytic infiltration but rarely nuclear follicular degeneration. The Hashitoxicosis variant initially presents as typical Graves' disease, but the hyperthyroidism only lasts a few months before progressing into chronic hypothyroidism consistent with HT. The juvenile form is more commonly diagnosed in women before age 18, who are often euthyroid despite having a goiter. The painless variant, also called silent, presents with more subtle and transient symptoms, and can be either sporadic, or more often, related to pregnancy and presenting within a year following delivery, for what is known as postpartum thyroiditis [127, 174].

Secondary Hashimoto's Thyroiditis

Secondary HT refers to cases where the underlying cause has been clearly determined. This classification often includes iatrogenic causes, as well as less clear cases induced by therapeutic

agents. It has been observed, for instance, that immunomodulatory drugs such Anti-CTLA-4 antibody therapy, interferon-alpha treatment, and some vaccines for cancer can lead to or exacerbate HT [175–177]. For instance, while CTLA-4 blocking antibody has been successfully used to treat certain tumors, animal and human studies have also shown an association with worsened autoimmune thyroiditis [178]. Similarly, some researchers have proposed the importance of screening for TAb's in patients about to undertake interferon treatment for hepatitis C virus since it has been demonstrated that preexisting high TAb's levels increase the risk of developing HT. About 15% of these patients have been found to develop thyroid disease, and although they can often be managed with T4 replacement, treatment discontinuation may be necessary to prevent further complications of interferon-induced thyroiditis [178, 179].

Diagnosis

The diagnosis of HT typically involves several steps, beginning with anatomical examination of relevant neck structures near the thyroid gland. This includes localized evaluation of the cervical structure, recurrent laryngeal nerve, trachea, and esophagus, as well as associated signs of functional compromise such as compression of the cervical vertebrae or spine, dysphonia, dyspnea, and dysphagia. Likewise, evaluation of clinical and subclinical hypothyroidism, as well as systemic clinical manifestations is crucial given that most organs are influenced by thyroid hormones. Thus, a thorough review of the gastrointestinal, skin and appendages, cardiovascular, skeletal, pulmonary, hematopoietic, reproductive, urinary, and nervous systems is necessary. Common symptoms experienced by patients with HT may include constipation, dry and cold skin, thin and frail nails, bradycardia, coronary artery disease, muscle soreness and hypertrophic appearance, bradypnea and hypoxia, anemia, oligomenorrhea and/or menometrorrhagia, urinary retention, as well as drowsiness, cognitive, and mood changes [127]. The thyroid gland's aspect is also often examined through ultrasound. In addition, radioactive iodine uptake (RIU) testing and fine needle cytology aspiration (FNCA), although less often used in clinical practice, can be helpful diagnostic tools to confirm and classify HT. Commonly associated thyroid autoantibodies are also evaluated, and they can differ between goitrous and non-goitrous thyroiditis. Lab work from individuals with HT typically reveals serum antibodies reacting to thyroid peroxidase (TPO) at a rate of 95%, and Tg at a rate of 60–80% [166].

Hashimoto's Encephalopathy and Behavioral Phenotypes

Hashimoto's encephalopathy (HE) also known as steroid-responsive autoimmune encephalopathy associated with autoimmune thyroiditis (SREAT) was first described in 1966 [180]. It is thought to be induced by inflammation, but still not fully understood and often misdiagnosed. It presents as an encephalopathy in the absence of a specific central nervous system (CNS) pathology such as a stroke, tumor, or infection, with typically normal brain imaging. Instead, it is associated with autoimmune thyroiditis, and characterized by elevation of anti-TPO antibodies, increased protein on CSF, and responsiveness to corticosteroid treatment. EEG findings are usually reported as nonspecific diffused slowing, typically seen in many other encephalopathies. Thus, its diagnosis remains a process of elimination of other pathologies that could potentially affect the central nervous system, including inflammatory, vascular, metabolic, and neoplastic causes [181]. It has been estimated that the prevalence of HE is 2.1 in 100,000 cases, and although it can range from pediatric to geriatric populations, it occurs most frequently in women in their mid-40s to mid-50s. Most cases are described as having a relapsing and remitting course irrespective of age and gender, and the underlying pathogenesis is unknown [182]. Important differential diagnoses should include autoimmune Anti-N-methyl-D-aspartate

receptor (anti-NMDAR) encephalitis, Creutzfeldt–Jakob disease (CJD), systemic lupus, primary CNS vasculitis, paraneoplastic limbic encephalitis (PLE), tumors, and stroke [183].

Clinically, HE is characterized by altered mental status, and manifest in two different, and potentially reversible, types: A vasculitic form with fairly localized neurocognitive symptoms resembling stroke-like events (i.e., somatosensory and other typical cortical syndromes), or a nonspecific continuous worsening of cognitive abilities, motor abnormalities such as opsoclonus or ataxia, and psychosis, eventually leading to a dementing state. Neurological symptoms frequently include seizures, including generalized and complex partial, which may result in complicated status epilepticus [184, 185]. Prevalence estimates for seizures (focal, generalized, complex-partial, and status epilepticus) in HT range from 60 to 70% of cases [185]. Other features may include mood disturbance, sleep disorder, and other diffused systemic symptoms [184, 185].

Behavioral changes are very common in HE, and in some cases, the initial presentation is psychiatric disturbance. Unfortunately, there is not a specific criterion or systematic protocol to help clarify the underlying cause of these symptoms and potentially result in an accurate diagnosis. A recent literature review examined 46 case reports of patients eventually diagnosed with HE, the majority of whom did not have preceding hypothyroidism, and who had presented with early psychiatric symptoms. The most commonly found symptoms were psychosis, including hallucinations, delusion, and paranoia (26.1%), as well as depression (23.9%), whereas dementia (10.9%) and schizophrenia (2.2%) were more rare [186, 187].

Treatment for Hypothyroidism and Hashimoto's Thyroiditis

Oral medication is the first line of treatment for overt and subclinical hypothyroidism, including that seen in various forms of HT. The most common treatment is replacement of thyroid hormone by synthetic levothyroxine (L-T4), which is a pharmacological agent typically prescribed as a lifetime daily treatment of clinical symptoms without actual impact on the underlying development of the disease. However, for the IgG4 variant of HT, glucocorticoids may be curative and prevent hypothyroidism from becoming permanent [188]. Although the literature has shown some inconsistent results, selenium supplements are increasingly recommended as they appear to provide the thyroid gland with shielding properties against autoimmune disease, even in patients already on L-T4 [189]. Partial or total, unilateral or bilateral, surgical removal of the thyroid gland, a procedure known as thyroidectomy, can be performed when there is cervical compression, suspicion of malignancy following FNCA, or in some cases for cosmetic purposes when patients request it. However, careful consideration is essential to avoid unnecessary complications in patients with HT, including hypoparathyroidism, which is less common when thyroidectomy is done for other thyroid disorders. Individuals with HT undergoing thyroidectomy often have to continue taking synthetic thyroid hormones thereafter, and while the surgery addresses some of the symptoms, it does not treat the underlying cause of hypothyroidism [190].

The main treatment for Hashimoto's Encephalopathy (HE) is high dose of corticosteroids, which can also help confirm the diagnosis. Oral prednisone or high-dose intravenous methylprednisolone are most often used. Patients often show improvement of clinical symptoms within the first few weeks, though a subset of them often shows resistance and requires additional boosts of medication. In many cases, early intervention and a short treatment course prove to be successful, yet a few patients remain on steroids for years, and other immunosuppressive therapy may be required as well. A common adverse effect of long-term steroid use is osteoporosis. Antiepileptic drugs, such as Levetiracetam, are frequently included for seizure treatment or prophylaxis. Psychotic symptoms, associated with HE, are usually managed with antipsychotic medications. The prognosis is

variable depending on how early diagnosis and treatment are established, and there are still many unresolved questions regarding this form of encephalopathy, including which treatment regimen is most adequate [191].

Neuropsychological Outcomes in Hashimoto's Thyroiditis

In addition to physical and mood symptoms, patients diagnosed with HT often complain of diffuse cognitive problems, memory, and speech issues. Complicated HT that progresses into autoimmune encephalopathy results in much greater cognitive dysfunction, reported in more than eighty percent of patients. Given that cognitive and mood issues have been inconsistently reported in patients with HT, who are well controlled with levothyroxine in euthyroid ranges, researchers have been interested in further studying the effects of levothyroxine treatment on these functions. One such study compared the neuropsychological performance of two groups of L-thyroxine treated patients, one with HT versus a control group receiving hormonal treatment for either goiter or following thyroidectomy. Interestingly, no differences were found between the two groups across measures of attention, executive control, verbal and visual memory, and acoustic working memory. However, only the HT group exhibited decreased performance on the "d2 Test of Attention," a measure of processing speed and attention [192]. Similar conclusions were made more recently in a group of patients with HT, well controlled at euthyroid levels, who demonstrated reduced sustained speeded attention in this same task. Through the use of high-resolution structural imaging techniques, an association was found between this cognitive weakness and reduced gray matter density in the left inferior frontal gyrus of these individuals. Thus, the results from this study indicate a possible influence of HT on the frontal cortex [193].

While some studies have found that patients with HT present with cognitive problems regardless of thyroid function disorder, the literature is mixed. At least one case of selective memory problems, with sparing of other cognitive functions, has been reported in a patient with subclinical hypothyroidism due to HT. Despite well-controlled hypothyroidism and normal medical examination, this individual showed decreased encoding of verbal information as well as mildly impaired visual retrieval on the WMS-III (Logical Memory and Visual Reproduction, respectively). Both issues had resolved on a five-month neuropsychological follow-up, after a course with dexamethasone [194]. Giannouli and colleagues (2014) found differing results in two patients with HT; neither patient showed any cognitive deficits on exam (one of whom was diagnosed with Major Depressive Disorder), using a battery of neuropsychological measures assessing the cognitive domains of attention, executive functioning, verbal and visual learning/memory, global cognitive functioning, and screening measures of depressive and anxiety symptoms [195]. In their study, baseline pretreatment versus one-year posttreatment neuropsychological findings did not reveal noteworthy changes in cognition, suggesting a benign course in well-treated hypothyroidism [195]. Others have also failed to identify any significant differences when comparing neuropsychological tests results, structural brain imaging, and functional connectivity in patients with HT undergoing biochemically adequate treatment for long-term hypothyroidism versus a healthy control group. In this study, Quinque and colleagues (2014) evaluated 18 patients ranging from 18 to 54 years of age, treated with levothyroxine for hypothyroidism. Neuropsychological domains included sustained attention, verbal learning/memory, working memory, and psychomotor speed [196]. Thus, variable findings regarding cognitive functioning of individuals with HT have been attributed to mediating factors such as depression, other mood issues, or cognitive reserve. However, further research is needed to explore these variables.

Social Factors and Quality of Life

Chronic illness has a significant negative impact on day-to-day functioning in patients, and long-lasting metabolic conditions such as thyroid

disorders are not the exception. In addition to determining physical, cognitive, and behavioral factors impacting patients during the progression and treatment of thyroid disease, identifying and grading other health-related quality of life factors is an important part of treatment. Hypothyroidism has been shown to have a considerable effect on the quality of life of patients resulting in additional symptom burden and decreased life satisfaction, irrespective of thyroid functioning and treatment. In hypothyroidism mood and cognitive symptoms, as aforementioned are often present, further impact other life areas such as self-concept and worth, relationships, and school and work performances. For instance, a study by Bektas-Uysal and Ayhan (2016) looked at the influence of anti-TPO and anti-TG antibodies on quality of life in euthyroid patients with HT. An inverse correlation was found between the antibody levels and quality of life, where patients with high levels of anti-TPO and anti-TG had lower quality of life ratings, independent of thyroid functioning [197].

Effect of treatment on symptoms: As clinical symptoms of HT have been shown to diminish quality of life, it has been suspected that thyroidectomy may result in improved physical health, and therefore enhanced life quality. However, a survey assessing several variables underlying quality of life (i.e., general health, physical functioning, bodily pain, vitality, as well as social, emotional, and mental functioning) in 248 women who underwent thyroidectomy for treatment of subclinical hypothyroidism with goiter, revealed unchanged responses 12 and 33 months post-surgically, without particular difference when compared to those living with euthyroid goiter [198].

Conclusions

This chapter has reviewed the epidemiology, underlying pathology, laboratory findings, clinical presentation, neuropsychological outcomes, and treatment for hypothyroidism and Hashimoto's thyroiditis (HT), as it is currently understood. Hypothyroidism is the result of a disturbance in the production of thyroid hormones, which can be associated with multiple etiologies and may result in a number of neurocognitive and psychiatric manifestations. There are concerns regarding the neurodevelopmental outcomes related to maternal hypothyroidism during pregnancy and child development. Even so, the literature still remains somewhat conflicted, as some studies have reported no association between low maternal T4 and offspring cognitive functioning, others report evidence of lower intellectual scores, as well as language and motoric abilities being below expectation. The adult literature on cognitive performances in individuals with primary hypothyroidism indicates these patients, compared to healthy controls tend to obtain lower scores across various cognitive domains, including intelligence, perceptual and visual-spatial abilities, mental speed, attention and concentration, verbal fluency, visual tracking and psychomotor speed, executive functions, and memory, with the latter being documented most often by authors. On the other hand, the adult literature in Hashimoto's Thyroiditis is limited and shows contrasting neuropsychological findings, which appears to be due to several factors, including small sample sizes, etiology of hypothyroidism, and other methodological differences. As of yet, there is no established cognitive pattern in adult hypothyroidism.

Early detection and intervention in all cases of hypothyroidism are key in order to adequately treat and monitor associated symptoms. Identifying an underlying etiology, such as in specific variants of primary HT, prove to be crucial in certain cases where specific interventions are required and levothyroxine may not be effective. Moreover, large-scale studies using screening measures typically fail to show a relationship between hypothyroidism and cognitive impairment, while other studies using more comprehensive cognitive batteries appear to be able to capture cognitive weaknesses and/or impairments in patients with hypothyroidism. Thus, future research and clinical neuropsychological evaluation of these individuals should include measures that assess all major cognitive domains, in addition to psychological functioning, and quality of life variables.

References

1. Choufoer JC, Van Rhijn M, Kassenaar AAH, Querido A. Endemic goiter in Western New Guinea: iodine metabolism in goitrous and non-goitrous subjects. J Clin Endocrinol Metab. 1963;23 (12):1203–17.
2. Choufoer JC, Van Rhijn M, Querido A. Endemic goiter in Western New Guinea. II. Clinical picture, incidence and pathogenesis of endemic cretinism. 1964.
3. Adams DD, Kennedy TH, Choufoer JC, Querido A. Endemic goiter in Western New Guinea. III. Thyroid-stimulating activity of serum from severely iodine-deficient people. 1968;28(August).
4. Man EB, Reid WA, Jones WS. Thyroid function in human pregnancy. I. The significance of serum butanol-extractable iodines in the last trimester. Am J Obstet Gynecol. 1964;90(4):474–81. http://dx.doi.org/10.1016/0002-9378(64)90804-X.
5. Man EB, Holden RH, Jones WS. Thyroid function in human pregnancy. Am J Obstet Gynecol. 1971;109(1):12–9. http://linkinghub.elsevier.com/retrieve/pii/0002937871908258.
6. Man EB, Reid WA, Hellegers AE, Jones WS. Thyroid function in human pregnancy. III. Serum thyroxine-binding prealbumin (TBPA) and thyroxine-binding globulin (TBG) of pregnant women aged 14 through 43 years. Am J Obstet Gynecol. 1969;103(3):338–47.
7. Man EB, Reid WA, Jones WS. Thyroid function in human pregnancy. IV. Serum butanol-extractable iodine drop with weight gain. Am J Obstet Gynecol. 1968;102(2):244–7. http://dx.doi.org/10.1016/0002-9378(68)90326-8.
8. Man EB, Jones WS. Thyroid function in human pregnancy. V. Incidence of maternal serum low butanol-extractable iodines and of normal gestational TBG and TBPA capacities; retardation of 8-month-old infants. Am J Obstet Gynecol. 1969;104(6):898–908. http://dx.doi.org/10.1016/0002-9378(69)90644-9.
9. Jones WS, Man EB. Thyroid function in human pregnancy. VI. Premature deliveries and reproductive failures of pregnant women with low serum butanol-extractable iodines: maternal serum TBG and TBPA capacities. Am J Obstet Gynecol. 1969;104(6):909–14. http://dx.doi.org/10.1016/0002-9378(69)90645-0.
10. Man EB, Holden RH, Jones WS. Thyroid function in human pregnancy. VII. Development and retardation of 4-year-old progeny of euthyroid and of hypothyroxinemic women. Am J Obstet Gynecol. 1971;109(1):12–9. http://dx.doi.org/10.1016/0002-9378(71)90825-8.
11. Man EB, Jones WS, Holden RH, David Mellits E. Thyroid function in human pregnancy. VIII. Retardation of progeny aged 7 years; relationships to maternal age and maternal thyroid function. Am J Obstet Gynecol. 1971;111(7):905–16. http://dx.doi.org/10.1016/0002-9378(71)90945-8.
12. Man EB, Serunian SA. Thyroid function in human pregnancy. IX. Development or retardation of 7-year-old progeny of hypothyroxinemic women. Am J Obstet Gynecol. 1976;125(7):949–57. http://dx.doi.org/10.1016/0002-9378(76)90494-4.
13. Openstax. Muscle tissue. In: Betts JG, Desaix P, Johnson E, Johnson JE, Korol O, Kruse D, et al., editors. Anatomy & Physiology; 2013. 405–30 p. https://openstax.org/details/books/anatomy-and-physiology.
14. Beckwith BE, Tucker DM. Medical neuropsychology: the impact of disease on behavior. In: Tarter RE, Van Thiel DH, Edwards KL, editors. Pittsburg, PA: Plenum Press; 1988. 197–221 p.
15. Mohebati A, Shaha AR. Anatomy of thyroid and parathyroid glands and neurovascular relations. Clin Anat. 2012;25(1):19–31.
16. Allen E, Bhimji S. Anatomy, neck, thyroid. StatPearls Publ. 2017. https://www.ncbi.nlm.nih.gov/books/NBK470452/.
17. Bergman RA, Afifi AK, Miyauchi R. Anatomy atlases: an anatomy digital library. Thyroidea Ima (of Neubauer) Artery; 2018. https://www.anatomyatlases.org/AnatomicVariants/Cardiovascular/Text/Arteries/ThyroideaIma.shtml.
18. Ritchie M, Yeap BB. Thyroid hormone: influences on mood and cognition in adults. Maturitas. 2015;81(2):266–75. http://dx.doi.org/10.1016/j.maturitas.2015.03.016.
19. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3(4):286–95.
20. WHO/UNICEF/ICCIDD. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. World Health Organization; 1996. p. 10.
21. WHO. Assessment of the iodine deficiency disorders and monitoring their elimination. WHO, Geneva; 2007. p. 1–107.
22. Hetzel BS. Iodine deficiency disorders (Idd) and their eradication. Lancet. 1983;322(8359):1126–9.
23. Delong G. Iodine and the brain. In: Delong G, Robbins J, Condliffe P, editors. New York; 1989. 231–8 p.
24. Delange F. The thyroid: a fundamental and clinical text. In: Braverman LE, Utiger RD, editors. Philidelphia: Lippincott; 2000. 743–54 p.
25. Zimmermann MB. Symposium on "Geographical and geological influences on nutrition"—Iodine deficiency in industrialised countries. Proc Nutr Soc. 2010;69(1):133–43.
26. Esselstyn CB, Gendy G, Doyle J, Golubic M, Roizen MF. A way to reverse CAD? J Fam Pract. 2014;63(7):356–64b. https://www.mdedge.com/jfponline/article/83345/cardiology/way-reverse-cad.
27. Esselstyn CB. A plant-based diet and coronary artery disease: a mandate for effective therapy. J Geriatr Cardiol. 2017;14(5):317–20.

28. Aburto NJ, Abudou M, Candeias V, Wu T. Effect of salt iodization to prevent iodine deficiency disorders: a systematic review with meta-analyses. WHO eLibrary Evid Nutr Actions. 2014;142. www.who.int/about/licensing/copyright_form/en/index.html; http://apps.who.int/iris/bitstream/10665/148175/1/9789241508285_eng.pdf.
29. Bougma K, Aboud FE, Harding KB, Marquis GS. Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. Nutrients. 2013;5(4):1387–416.
30. Gessl A, Lemmens-Gruber R, Kautzky-Willer A. Sex and Gender Differences in Pharmacology [Internet]. Regitz-Zagrosek V, editor. Sex and Gender Differences in Pharmacology. 2012. 361 p. Available from: http://books.google.com/books?hl=en&lr=&id=J3VxihGDh9wC&oi=fnd&pg=PR5&dq=Sex+and+Gender+Differences+in+Pharmacology&ots=IdkJGzUYsk&sig=r0qg0Y-GDdroABvYpKCQ7lH9T8k%; http://link.springer.com/10.1007/978-3-642-30726-3.
31. Garber J, Cobin R, Gharib H, Hennessey J, Klein I, Mechanick J, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18(6):988–1028.
32. Samuels MH. Thyroid disease and cognition. Endocrinol Metab Clin North Am. 2014;43(2):529–43. http://dx.doi.org/10.1016/j.ecl.2014.02.006.
33. Henrichs J, Ghassabian A, Peeters RP, Tiemeier H. Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? Clin Endocrinol (Oxf). 2013;79(2):152–62.
34. Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the MRC cognitive function and ageing study. Psychoneuroendocrinology. 2008;33(7):1013–22.
35. Mennemeier M, Garner RD, Heilman KM. Memory, mood and measurement in hypothyroidism. J Clin Exp Neuropsychol. 1993;15(5):822–31.
36. Osterweil D, Syndulko K, Cohen SN, Pettier-Jennings PD, Hershman JM, Cummings JL, et al. Cognitive function in non-demented older adults with hypothyroidism. J Am Geriatr Soc. 1992;40(4):325–35.
37. Burmeister LA, Ganguli M, Dodge HH, Toczek T, Dekosky ST, Nebes RD. Hypothyroidism and cognition: preliminary evidence for a specific defect in memory. Thyroid. 2001;11(12):1177–85. http://www.liebertonline.com/doi/abs/10.1089/10507250152741037.
38. Botella-Carretero J, Galán J, Caballero C, Sancho J, Escobar-Morreale H. Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. Endocr Relat Cancer. 2003;10(4):601–10. http://www.ncbi.nlm.nih.gov/pubmed/14713270.
39. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JGP, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005;153(6):747–53.
40. Constant EL, Adam S, Seron X, Bruyer R, Seghers A, Daumerie C. Anxiety and depression, attention, and executive functions in hypothyroidism. J Int Neuropsychol Soc. 2005;11(05):535–44. http://www.journals.cambridge.org/abstract_S1355617705050642.
41. Correia N, Mullally S, Cooke G, Tun TK, Phelan N, Feeney J, et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. J Clin Endocrinol Metab. 2009;94(10):3789–97.
42. Miller KJ, Parsons TD, Whybrow PC, Van Herle K, Rasgon N, Van Herle A, et al. Verbal memory retrieval deficits associated with untreated hypothyroidism. J Neuropsychiatry Clin Neurosci. 2007;19(2):132–6. http://www.ncbi.nlm.nih.gov/pubmed/17431058%; http://psychiatryonline.org/doi/abs/10.1176/jnp.2007.19.2.132.
43. Beydoun MA, Beydoun HA, Rostant OS, Dore GA, Fanelli-Kuczmarski MT, Evans MK, et al. Thyroid hormones are associated with longitudinal cognitive change in an urban adult population. Neurobiol Aging. 2015;36(11):3056–66. http://dx.doi.org/10.1016/j.neurobiolaging.2015.08.002.
44. Reid RE, Kim EM, Page D, O'Mara SM, O'Hare E. Thyroxine replacement in an animal model of congenital hypothyroidism. Physiol Behav. 2007;91(2–3):299–303.
45. De Jong FJ, Den Heijer T, Visser TJ, De Rijke YB, Drexhage HA, Hofman A, et al. Thyroid hormones, dementia, and atrophy of the medial temporal lobe. J Clin Endocrinol Metab. 2006;91(7):2569–73.
46. Forti P, Olivelli V, Rietti E, Maltoni B, Pirazzoli G, Gatti R, et al. Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. Gerontology. 2012;58(1):41–9.
47. Tan ZS, Beiser A, Vasan RS, Auerbach S, Kiel DP, Wolf PA, et al. NIH public access. Arch Intern Med. 2009;168(14):1514–20.
48. Jensovsky J, Ruzicka E, Spackova N, Hejdukova B. Changes of event related potential and cognitive processes in patients with subclinical hypothyroidism after thyroxine treatment. Endocr Regul. 2002;36(3):115–22.
49. kMonzani F, Del Guerra P, Caraccio N, Pruneti C, Pucci E, Luisi M, et al. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. Clin Investig. 1993;71(5):367–71.
50. Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg P, Lindstedt G. Double-blind cross-over 12-month study of L-thyroxine treatment of women with subclinical hypothyroidism. Clin Endocrinol (Oxf). 1988;29:63–75.
51. Aghili R, Khamseh ME, Malek M, Hadian A, Baradaran HR, Najafi L, et al. Changes of subtests of Wechsler Memory Scale and cognitive function in subjects with subclinical hypothyroidism

following treatment with levothyroxine. Arch Med Sci. 2012;8(6):1096–101.
52. Roberts LM, Pattison H, Roalfe A, Franklyn J, Wilson S, Hobbs FD, et al. Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Intern Med. 2006;145(8):573–81. http://www.ncbi.nlm.nih.gov/pubmed/17043339.
53. De Jongh RT, Lips P, Van Schoor NM, Rijs KJ, Deeg DJH, Comijs HC, et al. Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. Eur J Endocrinol. 2011;165(4):545–54.
54. Gussekloo J, van Exel E, de Craen AJM, Meinders AE, Frölich M, Westendorp RGJ. Thyroid status, disability and cognitive function, and survival in old age. JAMA. 2004;292(21):2591–9. http://www.ncbi.nlm.nih.gov/pubmed/15572717.
55. Bell RJ, Rivera-Woll L, Davison SL, Topliss DJ, Donath S, Davis SR. Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease—A community-based study. Clin Endocrinol (Oxf). 2007;66(4):548–56.
56. Engum A, Bjøro T, Mykletun A, Dahl A. An association between depression, anxiety and thyroid function—A clinical fact or an artefact? Acta Psychiatr Scand. 2002;106(1):27–34.
57. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab. 2006;91(1):145–53.
58. Kong WM, Sheikh MH, Lumb PJ, Freedman DB, Crook M, Doré CJ, et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Med. 2002;112(5):348–54. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2002111425.
59. Parle J, Roberts L, Wilson S, Pattison H, Roalfe A, Haque MS, et al. A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham elderly thyroid study. J Clin Endocrinol Metab. 2010;95(8):3623–32.
60. Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, Tokatlioglu B. Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. Arch Med Res. 2006;37(1):133–9.
61. Stagnaro-Green A. Overt hyperthyroidism and hypothyroidism during pregnancy. Clin Obstet Gynecol. 2011;54(3):478–87.
62. Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2011;366(6):1757–65.
63. Sutherland J, Esselborn V, Burket R, Skillman T, Benson JT. Familial nongoitrous cretinism apparently due to maternal antithyroid antibody: report of a family. N Engl J Med. 1960;263:336–41. https://www.nejm.org/doi/full/10.1056/NEJM196008182630703.
64. Connors MH, Styne DM. Transient neonatal 'athyreosis' resulting from thyrotropin-binding inhibitory immunoglobulins. Pediatrics. 1986;78(2):287–90. http://pediatrics.aappublications.org/content/78/2/287..info.
65. Cho BY, Shong YKEE, Lee HKYU, Uppsalla P. Transient neonatal hypothyroidism due to transplacental transfer of maternal immunoglobulins that inhibit TSH binding, cAMP increase and cell growth. Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, Korea; 1987. p. 110–744.
66. Fort P, Lifshitz F, Pugliese M, Klein I. Neonatal thyroid disease: differential expression in three successive offspring. J Clin Endocrinol Metab. 1988;66(3):645–7.
67. Goldsmith RE, McAdams AJ, Larsen PR, Mackenzie M, Hess EV. Familial autoimmune thyroiditis: maternal–fetal relationship and the role of generalized autoimmunity. J Clin Endocrinol Metab. 1973;37(2):265–75.
68. McCarrison R. The thyroid gland in health and disease. New York: William Wood & Company; 1917. http://www.archive.org/details/thyroidglandinheOOmcca.
69. Matsuura N, Konishi J. Transient hypothyroidism in infants born to mothers with chronic thyroiditis—a nationwide study of twenty-three cases. The Transient Hypothyroidism Study Group. Endocrinol Jpn. 1990;37(3):369–79.
70. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341(8):549–55. https://www.nejm.org/doi/pdf/10.1056/NEJM199908193410801.
71. Calvo R, Obregón M, del Rey F, de Escobar G. The rat placenta and the transfer of thyroid hormones from the mother to the fetus. Effects of maternal thyroid status. Endocrinology. 1992;131(1):357–65. https://watermark.silverchair.com/endo0357.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAcAwggG8BgkqhkiG9w0BBwaggGtMIIBqQIBADCCAaIGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMmaqVeYWTFpFt5BmQAgEQgIIBc_AM6arFgUZbj9gsCkACNjY4EaKWQYzvaBjBokCLLCJgUF.
72. Smit BJ, Kok JH, Vulsma T, Briët JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. Acta Paediatr Int J Paediatr. 2000;89(3):291–5.

73. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol (Oxf). 2010;72(6):825–9.
74. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf). 1999;50(2):149–55. http://www.ncbi.nlm.nih.gov/pubmed/10396355.
75. Den Ouden A, Kok J, Verkerk P, Brand R, Verloove-Vanhorick S. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. Pediatr Res. 1996;39(1):142–5. http://ovidsp.tx.ovid.com/sp-3.31.1b/ovidweb.cgi?&S=PCKGFPLMEFDDLHBGNCEKHFLBHGHLAA00&Link+Set=S.sh.22%7C1%7Csl_10.
76. Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med. 1996;334(13):821–7. http://www.nejm.org/doi/abs/10.1056/NEJM199603283341303.
77. Vulsma T, Kok J. Prematurity-associated neurologic and developmental abnormalities and neonatal thyroid function. Editorial. N Engl J Med. 1996;334(13):857–8. https://www.nejm.org/doi/pdf/10.1056/NEJM199603283341310.
78. Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis AJ, Neil J, et al. Volpe's neurology of the newborn, 6th ed. Philadelphia, PA: Elsevier Inc.; 2017. https://www.us.elsevierhealth.com/volpes-neurology-of-the-newborn-9780323428767.html#panel1.
79. Pop VJ, Brouwers EP, Vader HL, Vulsma T, Van Baar AL, De Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 2003;59(3):282–8.
80. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab. 2004;89(12):6054–60.
81. Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forns J, Garcia-Esteban R, et al. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. Epidemiology. 2013;24(1):150–7.
82. Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid. 2009;19(5):511–9. http://www.liebertonline.com/doi/abs/10.1089/thy.2008.0341.
83. Contempré B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, de Escobar G. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. J Clin Endocrinol Metab. 1993;17(6):1719–22. https://www.ncbi.nlm.nih.gov/pubmed/?term=Detection+of+thyroid+hormones+in+human+embryonic+cavities.
84. Delange F. Endemic cretinism. In: Werner SC, Ingbar SH, Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 7th ed. Philadelphia, PA: Lippincott-Raven; 1996. p. 756–67.
85. Foley T. Congenital hypothyroidism. In: Werner SC, Ingbar SH, Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 7th ed. Philadelphia, PA: Lippincott-Raven; 1996. p. 988–94.
86. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab. 2010;95(9):4227–34.
87. Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ. Neonatal effects of maternal hypothyroxinemia during early pregnancy. Pediatrics. 2006;117(1):161–7.
88. Mirabella G, Westall CA, Asztalos E, Perlman K, Koren G, Rovet J. Development of contrast sensitivity in infants with prenatal and neonatal thyroid hormone insufficiencies. Pediatr Res. 2005;57(6):902–7.
89. Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VWV, Visser TJ, Visser W, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatr Res. 2011;69(5 PART 1):454–9.
90. Brent G. The molecular basis of thyroid hormone action. N Engl J Med. 1994;331(13):846–51. https://www.nejm.org/doi/pdf/10.1056/NEJM199409293311306.
91. Glinoer D, Riahi M, Grun J, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab. 1994;79(1):197–204.
92. Oken E, Braverman LE, Platek D, Mitchell ML, Lee SL, Pearce EN. Neonatal thyroxine, maternal thyroid function, and child cognition. J Clin Endocrinol Metab. 2009;94(2):497–503.
93. Chevrier J, Harley KG, Kogut K, Holland N, Johnson C, Eskenazi B. Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age. J Thyroid Res. 2011;2011.

94. Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, et al. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. J Clin Endocrinol Metab. 2012;97(1):22–8.
95. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med. 2017;376(9):815–25. https://www.nejm.org/doi/10.1056/NEJMoa1606205?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov.
96. Lavado-Autric R, Ausó E, García-Velasco JV, Del Carmen Arufe M, Escobar del Rey F, Berbel P, et al. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest. 2003;111(7):1073–82. https://www.jci.org/articles/view/16262.
97. Ausó E, Lavado-Autric R, Cuevas E, Escobar Del Rey F, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology. 2004;145(9):4037–47.
98. Cherella CE, Wassner AJ. Congenital hypothyroidism: insights into pathogenesis and treatment. Int J Pediatr Endocrinol. 2017;2017(11):1–8. http://ijpeonline.biomedcentral.com/articles/10.1186/s13633-017-0051-0.
99. Deladoëy J, Ruel J, Giguère Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? a 20-year retrospective population-based study in Québec. J Clin Endocrinol Metab. 2011;96(8):2422–9.
100. Olivieri A, Fazzini C, Medda E, Hypothyroidism TISG for C. Multiple factors influencing the incidence of congenital hypothyroidism detected by neonatal screening. Horm Res Paediatr. 2015;83(2):86–93.
101. Wassner AJ, Brown RS. Congenital hypothyroidism: recent advances. Curr Opin Endocrinol Diabetes Obes. 2015;22(5):407–12.
102. Lanting CI, van Tijn DA, Loeber JG, Vulsma T, de Vijlder JJM, Verkerk PH. Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. pediatrics. 2005;116(1):168–73. http://pediatrics.aappublications.org/content/116/1/168..info.
103. Van Tijn DA, De Vijlder JJM, Verbeeten B, Verkerk PH, Vulsma T. Neonatal detection of congenital hypothyroidism of central origin. J Clin Endocrinol Metab. 2005;90(6):3350–9.
104. Fisher DA, Dussault JH, Foley TP, Klein AH, LaFranchi S, Larsen PR, et al. Screening for congenital hypothyroidism: results of screening one million North American infants. J Pediatr. 1979;94(5):700–5.
105. Hanna CE, Krainz PL, Skeels MR, Miyahira RS, Sesser DE, LaFranchi SH. Detection of congenital hypopituitary hypothyroidism: ten-year experience in the Northwest Regional Screening Program. J Pediatr. 1986;109(6):959–64.
106. Persani L. Central hypothyroidism: pathogenic, diagnostic and therapeutic challenges. J Clin Endocrinol Metab. 2012;97(9):3068–78.
107. Nebesio TD, McKenna MP, Nabhan ZM, Eugster EA. Newborn screening results in children with central hypothyroidism. J Pediatr. 2010;156(6):990–3. http://dx.doi.org/10.1016/j.jpeds.2009.12.011.
108. Ford G, Lafranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab. 2014;28(2):175–87. http://dx.doi.org/10.1016/j.beem.2013.05.008.
109. Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT. Recent advances in central congenital hypothyroidism. J Endocrinol. 2015;227(3):R51–71.
110. Sun Y, Bak B, Schoenmakers N, Van Trotsenburg ASP, Oostdijk W, Voshol P, et al. Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. Nat Genet. 2012;44(12):1375–81. http://dx.doi.org/10.1038/ng.2453.
111. Persani L, Bonomi M. The multiple genetic causes of central hypothyroidism. Best Pract Res Clin Endocrinol Metab. 2017;31(2):255–63. http://dx.doi.org/10.1016/j.beem.2017.04.003.
112. New England Congenital Hypothyroidism Collaborative. Elementary school performance of children with congenital hypothyroidism. New England Congenital Hypothyroidism Collaborative. J Pediatr. 1990;116(1):27–32. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med3&AN=2295961%; http://202.120.227.56:3210/sfxlcl3?sid=OVID:medline&id=pmid:2295961&id=doi:&issn=0022-3476&isbn=&volume=116&issue=1&spage=27&pages=27-32&date=1990&title=Journal+of+Ped.
113. Ilicki A, Larsson A. Psychological development at 7 years of age in children with congenital hypothyroidism: timing and dosage of initial treatment. Acta Paediatr Scand. 1991;80(2):199–204. https://www.ncbi.nlm.nih.gov/pubmed/?term=Psychological+development+at+7+years+of+age+in+children+with+congenital+hypothyroidism%3A+Timing+and+dosage+of+initial+treatment.
114. Glorieux J, Dussault J, Van Vliet G. Intellectual development at age 12 years of children with congenital hypothyroidism diagnosed by neonatal screening. J Pediatr. 1992;121(4):581–4. https://www.sciencedirect.com/science/article/pii/S0022347605811503?via%3Dihub#aep-article-footnote-id1.
115. Kooistra L, Laane C, Vulsma T, Schellekens JM, van der Meere JJ, Kalverboer AF. Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the

effects of neonatal treatment. J Pediatr. 1994;124 (6):903–9.
116. Simons WF, Fuggle PW, Grant DB, Smith I. Intellectual development at 10 years in early treated congenital hypothyroidism. Arch Dis Child. 1994;71(3):232–4.
117. Rovet JF, Ehrlich RM. Long-term effects of L-thyroxine therapy for congenital hypothyroidism. J Pediatr. 1995;126(3):380–6.
118. Heyerdahl S. Treatment variables as predictors of intellectual outcome in children with congenital hypothyroidism. Eur J Pediatr. 1996;155(5):357–61. http://www.ncbi.nlm.nih.gov/pubmed/8741030.
119. Bargagna S, Canepa G, Costagli C, Dinetti D, Marcheschi M, Millepiedi S, et al. Neuropsychological follow-up in early-treated congenital hypothyroidism: a problem-oriented approach. Thyroid. 2000;10(3):243–9.
120. Rovet J, Ehrlich R, Sorbara D. Intellectual outcome in children with fetal hypothyroidism. J Pediatr. 1987;110(5):700–4.
121. Fuggle PW, Grant DB, Smith I, Murphy G. Intelligence, motor skills and behaviour at 5 years in early-treated congenital hypothyroidism. Eur J Pediatr. 1991;150(8):570–4. https://www.ncbi.nlm.nih.gov/pubmed/?term=Intelligence%2C+motor+skills+and+behaviour+at+5+years+in+early-treated+congenital+hypothryoidism.
122. Rovet JF, Ehrlich RM, Sorbara DL. Neurodevelopment in infants and preschool children with congenital hypothyroidism: etiological and treatment factors affecting outcome. J Pediatr Psychol. 1992;17(2):187–213.
123. Simons WF, Fuggle PW, Grant DB, Smith I. Educational progress, behaviour, and motor skills at 10 years in early treated congenital hypothyroidism. Arch Dis Child. 2007;1997:219–22.
124. LaFranchi S. Congenital hypothyroidism: a newborn screening success story? Endocrinologist. 1994;4(6):477–86.
125. Lain SJ, Bentley JP, Wiley V, Roberts CL, Jack M, Wilcken B, et al. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diabetes Endocrinol. 2016;4(9):756–65. http://dx.doi.org/10.1016/S2213-8587(16)30122-X.
126. Walstad P, Gates C, Carlson E. Struma lymphomatosa (Hashimoto' s disease). Calif Med. 1951; 74(1):31–5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1520811/pdf/califmed00235-0033.pdf.
127. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4–5):391–7. http://dx.doi.org/10.1016/j.autrev.2014.01.007.
128. Sinclair D. Clinical and laboratory aspects of thyroid autoantibodies. Annu Clin Biochem. 2006;43:173–83 http://journals.sagepub.com/doi/pdf/10.1258/000456306776865043.
129. Bothra N, Shah N, Goroshi M, Jadhav S, Padalkar S, Thakkar H, et al. Hashimoto's thyroiditis: relative recurrence risk ratio and implications for screening of first-degree relatives. Clin Endocrinol (Oxf). 2017;87(2):201–6.
130. Mincer DL, Jialal I. Thyroid, hashimoto thyroiditis. StatPearls Publ. 2017;(November 16). https://www.ncbi.nlm.nih.gov/books/NBK459262/.
131. Parvathaneni A, Fischman D, Cheriyath P. Hashimoto' s thyroiditis. In: Springer D, editor. A new look at hypothyroidism; 2012. p. 46–60. http://www.intechopen.com/books/a-new-look-at-hypothyroidism/hashimoto-s-disease.
132. Zaletel K, Gaberscek S. Hashimotos thyroiditis: from genes to the disease. Curr Genomics. 2011;12 (8):576–88. http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1389-2029&volume=12&issue=8&spage=576.
133. Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. Epidemiol Clin Decis Mak. 1997;26(1):189–218.
134. Staii A, Mirocha S, Todorova-Koteva K, Glinberg S, Jaume JC. Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state. Thyroid Res. 2010;3 (1):1–7.
135. Brix TH, Kyvik KO, Hegedüs L. A population-based study of chronic autoimmune hypothyroidism in Danish twins. J Clin Endocrinol Metab. 2000;85(2):536–9.
136. Hari Kumar KVS, Modi K. Twins and endocrinology. Indian J Endocrinol Metab. 2014;18(1):S48–52. http://www.ijem.in/text.asp?2014/18/7/48/145074.
137. Villanueva R, Greenberg DA, Davies TF, Tomer Y. Sibling recurrence risk in autoimmune thyroid disease. Thyroid. 2003;13(8):761–4. http://www.liebertonline.com/doi/abs/10.1089/105072503768499653.
138. Marwaha RK, Sen S, Tandon N, Sahoo M, Walia RP, Singh S, et al. Familial aggregation of autoimmune thyroiditis in first-degree relatives of patients with juvenile autoimmune thyroid disease. Thyroid. 2003;13(3):297–300. http://www.liebertonline.com/doi/abs/10.1089/105072503321582114.
139. Nussinovitch U, Shoenfeld Y. The role of gender and organ specific autoimmunity. Autoimmun Rev. 2012;11(6–7):377–85.
140. Gómez López E, Nso-Roca AP, Juste Ruiz M, Cortés Castell E. Enfermedad de Hashimoto en una cohorte de 29 niños y adolescentes. Epidemiología, evolución y comorbilidad a corto y largo plazo. Arch Argent Pediatr. 2018;116(1):56–8. http://www.sap.org.ar/docs/publicaciones/archivosarg/2018/v116n1a17.pdf.
141. Zeitlin AA, Simmonds MJ, Gough SCL. Genetic developments in autoimmune thyroid disease: an evolutionary process. Clin Endocrinol (Oxf). 2008;68(5):671–82.

142. Tomer Y, Huber A. The eitiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun. 2009;32(3–4):1–22. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3561494/pdf/nihms118814.pdf.
143. Janeway CAJ, Travers P, Walport M, Shlomchik M. The major histocompatibility complex and its functions. In: Immunobiology: the immune system in health and disease, 5th ed. New York: Garland Science; 2001. https://www.ncbi.nlm.nih.gov/books/NBK27156/.
144. Huang H, Li X, Lin L, Shi Y, Lin X, Li L, et al. Upregulation of thyroid transcription factor-1 and human leukocyte antigen class I in Hashimoto's disease providing a clinical evidence for possible triggering autoimmune reaction. Eur J Endocrinol. 2011;164(5):795–800.
145. Bottazzo GF, Dean BM, McNally JM, MacKay EH, Swift PG, Gamble DR. In situ characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. N Engl J Med. 1985;313(6):353–60. https://www.nejm.org/doi/pdf/10.1056/NEJM198508083130604.
146. Singer D, Kohn L, Zinger H, Mozes E. Methimazole prevents induction of experimental systemic lupus erythematosus in mice. J Immunol. 1994;153:873–80. http://www.jimmunol.org/content/153/2/873.short.
147. Longhi MS, Ma Y, Mieli-Vergani G, Vergani D. Aetiopathogenesis of autoimmune hepatitis. J Autoimmun. 2010;34(1):7–14. http://dx.doi.org/10.1016/j.jaut.2009.08.010.
148. Tokić S, Štefanić M, Karner I, Glavaš-Obrovac L. Altered expression of CTLA-4, CD28, VDR, and CD45 mRNA in T cells of patients with Hashimoto's thyroiditis—a pilot study. Endokrynol Pol. 2017;68(3):274–82. https://www.researchgate.net/publication/318022377_Altered_expression_of_CTLA-4_CD28_VDR_and_CD45_mRNA_in_T_cells_of_patients_with_Hashimoto's_thyroiditis_-_a_pilot_study.
149. Narooie-Nejad M, Taji O, Kordi Tamandani DM, Kaykhaei MA. Association of CTLA-4 gene polymorphisms −318C/T and +49A/G and Hashimoto's thyroidits in Zahedan, Iran. Biomed Reports. 2017;6(1):108–12. https://www.spandidos-publications.com/.
150. McLachlan SM, Rapoport B. Why measure thyroglobulin autoantibodies rather than thyroid peroxidase autoantibodies? Thyroid. 2004;14(7):510–20.
151. Burn GL, Svensson L, Sanchez-Blanco C, Saini M, Cope AP. Why is PTPN22 a good candidate susceptibility gene for autoimmune disease? FEBS Lett. 2011;585(23):3689–98. http://dx.doi.org/10.1016/j.febslet.2011.04.032.
152. Hu S, Rayman MP. Multiple nutritional factors and the risk of hashimoto's thyroiditis. Thyroid. 2017;27(5):597–610. http://online.liebertpub.com/doi/10.1089/thy.2016.0635.
153. Duntas LH. Facteurs environnementaux et auto-immunité thyroïdienne. Ann Endocrinol (Paris). 2011;72(2):108–13. http://dx.doi.org/10.1016/j.ando.2011.03.019.
154. Effraimidis G, Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. Eur J Endocrinol. 2014;170(6).
155. Köhrle J. Selenium and the thyroid. Curr Opin Endocrinol Diabetes Obes. 2015;22(5):392–401.
156. Ravanbod M, Asadipooya K, Kalantarhormozi M, Nabipour I, Omrani GR. Treatment of iron-deficiency anemia in patients with subclinical hypothyroidism. Am J Med. 2013;126(5):420–4. http://dx.doi.org/10.1016/j.amjmed.2012.12.009.
157. Barbesino G. Drugs affecting thyroid function. Thyroid. 2010;20(7):763–70. http://www.liebertonline.com/doi/abs/10.1089/thy.2010.1635.
158. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology. 2006;43(4):661–72.
159. Tomer Y, Blackard JT, Akeno N. Interferon alpha treatment and thyroid dysfunction. Endocrinol Metab Clin North Am. 2007;36(4):1051–66.
160. Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J. 2009;6.
161. Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab. 2009;23(6):723–33. http://dx.doi.org/10.1016/j.beem.2009.06.002.
162. van Melick EJM, Wilting I, Meinders AE, Egberts TCG. Prevalence and determinants of thyroid disorders in elderly patients with affective disorders: lithium and nonlithium patients. Am J Geriatr Psychiatry. 2010;18(5):395–403. http://dx.doi.org/10.1097/JGP.0b013e3181c6584e.
163. Chiu CC, Shen WW, Chen KP, Lu ML. Application of the Cockcroft-Gault method to estimate lithium dosage requirement. Psychiatry Clin Neurosci. 2007;61(3):269–74.
164. Ross DS. Radioiodine therapy for hyperthyroidism—NEJMct1007101. 2011;19(2):1–12. http://www.nejm.org/doi/pdf/10.1056/NEJMct1007101.
165. Hyer S, Pratt B, Newbold K, Hamer C. Outcome of pregnancy after exposure to radioiodine in utero. Endocr Pract. 2011;(aop):1–10. http://journals.aace.com/doi/abs/10.4158/EP10237.RA.
166. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Front Immunol. 2017;8(May).
167. Li Y, Bai Y, Liu Z, Ozaki T, Taniguchi E, Mori I, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. Pathol Int. 2009;59(9):636–41.
168. Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. J Clin Endocrinol Metab. 2012;97(2):334–42.
169. Caturegli P, De Remigis A, Chuang K, Dembele M, Iwama A, Iwama S. Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records.

Thyroid. 2013;23(2):142–50. http://online.liebertpub.com/doi/abs/10.1089/thy.2012.0554.
170. De Luca F, Santucci S, Corica D, Pitrolo E, Romeo M, Aversa T. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. Ital J Pediatr. 2013;39(1):1.
171. Caturegli P, Ruggere C. Thyroid history: Karl Hürthle! Now, who was he? Thyroid. 2005;15 (2):121–3.
172. Iannaci G, Luise R, Sapere P, Coluccino V, Ronchi A, Faggiano A, et al. Fibrous variant of Hashimoto's thyroiditis as a diagnostic pitfall in thyroid pathology. Case Rep Endocrinol. 2013;2013:308908. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3870128&tool=pmcentrez&rendertype=abstract.
173. Luiz HV, Gonçalves D, Silva TN da, Nascimento I, Ribeiro A, Mafra M, et al. IgG4-related Hashimoto's thyroiditis—a new variant of a well known disease. Arq Bras Endocrinol Metabol. 2014;58 (8):862–8. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302014000800862&lng=en&tlng=en.
174. Alexander I, Eckhart H, Hahn G, Strobel D. Hashitoxicosis—three cases and a review of the literature. Eur Endocrinol. 2008;4:70. http://www.touchendocrinology.com/articles/hashitoxicosis-three-cases-and-review-literature.
175. Donner H, Braun J, Seidl C, Rau H. Codon 17 polymorphism of the cytotoxic T lymphocyte antigen 4 gene in Hashimoto's thyroiditis and Addison's disease. J Clin Endocrinol Metab. 1997;82(12):4130–2. http://jcem.endojournals.org/content/82/12/4130.short.
176. Braun J, Donner H, Siegmund T, Walfish PG, Usadel KH, Badenhoop K. CTLA-4 promoter variants in patients with Graves' disease and Hashimoto's thyroiditis. Tissue Antigens. 1998;51 (5):563–6.
177. Yagyu H, Okada K, Sato S, Yamashita Y, Okada N, Osuga JI, et al. Pegylated interferon-α2b and ribavirin combination therapy induces Hashitoxicosis followed by type 1 diabetes mellitus. Diabetes Res Clin Pract. 2012;95(3):e52–4. http://dx.doi.org/10.1016/j.diabres.2011.11.016.
178. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med. 2015;13(1):1–14. http://dx.doi.org/10.1186/s12916-015-0455-8.
179. Sharma R, Di Dalmazi G, Caturegli P. Exacerbation of autoimmune thyroiditis by CTLA-4 blockade: a role for IFNγ-induced indoleamine 2, 3-dioxygenase. Thyroid. 2016;26(8):1117–24. http://online.liebertpub.com/doi/10.1089/thy.2016.0092.
180. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet. 1966;307:512.
181. Liyanage CK, Munasinghe TMJ, Paramanantham A. Steroid-responsive encephalopathy associated with autoimmune thyroiditis presenting with fever and confusion. Case Rep Neurol Med. 2017;2017:1–4. https://www.hindawi.com/journals/crinm/2017/3790741/.
182. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. J Neurol Sci. 2004;217 (2):165–8.
183. Zhou JY, Xu B, Lopes J, Blamoun J, Li L. Hashimoto encephalopathy: literature review. Acta Neurol Scand. 2017;135(3):285–90.
184. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? Arch Neurol. 2003;60:164–71. https://jamanetwork.com/journals/jamaneurology/fullarticle/783630.
185. Mocellin R, Walterfang M, Velakoulis D. Hashimoto' s encephalopathy epidemiology, pathogenesis and management. CNS Drugs. 2007;21 (10):799–811.
186. Monti G, Pugnaghi M, Ariatti A, Mirandola L, Giovannini G, Scacchetti S, et al. Non-convulsive status epilepticus of frontal origin as the first manifestation of Hashimoto's encephalopathy. Epileptic Disord. 2011;13(3):253–8.
187. Menon V, Subramanian K, Thamizh J. Psychiatric presentations heralding Hashimoto's encephalopathy: a systematic review and analysis of cases reported in literature. J Neurosci Rural Pract. 2017;8 (2):261–7. https://www.ncbi.nlm.nih.gov/pubmed/28479803/.
188. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–751. http://online.liebertpub.com/doi/abs/10.1089/thy.2014.0028.
189. Ventura M, Melo M, Carrilho F. Selenium and thyroid disease: from pathophysiology to treatment. Int J Endocrinol. 2017;2017.
190. McManus C, Luo J, Sippel R, Chen H. Is thyroidectomy in patients with Hashimoto thyroiditis more risky? J Surg Res. 2012;178(2):529–32.
191. Laurent C, Capron J, Quillerou B, Thomas G, Alamowitch S, Fain O, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): characteristics, treatment and outcome in 251 cases from the literature. Autoimmun Rev. 2016;15(12):1129–33. http://dx.doi.org/10.1016/j.autrev.2016.09.008.
192. Leyhe T, Müssig K, Weinert C, Laske C, Häring HU, Saur R, et al. Increased occurrence of weaknesses in attention testing in patients with Hashimoto's thyroiditis compared to patients with other thyroid illnesses. Psychoneuroendocrinology. 2008;33(10):1432–6.
193. Leyhe T, Ethofer T, Bretscher J, Künle A, Säuberlich AL, Klein R, et al. Low performance in attention testing is associated with reduced grey

matter density of the left inferior frontal gyrus in euthyroid patients with Hashimoto's thyroiditis. Brain Behav Immun. 2013;27(1):33–7. http://dx.doi.org/10.1016/j.bbi.2012.09.007.

194. Koros C, Economou A, Mastorakos G, Bonakis A, Kalfakis N, Papageorgiou SG. A selective memory deficit caused by autoimmune encephalopathy associated with Hashimoto thyroiditis. Cogn Behav Neurol. 2012;25(3):144–8. https://journals.lww.com/cogbehavneurol/fulltext/2012/09000/A_Selective_Memory_Deficit_Caused_by_Autoimmune.6.aspx.
195. Giannouli V, Toulis KA, Syrmos N. Cognitive function in Hashimoto' s thyroiditis under levothyroxine treatment. Hormones (Athens). 2014;13(3):430–3.
196. Quinque EM, Karger S, Arélin K, Schroeter ML, Kratzsch J, Villringer A. Structural and functional MRI study of the brain, cognition and mood in long-term adequately treated Hashimoto's thyroiditis. Psychoneuroendocrinology. 2014;42:188–98.
197. Bektas Uysal H, Ayhan M. Autoimmunity affects health-related quality of life in patients with Hashimoto's thyroiditis. Kaohsiung J Med Sci. 2016;32(8):427–33. http://dx.doi.org/10.1016/j.kjms.2016.06.006.
198. Promberger R, Hermann M, Pallikunnel SJ, Seemann R, Meusel M, Ott J. Quality of life after thyroid surgery in women with benign euthyroid goiter: influencing factors including Hashimoto's thyroiditis. Am J Surg. 2014;207(6):974–9. http://dx.doi.org/10.1016/j.amjsurg.2013.05.005.

Chapter 26

Neuropsychological Functioning of Endocrinology Disorders: Gonadotropic Hormones and Corticosteroids

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The sex hormones and corticosteroids influence neuroelectrophysiology, neuroanatomy, and cognition [1–3] through their interaction with a variety of brain structures, particularly the hippocampus [2, 4]. Normative levels of estrogen and testosterone as well as homeostatic levels of corticosteroids are required for optimal cognitive functioning. The present review will focus on the neuropsychological sequelae of conditions resulting from elevated or insufficient levels of the primary sex hormones and corticosteroids as well as post-treatment neuropsychological response.

Sex Hormones

Overview of Sex Hormones

Estrogen and testosterone are the two primary sex hormones that influence neurons, brain structures, and cognition. Clinically low levels of each are relatively common in different medical conditions. For example, menopause is a normative developmental process for older women, although 20% of postmenopausal women receive hormone replacement therapy (HRT) [5]. Of men 70 years or older, 68% meet criteria for hypogonadism [6]. Estrogen and testosterone each can influence neurons as neuromodulators and permanently change synapse structure [7]. Each hormone binds to estradiol, androgen, and aromatase receptors that are located in brain regions associated with learning and memory, notably, the hippocampus, amygdala, and prefrontal cortex [1]. The neurocognitive profiles of individuals with low estrogen and testosterone levels will be summarized along with the effects of estrogen hormone replacement therapy (HRT) and testosterone supplementation on cognition. Two of the most common sex hormone abnormalities, characterized by clinically low levels of estrogen and testosterone, Turner syndrome (TS) in females [7] and Klinefelter syndrome (KS) in males [8, 9] will also be reviewed.

Estrogen

Estrogen impacts cognition via the hippocampus and its effect on synapse formation, cell morphology, cell signaling, and neuronal excitability [2]. Estrogen increases neural spine density in the rat hippocampus; correspondingly, ovariectomy decreases the density of hippocampal dendritic spines [10]. Estrogen's effect on synaptic density may be moderated by age, in that it promotes

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brain density in younger, but not older, rats [11]. Congruently, administration of estradiol to ovariectomized monkeys increases synaptic density in the hippocampus by up to 35% [12]. In rodents, estrogen impacts neurotransmitters and electrophysiology by activating cell signaling in hippocampal neurons [13]. Memory consolidation is enhanced through long-term potentiation of NMDA receptors and cholinergic systems [2, 14]. However, like dendritic density, age moderates memory improvement. Following estrogen administration, memory improvement occurs only in younger, but not older, rats [15, 16].

To date, study of hormone replacement therapy (HRT) and cognitive skills in aging women shows variable results. Only 45% of studies find a positive or protective effect of HRT on memory in meta-analysis [17]. However, multiple factors may have affected this low rate of efficaciousness. First, self-selection bias of women who choose HRT occurs; generally healthier women with higher education and socioeconomic levels select this option, all of which are protective factors against age-related cognitive decline [18]. Second, few studies assess or control the effect of age such that developmental confounds may occur with test ceiling effects. Many studies use cognitive screening measures such as the Mini-Mental Status Exam (MMSE) that do not adequately quantify abilities of individuals that are largely intact [17]. Younger women prescribed HRT may perform so well on cognitive screens that a ceiling effect can attenuate a relation between HRT and cognition [17]. Finally, the composition and dose of hormonal replacement is different across HRT regimens; some women are prescribed HRT of only estrogen, while others receive both estrogen and progesterone. Further, different types of HRT are often combined and compared to a "never-treated" group [18]. In short, randomized clinical trials (RCTs) of HRT may provide a more accurate picture of estrogen effects on women's cognition than meta-analysis.

Randomized trials reveal a range of improved cognitive abilities following hormone replacement. Generally, better verbal memory and learning is the most consistent finding following HRT [4, 19–23]. Better executive functioning [24], nonverbal reasoning, visuospatial and visuomotor skills [4, 25], and general cognitive functioning [26] are also reported. Longitudinal investigations find better verbal memory and fluency too [27–31], along with better visual memory [32], nonverbal reasoning [29, 30], attention/speed [33], and general cognitive ability [30, 33, 34]. Most notably, HRT cognitive improvement is found during a time in life when these skills otherwise typically decline.

One of the first RCTs to show maintenance of verbal memory abilities over time utilized intramuscular (IM) administration of estradiol valerate [35]. Women awaiting hysterectomy and ovariectomy received neuropsychological tests preoperatively; following surgery, women randomly received either estradiol valerate, testosterone, estradiol and testosterone, or placebo [35]. Women with any of the hormonal treatments maintained verbal memory postoperatively, while women on placebo showed a decline in skills [35]. Results were confirmed and extended to short- and long-term verbal memory with IM estradiol valerate in an additional RCT [36]. Others find that transdermal estradiol alone relates to better visual memory and spatial ability [37], and orally administered estradiol combined with progesterone relates to better verbal memory in postmenopausal women [25].

Despite these initial RCT outcomes, many other trials reveal inconsistent results. For example, several RCTs failed to find improved memory with HRT. Five of these studies used conjugated equine estrogen (CEE) [38–42], suggesting that different HRTs may be associated with differential memory outcomes. Additionally, three of the investigations [39–41] did not assess verbal memory, the primary cognitive ability most reliably related to improvement with estrogen [17, 18]. Finally, three of the RCTs studied older women who likely were menopausal at least several years prior to investigation [38–40].

Alzheimer Disease and HRT in Women

Women with Alzheimer disease (AD) have lower base rates of estradiol [17]. Epidemiological

studies show HRT buffers against development of Alzheimer disease (AD), despite heterogeneous methods including self-report of HRT, inclusion of women with early dementia, and failure to assess or to control for education level and history of HRT use. All of these factors are known to be influential confounds with cognitive outcomes [43]. Nevertheless, despite these wide-ranging potential confounds, results show that women with HRT experience a protective effect on verbal memory, language, and global cognition [17] which could have public health ramifications. Careful control of educational and socioeconomic status will be important in future studies.

Randomized clinical trials with AD women provide the most methodologically stringent tests of HRT effects. The Hogervorst et al. meta-analyses identified experimental studies of HRT effects on dementia [17] and five double-blind placebo-controlled trials of post-menopausal women with dementia [44]. HRT consisted of both conjugated equine estrogens and estradiol. Positive effects were found on global cognitive functioning and selected tests of verbal delayed recall, quantitative working memory, and speed of information processing; no significant effects were found for visual memory or general language [44]. Interestingly, the two Hogervorst [17, 44] analyses found inconsistent duration effects; some cognitive improvements became significant after a length of time, while others lost significance with elapsed time. The reason for this difference is unclear.

One RCT in particular warrants attention given its large scale and surprising results. The Women's Health Initiative Memory Study (WHIMS) is arguably the most influential investigation of HRT effects on cognition in women to date. The WHIMS was a multicenter, randomized, double-blind, placebo-controlled clinical trial which assigned CEE, CEE + medroxyprogesterone, and placebo treatments to 7,510 women 65 years of age and older [45]. Contrary to hypotheses, the WHIMS investigation found that HRT significantly increased the risk of dementias of any cause but not mild cognitive impairment [45].

Varying RCT results have spurred discussion about a potential "critical period" of HRT benefit on cognitive function. Initiation of HRT temporally near the time of menopause yields beneficial memory effects, while initiation after the age of 65 appears to result in diminished memory or, according to the WHIMS HRT, an increased risk of dementia [18, 45–47]. Results of human trials appear buttressed by the comparative literature which indicates that HRT effects on synaptic density [11] and the cholinergic system of the hippocampus [15] are moderated by age. A prospective descriptive study highlights this relation. Initiation of HRT after the age of 64 correlated with a higher risk of AD, whereas initiation prior to the age of 64 correlated with decreased risk [48]. A second study also found less cognitive decline with HRT initiated during menopause versus later [33]. Finally, RCTs in women younger than 65 years of age show that six of six studies find gains in verbal memory in treatment, but not placebo, groups [46]. In contrast, RCTs of women aged 65 years and older yield discrepant results [18, 46], possibly due to critical period theory. At this point, critical period theory remains the most universally accepted explanation for discrepant HRT results in the literature.

Turner Syndrome

Turner syndrome (TS; karyotype X0) is a sex chromosome abnormality in females characterized by the absence of all or part of one X chromosome. TS is a relatively common genetic disorder that occurs in 1 of every 2,500 live female births [7]. TS results in distinct physical and neuropsychological profiles [7] including short stature, gonadal dysgenesis and subsequent low estrogen levels, difficulties in nonverbal memory and reasoning, and diminished visuomotor and visuospatial skills [7, 49–52]. Thus far, it remains unclear if the TS neurocognitive profile relates to a genetic or endocrine underpinning or an interaction of the two [7]. A review of genetic contributions to the neurocognitive phenotype is beyond the scope of this chapter; refer instead to Ross et al. [7] or Zinn et al. [53].

The neurophysiological and neuroanatomical underpinnings of the TS neuropsychological profile are well described. TS produces atypical EEG patterns [54] and is related to volume reduction in predominantly right hemispheric brain structures, notably right parietal, temporal and occipital regions, the caudate nucleus, and the dorsolateral prefrontal cortex [7]. Some left hemisphere involvement is found in the left parietal–perisylvian region [7]. Neuropsychological investigations show corresponding deficits in spatial and nonverbal skills [51, 55, 56], specifically visual–spatial abilities and visual–perceptual abilities [51, 52, 55, 56], nonverbal memory [51, 57], visuospatial working memory [50, 58], and motor abilities [59], with significant arithmetic difficulties [60, 61]. Diminished executive functioning [52] and attention are also seen [55, 56, 62]. In contrast, the majority of studies show that general IQ, language, and verbal abilities are relatively unaffected by TS [63], although some investigations show minor difficulties in verbal abilities [56, 64], and minor depression in full-scale IQ scores, probably secondary to diminished nonverbal skills [55, 56, 59, 63]. Typically, a significant discrepancy exists between verbal and depressed performance IQ scores [56], thought to result from either poorer visual memory [65] or working memory deficits [66].

A closer look at the nonverbal difficulties associated with TS reveals diminished visual, spatial, and auditory working memory [52, 55–57]. Some investigations find equivalent deficits in visual and spatial aspects of working memory [67], while others suggest that the challenging components of nonverbal skills change across development [52, 56]. Girls with TS demonstrate difficulties in spatial relations [55] and motor-free visuospatial memory, while adolescents demonstrate difficulties in visuospatial working memory that has a motor component [56]. During late adolescence and emerging adulthood, deficits broaden and are seen in visual memory, working memory, visual–perceptual skills, spatial abilities, and visual–motor coordination [52].

Given known relations between memory and attention [68], it is not surprising that females with TS also experience significant difficulty in attentional skills; difficulties in visual and auditory attention are found in both youth and young adults [52, 56]. Specifically, errors of commission or increased impulsivity occurs in sustained attention tasks [56]. Attention deficit disorder (ADD) and ADHD diagnoses have an 18-fold increase in girls with TS compared to the general population [62].

Motor dysfunction is a well-described feature of TS from childhood through adulthood [52, 55, 59, 65]. A prospective investigation of TS from birth noted significant delays in walking [55]. Difficulties in visual–motor and perceptual–motor skills also are reported [55]. Motor development in 7- to 12-year olds shows difficulty in spatially mediated motor tasks [59]. Adolescents with TS do not increase their speed on motor tasks with age as expected. A “speed and accuracy tradeoff” [59] occurs such that efforts to increase speed result in more errors.

Given estrogen’s relation to speed and motor function [69] as well as the hippocampal and spatial abilities [2, 4], estrogen supplementation ameliorates motor delays [70, 71] via improvement in nonverbal speed and spatially mediated motor ability [70]. Women with TS also experience androgen insufficiency [72], which can affect cognition [73]. Androgen supplementation relates to improvements in verbal abilities, spatial cognition, executive functioning, and working memory [71]. Two years post-oxandrolone treatment, girls with TS maintain better executive function and verbal working memory [71].

Testosterone

Testosterone relates to increased concentrations of nerve growth factors in the hippocampus [74] and androgen plays a role in repairing hippocampal neurons after injury [75]. Studies show that androgen deprivation via gonadectomy in rats and non-human primates results in a 40–50% decrease in hippocampal synaptic density [76, 77], although testosterone replacement produces notable restoration [76].

Gonadectomized male rats treated with testosterone replacement show more efficient

operant [78] and classically conditioned learning skills [79, 80]. In humans, androgen deprivation therapy (ADT) or "chemical castration" reduces testosterone levels comparable to gonadectomy as an important component of prostate cancer treatment [81]. Dramatic decreases in testosterone, secondary to ADT, are associated with significant declines in visuomotor speed, in working memory reaction time, in sustained attention [82], and in spatial rotation abilities [83]. Discontinuation of ADT relates to improved verbal rote memory and general global cognitive ability [84]. ADT also relates to poorer verbal memory over longer intervals, suggesting that testosterone loss results in a steeper forgetting curve and difficulty in memory consolidation [85]. While several studies highlight the iatrogenic effects of ADT (82–85), others suggest a beneficial effect of ADT. Significant decline in bioavailable testosterone, noted during active ADT treatment, has also been found to relate to improved delayed object recall [82] and verbal memory [86].

One of the most common factors associated with low levels of serum testosterone is older age; 68% of men over 70 years of age can be characterized as hypogonadal based on bioavailable testosterone concentrations [6]. Higher testosterone levels among men of age 50 and older relate to better visual and verbal memory [87], delayed verbal recall, verbal learning, cognitive flexibility [88], and visuospatial functioning [87]. Men classified as hypogonadal have lower memory and visuospatial abilities and experience more rapid decline in visual memory. Higher levels of testosterone also relate to less decline in visual memory over time [87]. In older women, higher levels of endogenous testosterone relate to better global cognitive functioning [88]. However, in women the beneficial effect of testosterone is less reliable than the beneficial effect of estrogen, although there are fewer investigations of the former sex steroid than the latter. The relation between endogenous testosterone and cognitive functioning in older women warrants further investigation so that the gender by age by sex hormone interactions can be further studied.

Testosterone supplementation in hypogonadal men is associated with improved cognitive ability in a positive linear relation. Age appears to influence which cognitive abilities are improved by supplementary testosterone [86, 89]. Older hypogonadal men who received dihydrotestosterone (DHT) gel demonstrate improvements in spatial memory [86], while middle-aged hypogonadal men with supplementation exhibit better verbal fluency [89] and verbal memory [86], but not visuospatial ability [89]. Consistent with results in hypogonadal men, eugonadal older men with testosterone supplementation show memory improvement [41]. Moderate doses of testosterone supplementation are associated with modest improvements in verbal and spatial memory; however, smaller and larger doses show little to no gain in verbal or spatial memory [90], which suggests a quadratic or an inverted "u"-shaped relation [90].

A neuroprotective effect of testosterone is seen in Alzheimer disease (AD). On a cellular level, higher levels of testosterone are linked to lower plasma concentrations of B-amyloid peptide, the main component of "senile plaques" that characterize AD cognitive impairment [91]. The Baltimore Longitudinal Study of Aging found a lower free testosterone index or bioavailable serum testosterone in 574 men related to later diagnosis of AD after controlling for age, education, smoking history, body mass index, diabetes, cancer history, and hormonal supplements [92]. This protective relation is replicated across studies and ethnicities [93]. In older men with either mild cognitive impairment (MCI) or AD, weekly testosterone injections for those with lower to normal testosterone levels (15–20 nmol/L) showed a protective effect for spatial memory, constructional ability, and verbal memory; however, testosterone did not protect selective attention, divided attention, or language [18]. In contrast, two other studies with hypogonadal men diagnosed with MCI or AD failed to detect a testosteronebuffering effect [94, 95].

Testosterone supplements may exhibit differential cognitive protection for those with average testosterone levels versus those who are hypogonadal.

Klinefelter Syndrome

Youth born with Klinefelter syndrome (KS; XXY karyotype), a sex hormone abnormality defined by at least one additional X chromosome in phenotypic males, have low basal testosterone levels. Klinefelter syndrome affects 1 in 400–800 males [8, 9] and is the most frequently occurring sex hormone anomaly [96]. An additional X chromosome in males is responsible for infertility, gynecomastia, and small testes [96]. Klinefelter syndrome is associated with a distinct neuropsychological profile [9, 40, 97–105] and structural brain alterations [101, 106–108].

Males with Klinefelter syndrome show altered, or atypical, left hemispheric lateralization [101, 109], with a shift toward right hemisphere involvement and dominance [101]. MRI reveals smaller brain volumes [108, 110], enlarged lateral ventricles [108, 110], thinner cortex in the left inferior frontal, temporal, superior motor regions [110], and reduced amygdalar volumes [106]. A reduction in left temporal gray matter is found, although men who receive exogenous testosterone prior to or during puberty have less gray matter reduction [107]. Regardless of whether the origin is genetic or hormonal in nature [102], neuromorphological features may be partially responsible for a distinctive pattern of cognitive and learning difficulties [102, 107].

Klinefelter syndrome is associated with difficulties in language [9, 49, 97–104, 111], attention [102, 104, 105], executive function [49, 100, 105], and motor skills [102, 112]. General intellectual ability appears within normative limits [9, 102, 105]; however, several investigations reveal significantly weaker VIQ compared to PIQ [104, 111] and significant discrepancies between IQ and academic achievement [105]. Review of the neuropsychological and achievement sequelae of Klinefelter syndrome shows that language deficits are the most significant neurobehavioral difficulty [113]. Up to 77% experience difficulty in learning to read and require remedial reading assistance; 42% require speech therapy [113]. Significant and sustained language delays [114] are related to reading and spelling learning disabilities [9, 49, 97–99, 103, 104, 111], impaired language expression, verbal comprehension, and verbal processing speed [9, 49, 97–99, 103, 104, 111].

Boys with KS appear to demonstrate more impairments in linguistic competence such as semantics, syntax, and pragmatics [102] than in expressive or receptive language abilities [102]. On average, youth with KS score over 1 standard deviation below expectation on complex language skills such as expression and interpretation of intent, semantics, syntax, and pragmatics [102]. Contrary to expectation, adults with KS also have impaired language skills that are associated with right hemispheric function [115]. Given deficient left hemispheric functioning, right hemispheric function such as comprehension of affective prosody should be relatively unaffected; however, at least one investigation shows impairments on language tasks of emotional discrimination [115]. This counterintuitive phenomenon may reflect a bihemispheric deficit in integrated language processing [115]. Alternatively, difficulties in emotion-based language may reflect amygdala abnormalities [106]; KS is associated with reduced amygdalar volumes [106].

Executive and attentional impairments are found in children with KS who have problems with sustained attention [102] and impaired inhibitory processes [102, 105]. Youth [102] and adults [105] with KS demonstrate relative inability to inhibit irrelevant or distracting information [102, 104, 212]. Since attention is an important prerequisite for working memory, it is not surprising that working memory difficulties are also found [116].

Although verbal comprehension and processing difficulties remain stable before and after puberty, nonverbal performance abilities may worsen with puberty [103, 117, 118]. Future studies could benefit from careful delineation and statistical treatment of pubertal stage as well as

length of time post-pubertally. Age or pubertal status may moderate neurocognitive profiles. Evidence suggests that pre-pubertal boys may experience difficulties in sustained attention and post-pubertal boys show impaired language and motor skills [102]. Although pubertal effects are related to low testosterone levels, no changes follow hormonal supplementation [102]. Future investigation of testosterone supplementation, perhaps with a randomized clinical trial, could better determine which cognitive difficulties might be testosterone responsive.

Corticosteroids, Cushing Syndrome, and Addison Disease

Overview of Corticosteroids

Corticosteroids are hormones endogenously released by the adrenal cortex upon activation of the autonomic nervous system. As exogenous supplements, they are widely prescribed for their anti-inflammatory and immunosuppressive properties. Available evidence suggests that intact cognitive functioning relies on an "ideal" level of steroids, since both excessive and insufficient levels are related to cognitive difficulties [3].

The brain is a major target organ of corticosteroids [3]. Glucocorticoids and mineralocorticoids are the two primary types of corticosteroids [119], both of which have receptors in the hippocampus and are thought necessary for intact encoding of learned material [3, 119]. Elevated levels of glucocorticoids are consistently related to hippocampal damage [3], including neuroanatomical changes in the hippocampus such as loss of hippocampal volume and increased ventricular volume [120]. Sapolsky [120] generated the "glucocorticoid hypothesis" which posits that excessive, chronic release of glucocorticoids leads to reduction in glucocorticoid receptors in the hippocampus. As the number of receptors becomes too few, the hippocampal feedback system inhibits the adrenocortical axis and results in continuous glucocorticoid hypersecretion. Ultimately, continuous hypersecretion results in hippocampal neuronal necrosis or death [121]. More recently, however, several comparative studies suggest that chronically elevated levels of glucocorticoids result in declining function, but not death, of hippocampal neurons [3]. Reduced dendritic length in hippocampal neurons [122], altered dendritic shape [123], decreased plasticity [124], impaired long-term potentiation [125], and altered glucose or energy metabolism [126] all are associated with elevated corticosteroids.

The effects of both excessive and insufficient corticosteroids will be reviewed. Cognitive profiles related to elevated corticosteroids will be discussed as will the effects of exogenous steroids and Cushing syndrome (CS), a case of cortisol hypersecretion. Next, corticosteroid insufficiency will be reviewed with emphasis on Addison disease and adrenal insufficiency. Finally, effects from cessation of exogenous steroids and medical treatment of CS also will be addressed.

Effects of Administration of Exogenous Steroids

The cognitive sequelae of excessive corticosteroids are studied through short-term exogenous administration to healthy subjects in comparison to placebo. Elevated steroids relate to compromised verbal declarative memory, working memory, spatial reasoning skills, and error processing, in addition to dysphoria [127–133].

Individuals administered exogenous corticosteroids demonstrate verbal memory impairments [127]. Short courses of corticosteroids, such as a 5-day course of prednisone or a single dose of dexamethasone, result in more errors of commission, but not omission in verbal declarative memory [127]. Cortisol is posited to affect discrimination between relevant and irrelevant information in verbally mediated memory [127]. Further, a dose–response effect is found in verbal memory [128, 129]. A higher versus lower dose of cortisol relates to poorer verbal declarative memory; however, no dose effect is found on

nonverbal memory, attention, or executive skills [129]. Further, the corticosteroid-related memory suppression is reversible; differences disappear after a 6-day "washout period" [129]. Neuroelectric activity and mood may also be disrupted by corticosteroids. Prednisone given for 4 consecutive days produces greater right frontal EEG activity, more severe negative affect, and poorer memory recall, consistent with patterns seen in depression [130].

Beyond verbal declarative memory, other cognitive skills are affected by excessive exogenous cortisol [131]. Following a single cortisol dose, episodic memory errors increase along with amplitude of incorrectresponse event-related potentials (ERPs) [134]. Higher levels of hydrocortisone relate to poorer working memory but not to verbal declarative memory which may explain poorer memory consolidation versus acquisition of information [132].

An intriguing disparity is found between studies of corticosteroid memory suppression and improvements in cognitive performance [133, 135, 136]. Cortisol twice a day for 10 consecutive days causes improved spatial pattern recognition but also poorer spatial working memory and increased associative memory errors [133]. Verbal fluency and nonverbal attention may also improve [137]. Further, an age effect may exist. When cortisol is administered before a task of verbally mediated working memory, young men demonstrate impaired performance, whereas older participants maintain performance [137].

Meta-analysis suggests that timing of glucocorticoid administration may be important [136]. When corticosteroids are administered prior to a learning task, a nominal memory effect ($d = 0.08$) is found; when corticosteroids are administered prior to recall retrieval a significant decrease in memory performance is found ($d = –0.49$). Time of day of corticosteroid administration may also matter. Cortisol administered in the morning yields significant memory impairment ($d = –0.40$) versus its administration in the afternoon which relates to modest memory improvement ($d = 0.22$). Discrepancies in the literature may be reconciled in the future by inclusion of time of day of drug administration as a significant independent variable [136].

Cushing Syndrome

Cushing syndrome (CS) results from chronic exposure to excess endogenous glucocorticoids produced by the adrenal cortex [138]. Overproduction of corticosteroids can result from pituitary adenoma, a condition specifically referred to as Cushing disease (CD), or from a unilateral adrenocortical tumor, an extrapituitary tumor, or a bilateral adrenal hyperplasia or dysplasia [138]. CS results in fatigue, altered sleep, high blood pressure, glucose intolerance, proximal muscle weakness, menstrual irregularities, and growth retardation in children [138]. CS is also associated with a variety of neuroanatomical and neuropsychological sequelae including loss of brain volume [139], difficulties in verbal memory, diminished learning and IQ [140–142], problems with nonverbal skills [143, 144], and mood disorders, particularly depression [143, 144]. CS treatment includes surgical resection of pituitary adenoma, bilateral adrenalectomy for adrenal adenoma, and pituitary irradiation and thoracotomy for an ectopic ACTH-secreting tumor [138]. Several prospective, longitudinal studies of post-surgical memory status of CS patients show that cognitive deficits remain after surgical intervention but problems are attenuated [141, 142, 144, 145]. Regularly cooccurring depression, which can also be associated with cognitive impairments [146], does not correlate with learning problems [140, 142, 143, 147].

CS is related to loss of brain volume before surgical intervention in 83% of individuals with CD and 100% of individuals with CS [145]. Clinical estimates of brain volume loss are quantified on both CT and MRI scans [139, 145]. Loss of brain volume is related to greater third ventricle and bicaudate diameter [145] and is mediated by age [139]. A retrospective investigation compared perioperative CT scans for individuals with CS.

Loss of 1 SD in volume was found but only for individuals <25 years and those greater than 41 and less than 60 years [139]. Interestingly, loss of brain volume was partially reversible following restoration of eucortisolism post-surgically [145, 148]. CT and MRI scans conducted up to 40 months after surgical resection continued to show reduction of the third ventricle and bicaudate diameter but improvement on subjective estimates of brain volume [145]. After controlling for age, duration of disease, and months since surgery, comparison of MRI pre- and post-adenomectomy showed a 10% increase in hippocampal formation volume (HFV) postoperatively [148]. Increased HFV related to urinary free cortisol levels, further tying decreases in cortisol levels to increases in brain volume.

Compromised verbal memory, learning, and intelligence are related to CS [140–142]. Similarly, untreated CD is related to lower verbal IQ, and verbal, but not visual, learning and delayed recall [140]. Verbal impairments appear reversible after treatment [141, 142]. Improvement in verbal memory is related to greater increase in hippocampal volume 17 months post-surgically after controlling for the effects of age, education, duration of illness [141]. Improvements in verbal working memory and learning are also found post-treatment but are unrelated to hippocampal volume [141]. Other cortical regions beyond the hippocampus may be involved in working memory and learning problems. Hook et al. [142] found 1 year after surgical intervention that improvements in verbal recall are associated with increased brain volume and reduced cortisol levels, an effect that was moderated by younger age. Younger patients with CD made more rapid verbal improvements than did older individuals [142].

CS has also been related to lower nonverbal and visual cognitive abilities [143, 144]. Individuals with untreated CS show poorer attention, visual memory, nonverbal and verbal concept formation as well as poorer abstract reasoning [143]. However, nonverbal abilities improve following adenoma resection or other surgical intervention [144]. For example, prior to surgery, patients with CS have diminished problem solving, visual construction ability and psychomotor efficiency [144]. After surgery, attention and psychomotor efficiency improve congruent with decreased cortisol levels [144]. Duration effects indicate that longer periods of hypercortisolism relate to less improvement in psychomotor efficiency.

Given the established relations between major depression and cognition [146], depression and cortisol [149], and overproduction of corticosteroids and CS [144], one might expect a relation between mood and cognition in this population. However, multiple investigations have failed to find significant ties between the two. Depression does not relate to poorer verbal skills [140], poorer verbal declarative memory [147], or impaired nonverbal skills [143]. If a relation exists between depression and cognitive abilities in CS, it may be mediated by cortisol levels [149]; however, this possibility remains to be assessed.

Adrenal and Corticosteroid Insufficiency

In direct opposition to CS, Addison disease, or primary adrenal insufficiency, is characterized by the inability of the adrenal cortex to produce and secrete glucocorticoid and mineralocorticoid hormones. Addison disease is primarily caused by autoimmune adrenalitis, tuberculosis, systemic fungal infections, AIDS, metastatic carcinoma, adrenal hemorrhage, or glucocorticoid deficiency. Addison disease also increases secretion of adrenocorticotropin (ACTH), a hormone released by the pituitary corticotropes in an attempt to stimulate the adrenal glands [150].

Secondary adrenal insufficiency has a different pathophysiology than Addison disease. Secondary adrenal insufficiency is classified by glucocorticoid and ACTH deficiencies, but is associated with normative mineralocorticoid [150]. Secondary adrenal insufficiency can be caused by pituitary or metastatic tumor, craniopharyngioma, sarcoidosis, hypothalamic tumors, head trauma, or long-term glucocorticoid therapy. See Oelkers et al. [151] for a more complete review of different etiologies.

Despite the hormonal differences in primary and secondary adrenal insufficiency, the clinical features of these two conditions are quite similar [150]. Individuals with untreated adrenal

insufficiency typically present with orthostatic hypotension, fatigue, weight loss, nausea, abdominal pain, agitation, fever, hyponatremia, hypoglycemia, and hyperkalemia, as well as cognitive and behavioral changes [150–153]. Treatment of adrenal insufficiency typically includes oral glucocorticoids such as prednisone [150].

Few studies of neuropsychological and affective sequelae exist for corticosteroid insufficiencies [119, 152]. Available evidence suggests that corticosteroid deficiency is associated with impaired cognitive or neuropsychological function that improves following replacement therapy [119, 154]. In animals, adrenal insufficiency established by adrenalectomy or administration of mineralocorticoid or glucocorticoid receptor antagonists [155] is associated with spatial memory and learning difficulties [154, 155]. Adrenalectomized rats release less dopamine in the prefrontal cortex and demonstrate impaired spatial working memory [154]. However, deficiencies are attenuated with supplementation administered directly to the prefrontal cortex [154]. Preliminary comparative data indicate that endogenous corticosteroids, including both glucocorticoids and mineralocorticoids, are necessary for spatial memory [154, 155]. Evidence also suggests that the effect of glucocorticoids on memory is related, in part, to dopaminergic pathways in the prefrontal cortex [154].

Studies of adrenal insufficiency in humans primarily consist of administration of corticosteroid antagonists in healthy populations [156] or exogenous steroid administration to individuals with Addison disease [119]. A relation is found between steroid availability and attention, memory, learning, and executive functioning [119, 156]. Healthy men treated with spironolactone, a mineralocorticoid antagonist, showed a trend toward impaired selective attention, executive functioning, and delayed visuospatial recall [156]. When individuals with Addison disease are administered exogenous replacement of glucocorticoids such as dexamethasone and/or mineralocorticoids like fluorohydrocortisone, improved cognitive skills are found in attention, working memory, verbal learning, and executive function [119, 156]. Activation of both glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) appears necessary for normative cognitive function.

Similar to CS, individuals with untreated adrenal insufficiency may also exhibit affective problems [152, 153]. While exogenous replacement of corticosteroids attenuates the cognitive sequelae of adrenocortical insufficiency, affective status appears less amenable to treatment [152]. Multiple case studies of psychiatric symptoms date back to 1942. A majority of affective problems remitted within 1 week of cortisone treatment [153]. However, another case study review found that patients with adrenocortical insufficiency or Addison disease are twice more likely to be hospitalized for psychiatric diagnosis of an affective disorder after surgery [153]. Experimental studies of adrenal insufficiency have not examined the association between an elevated prevalence of mood disorders and cognitive problems which could expand an understanding of the interplay between these two frequent sequelae.

Sex Hormones and Corticosteroids: Summary and Future Directions

Optimal cognitive functioning requires normative levels of estrogen, testosterone, and corticosteroids. Clinically low levels of any of three steroids result in impaired attention, verbal memory, and spatial abilities. Cognitive impairments appear modestly amenable to treatment; exogenous supplementation appears to attenuate many of these difficulties. Clinically elevated levels of steroids, particularly corticosteroids, also produce cognitive difficulties. Resumption of normative corticosteroids, typically achieved through surgery, results in significant improvements.

As part of the natural aging process, women and men experience increasingly low levels of estrogen and testosterone, respectively [5, 6]. Estrogen hormone replacement therapy (HRT) administered to postmenopausal women and testosterone supplementation administered to hypogonadal men yield improved memory and visuospatial skills, respectively [4, 19–23, 86, 89]. These findings are consistent with the

known effects of sex steroids on hippocampal neurons [6, 7]. Higher levels of estrogen and testosterone also appear to buffer against the development of Alzheimer disease (AD) and mild cognitive impairment (MCI) [17, 18]; however, age at time of supplementation determines the magnitude and direction of beneficial effects. Specifically, a "critical period" may exist for women such that, if HRT is administered perimenopausally, HRT may buffer against MCI or AD. However, HRT administered after age 65 may, in fact, be detrimental and increase the risk of MCI or AD [45–47]. Future research that examines mechanisms behind this apparent critical period could yield insights into hormones and brain function, particularly in the hippocampus, and may lead to prophylactic treatments.

Klinefelter and Turner syndromes (KS and TS) are two common sex-linked abnormalities that result in clinically low levels of testosterone and estrogen, respectively [7–9]. KS results in disrupted left hemisphere neuroanatomy [108–110] and TS results in disrupted right hemisphere neuroanatomy [7]; as a result, several of the cognitive sequelae of these two conditions appear to mirror or complement one another. Congruent with left hemispheric abnormalities, KS is associated with difficulties primarily in language, and secondarily with attention, and motor skills [102, 104, 105]. Consistent with right hemispheric sequelae, females with TS primarily experience difficulties in nonverbal/visual skills of spatial reasoning, visuomotor and visuospatial skills, with secondary effects on working memory and attention [55–60]. Puberty appears to alter the neurocognitive and motor presentation associated with both KS [59] and TS [102]. Motoric and linguistic problems associated with KS and motoric problems of TS [59] are exacerbated as youth mature into adolescence [102]. Contrary to the beneficial effects of HRT and testosterone supplementation noted above, the effect of hormone supplementation for TS individuals shows improvements in nonverbal speed and spatially mediated motor ability during adolescence [70, 71], but no complementary beneficial effects are found for KS [102]. Future investigations of the cognitive benefits of hormonal supplementation may help modulate neurocognitive performance and yield further information about normative hormonal influences on brain and neurocognitive profiles.

Excessive and insufficient corticosteroids result in a myriad of neuropsychological problems such as impaired verbal memory, spatial memory, attention, and affective problems [127–133, 140–144, 156]. Many of these neuropsychological effects appear greatly diminished with return to normative levels of corticosteroids [129, 141, 142, 144]. Pre-treatment reduction in brain volume, verbal memory, attenuated IQ, nonverbal skills, and depression associated with Cushing's syndrome (CS) are ameliorated post-surgically [141, 142, 144]. Consistent with conditions of elevated corticosteroids, individuals with Addison's disease who receive treatment with corticosteroids show gains in attention, working memory, verbal learning, and executive functioning [119, 156]. Age at which excessive corticosteroids are experienced can impact their effect on cognition. Exogenous administration appears to have a greater negative impact on verbal memory among young adults compared to older adults [137], although younger adults with CS regain verbal memory abilities more rapidly post-surgically than do their older counterparts [142]. Future investigations of corticosteroids and cognition may investigate the relation between depression and cognition. Excessive and insufficient steroid levels have been associated with elevated depressive symptoms [130, 143, 153], yet the relation between negative affect, corticosteroids, and cognition has yet to be clearly defined or understood.

Future investigations of the sex hormones and corticosteroids would benefit from inclusion of age, pubertal development, and affective functioning. Despite the general conclusions described above, a review of the literature on endocrine conditions and cognition reveals considerable discrepancies and inconsistencies. Assessment of the direct and indirect effects of age, pubertal status, and affect [45–47, 49, 102, 137, 142] on the relation between endocrine conditions and

cognition could yield further treatment information.

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References

1. Janowsky JS. Thinking with your gonads: testosterone and cognitive. Trends Cog Sci. 2006;10 (2):77–82.
2. Spencer JL, Waters EM, Romeo RD, et al. Uncovering the mechanisms of estrogen effects on hippocampal function. Front Neuroendocrinol. 2008;29(2):219–37.
3. Belanoff JK, Gross K, Yager A, Schatzberg AF. Corticosteroids and cognition. J Psychiatr Res. 2001;35:127–45.
4. Verghese J, Kusansky G, Katz MJ, et al. Cognitive performance in surgical menopausal women on estrogen. Neurology. 2000;55:872–4.
5. Brett KM, Madan JH. Use of posthormonal hormone replacement therapy estimates from a nationally representative cohort study. Am J Epidemiol. 1997;145:536–45.
6. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men: Baltimore Aging Study. J Clin Endocrinol Metab. 2001;86:724–31.
7. Ross J, Roeltgen D, Zinn A. Cognition and the sex chromosomes: studies in Turner Syndrome. Horm Res. 2006;65(1):47–56.
8. Geschwind DH, Boone KB, Miller BL, Swerdloff RS. Neurobehavioral phenotype of Klinefelter syndrome. Ment Retard Dev Disabil Res Rev. 2000;6:107–16.
9. Mandoki MW, Sumner GS, Hoffman RP, Riconda DL. A review of Klinefelter's syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1991;30(2):167–72.
10. Gould E, Woolley CS, Frankfurt M, McEwen BS. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J Neurosci. 1990;10:1286–91.
11. Adams MM, Shah RA, Janssen WG, Morrison JH. Different modes of hippocampal plasticity in response to estrogen in young and aged female rats. Proc Natl Acad Sci USA. 2001;98:8071–6.
12. Hao J, Janssen WG, Tang Y, et al. Estrogen increases the number of spinophilin-immunoreactive spines in the hippocampus of young and aged female rhesus monkeys. J Comp Neurol. 2003;465(4):540–50.
13. Woolley CS, Wentzel HJ, Schwartzkroin PA. Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region of the adult female rat. J Comp Neurol. 1996;373:108–17.
14. Cordoba Montoya DA, Carrer HF. Estrogen facilitates induction of long term potentiation in the hippocampus of awake rats. Brain Res. 1997;778:430–8.
15. Markowska AL, Savonenko AV. Effectiveness of estrogen replacement in restoration of cognitive function after long-term estrogen withdrawal in aging rats. J Neurosci. 2002;22:10985–95.
16. Savonenko AV, Markowska AL. The cognitive effects of ovariectomy and estrogen replacement are modulated by aging. Neuroscience. 2003;19:821–30.
17. Hogervorst E, Williams J, Budge M, et al. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience. 2000;101(3):485–512.
18. Sherwin BB. Estrogen and cognitive aging in women. Neuroscience. 2006;138:1021–6.
19. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. Obstet Gynecol. 1994;83(6):979–83.
20. Kimura D. Estrogen replacement therapy may protect against intellectual decline in post-menopausal women. Horm Behav. 1995;29 (3):312–21.
21. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry. 2001;158(2):227–33.
22. Robinson D, Friedman L, Marcus R, et al. Estrogen replacement therapy and memory in older women. J Am Geriatr Soc. 1994;42(9):919–22.
23. Resnick SM, Maki PM, Golski S, et al. Effects of estrogen replacement therapy on PET cerebral blood flow and neuropsychological performance. Horm Behav. 1998;34(2):171–82.
24. Schmidt R, Fazekas F, Reinhart B, et al. Estrogen replacement therapy in older women: a neuropsychological and brain MRI study. J Am Gerontol Soc. 1996;44:1307–13.
25. Hogervorst E, Boshuisen M, Riedel W, et al. The effect of hormone replacement therapy on cognitive function in elderly women. Psychoneuroendocrinology. 1999;24:43–68.
26. Steffans DC, Norton MC, Plassman BL, et al. Enhanced cognitive performance with estrogen use in nondemented community-dwelling older women. J Am Geriatr Soc. 1999;47:1171–5.
27. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. JAMA. 1993;269:2637–41.
28. Grodstein F, Chen J, Pollen DA, et al. Post-menopausal hormone therapy and cognitive function in healthy older women. J Am Gerontol Soc. 2000;48:746–52.
29. Jacobs DM, Tag M-X, Stern Y, et al. Cognitive function in nondemented older women who took

estrogen after menopause. Neurology. 1998;50:368–73.
30. Rice MM, Graves AB, McCurry SM, et al. Postmenopausal estrogen and estrogen–progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: the Kame project. Arch Intern Med. 2000;160:1641–9.
31. Szklo M, Cerhan J, Diez-Roux AV, et al. Estrogen replacement therapy and cognitive functioning in the artherosclerotic risk in communities (ARIC) study. Am J Epidemiol. 1996;144:1048–57.
32. Resnick SM, Metter EJ, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? Neurology. 1997;49(6):1491–7.
33. Matthews K, Cauley J, Yaffe K, Zmuda J. Estrogen replacement therapy and cognitive decline in older community women. J Am Gerontol Soc. 1999;47:518–23.
34. Yaffe K, Haan M, Byers A, et al. Estrogen use, ApoE, and cognitive decline. Neurology. 2000;54:1949–53.
35. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. Psychoneuroendocrinology. 1988;13:345–57.
36. Phillips SM, Sherwin BB. Effects on estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology. 1992;17:485–95.
37. Duka T, Tasker R, McGowan JF. The effects of 3-week estrogen hormone replacement on cognition in elderly healthy females. Psychopharmacology. 2000;149:129–39.
38. Binder EF, Schectman KB, Birge SJ, et al. Effects of hormone replacement therapy on cognitive performance in elderly women. Maturitas. 2001;38:137–46.
39. Ditkoff EC, Crary WG, Cristo M, Lobo RA. Estrogen improves psychological function in asymptomatic postmenopausal women. Obstet Gynecol. 1991;78:459–66.
40. Goebel JA, Birge SJ, Price SC, et al. Estrogen replacement therapy and postural stability in the elderly. Am J Otol. 1995;16(4):470–4.
41. Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. J Cogn Neurosci. 2000;12(3):407–14.
42. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. JAMA. 1999;281:1197–202.
43. LeBlanc ES, Janowsky J, Chan BKS, Nelson HD. Hormone replacement therapy and cognition: systemic review and meta-analysis. J Am Med Dir Assoc. 2001;285:1489–99.
44. Hogervorst E, Yaffee K, Richards M, Huppert F. Hormone replacement therapy to maintain cognitive function in women with dementia. Cochrane Database Syst Rev Issue. 2008;3:1–9.
45. Craig MC, Maki PM, Murphy DGM. The women's health initiative memory study: findings and implications for treatment. Lancet Neurol. 2005;4:190–4.
46. Maki PM. Hormone Therapy and cognitive function: is there a critical period for benefit? Neuroscience. 2006;138:1027–30.
47. Resnick SM, Coker LH, Maki PM, et al. The Women's Health Initiative Study of Cognitive Aging (WHISCA): a randomized clinical trial of the effects of hormone therapy on age-associated cognitive decline. Clin Trials. 2004;1:440–50.
48. Zandi PP, Carlson MC, Plassman ML, et al. Hormone replacement therapy and incidence of Alzheimer's disease is older women: Te Cache County Study. JAMA. 2002;288:2123–9.
49. Bender B, Linden M, Robinson A. Neuropsychological impairment in 42 adolescents with sex chromosome abnormalities. Am J Genet B Neuropsychiatr Genet. 1993;48:169–73.
50. Haberecht MF, Menon V, Warsofsky IS, et al. Functional neuroanatomy of visuo-spatial working memory in Turner syndrome. Hum Brain Mapp. 2001;14:96–107.
51. McCauley EM, Kay T, Ito J, Treder R. The Turner syndrome: cognitive deficits, affective discrimination, and behavior problems. Child Dev. 1987;58:464–73.
52. Romans SM, Stefanatos G, Roeltgen DP, et al. Transition to young adulthood in Ullrich-Turner syndrome: neurodevelopmental changes. Am J Med Genet A. 1998;79:140–9.
53. Zinn AR, Roeltgen D, Stefanatos G, et al. A Turner syndrome neurocognitive phenotype maps to Xp22.3. Behav Brain Funct. 2007;21:3–24.
54. Tsoubi T, Nielsen J, Nagayama I. Turner's syndrome: a qualitative and quantitative analysis of EEG background activity. Hum Genet. 1998;78:206–15.
55. Bender B, Puck M, Salbenblatt J, Robinson A. Cognitive development of unselected girls with complete and partial X monosomy. Pediatrics. 1984;73:175–82.
56. Ross JL, Stefanatos G, Roeltgen D, et al. Ullrich-Turner syndrome: neurodevelopmental changes from childhood through adolescence. Am J Med Genet. 1995;58:74–82.
57. Cornoldi C, Marconi F, Vecchi T. Visuospatial working memory in Turner's syndrome. Brain Cogn. 2001;46(1–2):90–4.
58. Ross J, Zinn A, McCauley E. Neurodevelopmental and psychosocial aspects of Turner syndrome. Ment Retard Dev Disabil Res Rev. 2000;6:135–41.
59. Ross JL, Kushner H, Roeltgen DP. Developmental changes in motor function in girls with Turner Syndrome. Pediatr Neurol. 1996;15:317–32.
60. Kesler SR, Menon V, Reiss AI. Neurofunctional differences associated with arithmetic processing in Turner Syndrome. Cereb Cortex. 2006;16:849–56.
61. Kesler SR, Haberecht MF, Menon V, et al. Functional neuroanatomy of spatial orientation

processing in Turner Syndrome. Cereb Cortex. 2004;14(2):174–80.
62. Russell HF, Wallis D, Mazzocco MMM, et al. Increasing prevalence of ADHD in Turner syndrome with no evidence of imprinting effects. J Pediatr Psychol. 2006;31(9):945–55.
63. Nijhuis van der Sanden MWG, Eling PATM, Otten BJ. A review of neuropsychological and motor studies in Turner syndrome. Neurosci Biobehav Rev. 2003;27:329–38.
64. Pennington B, Bender B, Puck M, et al. Learning disabilities in children with sex chromosome anomalies. Child Dev. 1982;53:1182–92.
65. Waber DP. Neuropsychological aspects of Turner's syndrome. Dev Med Child Neurol. 1979;21:58–70.
66. Rovet J, Netley C, Bailey J, et al. Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. Am Med Genet B Neuropsychiatr Genet. 1995;60:356–63.
67. Cornoldi C, De Beni R, Giusberti F, Massironi M. Memory and imagery: A visual trace is not a mental image. In: Conway's MA, Gatherode SE, Cornoldi C, editors. Theories of memory. Hove, UK: Psychology Press. Volume 2, pp 187–210.
68. Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. New York, NY: Oxford University Press; 2004.
69. Hampson E. Estrogen-related variations in human spatial and articulatory-skills. Psychoneuroendocrinology. 1990;15:97–111.
70. Ross JL, Roeltgen D, Feuillan P, et al. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. J Clin Endocrinol Metab. 1998;83(9):3198–204.
71. Ross JL, Roeltgen D, Stefanatos GA, et al. Androgenresponsive aspects of cognition in girls with Turner syndrome. J Clin Endocrinol Metab. 2003;88(1):292–6.
72. Gravholt CH, Svenstrup B, Bennett P, Sandahl Christiansen J. Reduced androgen levels in adult Turner syndrome: influence of female sex steroids and growth hormone status. Clin Endocrinol. 1999;50:791–800.
73. Shute VJ, Pellegrino JW, Hubert L, Reynolds RW. The relationship between androgen levels and human spatial ability. Bull Psychon Soc. 1983;21:465–8.
74. Tirassa P, Thilbin I, Angren G, et al. High-dose anabolic androgenic steroids modulate concentrations of nerve growth factor and expression of its low affinity receptor in male rat brain. J Neurosci Res. 1997;47:198–207.
75. Morse JK, DeKosky ST, Scheff SW. Neurotrophic effects of steroids on lesion-induced growth in the hippocampus-II. Exp Neurol. 1992;118:47–52.
76. Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J Neurosci. 2003;23(5):1588–92.
77. Leranth C, Prange-Kiel J, Frick K, Horvath TL. Low CA1 spine synapse density is further reduced by castration in male non-human primates. Cereb Cortex. 2004;14:503–10.
78. Kritzer ME, McLaughlin PJ, Smirlis T, Robinson JK. Gonadectomy impairs T-maze acquisition in adult male rats. Horm Behav. 2001;39:167–74.
79. Edinger KL, Frye CA. Testosterone's analgesic, anxiolytic, and cognitive-enhancing effects may be due in part to actions of its 5alpha-reduced metabolites in the hippocampus. Behav Neurosci. 2004;118(6):1352–64.
80. Kritzer ME, Brewer A, Montalmant F, et al. Effects of gonadectomy on performance in operant tasks measuring prefrontal cortical function in adult male rats. Horm Behav. 2007;51(2):183–94.
81. Kawakami J, Cowan JE, Elkin EP, et al. Androgen-deprivation therapy as primary treatment for localized prostate cancer: data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). Cancer. 2006;106(8):1708–14.
82. Salminen EK, Portin RI, Koskinen A, et al. Associations between serum testosterone fall and cognitive function in prostate cancer patients. Clin Cancer Res. 2004;10:7575–82.
83. Cherrier M, Rose AL, Higano C. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. J Urol. 2003;170:1808–11.
84. Almeida OP, Waterreus A, Spry N, et al. One year follow-up study of the associations between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology. 2004;29:1071–81.
85. Bussiere JR, Beer TM, Neiss MB, Janowsky JS. Androgen deprivation impairs memory in older men. Behav Neurosci. 2005;119(6):429–1437.
86. Cherrier MM, Craft S, Matsumoto AH. Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: a preliminary report. J Androl. 2003;24(4):568–76.
87. Moffat SD, Zonderman AB, Metter EJ, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab. 2002;87:5001–7.
88. Barrett-Connor E, Goodman-Gruen D. Cognitive function and endogenous sex hormones in older women. J Am Geriatr Soc. 1999;47:1289–93.
89. Alexander GM, Swerdloff RS, Wang C, et al. Androgenbehavior correlations in hypogonadal men and eugonadal men: II. Cognitive abilities. Horm Behav. 1998;33:85–94.
90. Cherrier MM, Matsumoto AM, Amory JK, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological

increases in serum testosterone in healthy older men. Psychoneuroendocrinology. 2007;32:72–9.
91. Gandy S, Almeida OP, Fonte J, et al. Chemical andropause and amyloid-beta peptide. JAMA. 2001;285:2195–6.
92. Moffat SD, Zonderman AB, Metter EJ, Kawas C, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004;62(2):170–1.
93. Chu L, Tam S, Lee PWH, et al. Bioavailable testosterone is associated with a reduced risk of amnestic mild cognitive impairment in older men. Clin Endocrinol. 2008;68(4):589–98.
94. Kenny AM, Fabregas G, Song C, et al. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. J Gerontol. 2004;59A(1):75–8.
95. Lu PH, Masterman DA, Mulnard R, et al. Effects of testosterone on cognition and mod in male patients with mild Alzheimer disease and healthy elderly men. Arch Neurol. 2006;63:177–85.
96. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet. 2004;364:273–83.
97. Bender B, Fry E, Pennington B, et al. Speech and language development in 41 children with sex chromosome anomalies. Pediatrics. 1983;71:262–7.
98. Bender BG, Puck MH, Salbenblatt JA, Robinson A. Dyslexia in 47, XXY boys identified at birth. Behav Genet. 1986;16:343–54.
99. Bender B, Linden M, Robinson A. Verbal and spatial processing efficiency in 32 children with sex chromosome abnormalities. Pediatr Res. 1989;25:577–9.
100. Itti E, Gonzalo ITG, Pawlikowska-Haddal A, et al. The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. J Clin Endocrinol Metab. 2006;91(4):1423–7.
101. Netley C, Rovet J. Hemispheric lateralization in 47. XXY Klinefelter's syndrome boys. Brain Cogn. 1984;3(1):10–8.
102. Ross JL, Roeltgen DP, Benecke R, et al. Cognitive and motor development during childhood in boys with Klinefelter syndrome. Am J Med Genet A. 2008;146A(6):708–19.
103. Rovet J, Netley C, Bailey J, Keenan M, Stewart D. Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. Am J Med Genet. 1995;60:356–63.
104. Rovet J, Netley C, Neenan M. The psychoeducational profile of boys with Klinefelter syndrome. J Learn Disabil. 1996;29:180–96.
105. Temple CM, Sanfilippo PM. Executive skills in Klinefelter's syndrome. Neuropsychologia. 2003;41:1547–59.
106. Patwardhan AJ, Brown WE, Bender BG, et al. Reduced size of the amygdale in individuals with 47, XXY and 47. XXX karyotypes. Am J Med Genet. 2002;114(1):93–8.
107. Patwardhan AJ, Eliez S, Bender B, et al. Brain morphology in Klinefelter syndrome: extra X chromosome and testosterone supplementation. Neurology. 2000;54(12):2218–28.
108. Warwick MM, Doody GA, Lawrie SM, et al. Volumetric magnetic resonance imaging study of the brain in subjects with sex chromosome aneuploidies. J Neurol Neurosurg Psychiatry. 1999;66(5):628–32.
109. Geschwind DH, Gregg J, Boone K, et al. Klinefelter's syndrome as a model of anomalous cerebral laterality: testing gene dosage in the X chromosome pseudoautosomal region using a DNA microarray. Dev Genet. 1998;23(3):215–29.
110. Geidd JN, Clasen LS, Wallace GL, et al. XXY (Klinefelter syndrome): a pediatric quantitative brain magnetic resonance imaging case–control study. Pediatrics. 2007;119:232–40.
111. Waltzer S, Bashir AS, Silbert AR. Cognitive and behavioral factors in the learning disabilities of 47, XXY and 47. XYY boys. Birth Defects. 1991;26:45–58.
112. Robinson A, Bender BG, Borelli JB. Sex chromosome aneuploidy: prospective and longitudinal studies. Birth defects: original article series. 1986;22:23–71.
113. Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Arch Dis Child. 1999;80:192–5.
114. Leonard MF, Sparrow S. Prospective study of development of children with sex abnormalities: New Haven study IV. Adolescence. In: Ratcliffe SG, Paul N, editors. Birth defects: original article series, vol. 22(3). New York, NY: Alan R. Liss, Inc.; 1986. p. 221–49.
115. Van Rijn S, Aleman A, Swaab H. What it is said versus how it is said: comprehension of affective prosody in men with Klinefelter (47, XXY) syndrome. J Int Neuropsychol Soc. 2007;13:1065–70.
116. Fales CL, Knowlton BJ, Holyoak K, et al. Working memory and relational reasoning in Klinefelter syndrome. J Int Neuropsychol. 2003;9:839–46.
117. Boone KB, Swerdloff RS, Miller BL. Neuropsychological profiles of adults with Klinefelter syndrome. J Int Neuropsychol Soc. 2001;7:446–56.
118. Stewart DA, Bailey JD, Netley CT, Park E. Growth, development, and behavioral outcome from mid-adolescence to adulthood in subjects with chromosome aneuploidy: the Toronto Study. Birth Defects. 1991;26:131–88.
119. Tytherleigh MY, Vedhara K, Lightman SL. Mineralocorticoid and glucocorticoid receptors and their differential effects on memory performance in people with Addison's disease. Psychoneuroendocrinology. 2004;29:712–23.
120. Sapolsky R, Krey L, McEwen BS. Prolonged glucocorticoid exposure reduces hippocampal neuronal number: implications for aging. J Neurosci. 1985;5:1222–7.

121. Sapolsky R, Krey L, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev. 1986;7:284–301.
122. Woolley CS, Gould R, McEwen BS. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. Brain Res. 1990;531:225–31.
123. Wantabe Y, Gould E, McEwen BS. Exposure to excess glucocorticoids alters dendritic morphology of the adult hippocampal pyramidal neurons. Brain Res. 1990;531:225–31.
124. Bodnoff SR, Humphreys AG, Lehman JC, et al. Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-age rats. J Neurosci. 1995;15:61–9.
125. Kerr DS, Campbell LW, Applegate MD, et al. Chronic stress-induced acceleration of electrophysiologic and morphometric biomarkers of hippocampal aging. J Neurosci. 1991;11:1316–24.
126. DeLeon MJ, Rusinek H, McRae T, de Santi S, et al. Cortisol reduces hippocampal glucose metabolism in normal elderly, but not in Alzheimer's Disease. J Clin Endocrinol Metab. 1997;82:3251–9.
127. Wolkowitz OM, Reus M, Weingartner H, et al. Cognitive effects of corticosteroids. Am J Psychiatry. 1990;147(10):1297–303.
128. Newcomer JW, Craft S, Hershey T, et al. Glucocorticoid-induced impairment in declarative memory performance in adults humans. J Neurosci. 1994;14(4):2047–53.
129. Newcomer JW, Sella H, Melson AK. Decreased memory performance in health humans induced by stress-level cortisol treatment. Arch Gen Psychiatry. 1999;56:527–33.
130. Schmidt LA, Fox NA, Goldberg MC, et al. Effects of acute prednisone administration on memory, attention and emotion in healthy human adults. Psychoneuroendocrinology. 1999;24:461–83.
131. Kirschbaum C, Wolf OT, May M, et al. Stress-and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci. 1996;58(17):1475–83.
132. Lupien S, Gillin CJ, Hauger RL. Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose–response study in humans. Behav Neurosci. 1999;113 (3):420–30.
133. Young AH, Sahakian BJ, Robbins TW. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. Psychopharmacology. 1999;145:260–6.
134. Hsu FC, Garside MJ, Massey AE, et al. Effects of a single dose of cortisol on the neural correlates of episodic memory and error processing in healthy volunteers. Psychopharmacology. 2003;167:431–42.
135. Naber D, Sand P, Heigl B. Psychological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;21:25–31.
136. Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology. 2005;30:771–84.
137. Wolf OT, Convit A, McHugh PF, et al. Cortisol differentially affects memory in young and elderly men. Behav Neurosci. 2001;115:1002–11.
138. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003;88:5593–602.
139. Simmons NE, Do HM, Lipper MH, Laws ER Jr. Cerebral atrophy in Cushing's disease. Surg Neurol. 2000;53:72–6.
140. Starkman MN, Giordani B, Berent S, et al. Elevated cortisol levels in Cushing's Disease are associated with cognitive decrements. Psychosom Med. 2001;63:985–93.
141. Starkman MN, Giordani B, Gebarski SS, Schteingart DE. Improvement in learning associated with increase in hippocampal formation volume. Biol Psychiatry. 2003;53:233–8.
142. Hook J, Giordani B, Schteingart DE, et al. Patterns of cognitive change over time and relationship to age following successful treatment of Cushing's disease. J Int Neuropsychol Soc. 2007;13:21–9.
143. Forget H, Lacroix A, Somma M, et al. Cognitive decline in patients with Cushing's syndrome. J Int Neuropsychol Soc. 2000;6:20–9.
144. Dorn LD, Burgess ES, Dubbert B, et al. Psychopathology in patients with endogenous Cushing's syndrome: "atypical" or melancholic features. Clin Endocrinol. 1995;43:433–42.
145. Bourdeau I, Bard C, Noel B, et al. Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab. 2002;87:1949–54.
146. Porter RJ, Bourke C, Gallagher P. Neuropsychological impairment in major depression: its nature, origin and clinical significance. Aust NZ J Psychiatry. 2007;41:115–28.
147. Grillon C, Smith K, Haynos A, Nieman LK. Deficits in hippocampus-mediated Pavlovian conditioning in endogenous hypercortisolism. Biol Psychiatry. 2004;56:837–43.
148. Starkman MN, Giordani B, Gebarski SS, et al. Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry. 1999;46:1595–602.
149. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? Biol Psychiatry. 2004;55:1–9.
150. Nieman LK, Chanco Turner ML. Addison's disease. Clin Dermatol. 2006;24:276–80.
151. Oelkers W. Adrenal insufficiency. N Engl J Med. 1996;335:1206–12.

152. Thomsen AF, Kvist TK, Andersen PK, Kessing LV. The risk of affective disorders in patients with adrenocortical insufficiency. Psychoneuroendocrinology. 2006;31:614–22.
153. Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci. 2006;18:450–9.
154. Mizoguchi K, Ishige A, Takeda S, et al. Endogenous glucocorticoids are essential for maintaining prefrontal cortical cognitive function. J Neurosci. 2004;23:5492–9.
155. Oitzl MS, De Kloet ER. Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning. Behav Neurosci. 1992;106:62–71.
156. Otte C, Moritz S, Yassouridis A, et al. Blockade of the mineralocorticoid receptor in healthy men: effects on experimentally induced panic symptoms, stress, hormones, and cognition. Neuropsychopharmacology. 2007;32:232–8.

Chapter 27

Neuropsychological Assessment of Posttraumatic Stress Disorder (PTSD)

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Posttraumatic stress disorder (PTSD) is a mental disorder that sometimes develops after exposure to a life-threatening, psychologically traumatic event. Reflecting empirical advances relevant to the neurobiology and cognitive neuroscience of PTSD, this chapter will focus on PTSD as a neurobehavioral syndrome. We begin by describing PTSD, including a brief review of its clinical presentation and underlying neuropathology. We next review the neurocognitive characteristics of the disorder, common neuropsychological approaches to its assessment, and key clinical considerations in conducting neuropsychological evaluations when PTSD is a possible diagnosis. The chapter additionally addresses treatment implications, concluding with family and social considerations.

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Description of the Disorder

Diagnostic Criteria and Prevalence

Although numerous psychosocial and biological factors increase the risk of developing PTSD following exposure to a psychologically traumatic event [1–5], PTSD is unique among psychiatric disorders in that the diagnosis cannot be made without exposure to an environmental event (i.e., the trauma event). The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [6] defines a traumatic event as one in which a person "experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (Criterion A1) and had a subjective response that involved "intense fear, helplessness, or horror" in adults or "disorganized or agitated behavior" in children (Criterion A2). Epidemiological studies indicate that at least one of every two Americans (ages 15–54) have been exposed over the course of their lifetimes to a psychologically traumatic event and the majority of those exposed have faced two or more traumas in their lifetime [7].

As defined by DSM-IV, symptoms are grouped into three symptom criteria: (1) reexperiencing of the traumatic event (e.g., nightmares, physiological and emotional responsivity to trauma reminders); (2) avoidance of external reminders or thoughts

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associated with the trauma and numbing of general responsiveness (e.g., inability to have loving feelings); and (3) hyperarousal (e.g., concentration impairment, hypervigilance to threat, difficulty in sleeping). Factor analytic studies, however, suggest that a four-factor solution in which avoidance symptoms are separated from numbing and other symptoms may be more appropriate [8, 9]. DSM-IV additionally requires that symptoms endure for at least 1 month and cause clinically significant distress or functional impairment. Despite the frequency of trauma exposure, only about 25% of individuals confronted with trauma develop core PTSD symptoms [10]. The lifetime prevalence of PTSD among US adults has been estimated to be 6.8% [7]. Not surprisingly, prevalence is higher in at-risk populations such as combat veterans [11–14], inner-city children [15], and mass violence survivors [16].

Course and Associated Clinical Features

Course. PTSD typically begins with symptom emergence immediately following the traumatic event [17, 18], although it is possible for symptoms to have a delayed onset. Whereas a subset of individuals recover within a few months [19], PTSD can persist for decades or even for an individual's lifetime [20]. For example, approximately 90% of National Comorbidity Study (NCS) participants retrospectively reported that their PTSD symptoms were still present at 3 months, more than 70% continued to experience symptoms 1 year following the traumatic event, and more than one-third of the sample continued to experience PTSD symptoms 10 years or more, including those individuals who had received treatment [7]. Symptoms may also be cyclical, waxing and waning over time.

Comorbidities. PTSD rarely occurs in isolation from other emotional and behavioral symptoms. Kessler et al. [7], for example, reported that 88% of men and 79% of women with a lifetime diagnosis of PTSD met criteria for at least one other psychiatric diagnosis. Most common among these comorbid disorders are alcohol and substance use, mood, and non-PTSD anxiety disorders [21] (see Brady et al. for a review). Comorbidity rates of PTSD with other anxiety disorders (e.g., generalized anxiety disorder, panic disorder, simple phobia) ranged in the NCS from 7.3 to 31.4%, and lifetime prevalence rates of alcohol and drug use disorders were 51.9 and 34.5%, respectively, for men and 27.9 and 26.9%, respectively, for women with histories of PTSD [7]. Rates of comorbid major depression are likewise high, typically ranging from 30 to 50% (see [18]), with rates as high as 77% in treatment-seeking populations [22].

Traumatic stress exposures and PTSD also have been linked to health problems, such as cardio-and cerebrovascular disease, depressed immune functioning, pain disorders, increased health complaints, and decrements in health-related functioning [23–25]. Subsets of individuals diagnosed with PTSD may also experience physiological sleep abnormalities [26–29], potentially further damaging somatic, emotional, and cognitive health. Although some health problems may result from health risk behaviors such as increased tobacco use [28], as described below, others may be a direct consequence of neurobiological alterations.

Neurobiological Basis of PTSD

When confronted with life threat, the body responds with a state of physiological arousal, including acute increases in stress-related neurotransmitters and neuropeptides, such as corticotropin-releasing factor, norepinephrine, serotonin, dopamine, endogenous benzodiazepines, and endogenous opiates [30]. Although this response often serves an adaptive function in the immediate context of danger by facilitating actions that promote survival (i.e., "flight or fight" responses), the chronic dysregulation of these systems is believed to play an important role in both the pathogenesis and the maintenance of PTSD [31, 32] and is distinct from the pattern of neurobiological abnormalities associated with other stress-related psychiatric disorders such as anxiety and depression [32]. Unlike the profile of attenuated responsivity associated with habituation and adaptation to chronic stress [33] and major depression [34], PTSD is associated with

exaggerated neurobiological responsiveness to cues (now often harmless) of the original trauma [30] and the general sensitization of several neurobiological systems [32, 35]. This sensitization in turn can lead to over-responsiveness to subsequent stress and fear cues. Over time, the cumulative biological strain produced by repeated stress responses, known as "allostatic load," [36] can accelerate pathophysiology, including neuroimmune suppression and possibly neuronal damage.

Of particular relevance to the neuropsychology of PTSD is the dysregulation of the noradrenergic system, hypothalamic–pituitary–adrenal (HPA) axis, and serotonergic system [35]. These systems are believed to influence brain functioning in regions involved in the fear response, including the prefrontal cortex (PFC), amygdala, hippocampus, dorsal raphe nucleus, and locus coeruleus. In short, the combined dysregulation of these systems is thought to result in dampened prefrontal and hippocampal functioning and reduced medial prefrontal inhibition of the amygdala, a limbic structure central to fear-based emotion. Multiple reviews of the vast neurobiological literature relevant to PTSD are available [30, 35, 37–40].

Neuroimaging Findings

In this section, we present a brief overview of findings from structural and functional neuroimaging studies relevant to three critical brain regions (amygdala, medial prefrontal cortex, hippocampus) thought to be involved in the pathophysiology of PTSD. Several extensive reviews of these literatures are available [41–45].

Structural Imaging and Magnetic Resonance Spectroscopy (MRS)

Volumetric studies generally have revealed smaller hippocampal volumes in participants diagnosed with PTSD as compared to both no-PTSD trauma-exposed [43, 46–49] and non-trauma-exposed [43, 46–48, 50, 51] participants, although this finding has not been uniform [52], especially when samples with more recent trauma exposure were examined [53–55]. Gilbertson et al. [56] suggested that hippocampal volume may be a vulnerability for PTSD, rather than a consequence of the disorder, based on the finding that both the trauma-exposed and the non-trauma-exposed "co-twins" of veterans with PTSD showed smaller hippocampal volumes than non-PTSD trauma-exposed veterans and their non-exposed co-twins. Moreover, hippocampal volumetric differences may not become apparent until adulthood (see [43] for a review) and are not necessarily associated with neurocognitive performances, including on tasks of learning and memory [57]. Paralleling the volumetric findings, MRS studies examining the relative concentration of select compounds within the hippocampus have suggested that PTSD is associated with decreased neuronal health in the hippocampus [52, 58, 59].

A growing number of structural imaging studies have begun to examine the PFC and amygdala in relation to PTSD. In a meta-analysis of structural brain abnormalities in PTSD, Karl and colleagues [43] found significantly smaller left amygdala volumes in adults with PTSD compared to both healthy and trauma-exposed controls and significantly smaller anterior cingulate cortex compared to trauma-exposed controls. Not all studies examining amygdala volumes, however, have revealed differences between PTSD-diagnosed trauma survivors and comparison samples [47, 51, 53–55]. In contrast, those measuring frontal cortex volumes have revealed reduced volumes of the frontal cortex in PTSD [54, 60, 61], including decreased volumes in medial PFC structures [62–65] and reduced cortical thickness in much of the frontal gyri [66].

Functional Imaging

Functional neuroimaging studies of PTSD typically have demonstrated that individuals with PTSD, relative to comparison samples, show heightened amygdala responsivity and

deactivation or decreased activation of the hippocampal, anterior cingulate, and orbital frontal cortex in response to symptom provocation such as that elicited by combat sounds and trauma-related words [67–69], script-driven imagery [70–74], and administration of yohimbine, an alpha-2 adrenergic receptor antagonist [75]. A similar pattern has surfaced in studies using cognitive activation paradigms such as encoding and retrieval of threat-related words [76], the emotional Stroop task [77], and presentation and memory of emotional facial expressions [78–80]. Relationships between activation in the amygdala and medial prefrontal cortex in response to traumatic imagery [74, 81] and fear-related stimuli [80] suggest that these two structures are functionally related in PTSD.

Summary and Related Literatures

Although beyond the scope of this chapter, there is also significant evidence of electrophysiological abnormalities in PTSD suggestive of neural processing abnormalities to both neutral and trauma-relevant stimuli [82]. Taken together, multiple methodologies provide converging evidence of biological, physiological, and neuroanatomical abnormalities associated with PTSD that would be expected to be associated with neuropsychological impairment.

Neuropsychological Functioning in PTSD

Empirical Findings

In this section, we review the now sizable literature on clinical neuropsychological test performances in PTSD and organize our review by domains commonly assessed in clinical neuropsychological evaluations, emphasizing those domains with the strongest empirical bases. Other recent reviews are also available [83–87].

Intellectual functioning. PTSD in both children [88] and adults [89–96] is associated with lower estimated and omnibus IQ scores as compared to no-PTSD trauma-exposed and non-exposed comparison groups. Likewise, correlational studies indicate an inverse relationship between PTSD and intellectual performance, even after controlling for stressor severity [90, 94, 97]. Few studies have examined intellectual functioning comprehensively with multi-faceted tasks, but those that have suggested that performance on verbal, as compared to visual–spatial, intellectual tasks may be more strongly associated with PTSD status [88, 90, 95]. In children, intellectual performance decrements have been associated with both early trauma exposure [98] and cortisol-induced neuronal loss associated with trauma exposure [55].

Earlier work using archival records suggests a directional relationship in which higher IQ serves a protective role following trauma exposure, reducing risk of PTSD [94]. Gilberston et al. [99] provided additional support for this hypothesis by examining twin pairs composed of one Vietnam War-exposed and one non-exposed brother. Intellectual performance did not differ between trauma-exposed brothers and their non-exposed co-twins. Instead, no-PTSD exposed brothers and their non-exposed co-twins performed more proficiently on intellectual tasks than both exposed brothers with PTSD and their non-exposed co-twins. A recent study of combat veterans using archival data, however, suggests that this relationship may be more complex: pre-exposure intellectual performance appeared to be protective against development of PTSD symptoms only at lower levels of trauma severity [100]. Using combat exposure as an index of combat severity, at lower levels of combat exposure, pre-exposure intellectual scores were negatively correlated with post-exposure PTSD symptom levels. In contrast, at higher levels of trauma exposure, pre-combat intellectual performances were not significantly associated with post-exposure PTSD severity.

New learning and memory. Anterograde memory on episodic, declarative memory tasks is perhaps the most thoroughly examined

neuropsychological domain in the PTSD literature. Although several studies have yielded negative findings regarding the relationship of PTSD to anterograde memory functioning [101–103], the majority of studies have found that both children [104, 105] and adults [89–91, 93, 96, 106–117] with PTSD perform less proficiently than those without PTSD on one or more measures of learning or memory, with initial acquisition being the most frequently impaired aspect of memory dysfunction. There is also evidence of heightened sensitivity to proactive [118] and retroactive [96, 115, 117] interference in persons with PTSD. Whether PTSD is associated with degraded retention of newly learned information over longer delayed intervals is more ambiguous. Whereas PTSD was associated with less proficient memory retention in select studies [107], several studies failed to reveal PTSD-related deficits in memory retention [89, 91, 115, 119–121].

Two recent independent meta-analyses have attempted to address inconsistencies across studies through the advantages gained by pooling data. Both found that PTSD was associated with less proficient performance on verbal memory tasks. Brewin et al. [122] found small to moderate effect sizes for PTSD diagnostic status across different civilian and military trauma samples. The association between PTSD and memory impairment, which were more pronounced on verbal as compared to non-verbal memory tasks, could not be attributed to head injury and did not differ significantly according to immediate versus delayed recall conditions. Johnsen and Asbjornsen [111] extended these findings in a meta-analysis of immediate verbal memory performance, likewise finding a moderate effect size for PTSD diagnostic status. The effect was larger in military as compared to interpersonal trauma samples and when specific memory instruments (Wechsler Memory Scale subtests and the Rey Auditory Verbal Learning Test, as compared to the California Verbal Learning Test) were used.

Autobiographical memory. In addition to anterograde memory deficits, PTSD is associated with autobiographical memory abnormalities. On autobiographical memory tasks that require recall of a specific memory in response to a cue word, trauma survivors with PTSD, as compared to trauma-exposed participants without PTSD, are more likely to produce "over-general" memories (i.e., reflecting categories of events rather than a specific event) [123–126]. Overgeneral memory recall appears to be particularly pronounced for emotionally positive memories [124, 125, 127], suggesting a possible emotion-based cognitive bias. Although beyond the scope of this chapter, considerable controversy exists regarding whether traumatic autobiographical memories are encoded differently than non-traumatic memories or whether they differ only in the severity of impairment [128–132].

Attentional, executive, and prefrontal functioning. Despite the inclusion of concentration difficulties as a core PTSD diagnostic feature, PTSD does not appear to be associated with a general concentration deficit but instead appears to be associated with a specific pattern of attentional deficits. PTSD-related performance decrements have been documented repeatedly on working memory and divided attention tasks [89, 91, 95, 133, 134] and to a lesser extent [135] on tasks of sustained attention [96, 115, 136–138]. In contrast, some aspects of attention, such as shift of set (as measured by card sorting and visual selective attention tasks) and focus of attention (as measured by letter cancellation and the standard Stroop) appear to be relatively impervious to PTSD in non-elderly adults [93, 96, 115, 116, 136, 138–141], although PTSD-related deficits on card sorting tasks have been documented in elderly former prisoners of war [142] and children [104].

Contemporary neuroanatomical conceptualizations of PTSD implicate dysfunction of the prefrontal cortex, especially regarding its inhibitory functions. Consistent with this notion, PTSD has been shown to be associated with cognitive disinhibition [115, 140] and perseveration [99, 143]. Also suggesting prefrontal dysfunction, Vasterling et al. [116] found that, as compared to combat-exposed veterans without PTSD and non-combat-exposed veterans, Vietnam veterans with PTSD displayed relative performance deficits in olfactory recognition, a task sensitive to orbitofrontal integrity [144].

Language, visual–spatial, and motor functioning. The few studies examining basic language, visual– spatial, and motor functions in PTSD have failed to reveal PTSD-related deficits [145, 146] with the exception of performances on those tasks with a strong executive component, such as complex figural copying [92, 139, 147, 148], word list generation [104, 108, 118], and motor sequencing [92, 93]. Error analysis of clinical visuo-constructive tasks [149] and performance patterns on experimental visuo-spatial tasks [150] have also revealed PTSD-related deficits in processing local, as compared to global, stimulus attributes and distal contextual elements.

Summary. The existing literature indicates subtle, yet specific, cognitive deficits on tasks with significant executive demands (e.g., strategic learning, working memory, and inhibition tasks). Consistent with neuroimaging [46, 152], electrophysiological [153], and behavioral [149, 151] data implicating a cerebral asymmetry favoring the non-dominant hemisphere, neuropsychological studies of PTSD point to a modality-specific deficit in processing verbally mediated information. Although much of the neuropsychological literature relevant to PTSD is derived from non-elderly adult samples, existing studies of children and older adults suggest that the observed neuropsychological deficits are relatively consistent across the lifespan, although age may interact with PTSD such that the performance of older individuals possibly reflects aspects of both PTSD and aging [154, 155]. With rare exception [94, 99, 100], few studies have attempted to examine causal direction between cognitive dysfunction and PTSD in humans, leaving it an area ripe for further exploration via prospective methodology.

Implications for Clinical Evaluation

In our experience, PTSD referrals for neuropsychological evaluation typically center on requests to rule out alternative etiologies (e.g., degenerative disease, traumatic brain injury, cerebrovascular disease) for cognitive dysfunction and/or to document the extent of cognitive dysfunction associated with PTSD. Neuropsychological evaluation of PTSD patients can be used to inform treatment planning, including cognitive rehabilitation efforts. Occasionally, neuropsychologists also are referred cases in which the primary diagnosis of PTSD is not yet established or requires confirmation.

Confirming or establishing a PTSD diagnosis. As summarized in previous sections, empirical findings reveal that PTSD is associated with a pattern of mild cognitive deficits that are not necessarily specific to the disorder. Therefore, the primary diagnosis of PTSD is not made on the basis of neurocognitive testing, but instead requires the use of psychological assessment methods developed specifically for PTSD diagnosis. At its most basic level, the PTSD evaluation includes solicitation of the trauma event(s), assessment of the full range of PTSD symptoms and their linkage to the trauma event(s), and documentation of the duration and functional impact of the symptoms. State-of-the-art assessments typically incorporate multiple methods, including interview-based and paper-and-pencil self-report measures, allowing the examiner to capitalize on the strengths of each, while mitigating the relative weaknesses of each. An excellent summary of these measures can be found on the Department of Veterans Affairs National Center for PTSD website (www.ncptsd.va.gov).

Commonly employed structured interviews include measures focused solely on PTSD such as the Clinician-Administered PTSD Scale (CAPS) [156], Structured Interview for PTSD [157], the PTSD Symptom Scale Interview [158], and the PTSD Module of the Structured Clinical Interview for DSM-IV [159]. The CAPS is often considered the "gold standard" due to its inclusion of trauma assessment, linkage of symptoms to trauma events, assessment of associated features, and assessment of functional impact. Self-report measures often focus on symptom assessment and include those that are DSM-congruent, such as the PTSD Checklist [160], Davidson Trauma Scale [161], Impact of Events Scale – Revised [162], and the Posttraumatic Diagnostic Scale [163], as well as those that are considered less face valid because they do not show one-to-one DSM

symptom correspondence but as a result may be less specific to PTSD [164]. Examples of the latter group include the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder [165], Los Angeles Symptom Checklist [166], Penn Inventory for Posttraumatic Stress Disorder [167], and the Trauma Symptom Inventory [168].

A smaller subset of measures with demonstrated psychometric properties have been designed for use with young trauma patients. Examples include the Clinician-Administered PTSD Scale for Children and Adolescents [169], Trauma Symptom Checklist for Children [170], Posttraumatic Stress Disorder Semi-Structured Interview and Observation Record [171], and the Child Post-Traumatic Stress Disorder Reaction Index [172]. Detailed discussions of the strengths and weaknesses of various adult and child assessment measures and approaches can be found elsewhere [173–176].

Assessment of comorbid conditions and other contributory factors. As described earlier, PTSD commonly is associated with other psychiatric and somatic disorders. Complicating the primary diagnosis, overlap in symptom criteria (e.g., concentration difficulties) between PTSD and other psychiatric (e.g., depression) and somatic (e.g., post-concussion syndrome) disorders often create diagnostic ambiguities. Comorbid conditions also potentially impact cognitive performance both directly and indirectly (through other mediating factors). For example, when accompanied by certain comorbidities (e.g., depression), trauma survivors may be at greater risk for suicidal and other harmful behaviors [177], some of which (e.g., gunshots wounds to the head, drug overdoses resulting in coma) may result in lasting neuropsychological impairment. Further, pharmacological treatment of PTSD and associated conditions may result in iatrogenic effects that either enhance or impair cognitive functioning, depending on the specific agent [178–182]. Finally, certain comorbidities (e.g., alcohol use disorders, depression, traumatic brain injury, sleep disturbance) may influence neuropsychological performance directly [134, 183–186].

As such, clinical neuropsychological evaluation of PTSD requires assessment of comorbid conditions (e.g., depression), health risk behaviors (e.g., suicide attempts, excessive alcohol consumption), and contextual factors (e.g., concurrent pharmacological treatment, sleep) that potentially complicate interpretation of the assessment data. When such complicating factors occur, it becomes important to document the timeline of their onset relative to the onset and course of PTSD as well as any neuropsychological deficits. For example, knowing the chronology of substance abuse in relation to the onset of cognitive impairment and PTSD symptoms may help determine that cognitive decline began only after substance use increased. This information in turn can be used to project prognosis under a range of different circumstances (e.g., once substance use is discontinued). Preliminary evidence that neurodevelopmental disorders (e.g., attention deficit hyperactivity disorder) may be associated with increased risk of PTSD [91–93] also highlights the need to assess mental disorders that predate PTSD onset. Likewise, neurobehavioral disorders (e.g., dementia) with onset postdating trauma exposure may be associated with recurrence or exacerbation of PTSD symptoms [187].

As an example of a complex clinical constellation, we highlight traumatic brain injury (TBI) occurring in the context of PTSD. TBI may have considerable overlap with PTSD in regard to neuropsychological deficits [188–198], associated somatic symptoms [199, 200], and underlying neural abnormalities [201, 202]. Depending on the relative severity of the two disorders, the overlap between PTSD and TBI on these dimensions can make differentiation of the relative contributions of each to neuropsychological deficits challenging [203]. Perhaps of greater relevance to the patient's day to day functioning, however, is that TBI may exacerbate existing PTSD and depression symptoms in trauma survivors [204–206], complicating the clinical presentation. In such cases, it becomes essential to understand the recency of the TBI(s), the onset of PTSD relative to the TBI(s), the relative severity of each disorder, and the degree to which there may be other complicating factors (e.g., headaches) that influence current cognitive

status and the course and prognosis of neuropsychological deficits.

Neurobehavioral Instrument Selection

As with neuropsychological evaluation of most disorders, we recommend incorporating at least cursory assessment of a broad range of cognitive domains, evaluating domains anticipated to be sensitive to PTSD diagnosis as well as those not expected to be affected. This approach allows evaluation of both confirmatory and disconfirmatory evidence of the hypothesized etiology of neuropsychological dysfunction and facilitates detection of non-PTSD etiologies. Screening multiple domains additionally identifies potential cognitive strengths that can be utilized to help compensate for observed deficits. Because the empirical literature suggests that PTSD-related deficits are relatively subtle, we recommend more comprehensive assessment of domains thought to be impaired in PTSD (e.g., learning, memory, inhibitory functions) using tasks that are reasonably challenging. Unfortunately, research examining neuropsychological functioning in PTSD only rarely has included assessment of effort, but the clinical context necessitates evaluation of cognitive effort for interpretation of the results. In the following paragraphs, we integrate findings from the empirical literature in considering clinical test selection in the two domains most commonly found to differ according to PTSD diagnosis (i.e., learning/memory and attention/executive functioning).

Learning and memory. Although both visual–spatial and verbal–auditory learning and memory deficits have been found to be associated with PTSD diagnosis, deficits have been more commonly documented on verbal–auditory tasks, and effect sizes appear larger on verbal–auditory as compared to visual–spatial tasks [122], suggesting that learning and memory should be assessed in both modalities. As with any disorder, it is typically useful to include both single- and multiple-exposure tasks, and to include tasks that assess both initial registration and retention. Although PTSD-related deficits have been observed on delayed recall [106], they less commonly have been observed when retention is computed relative to initial acquisition [91, 115, 116, 119, 154], suggesting that computation of difference scores or retention ratios may be clinically informative. Similarly, empirical findings indicating that PTSD is associated with heightened sensitivity to proactive and retroactive interference [115, 117, 118] suggest that tasks incorporating interference trials may provide clinically useful information.

The memory deficits associated with PTSD have been conceptualized as stemming in part from difficulties related to strategic learning [132, 207], highlighting the potential utility of administering tasks that vary in their demands on self-initiated strategy. For example, it may be helpful to compare performance on tasks with unrelated stimuli (placing additional burden on strategic memory processes) to performance on tasks in which there is an underlying categorical structure (demanding less strategic processing). Finally, we recommend analyzing errors (e.g., perseverations, intrusions) in memory assessments, given the mounting evidence that executive components of memory encoding and retrieval may be central to the memory deficit observed in PTSD.

Attentional and executive functions. One of the most theoretically interesting neuropsychological findings in PTSD (i.e., decreased response inhibition) may also be among the most clinically significant. The failure to gate information and regulate emotions strikes at the heart of PTSD with direct implications for the development and maintenance of the disorder. Specifically, it may be that frontally mediated deficits in inhibitory regulation influence how patients with PTSD process, encode, and retrieve trauma events and related memories [132]. Similarly, regulatory deficits of the limbic system have far-reaching implications for how emotions are experienced and managed. Therefore, we recommend that evaluation of attention/executive functions in PTSD include at a minimum a thorough assessment of response inhibition. Because

the full extent of executive and attentional deficits associated with PTSD is not yet fully understood (especially in terms of their interactions with developmental stage), neuropsychological evaluation of PTSD ideally will include a broad range of attention and executive tasks.

Summary. Neuropsychological evaluation of the PTSD patient poses specific challenges. Whereas there are observable group-level deficits on neurobehavioral measures, they are likely to be mild and difficult to interpret at the individual level. In addition, a number of other potential contributory factors (e.g., other medical conditions, medications, comorbid substance abuse) may complicate the clinical picture. However, even subtle deficits may have a significant impact on daily functioning [148]. Moreover, as described below under the "Treatment Implications" section, such deficits may also have as yet undocumented effects on treatment response, suggesting that neuropsychological evaluation of PTSD offers information of potential value to the overall clinical management of the patient.

The Emotional Stroop Paradigm

As suggested by the previous section, the performance deficits on standardized clinical neuropsychological tests that accompany PTSD are typically mild and overlap to some extent with comorbid disorders. In contrast to standardized neuropsychological assessment instruments, experimental information processing, electrophysiological, and functional imaging studies have yielded results suggesting that some types of information processing abnormalities may be specific to PTSD, especially when trauma-relevant stimuli are employed. In this section, we highlight the emotional Stroop task, an experimental paradigm that has been particularly robust in detecting information processing biases to trauma-relevant stimuli in PTSD [208]. Although we anticipate that functional imaging and electrophysiological paradigms will continue to generate findings that will move the field closer toward understanding the neuropsychology of PTSD, we focus on the emotional Stroop task because of its extensive empirical history and, because it does not require specialized equipment, its potential feasibility and widespread accessibility. The functional imaging literature has been reviewed briefly in previous sections, and comprehensive reviews of the electrophysiological and cognitive information processing PTSD literatures are available elsewhere [82, 209, 210].

The emotional Stroop is a variant of the Stroop color-naming task [211], in which respondents are shown color-congruent (e.g., the word "red" printed in red ink) and color-incongruent (e.g., the word "red" printed in blue ink) words and asked to name as quickly as possible the color of ink in which the word is printed. In the classic Stroop, respondents are slower to name color-incongruent words than color-congruent words [211]. The emotional Stroop variation modifies the paradigm by varying the emotional valence and relevance of the words (e.g., "chair" as a neutral word, "combat" as a trauma-relevant word for combat veterans). Slower naming of any particular class of words is interpreted as an attentional bias (i.e., an attentional preference or "pull") to the particular semantic category.

Relative to non-trauma-exposed and trauma-exposed individuals without PTSD, individuals with PTSD are slower to color-name trauma-related words as compared to emotionally neutral words or emotional words that are unrelated to their trauma [208, 212–216]. This attentional bias is thought to occur when the mild threat inherent to the semantic content of trauma words interferes with normal functioning and diverts cognitive resources to the threat-related information [208]. Attentional bias to trauma words in PTSD has been documented across a range of trauma populations, including rape victims [212, 213], combat veterans [214, 215, 217], and motor vehicle accident survivors [218, 219].

Although attentional biases to threat words on the Stroop have been well replicated, there continue to be several factors that limit its application as a clinical task. First, whereas idiographic lists are not required to show an effect, the trauma

words nonetheless need to be generally related to the respondent's trauma experience to elicit an effect. Thus, prior to clinical use, different versions of the task must be developed to accommodate diverse trauma populations. Second, and likely related to the diversity of stimuli necessary across trauma populations, clinical normative data do not yet exist. Such normative data will be critical, as biases to emotionally relevant words are not absolute but are instead relative to normal controls. Finally, theoretical debate continues regarding the parameters in which the emotional Stroop effect is most likely to occur and the degree to which it reflects automatic (i.e., involuntary and without conscious awareness or effort) versus strategic (i.e., requiring cognitive effort) processing [208, 220–222].

In sum, the emotional Stroop and other information processing paradigms continue to generate findings that elucidate the cognitive processes that underlie the development and perpetuation of PTSD (e.g., through reinforcement of fear networks) and explain PTSD symptoms such as hypervigilance and decreased concentration. Moreover, because of the specificity of attentional bias to threat-relevant information, some of these paradigms also hold potential for future clinical application; however, the field awaits further development of these tasks prior to widespread clinical implementation.

Treatment Implications

There are a number of psychosocial and psychopharmacological interventions used to treat PTSD. Below, we discuss the neuropsychological relevance of some of the more common of these interventions.

Pharmacological Treatment

Several psychotropic medications have been employed in the treatment of PTSD, including selective serotonin reuptake inhibitors (SSRIs), other antidepressants (e.g., tricyclics, monoamine oxidase inhibitors), anti-psychotic medications, and antiepileptic medications [180, 223]. However, the only two pharmacological agents approved by the US Food and Drug Administration specifically for treatment of PTSD are the SSRIs sertraline, and paroxetine [224]. Likewise, the Department of Veterans Affairs/Department of Defense Guidelines (VA/DOD) [225], the American Psychiatric Association [226], and the International Society of Traumatic Stress Studies (ISTSS) [227] endorsed SSRIs as the initial choice for the pharmacological treatment of PTSD. SSRIs impact multiple neurotransmitter systems [e.g., serotonin, glutamate, and gamma-aminobutyric acid (GABA)] that are thought to potentially impact cognitive functioning by improving inhibition of distracting recollections [223]. Supporting this hypothesis, preliminary evidence from single group designs suggests that SSRIs used in the treatment of PTSD may enhance performance on anterograde memory tasks [228] and alter neural activation from pre- to post-treatment in frontal, limbic, and paralimbic regions, particularly among treatment responders [229].

Psychotherapy

Psychological treatment approaches for PTSD include but are not limited to exposure-based interventions, cognitive–behavioral therapy, psychodynamic therapy, supportive counseling, anxiety management, and eye movement desensitization and reprocessing (EMDR). Of the many treatment approaches available, exposure-based and cognitive–behavioral interventions have been identified as the most efficacious in the treatment of PTSD [230–232], with exposure-based therapy named as the treatment of choice by the Institutes of Medicine [233].

Cognitive–behavioral interventions target modification of negative or distorted thoughts attached to trauma experiences, with the goal of generating more realistic explanations and thoughts associated with the trauma and trauma experience. Such modifications could be reasoned to require both the inhibition of

maladaptive thoughts and sufficient cognitive flexibility to reappraise thoughts and memories. In addition, the degree to which trauma memories can be retrieved and modified may be important to treatment, especially when exposure is included in the intervention. Although not directly measuring neurocognitive functioning, recent neuroimaging studies have demonstrated that activation levels of the amygdala and anterior cingulate cortex [234, 235] and anterior cingulate volumes [236] helped predict treatment response for cognitive–behavioral and exposure therapies, raising the question of whether associated cognitive functions also may be useful in predicting treatment response to common psychological PTSD interventions. Supporting this notion, Wild and Gur [237] reported that more proficient verbal encoding and recall performances at pre-treatment were associated with better PTSD treatment outcomes.

EMDR is a multi-phase treatment incorporating trauma visualization, simultaneous lateral eye movements, and the coupling of positive cognitions with trauma visualization [238], with the latter repeated until the patient reports a high level of belief in the positive cognition [239]. Thus, like exposure-based interventions and some forms of CBT, EMDR incorporates an exposure component. Significant debate exists regarding the incremental benefits of EMDR over other exposure-based interventions, and the underlying mechanism of change (i.e., imagined exposure, ocular movement) is not well understood [239–241].

Preliminary work suggests that cognitive–behavioral and other psychological interventions may alter neural functioning. Sutherland and Bryant reported improved recollection of specific memories and reduced recollection of overgeneral, categorical memories following cognitive–behavioral treatment, as well as reduced bilateral amygdala and anterior cingulate activation [126]. Although not measuring neuropsychological outcomes, in a randomized trial, Lindauer et al. likewise demonstrated changes in neural activation in frontal and paralimbic regions following brief eclectic psychotherapy as compared to a wait-list control condition [242].

Family Considerations

Neuropsychological evaluations often consider how disorders impact the family. In PTSD, emotional, and possibly cognitive, dysfunction may lead to significant disruptions of social and family functioning. PTSD patients have the most difficulty in their closest relationships, such as those with a partner or significant other and children. In intimate relationships, trauma survivors with PTSD report lower levels of marital satisfaction [243, 244], poor cohesion and expressiveness [244, 245], high levels of conflict, which sometimes include physical aggression [246–248], and less intimacy and sexual satisfaction [246, 249, 250]. In turn, their partners report significant marital problems and often show somatic symptoms, anxiety, depression, and insomnia [244, 251, 252].

Regarding relationships with their children, trauma survivors suffering PTSD, particularly those who experience high levels of PTSD numbing and avoidance symptoms, have poorer parent–child relationships and less satisfaction with parenting [253, 254]. Children who have a parent with PTSD live in households with significantly higher conflict and lower cohesiveness [245, 252]. These children are also more likely to have behavioral problems [244] and are at a greater risk for mental disorders, including PTSD [255]. Some literature suggests that partners and children may exhibit secondary PTSD in which family members take on some symptoms of PTSD [256–259].

These negative family outcomes are relevant not only to the family member but also to the patient, especially in light of robust findings that social support is a key resource and determinant of mental health outcomes for those suffering from PTSD [260, 261]. Because social relationships may be affected adversely by PTSD symptoms, without intervention, individuals with

PTSD may find themselves in a downward spiral in which one of the most valuable resources (i.e., social support) is less likely to be available. This reduction of social resources leads to ineffective coping behaviors (e.g., avoidance and isolation), which further deplete available resources, thus continuing the cycle. Therefore, in clinical settings, it is critical to assess family and social resources available to patients with PTSD. Fortunately, a number of interventions are emerging that may be particularly promising to address social dysfunction within intimate partner and family relationships [262–264].

Conclusions

Neuropsychological research, along with converging evidence from neurobiological, neuroimaging, and electrophysiological studies, suggests that the neural underpinnings of PTSD are integral to the disorder. Neuropsychological abnormalities include impairment of executive aspects of attention, sustained attention, learning, and memory. Performance on verbally mediated tasks, including IQ and anterograde memory tasks, is less likely to be proficient among trauma survivors who develop PTSD as compared to those who do not. The pattern of results is consistent with neuroanatomical models of PTSD that emphasize the prefrontal cortex and limbic/paralimbic areas, including the amygdala and the hippocampus. There is much about PTSD as a neurobehavioral disorder, however, that remains unresolved. For example, the degree to which neurobiological and neuropsychological abnormalities represent predispositional factors versus sequelae of trauma exposure is uncertain. Likewise, the extent to which comorbidity and treatment-related factors contribute to neuropsychological dysfunction in PTSD is not fully resolved. Inconsistencies in measurement and sampling methodology across studies have not permitted sufficient replication to create a highly delineated neuropsychological profile, although recent meta-analytic and longitudinal studies have begun to help address some of these issues. Finally, the addition of clinical neuropsychological measures within clinical trial research represents a particularly exciting application of neuropsychology. Inclusion of such assessment tools, both as outcome measures and as potential predictors of treatment response, will potentially have significant impact on the care of patients with PTSD.

References

1. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol. 2000;68:748–66.
2. McFarlane AC, Yehuda R. Risk factors for the acute biological and psychological response to trauma. In: Yehuda R, editor. Risk factors for posttraumatic stress disorder. Washington, DC: American Psychiatric Association; 1999. pp. 163–90.
3. Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull. 2003;129:52–73.
4. Yehuda R. Biological factors associated with susceptibility to posttraumatic stress disorder. Can J Psychiatry/La Revue Canadienne de Psychiatrie. 1999;44:34–39.
5. Vogt DS, King DW, King LA. Risk pathways for PTSD: making sense of the literature. In: Friedman MJ, Keane TM, Resick PA, editors. Handbook of PTSD: science and practice. New York, NY: Guilford Press; 2007. pp. 99–115.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
7. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the national comorbidity survey. Arch Gen Psychiatry. 1995;52:1048–60.
8. King DW, Leskin GA, King LA, Weathers FW. Confirmatory factor analysis of the clinician-administered PTSD Scale: evidence for the dimensionality of posttraumatic stress disorder. Psychol Assess. 1998;10:90–96.
9. Simms LJ, Watson D, Doebbeling BN. Confirmatory factor analyses of posttraumatic stress symptoms in deployed and nondeployed veterans of the Gulf War. J Abnorm Psychol. 2002;111:637–47.
10. Green BL. Psychosocial research in traumatic stress: an update. J Trauma Stress. 1994;7:341–62.
11. Dohrenwend BP, Turner JB, Turse NA, et al. The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science. 2006;313:979–82.
12. Hoge CW, Castro CA, Messer SC, et al. Combat duty in Iraq and Afghanistan, mental health

problems, and barriers to care. N Engl J Med. 2004;351:13–22.
13. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA. 2006;295:1023–32.
14. Kulka RA, Schlenger WE, Fairbank JA, et al. Trauma and the Vietnam war generation: report of findings from the National Vietnam Veterans Readjustment Study. Philadelphia, PA: Brunner/Mazel; 1990.
15. Silva RR, Alpert M, Munoz DM, et al. Stress and vulnerability to posttraumatic stress disorder in children and adolescents. Am J Psychiatry. 2000;157:1229–35.
16. de Jong JT, Komproe IH, Van Ommeren M, et al. Lifetime events and posttraumatic stress disorder in four postconflict settings. JAMA. 2001;286:555–62.
17. Flouri E. Post-traumatic stress disorder (PTSD): what we have learned and what we still have not found out. J Interpers Violence. 2005;20:373–79.
18. Shalev AY. What is posttraumatic stress disorder? J Clin Psychiatry. 2001;62(Suppl 17):4–10.
19. Breslau N. Outcomes of posttraumatic stress disorder. J Clin Psychiatry. 2001;62(Suppl 17):55–9.
20. Yule W. Posttraumatic stress disorder in the general population and in children. J Clin Psychiatry. 2001;62(Suppl 17):23–8.
21. Brady KT, Killeen TK, Brewerton T, Lucerini S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry. 2000;61 (Suppl 7):22–32.
22. Brown TA, Campbell LA, Lehman CL, et al. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol. 2001;110:585–99.
23. Schnurr PP, Green BL. Trauma and health: physical health consequences of exposure to extreme stress. Washington, DC: American Psychological Association; 2004.
24. Taft CA, Stern AS, King LA, King DW. Modeling physical health and functional health status: the role of combat exposure, posttraumatic stress disorder, and personal resource attributes. J Trauma Stress. 1999;12:2–23.
25. Vasterling JJ, Schumm J, Proctor SP, et al. Posttraumatic stress disorder and health functioning in a non-treatment-seeking sample of Iraq war veterans: a prospective analysis. J Rehabil Res Dev. 2008;45:347–58.
26. Breslau N, Roth T, Burduvali E, et al. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. Arch Gen Psychiatry. 2004;61:508–16.
27. Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152:110–15.
28. Schnurr PP, Spiro A 3rd. Combat exposure, posttraumatic stress disorder symptoms, and health behaviors as predictors of self-reported physical health in older veterans. J Nerv Ment Dis. 1999;187:353–59.
29. Singareddy RK, Balon R. Sleep in posttraumatic stress disorder. Ann Clin Psychiatry. 2002;14: 183–90.
30. Bremner JD, Southwick SM, Charney DS. The neurobiology of posttraumatic stress disorder: an integration of animal and human research. In: Saigh PA, Bremner JD, editors. Posttraumatic stress disorder: a comprehensive text. Needham Heights, MA: Allyn & Bacon; 1999. pp. 103–43.
31. Charney DS, Deutch AY, Krystal JH, et al. Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry. 1993;50: 295–305.
32. Yehuda R, McFarlane AC. Conflict between current knowledge about posttraumatic stress disorder and its original conceptual basis. Am J Psychiatry. 1995;152:1705–13.
33. Selye H. The stress of life. New York, NY: McGraw-Hill; 1956.
34. Siever LJ, Davis KL. Overview: toward a dysregulation hypothesis of depression. Am J Psychiatry. 1985;142:1017–31.
35. Southwick SM, Rasmusson A, Barron J, Arnsten A. Neurobiological and neurocognitive alterations and PTSD: a focus on norepinephrine, serotonin, and the HPA axis. In: Vasterling JJ, Brewin CR, editors. The neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005.
36. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology. 2000;22:108–24.
37. Bonne O, Grillon C, Vythilingam M, et al. Adaptive and maladaptive psychobiological responses to severe psychological stress: implications for the discovery of novel pharmacotherapy. Neurosci Biobehav Rev. 2004;28:65–94.
38. Charney DS, Deutch AY, Southwick SM, Krystal JH. Neural circuits and mechanisms of posttraumatic stress disorder. In: Friedman MJ, Charney DS, Deutch AY, editors. Neurobiological and clinical consequences of stress: from normal adaptation to posttraumatic stress disorder. Philadelphia, PA: Lippincott-Raven; 1995. pp. 271–87.
39. Rasmusson AM, Vythilingam M, Morgan CA 3rd. The neuroendocrinology of posttraumatic stress disorder: new directions. CNS Spectr. 2003;8(651–656):665–657.
40. Yehuda R. Current status of cortisol findings in posttraumatic stress disorder. Psychiatr Clin North Am. 2002;25(341–68):vii.
41. Francati V, Vermetten E, Bremner JD. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. Depress Anxiety. 2007;24:202–18.

42. Grossman R, Buchsbaum MS, Yehuda R. Neuroimaging studies in post-traumatic stress disorder. Psychiatr Clin N Am. 2002;25:317–40.
43. Karl A, Schaefer M, Malta LS, et al. A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev. 2006;30:1004–31.
44. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. Biol Psychiatry. 2006;60:376–82.
45. Shin LM, Rauch SL, Pitman RK. Structural and functional anatomy of PTSD: findings from neuroimaging research. In: Vasterling JJ, Brewin CR, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. pp. 59–82.
46. Bremner JD, Vythilingam M, Vermetten E, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry. 2003;160:924–32.
47. Gurvits TV, Shenton ME, Hokama H, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry. 1996;40:1091–99.
48. Kitayama N, Vaccarino V, Kutner M, et al. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. J Affect Disord. 2005;88:79–86.
49. Stein MB, Koverola C, Hanna C, et al. Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med. 1997;27:951–59.
50. Bremner JD, Randall P, Scott TM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry. 1995;152:973–81.
51. Bremner JD, Randall P, Vermetten E, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. Biol Psychiatry. 1997;41:23–32.
52. Schuff N, Neylan TC. Lenoci MA et al. Decreased hippocampal *N*-Acetylaspartate in the absence of atrophy in posttraumatic stress disorder. Biol Psychiatry. 2001;50:952–59.
53. Bonne O, Brandes D, Gilboa A, et al. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am J Psychiatry. 2001;158:1248–51.
54. Carrion VG, Weems CF, Eliez S, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry. 2001;50(12):943–51.
55. De Bellis M, Keshavan MS, Clark D, et al. Developmental traumatology part II: brain development. Biol Psychiatry. 1999;45:1271–84.
56. Gilbertson MW, Shenton ME, Ciszewski A, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 2002;5:1242–47.
57. Lindauer RJ, Olff M, van Meijel EP, et al. Cortisol, learning, memory, and attention in relation to smaller hippocampal volume in police officers with posttraumatic stress disorder. Biol Psychiatry. 2006;59:171–77.
58. Freeman TW, Cardwell D, Karson CN, Komoroski RA. In vivo proton magnetic resonance spectroscopy of the medial temporal lobes of subjects with combat-related posttraumatic stress disorder. Magn Reson Med. 1998;40:66–71.
59. Menon PM, Nasrallah HA, Lyons JA, et al. Single-voxel proton MR spectroscopy of right versus left hippocampi in PTSD. Psychiatry Res. 2003;123:101–08.
60. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry. 2002;52:1066–78.
61. Fennema-Notestine C, Stein MB, Kennedy CM, et al. Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. Biol Psychiatry. 2002;52:1089–101.
62. Kasai K, Yamasue H, Gilbertson MW, et al. Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. Biol Psychiatry. 2008;63:550–56.
63. Rauch SL, Shin LM, Segal E, et al. Selectively reduced regional cortical volumes in post-traumatic stress disorder. Neuroreport. 2003;14:913–16.
64. Woodward SH, Kaloupek DG, Streeter CC, et al. Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry. 2006;59:582–87.
65. Yamasue H, Kasai K, Iwanami A, et al. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. Proc Natl Acad Sci USA. 2003;100:9039–43.
66. Geuze E, Westenberg HG, Heinecke A, et al. Thinner prefrontal cortex in veterans with posttraumatic stress disorder. Neuroimage. 2008;41:675–81.
67. Bremner JD, Staib LH, Kaloupek D, et al. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry. 1999;45:806–16.
68. Driessen M, Beblo T, Mertens M, et al. Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. Biol Psychiatry. 2004;55:603–11.
69. Liberzon I, Taylor SF, Amdur R, et al. Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry. 1999;45:817–26.
70. Bremner JD, Narayan M, Staib LH, et al. Neural correlates of memories of childhood sexual abuse in

women with and without posttraumatic stress disorder. Am J Psychiatry. 1999;156:1787–95.
71. Lanius RA, Williamson PC, Densmore M, et al. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. Am J Psychiatry. 2001;158:1920–22.
72. Liberzon I, Britton JC, Phan KL. Neural correlates of traumatic recall in posttraumatic stress disorder. Stress. 2003;6:151–56.
73. Rauch SL, van der Kolk BA, Fisler RE, et al. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Arch Gen Psychiatry. 1996;53:380–87.
74. Shin LM, Orr SP, Carson MA, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry. 2004;61:168–76.
75. Bremner JD, Innis RB, Ng CK, et al. Positron emission tomography measurement of cerebral metabolic correlates of yohimbine administration in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54:246–54.
76. Bremner JD, Vythilingam M, Vermetten E, et al. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biol Psychiatry. 2003;53:879–89.
77. Shin LM, Whalen PJ, Pitman RK, et al. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biol Psychiatry. 2001;50:932–42.
78. Dickie EW, Brunet A, Akerib V, Armony JL. An fMRI investigation of memory encoding in PTSD: influence of symptom severity. Neuropsychologia. 2008;46:1522–31.
79. Rauch SL, Whalen PJ, Shin LM, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biol Psychiatry. 2000;47:769–76.
80. Shin LM, Wright CI, Cannistraro PA, et al. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry. 2005;62:273–81.
81. Gilboa A, Shalev AY, Laor L, et al. Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. Biol Psychiatry. 2004;55:263–72.
82. Metzger LJ, Gilbertson MW, Orr SP. Electrophysiology of PTSD. In: Vasterling JJ, Brewin CR, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. p. 83–102.
83. Danckwerts A, Leathem J. Questioning the link between PTSD and cognitive dysfunction. Neuropsychol Rev. 2003;13:221–35.
84. De Bellis MD, Hooper SR, Sapia JL. Early trauma exposure and the brain. In: Vasterling JJ, Brewin CR, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. pp. 153–77.
85. Horner MD, Hamner MB. Neurocognitive functioning in posttraumatic stress disorder. Neuropsychol Rev. 2002;12:15–30.
86. MacDonald HZ, Vasterling JJ, Rasmusson A. Neuropsychological underpinnings of PTSD in children and adolescents. In: Ardino V, editor. Post-traumatic syndromes in children and adolescents. London: Wiley–Blackwell, in press.
87. Vasterling JJ, Brailey K. Neuropsychological findings in adults with PTSD. In: Vasterling JJ, Brewin CR, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. pp. 178–207.
88. Saigh PA, Yasik AE, Oberfield RA, et al. The intellectual performance of traumatized children and adolescents with or without posttraumatic stress disorder. J Abnorm Psychol. 2006;115:332–40.
89. Brandes D, Ben-Schachar G, Gilboa A, et al. PTSD symptoms and cognitive performance in recent trauma survivors. Psychiatry Res. 2002;110:231–38.
90. Gil T, Calev A, Greenberg D, et al. Cognitive functioning in post-traumatic stress disorder. J Trauma Stress. 1990;3:29–45.
91. Gilbertson MW, Gurvits TV, Lasko NB, et al. Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. J Trauma Stress. 2001;14:413–31.
92. Gurvits TV, Gilbertson MW, Lasko NB, et al. Neurologic soft signs in chronic posttraumatic stress disorder. Arch Gen Psychiatry. 2000;57:181–86.
93. Gurvits TV, Lasko NB, Schachter SC, et al. Neurological status of Vietnam veterans with chronic posttraumatic stress disorder. J Neuropsychiatry Clin Neurosci. 1993;5:183–88.
94. Macklin ML, Metzger LJ, Litz BT, et al. Lower precombat intelligence is a risk factor for posttraumatic stress disorder. J Consult Clin Psychol. 1998;66:323–26.
95. Vasterling JJ, Brailey K, Constans JI, et al. Assessment of intellectual resources in Gulf War veterans: relationship to PTSD. Assessment. 1997;4:51–59.
96. Vasterling JJ, Duke LM, Brailey K, et al. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. Neuropsychology. 2002;16:5–14.
97. McNally RJ, Shin LM. Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam Combat veterans. Am J Psychiatry. 1995;152:936–38.
98. Koenen KC, Moffitt TE, Caspi A, et al. Domestic violence is associated with environmental suppression of IQ in young children. Dev Psychopathol. 2003;15:297–311.
99. Gilbertson MW, Paulus LA, Williston SK, et al. Neurocognitive function in monozygotic twins

discordant for combat exposure: relationship to posttraumatic stress disorder. J Abnorm Psychol. 2006;115:484–95.
100. Thompson WW, Gottesman II. Challenging the conclusion that lower preinduction cognitive ability increases risk for combat-related post-traumatic stress disorder in 2,375 combat-exposed Vietnam War veterans. Mil Med. 2008;173:576–82.
101. Neylan TC, Lenoci M, Rothlind J, et al. Attention, learning, and memory in posttraumatic stress disorder. J Trauma Stress. 2004;17:41–46.
102. Pederson CL, Maurer SH, Kaminski PL, et al. Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. J Trauma Stress. 2004;17:37–40.
103. Zalewski C, Thompson W, Gottesman II. Comparison of neuropsychological test performance in PTSD, generalized anxiety disorder, and control Vietnam veterans. Assessment. 1994;1:133–42.
104. Beers SR, De Bellis M. Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. Am J Psychiatry. 2002;159:483–86.
105. Yasik AE, Saigh PA, Oberfield RA, Halamandaris PV. Posttraumatic stress disorder: memory and learning performance in children and adolescents. Biol Psychiatry. 2007;61:382–88.
106. Bremner JD, Scott TM, Delaney RC, et al. Deficits in short-term memory in posttraumatic stress disorder. Am J Psychiatry. 1993;150:1015–19.
107. Bremner JD, Randall P, Scott TW, et al. Deficits in short-term memory in adult survivors of childhood abuse. Psychiatry Res. 1995;59:97–107.
108. Bustamante V, Mellman TA, David D, Fins AI. Cognitive functioning and the early development of PTSD. J Trauma Stress. 2001;14:791–97.
109. Golier JA, Yehuda R, Lupien SJ, et al. Memory performance in Holocaust survivors with posttraumatic stress disorder. Am J Psychiatry. 2002;159:1682–88.
110. Jenkins MA, Langlais PJ, Delis D, Cohen R. Learning and memory in rape victims with posttraumatic stress disorder. Am J Psychiatry. 1998;155:278–279.
111. Johnsen GE, Asbjornsen AE. Consistent impaired verbal memory in PTSD: a meta-analysis. J Affect Disord. 2008;111:74–82.
112. Moradi AR, Doost HT, Taghavi MR, et al. Everyday memory deficits in children and adolescents with PTSD: performance on the Rivermead Behavioural Memory Test. J Child Psychol Psychiatry. 1999;40:357–61.
113. Parslow RA, Jorm AF. Pretrauma and posttrauma neurocognitive functioning and PTSD symptoms in a community sample of young adults. Am J Psychiatry. 2007;164:509–15.
114. Sachinvala N, Von Scotti H, McGuire M, et al. Memory, attention, function, and mood among patients with chronic posttraumatic stress disorder. J Nerv Ment Dis. 2000;188:818–23.
115. Vasterling JJ, Brailey K, Constans JI, Sutker PB. Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology. 1998;12:125–33.
116. Vasterling JJ, Brailey K, Sutker PB. Olfactory identification in combat-related posttraumatic stress disorder. J Trauma Stress. 2000;13:241–53.
117. Yehuda R, Keefe RSE, Harvey PD, et al. Learning and memory in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1995;152:137–39.
118. Uddo M, Vasterling JJ, Brailey K, Sutker PB. Memory and attention in combat-related post-traumatic stress disorder (PTSD). J Psychopathol Behav Assess. 1993;15:43–53.
119. Jelinek L, Jacobsen D, Kellner M. Verbal and nonverbal memory functioning in posttraumatic stress disorder. J Clin Exp Neuropsychol. 2006;28:940–48.
120. Stein MB, Hanna C, Vaerum V, Koverola C. Memory functioning in adult women traumatized by childhood sexual abuse. J Trauma Stress. 1999;12:527–34.
121. Yehuda R, Golier JA, Harvey PD, et al. Relationship between cortisol and age-related memory impairments in Holocaust survivors with PTSD. Psychoneuroendocrinology. 2005;30:678–87.
122. Brewin CR, Kleiner JS, Vasterling JJ, Field AP. Memory for emotionally neutral information in posttraumatic stress disorder: a meta-analytic investigation. J Abnorm Psychol. 2007;116:448–63.
123. Dalgleish T, Rolfe J, Golden A-M, et al. Reduced autobiographical memory specificity and posttraumatic stress: exploring the contributions of impaired executive control and affect regulation. J Abnorm Psychol. 2008;117:236–41.
124. McNally RJ, Lasko NB, Macklin ML, Pitman RK. Autobiographical memory disturbance in combat-related posttraumatic stress disorder. Behav Res Ther. 1995;33:619–30.
125. McNally RJ, Litz BT, Prassas A, Shin LM. Emotional priming of autobiographical memory in post-traumatic stress disorder. Cogn Emot. 1994;8:351–67.
126. Sutherland K, Bryant RA. Autobiographical memory in posttraumatic stress disorder before and after treatment. Behav Res Ther. 2007;45:2915–23.
127. Schönfeld S, Ehlers A, Böllinghaus I, Rief W. Overgeneral memory and suppression of trauma memories in posttraumatic stress disorder. Memory. 2007;15:339–52.
128. Christianson S. Emotional stress and eyewitness memory: a critical review. Psychol Bull. 1992;112:284–309.
129. Conway MA. Memory and the self. J Mem Lang. 2005;53:594–628.
130. Golden A-M, Dalgleish T, Mackintosh B. Levels of specificity of autobiographical memories and of

biographical memories of the deceased in bereaved individuals with and without complicated grief. J Abnorm Psychol. 2007;116:786–95.
131. Safer MA, Christianson S, Autry MW, Österlund K. Tunnel memory for traumatic events. Appl Cogn Psychol. 1998;12:99–117.
132. Verfaellie M, Vasterling JJ. Memory in PTSD: a neurocognitive approach. In: Shiromani P, Keane TM, LeDoux J, editors. Neurobiology of PTSD. Totowa, NJ: Humana Press; 2009. pp. 105–132.
133. Beckham JC, Crawford AL, Feldman ME. Trail making test performance in Vietnam combat veterans with and without posttraumatic stress disorder. J Trauma Stress. 1998;11:811–9.
134. Meewisse ML, Nijdam MJ, de Vries GJ, et al. Disaster-related posttraumatic stress symptoms and sustained attention: evaluation of depressive symptomatology and sleep disturbances as mediators. J Trauma Stress. 2005;18:299–302.
135. Golier J, Yehuda R, Cornblatt B, et al. Sustained attention in combat-related posttraumatic stress disorder. Integr Physiol Behav Sci. 1997;32:52–61.
136. Jenkins MA, Langlais PJ, Delis DA, Cohen RA. Attentional dysfunction associated with posttraumatic stress disorder among rape survivors. Clin Neuropsychol. 2000;14:7–12.
137. McFarlane AC, Weber DL, Clark CR. Abnormal stimulus processing in posttraumatic stress disorder. Biol Psychiatry. 1993;34:311–20.
138. Veltmeyer MD, Clark CR, McFarlane AC, et al. Integrative assessment of brain and cognitive function in post-traumatic stress disorder. J Integr Neurosci. 2005;4:145–59.
139. Barrett DH, Green ML, Morris R, et al. Cognitive functioning and posttraumatic stress disorder. Am J Psychiatry. 1996;153:1492–94.
140. Leskin LP, White PM. Attentional networks reveal executive function deficits in posttraumatic stress disorder. Neuropsychology. 2007;21:275–84.
141. Twamley EW, Hami S, Stein MB. Neuropsychological function in college students with and without posttraumatic stress disorder. Psychiatry Res. 2004;126:265–74.
142. Sutker PB, Vasterling JJ, Brailey K, Allain AN. Memory, attention, and executive deficits in POW survivors: contributing biological and psychological factors. Neuropsychology. 1995;9:118–25.
143. Koenen KC, Driver KL, Oscar-Berman M, et al. Measures of prefrontal system dysfunction in posttraumatic stress disorder. Brain Cogn. 2001;45:64–78.
144. Savic I, Bookheimer SY, Fried I, Engel J Jr. Olfactory bedside test: a simple approach to identify temporo-orbitofrontal dysfunction. Arch Neurol. 1997;54:162–68.
145. Crowell TA, Kieffer KM, Siders CA. Neuropsychological findings in combat-related posttraumatic stress disorder. Clin Neuropsychol. 2002;16:310–21.
146. Sullivan K, Krengel M, Proctor SP, et al. Cognitive functioning in treatment-seeking Gulf War veterans: pyridostigmine bromide use and PTSD. J Psychopathol Behav Assess. 2003;25:95–103.
147. Gurvits TV, Lasko NB, Repak AL, et al. Performance on visuospatial copying tasks in individuals with chronic posttraumatic stress disorder. Psychiatry Res. 2002;112:263–68.
148. Stein MB, Kennedy CM, Twamley EW. Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. Biol Psychiatry. 2002;52:1079–88.
149. Vasterling JJ, Rogers C, Kaplan E. Qualitative block design analysis in posttraumatic stress disorder. Assessment. 2000;7:217–26.
150. Gilbertson MW, Williston SK, Paulus LA, et al. Configural cue performance in identical twins discordant for posttraumatic stress disorder: theoretical implications for the role of hippocampal function. Biol Psychiatry. 2007;62:513–20.
151. Vasterling JJ, Duke LM, Tomlin H, et al. Global-local visual processing in posttraumatic stress disorder. J Int Neuropsychol Soc. 2004;10:709–18.
152. Villarreal G, Hamilton DA, Petropoulos H, et al. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. Biol Psychiatry. 2002;52:119–25.
153. Metzger LJ, Paige SR, Carson MA, et al. PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. J Abnorm Psychol. 2004;113:324–29.
154. Yehuda R, Golier JA, Tischler L, et al. Learning and memory in aging combat veterans with PTSD. J Clin Exp Neuropsychol. 2005;27:504–15.
155. Yehuda R, Tischler L, Golier JA, et al. Longitudinal assessment of cognitive performance in Holocaust survivors with and without PTSD. Biol Psychiatry. 2006;60:714–21.
156. Weathers FW, Keane TM, Davidson JR. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety. 2001;13:132–56.
157. Davidson J, Smith R, Kudler H. Validity and reliability of the DSM-III criteria for posttraumatic stress disorder. Experience with a structured interview. J Nerv Ment Dis. 1989;177:336–41.
158. Foa D, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. J Trauma Stress. 1993;6:459–74.
159. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders, clinician version. Arlington, VA: American Psychiatric Publishing, Inc; 1997.
160. Weathers FW, Litz BT, Herman D, et al. The PTSD Checklist (PCL): reliability, validity, and diagnostic utility. San Antonio, TX: Annual Convention of the

International Society for Traumatic Stress Studies; 1993.
161. Davidson JR, Book SW, Colket JT, et al. Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med. 1997;27:153–60.
162. Weiss DS, Marmar CR. The Impact of Event Scale – Revised. In: Wilson J, Keane TM, editors. Assessing psychological trauma and PTSD. New York, NY: Guilford Press; 1996. pp. 399–411.
163. Foa EB, Cashman L, Jaycox LH, Perry BD. The validation of a self-report measure of posttraumatic stress disorder: The Posttraumatic Diagnostic Scale. Psychol Assess. 1997;9:445–51.
164. Weathers FW, Keane TM, King LA, et al. Psychometric theory in the development of posttraumatic stress disorder assessment tools. Assessing psychological trauma and PTSD. New York, NY: Guilford Press; 1997. pp. 98–135.
165. Keane TM, Caddell JM, Taylor KL. Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: three studies in reliability and validity. J Consult Clin Psychol. 1988;56:85–90.
166. King LA, King DW, Leskin G, Foy DW. The Los Angeles Symptom Checklist: a self-report measure of posttraumatic stress disorder. Assessment. 1995;2:1–17.
167. Hammarberg M. Penn Inventory for Posttraumatic Stress Disorder: psychometric properties. Psychol Assess. 1992;4:67–76.
168. Briere J. Trauma Symptom Inventory Professional manual. Odessa, FL: Psychological Assessment Resources; 1995.
169. Nader K, Kriegler JA, Blake DD, et al. Clinician Administered PTSD Scale, child and adolescent version. White River Junction, VT: National Center for PTSD; 1996.
170. Briere J. Trauma Symptom Checklist for children: professional manual. Odessa, FL: Psychol Assess Resources; 1996.
171. Scheeringa MS, Zeanah CH. PTSD semi-structured interview and observation record for infants and young children. New Orleans, LA: Department of Psychiatry and Neurology, Tulane University Health Sciences Center; 1994.
172. Frederick C, Pynoos R, Nader K. Child Post-traumatic Stress Disorder Reaction Index. Los Angeles, CA: Trauma Psychiatry Service, University of California at Los Angeles; 1992.
173. Hawkins SS, Radcliffe J. Current measures of PTSD for children and adolescents. J Pediatr Psychol. 2006;31:420–30.
174. Keane TM, Brief DJ, Pratt EM, et al. Assessment of PTSD and its comorbidities in adults. In: Friedman MJ, Keane TM, Resick PA, editors. Handbook of PTSD: science and practice. New York, NY: Guilford Press; 2007. pp. 279–305.
175. Norris FH, Hamblen JL. Standardized self-report measures of civilian trauma and PTSD. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD. 2nd ed. New York, NY: Guilford Press; 2004. pp. 63–102.
176. Stover CS, Berkowitz S. Assessing violence exposure and trauma symptoms in young children: a critical review of measures. J Trauma Stress. 2005;18:707–17.
177. Oquendo MA, Friend JM, Halberstam B, et al. Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. Am J Psychiatry. 2003;160:580–82.
178. Bremner JD, Yehuda R. The relationship between cognitive and brain changes in posttraumatic stress disorder. In: Yehuda R, editor. Psychobiology of posttraumatic stress disorders: a decade of progress, vol. 1071. Malden, MA: Blackwell; 2006. pp. 80–6.
179. Constant EL, Adam S, Gillain B, et al. Effects of sertraline on depressive symptoms and attentional and executive functions in major depression. Depress Anxiety. 2005;21:78–89.
180. Davis LL, Frazier EC, Williford RB, Newell JM. Long-term pharmacotherapy for post-traumatic stress disorder. CNS Drugs. 2006;20:465–76.
181. Siepmann M, Grossmann J, Muck-Weymann M, Kirch W. Effects of sertraline on autonomic and cognitive functions in healthy volunteers. Psychopharmacology (Berl). 2003;168:293–98.
182. Wadsworth EJ, Moss SC, Simpson SA, Smith AP. SSRIs and cognitive performance in a working sample. Hum Psychopharmacol. 2005;20:561–72.
183. Austin MP, Mitchell P, Wilhelm K, et al. Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? Psychol Med. 1999;29:73–85.
184. Himanen L, Portin R, Isoniemi H, et al. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. Neurology. 2006;66:187–92.
185. Leroi I, Sheppard JM, Lyketsos CG. Cognitive function after 11.5 years of alcohol use: relation to alcohol use. Am J Epidemiol. 2002;156:747–52.
186. Ravnkilde B, Videbech P, Clemmensen K, et al. The Danish PET/depression project: cognitive function and regional cerebral blood flow. Acta Psychiatr Scand. 2003;108:32–40.
187. van Achterberg ME, Rohrbaugh RM, Southwick SM. Emergence of PTSD in trauma survivors with dementia. J Clin Psychiatry. 2001;62:206–7.
188. Chen JK, Johnston KM, Petrides M, Ptito A. Neural sub-strates of symptoms of depression following concussion in male athletes with persisting post-concussion symptoms. Arch Gen Psychiatry. 2008;65:81–9.
189. Drake AI, Gray N, Yoder S, et al. Factors predicting return to work following mild traumatic brain injury: a discriminant analysis. J Head Trauma Rehabil. 2000;15:1103–12.
190. Kennedy JE, Jaffee MS, Leskin GA, et al. Posttraumatic stress disorder and posttraumatic stress

disorder-like symptoms and mild traumatic brain injury. J Rehabil Res Dev. 2007;44:895–920.
191. King KA, Hough MS, Vos P, et al. Word retrieval following mild TBI: implications for categorical deficits. Aphasiology. 2006;20:233–45.
192. Malojcic B, Mubrin Z, Coric B, et al. Consequences of mild traumatic brain injury on information processing assessed with attention and short-term memory tasks. J Neurotrauma. 2008;25:30–7.
193. Milders M, Fuchs S, Crawford JR. Neuropsychological impairments and changes in emotional and social behaviour following severe traumatic brain injury. J Clin Exp Neuropsychol. 2003;25:157–72.
194. Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: a review of the literature. Brain Inj. 2006;20:117–32.
195. Raskin SA, Rearick E. Verbal fluency in individuals with mild traumatic brain injury. Neuropsychology. 1996;10:416–22.
196. Ryan LM, Warden DL. Post concussion syndrome. Int Rev Psychiatry. 2003;15:310–6.
197. Vanderploeg RD, Curtiss G, Luis CA, Salazar AM. Long-term morbidities following self-reported mild traumatic brain injury. J Clin Exp Neuropsychol. 2007;29:585–98.
198. Yang CC, Tu YK, Hua MS, Huang SJ. The association between the postconcussion symptoms and clinical outcomes for patients with mild traumatic brain injury. J Trauma. 2007;62:657–63.
199. Fear NT, Jones E, Groom M, et al. Symptoms of post-concussional syndrome are non-specifically related to mild traumatic brain injury in UK Armed Forces personnel on return from deployment in Iraq: an analysis of self-reported data. Psychol Med. 2008;39(8):1379–87.
200. Hoge CW, McGurk D, Thomas JL, et al. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med. 2008;358:453–63.
201. Bigler ED. Mild traumatic brain injury: causality considerations from a neuroimaging and neuropathology perspective. In: Young G, Kane AW, Nicholson K, editors. Psychological knowledge in court: PTSD, pain, and TBI. New York, NY: Springer Science + Business Media; 2006. pp. 308–34.
202. Wilde EA, Bigler ED, Hunter JV, et al. Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. Dev Med Child Neurol. 2007;49:294–9.
203. Gaylord KM, Cooper DB, Mercado JM, et al. Incidence of posttraumatic stress disorder and mild traumatic brain injury in burned service members: preliminary report. J Trauma. 2008;64:S200–5, discussion S205–6.
204. Chemtob CM, Muraoka MY, Wu-Holt P, et al. Head injury and combat-related posttraumatic stress disorder. J Nerv Ment Dis. 1998;186:701–8.
205. Mollica RF, Henderson DC, Tor S. Psychiatric effects of traumatic brain injury events in Cambodian survivors of mass violence. Br J Psychiatry. 2002;181:339–47.
206. Vasterling JJ, Constans JI, Hanna-Pladdy B. Head injury as a predictor of psychological outcome in combat veterans. J Trauma Stress. 2000;13:441–51.
207. Isaac CL, Cushway D, Jones GV. Is posttraumatic stress disorder associated with specific deficits in episodic memory? Clin Psychol Rev. 2006;26:939–55.
208. Constans JI. Information-processing biases in PTSD. In: Vasterling JJ, CR Brewin, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. pp. 105–30.
209. Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: a review of the empirical literature. Clin Psychol Rev. 2000;28:1041–65.
210. Karl A, Malta LS, Maercker A. Meta-analytic review of event-related potential studies in post-traumatic stress disorder. Biol Psychol. 2006;71:123–47.
211. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643–62.
212. Cassiday KL, McNally RJ, Zeitlin SB. Cognitive processing of trauma cues in rape victims with post-traumatic stress disorder. Cogn Ther Res. 1992;16:283–95.
213. Foa EB, Feske U, Murdock TB, et al. Processing of threat-related information in rape victims. J Abnorm Psychol. 1991;100:156–62.
214. Kaspi SP, McNally RJ, Amir N. Cognitive processing of emotional information in posttraumatic stress disorder. Cogn Ther Res. 1995;19:433–44.
215. McNally RJ, Kaspi SP, Riemann BC, Zeitlin SB. Selective processing of threat cues in posttraumatic stress disorder. J Abnorm Psychol. 1990;99:398–402.
216. Williams JMG, Mathews A, MacLeod C. The emotional Stroop task and psychopathology. Psychol Bull. 1996;120:3–24.
217. Constans JI, McCloskey MS, Vasterling JJ, et al. Suppression of attentional bias in PTSD. J Abnorm Psychol. 2004;113:315–23.
218. Bryant RA, Harvey A. Posttraumatic stress reaction in volunteer fire fighters. Scand J Work Environ Health. 1996;19:121–5.
219. Buckley TC, Blanchard EB, Hickling EJ. Automatic and strategic processing of threat stimuli: a comparison between PTSD, panic disorder, and nonanxiety controls. Cogn Ther Res. 2002;26:97–115.
220. Bar-Haim Y, Lamy D, Pergamin L, et al. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol Bull. 2007;133:1–24.
221. Mathews A, MacLeod C. Induced processing biases have causal effects on anxiety. Cogn Emot. 2002;16:331–54.
222. Mobini S, Grant A. Clinical implications of attentional bias in anxiety disorders: an integrative

literature review. Psychother Theory Res Pract Training. 2007;44:450–62.
223. Friedman MJ. Pharmacological approaches to cognitive deficits associated with PTSD. In: Vasterling JJ, Brewin CR, editors. Neuropsychology of PTSD: biological, cognitive, and clinical perspectives. New York, NY: Guilford Press; 2005. pp. 292–325.
224. Friedman MJ, Davidson JRT. Pharmacotherapy for PTSD. In: Friedman MJ, Keane TM, Resick PA, editors. Handbook of PTSD: science and practice. New York, NY: Guilford Press; 2007. pp. 376–405.
225. Department of Veterans Affairs/Department of Defense. VA/DoD clinical practice guideline for the management of post-traumatic stress. Version 1.0. Washington, DC: Veterans Health Administration, Department of Defense; 2004.
226. American Psychiatric Association. Practice guidelines for the treatment of patients with acute stress disorder and posttraumatic stress disorder. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders: compendium 2006. Arlington, VA: American Psychiatric Association; 2006. pp. 1003–71.
227. Friedman MJ, Davidson JRT, Mellman TA, Southwick SM. Psychotherapy. In: Foa EB, Keane TM, Friedman MJ, Cohen JA, editors. Effective treatments for PTSD: practice guidelines from the International Society for Traumatic Stress Studies. New York, NY: Guilford Press; 2004. pp. 84–105.
228. Vermetten E, Vythilingam M, Southwick SM, et al. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry. 2003;54:693–702.
229. Seedat S, Warwick J, van Heerden B, et al. Single photon emission computed tomography in posttraumatic stress disorder before and after treatment with a selective serotonin reuptake inhibitor. J Affect Disord. 2004;80:45–53.
230. Friedman MJ. What might the psychobiology of posttraumatic stress disorder teach us about future approaches to pharmacotherapy? J Clin Psychiatry. 2000;61(Suppl 7):44–51.
231. Nemeroff CB, Bremner JD, Foa EB, et al. Posttraumatic stress disorder: a state-of-the-science review. J Psychiatr Res. 2006;40:1–21.
232. Resick PA, Monson CM, Gutner C. Psychosocial treatments for PTSD. In: Friedman MJ, Keane TM, Resick PA, editors. Handbook of PTSD: science and practice. New York, NY: Guilford Press; 2007. pp. 330–58.
233. Institutes of Medicine. Treatment of PTSD: an assessment of the evidence. Washington, DC: Institutes of Medicine of the National Academies; 2007.
234. Bryant RA, Felmingham K, Kemp A, et al. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med. 2008;38:555–61.
235. Felmingham K, Kemp A, Williams L, et al. Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. Psychol Sci. 2007;18:127–9.
236. Bryant RA, Felmingham K, Whitford TJ, et al. Rostral anterior cingulate volume predicts treatment response to cognitive–behavioural therapy for posttraumatic stress disorder. J Psychiatry Neurosci. 2008;33:142–6.
237. Wild J, Gur RC. Verbal memory and treatment response in post-traumatic stress disorder. Br J Psychiatry. 2008;193:254–5.
238. Shapiro DA. 'Validated' treatments and evidence-based psychological services. Clin Psychol (New York). 1996;3:256–9.
239. Cahill SP, Carrigan MH, Frueh BC. Does EMDR work? and if so, why?: a critical review of controlled outcome and dismantling research. J Anxiety Disord. 1999;13:5–33.
240. Perkins BR, Rouanzoin CC. A critical evaluation of current views regarding eye movement desensitization and reprocessing (EMDR): clarifying points of confusion. J Clin Psychol. 2002;58:77–97.
241. McNally RJ. EMDR and mesmerism: a comparative historical analysis. J Anxiety Disord. 1999;13:225–36.
242. Lindauer RJ, Booij J, Habraken JB, et al. Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial. Psychol Med. 2008;38:543–54.
243. Gold JI, Taft CT, Keehn MG, et al. PTSD symptom severity and family adjustment among female Vietnam veterans. Mil Psychol. 2007;19:71–81.
244. Jordan BK, Marmar CR, Fairbank JA, et al. Problems in families of male Vietnam veterans with posttraumatic stress disorder. J Consult Clin Psychol. 1992;60:916–26.
245. Taft CT, Schumm JA, Panuzio J, Proctor SP. An examination of family adjustment among Operation Desert Storm veterans. J Consult Clin Psychol. 2008;76:648–56.
246. Dekel R, Solomon Z. Marital relations among former prisoners of war: contribution of posttraumatic stress disorder, aggression, and sexual satisfaction. J Fam Psychol. 2006;20:709–12.
247. Sherman MD, Sautter F, Jackson MH, et al. Domestic violence in veterans with posttraumatic stress disorder who seek couples therapy. J Marital Fam Ther. 2006;32:479–90.
248. Taft CT, Street AE, Marshall AD, et al. Posttraumatic stress disorder, anger, and partner abuse among Vietnam combat veterans. J Fam Psychol. 2007;21:270–7.
249. Riggs DS, Byrne CA, Weathers FW, Litz BT. The quality of the intimate relationships of male Vietnam veterans: problems associated with

posttraumatic stress disorder. J Trauma Stress. 1998;11:87–101.
250. Roberts WR. Interpersonal problems of Vietnam combat veterans with symptoms of posttraumatic stress disorder. J Abnorm Psychol. 1982;91:444–50.
251. Beckham JC, Lytle BL, Feldman ME. Caregiver burden in partners of Vietnam War veterans with posttraumatic stress disorder. J Consult Clin Psychol. 1996;64:1068–72.
252. Westerink J, Giarratano L. The impact of posttraumatic stress disorder on partners and children of Australian Vietnam veterans. Aust N Z J Psychiatry. 1999;33:340.
253. Lauterbach D, Bak C, Reiland S, et al. Quality of parental relationships among persons with a lifetime history of posttraumatic stress disorder. J Trauma Stress. 2007;20:161–72.
254. Samper RE, Taft CT, King DW, King LA. Posttraumatic stress disorder symptoms and parenting satisfaction among a national sample of male Vietnam veterans. J Trauma Stress. 2004;17:311–5.
255. Yehuda R, Halligan SL, Bierer LM. Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring. J Psychiatr Res. 2001;35:261–70.
256. Ben Arzi N, Solomon Z, Dekel R. Secondary traumatization among wives of PTSD and post-concussion casualties: distress, caregiver burden and psychological separation. Brain Inj. 2000;14:725–36.
257. Dirkzwager AJE, Bramsen I, Ader H, van der Ploeg HM. Secondary traumatization in partners and parents of Dutch peacekeeping soldiers. J Fam Psychol. 2005;19:217–26.
258. Goff BSN, Reisbig AMJ, Bole A, et al. The effects of trauma on intimate relationships: a qualitative study with clinical couples. Am J Orthopsychiatry. 2006;76:451–60.
259. Solomon Z, Waysman M, Levy G, et al. From front line to home front: a study of secondary traumatization. Fam Process. 1992;31:289–302.
260. Dirkzwager AJE, Bramsen I, van der Ploeg HM. Social support, coping, life events, and posttraumatic stress symptoms among former peacekeepers: a prospective study. Pers Individ Dif. 2003;34:1545–59.
261. King LA, King DW, Fairbank JA, et al. Resilience-recovery factors in post-traumatic stress disorder among female and male Vietnam veterans: hardiness, postwar social support, and additional stressful life events. J Pers Soc Psychol. 1998;74:420–34.
262. Monson CM, Rodriguez BF, Warner R. Cognitive–behavioral therapy for PTSD in the real world: do interpersonal relationships make a real difference? J Clin Psychol. 2005;61:751–61.
263. Monson CM, Schnurr PP, Stevens SP, Guthrie KA. Cognitive–behavioral couple's treatment for posttraumatic stress disorder: initial findings. J Trauma Stress. 2004;17:341–4.
264. Sherman MD, Zanotti DK, Jones DE. Key elements in couples therapy with veterans with combat-related posttraumatic stress disorder. Prof Psychol Res Pr. 2005;36:626–33.

Part VII
Metabolic Disease

Chapter 28

Nutrition in Neurocognition and Mental Health

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Introduction

While it is widely known and accepted that proper nutrition is vital to physical health throughout the lifecycle [1, 2], the relationship between nutrition and neurocognition and mental health has been less acknowledged [3]. This chapter will review and summarize the current literature on the impact of nutrition on neurocognition and mental health. Folate, vitamin B12, vitamin D, choline, iodine, iron, zinc, omega-3 fatty acids, and overall diet quality show the most evidence suggesting potential influences, and will therefore be targeted here. Their effects on neurocognition and mental health throughout the lifespan (prenatal development, childhood, adolescence, and adulthood) will be reviewed. Detailed explanations of the involved biological processes and metabolism of nutrients are beyond the scope of this chapter and interested readers can see [4–8] for further reading. Additional aspects of nutrition including the role of probiotics, hydration, and nutraceuticals (other than l-methyl-folate) are also outside the scope of this chapter [see [9–11]] for further reading. Implications of the existing evidence, recommendations for advancing future research, and public health policy matters will also be discussed. Overall, it is hoped that this chapter will enhance understanding and consideration of the potential role of nutritional factors in psychological and neuropsychological evaluations.

Approach

A PubMed and Cochrane Library search using a combination of the following key terms: "prenatal," "pregnancy," "maternal," "children," "adolescents," "adults," "nutrition," "diet," "folate or folic acid," "vitamin B12," "vitamin D," "iron," "iodine," "choline," "zinc," "multivitamins," "omega-3 fatty acids," "BMI" AND "cognition," "neurocognition," "neurodevelopment," "depression," "schizophrenia," "attention deficit hyperactivity disorder," "autism," yielded 185 useable papers including several systematic reviews [11] and meta-analyses [23], included in this paper. Both animal and human studies were included. It was notable that literature included a combination of nutrition and psychological or psychiatric journals.

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Overall, the available literature indicates that the research related to nutrition and neurocognition and mental health is steadily increasing, but high--quality, robust studies are still needed.

Background

Increasing evidence indicates that both nutritional deficiencies and excesses have deleterious effects on brain development and functionality, potentially resulting in impairments in neurocognitive functioning or psychiatric/psychological disorders [3, 12]. Other emerging evidence suggests that conversely, adequate nutrition promotes optimal brain development, neurocognition, and mental health by preventing, mitigating, and/or reversing negative effects [13].

One of the earliest studies identifying links between nutrition and neurocognition and mental health was in 1915 by psychiatrist, H. Douglas Singer, who found that adults with Pellegra, a disease from niacin (Vitamin B-3) deficiency causing dermatitis and diarrhea, also experienced dementia and negative changes in mental health, including anxiety and depression [14]. In 1992, a landmark study based on data from the Dutch Winter Famine of 1944–1945 during World War II, examined a cohort of children born to mothers exposed to starvation (400–800 calories per day) throughout their pregnancy, and found that these offspring had a twofold increased risk of developing schizophrenia compared to controls [15]. Utilizing the same birth cohort, later research found that other subjects without schizophrenia experienced impaired cognitive function (selective attention) at ages 56–59, but did not have impaired cognition when tested at 19 years of age [16]. Although the degree of vitamin deficiency and malnutrition was extreme in these studies, they elicited important clues about the crucial role of nutrition in neurodevelopment and long-term neurocognitive and mental health and prompted subsequent research in this area. More recent evidence has suggested that these nutritional effects are mediated through multiple interrelated biological processes and pathways including methylation, inflammation, neuroplasticity, epigenetics, oxidative stress, gut microbiota, and the immune system [10, 17, 18], but the exact physiological mechanisms are still not yet fully elucidated.

Given the increasing evidence supporting the intricate relationship between nutrition and neurocognitive and neuropsychiatric disorders, it is essential to expand our understanding and awareness of these important links. Moreover, neurocognitive and neuropsychiatric disorders are an enormous emotional and economic burden to individuals, families, and society. According to the World Health Organization (WHO), neuropsychiatric disorders are the leading cause of global disability and projected to grow exponentially, potentially becoming a worldwide epidemic [19, 20]. Pharmacotherapy and psychotherapy are predominate treatment modalities for neuropsychiatric disorders but can be cost-prohibitive. Pharmacotherapy may also lead to undesirable side effects, which, in addition to expense, may interfere with compliance and therefore, proper treatment. Cognitive impairment and dementia are also increasing worldwide and predicted to increase significantly more in developing regions where four-fifths of the people older than 60 years will be living in developing countries in Africa, Asia, or Latin America [19–22]. Currently, no medications have been shown to effectively prevent progression or conversion to Alzheimer's disease (AD). Therefore, the role of nutritional factors as alternative preventative and therapeutic opportunities, for both current and future generations, is worth examining.

Micronutrients (*Vitamins and Minerals*)

The brain begins to develop three weeks after fertilization and grows rapidly during pregnancy. Therefore, adequate prenatal nutrition including specific micro/macronutrients and fats are vital, particularly during critical periods of growth and development [23]. Both individual and synergistic actions of nutrients affect brain development and functionality. For example, a deficiency in copper may lead to alterations in neuronal metabolism and

also interfere with iron storage and utilization in fetal and neonatal stages of brain development [24, 25]. Copper (food sources include beef liver, sunflower seeds, lentils, almonds, and apricots) and vitamin A (food sources include beef liver, carrots, and green leafy vegetables) play a critical role in the development of brain substrates for cognition, and their deficiencies may result in adverse effects on cognitive and psychological health. While research has been lacking regarding the specific subsequent effects on cognition, a recent animal study demonstrated that prenatal marginal vitamin A deficiency (mVAD) was associated with impaired learning and memory in adult rats [26]. In a follow-up of a placebo-controlled, randomized trial (n = 1,577) Ali et al. [27] found that at 8 years of age, Bangladeshi children of mothers who took vitamin A supplements (from the first trimester through 12 weeks postpartum) and who also received neonatal vitamin A supplementation (single dose at birth), had better executive function as measured by the Developmental NEuroPSYchological Assessment, 2nd edition, (NEPSY-II), as well as better performance in reading, spelling, and math as measured by a scholastic achievement test compared to the placebo group. The story was translated to Bangladesh and the pictures were modified for cultural appropriateness, but this may still be a limitation and potentially skew results. Also, since the study was conducted in rural Bangladesh, it is only generalizable to similar regions. Therefore, additional research is needed in more heterogeneous populations to further investigate these preliminary findings.

Folate and ***Folic Acid*** **(*FA*)** are natural and synthetic forms of vitamins, respectively, which are important for brain and central nervous system (CNS) development as they are involved in methylation, myelin formation, and neurotransmitter synthesis [28, 29]. Foods containing folate include liver, spinach, black-eyed peas, fortified cereals, rice, asparagus, pasta, and brussels sprouts, from highest to lowest amount per serving, respectively. Folic acid supplementation (FAS) is routinely recommended periconceptionally and prenatally to prevent neural tube defects (NTDs) [30], but recent research suggests that prenatal folate status and/or supplementation also affects cognition in children [31]. One systematic review of 14 studies found mixed results regarding the benefit of prenatal FAS, and cognition in children [32]. However, a recent subsequent systematic review of 22 studies found 15 studies showing that FAS during pregnancy may have beneficial effects on neurodevelopment, cognitive function, intellectual motor function, and risk of Autism Spectrum Disorders (ASDs). Notably, one of the 22 studies showed potential detrimental effects with excessive doses [33]. Similarly, a recent large population study (n = 1682) found that adequate folate or folic acid may be beneficial to cognition, but excessive levels were associated with negative effects on cognition including lower scores on verbal, verbal memory, posterior cognitive functions, and cognitive function of left posterior cortex in young children assessed using the adapted McCarthy Scales of Children's Abilities (MSCA) [30].

In contrast, low folate levels in early pregnancy may increase the risk of internalizing and externalizing problems in children [31, 34]. Steenweg-de Graaff et al. [35] found that children (aged 3 years) whose mothers had prenatal folate deficiency had a higher risk of emotional symptoms (anxiety/depression, withdrawal, and somatic complaints) but not behavioral problems (attention problems and aggressive behavior) as assessed using the Child Behavior Checklist (CBCL). Additionally, all children of mothers who did not use prenatal FAS or began supplementation late in pregnancy were at higher risk of emotional problems than offspring of mothers who began FAS periconceptionally. Authors state, however, that possibly not only higher socioeconomic status, but also better home environment or other indicators of social status, which are associated with higher plasma folate concentrations, account for the association with child emotional problems. In another study, prenatal folic acid supplementation, but not prenatal folate status (at 13 weeks of pregnancy) was associated with a reduction in autistic traits in children compared to children whose mothers did not take folic acid supplements prenatally or during pregnancy [36]. This suggests that folic acid supplements may have protective effects on mental health of offspring if it is introduced periconceptually or early in pregnancy.

An important consideration with respect to FAS in pregnant women is the methylenetetrahydrofolate reductase (MTHFR) 677 gene mutations which result in a defect in the enzyme that metabolizes folic acid and requires supplementation with the methylated form of folate (l-methylfolate) for proper metabolism and absorption [37]. This is particularly significant as maternal MTHFR 677 T allele has been associated with problems in neurodevelopment [38] and increased risk of depression, bipolar disorder, and schizophrenia [39, 40]. This may be partially due to a lower baseline folate status [41, 42]; therefore, affected women would require a significant (and potentially unrealistic) amount of folate from food and/or supplementation with l-methylfolate to compensate. Folate/FA intake may also play an important role in psychological health for adults. A recent systematic review and meta-analysis of 11 studies (n = 7,949 both gender data; 3,409 gender-specific data) reported a statistically significant association between low folate levels and depression in older adults (55–99 years) [42]. Similarly, a recent meta-analysis of 43 studies also reported a significant but small effect where individuals with depression had lower folate levels and intake than those without depression. Additionally, patients with depression had lower folate intake compared to those without depression [43]. In support of these findings, higher doses of folate, specifically l-methylfolate, may be effective as adjunctive antidepressant (SSRI) therapy [44, 45]. Although subjects were not specifically tested for MTHFR polymorphisms in the aforementioned studies, these findings are especially significant for individuals with the MTHFR C677T genotype as they have been shown to have lower baseline folate levels, an increased risk of depression [46], and require l-methylfolate versus regular FAS for effectiveness.

In summary, FAS may have protective effects on cognition and mental health of children if it is introduced periconceptually or early in pregnancy. More studies are needed to validate these findings and elucidate why prenatal FAS, but not folate status, may lessen traits of autism in children. Furthermore, given the genetic predisposition of mental illness in individuals with MTHFR polymorphisms, additional research utilizing l-methylfolate prenatally in this population is warranted. In adults, folate/FA seems to help to prevent depression and supplementation with l-methylfolate may augment effectiveness of SSRI therapy, particularly in those with MTHFR polymorphisms. While additional research is needed to support these findings, prenatal education regarding appropriate FAS dosage and type seems prudent to prevent potential detrimental effects on children's cognition and psychological health.

Vitamin B12 (cobalamin) is an essential vitamin found in fish, meat, poultry, eggs, milk, and other dairy products [47]. Therefore, strict vegans (no consumption of any animal products) are at risk for vitamin B12 deficiency. Vitamin B12 plays an important role in methylation reactions [48, 49], brain development, neural myelination, and subsequent cognitive function [48–53]. However, a recent systematic review of seven observational studies reported inconsistent findings regarding prenatal vitamin B12 status or supplementation and its benefits on children's cognition [32]. Only two studies included in the review showed possible negative cognitive impact of severe maternal deficiency. One study found negative effects on children's short-term working memory as measured by the Digit Span Backward Test [54]. Another study found that prenatal vitamin B12 deficiency was negatively associated with mental development as measured by the Spanish version of the Bayley Scales of Infant Development (BSID-II), only among children of mothers who were carriers of the MTHFR TT genotype [55]. Additional studies are needed to examine why effects were shown only in the MTHFR TT genotype group, as this may involve the previously mentioned genetic predisposition toward impaired neurodevelopment and/or lower baseline folate levels in this population, and the interdependence of folate and vitamin B12 for optimal metabolism and utilizations in the body.

In infancy and early childhood, vitamin B12 deficiency may negatively impact neurodevelopment, and subsequent short- or long-term cognition [56–58]. In a study in Nepal by Kvestad et al. [59], vitamin B-12 levels in infancy were associated with poor neurodevelopment and performance on social perception tasks and visuospatial abilities at 5 years of age, as measured by the Ages

and Stages Questionnaire, 3rd edition (ASQ-3) scores, and the Developmental Neuropsychological Assessment, 2nd edition (NEPSY-II), respectively. However, this study was conducted in a very rural area which limits its generalizability. Although a recent review of 17 studies reported that both normal B12 levels and B12 intake from food or supplements were positively associated with improved cognition in children [60], a study in India found that children (6–30 months old) who received vitamin B12 showed significant improvement on gross motor scores. Additionally, children who received both vitamin B-12 and FAS had higher scores in gross motor and problem-solving functioning domains as measured by the ASQ-3 compared to a placebo group [61]. This suggests that vitamin B-12 and folic acid may act synergistically, enhancing their beneficial effects.

In adults, a review of 43 studies [62] found associations between low vitamin B12 levels of cognitive impairment. Also, vitamin B12 supplements improved cognition (as assessed by MMSE, MMSE Syndrom-Kurztest (SKT), MMSE (Chinese version), and Mattis Dementia Rating Scale (MDRS)) only in those with pre--existing vitamin B12 deficiency. Authors stated that there is a small subset of dementias that are reversible with vitamin B12 supplements. A large systematic review and meta-analysis (n = 6,308 both gender data; n = 1,934 gender-specific data) reported a statistically significant overall association between low vitamin B12 and folate levels and depression in older adults (55–99 years), and a statistically significant positive association between low vitamin B12 levels and depression only among women [42].

In summary, findings regarding the benefits of prenatal vitamin B12 supplementation on children's cognition are mixed and inconclusive, but prenatal vitamin B12 deficiency negatively impacts cognition in offspring. In infancy and early childhood, evidence indicates that vitamin B12 status potentially improves aspects of cognition and FA may enhance its beneficial effects. Therefore, supplementation in infants and children with deficiency may improve cognition. Vitamin B12 deficiency has been shown to be associated with cognitive decline and depression in older adults. Notably, in a small subset of dementias, vitamin B12 supplementation may reverse symptomology, but only in those with pre-existing deficiency.

Choline is an essential nutrient involved in modulating gene expression and in production of acetylcholine, and plays an important role in early brain development [63, 64]. It is derived from the diet and from de novo synthesis. It is necessary for overall fetal development in part because it influences stem cell proliferation and apoptosis; therefore, needs are greatly increased during pregnancy. Consequently, approximately 30% of pregnant women tend to be choline deficient [65]. Foods containing the highest amount of choline include liver, eggs, peanuts, beef, soybeans, broccoli, chicken, and fish, respectively [66]. In rodents, low prenatal choline levels have been associated with negative effects on brain development and long-term cognition and behavior in offspring [67]. In humans, however, one randomized, double-blind, placebo-controlled trial study of moderate choline supplementation reported no benefits [68]. Yet, Boeke and colleagues [69] found that children of mothers with the highest intake of choline in the second trimester had better visual memory, as assessed using the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2), at 7 years of age than offspring of mothers with the lowest intake. Similar results were found with choline intake in the first trimester, but effects were not as strong. Authors note that dietary intake data was only noted for the first and second trimesters of pregnancy not for third-trimester or postnatal periods, nor did it consider the child's diet. Also, there was the potential for unmeasured confounding factors, particularly from maternal and paternal memory capacity in the WRAML2 analysis. A more recent randomized, double-blind, controlled feeding study tested reaction time to a visual attention task designed to measure rate of eye movements to locations on a display screen of animated pictures. Findings indicated that infants born to mothers who took twice the recommended amount of choline had a

significantly faster mean reaction time than infants born to mothers who took the recommended amount. Additionally, in the group who received the recommended amount, infants exposed to a longer duration of choline intake were faster. This study was limited by a small sample size of 24 and use of only one type of experimental measure of visual attention.

In another study with a larger sample size (n = 100), there was a significant improvement on measures of inhibition as related to poor sensory gating and attention in infants whose mothers took choline supplements (twice the recommended amount) during pregnancy and received choline for three months after birth [70]. A review of 8 studies examining prenatal choline supplementation and risk of schizophrenia in offspring reported that compared to the placebo group, choline supplementation in the second and third trimesters improved fetal inhibitory neuronal functions, a deficit which has been associated with schizophrenia and ADHD [71]. Therefore, the authors suggest that prenatal choline supplementation could reduce the risk of schizophrenia and ADHD in children, but this has not been examined directly.

An important concern is women with PEMT, (phosphatidylethanolamine N-methyltransferase—choline's principal regulatory enzyme), which are polymorphisms associated with inability to produce additional choline in periods of deprivation. In studies of Asian samples, PEMT polymorphisms have been associated with increased rates of schizophrenia [72]. Given the increased risk of schizophrenia in individuals with PEMT gene mutations and their potential for decreased choline levels during pregnancy, consideration of prenatal choline supplementation is supported; studies of populations in other parts of the world are also justified by these findings.

In summary, these findings indicate that higher doses and a longer duration of choline supplementation prenatally may improve some aspects of cognition in children and potentially reduce the risk of schizophrenia and ADHD later in life for certain groups. However, future longitudinal studies are needed before recommendations to increase prenatal choline intake can be implemented in practice. Also, additional studies investigating PEMT gene mutations in diverse populations are needed.

Vitamin D is important in brain development and function [73], neuromuscular function, and for reduction of inflammation [74, 75]. Fatty fish such as salmon, tuna, and mackerel are the best food sources, but fortified foods such as milk and cereal provide most of the vitamin D in a North American diet [76]. For vegans, mushrooms contain a vitamin D precursor that is activated by the sun's ultraviolet radiation as human skin produces vitamin D when it is exposed to ultraviolet B in sunlight. Vitamin D deficiency is a global problem with an estimated one billion people worldwide suffering from vitamin D deficiency or insufficiency [74, 77, 78]. In one population-based case–control study, neonatal vitamin D levels in both the lowest three quintiles and highest quintile were found to be significantly associated with a twofold elevated risk of schizophrenia in adulthood [79]. The association between high levels of neonatal vitamin D and schizophrenia was an unexpected finding, but authors theorize that a genetic variant in neonates in the highest quintile may affect their ability to convert 25OHD (prohormone in blood that measures vitamin D status) into the active form, 1,25OHD. However, no studies to date have replicated these findings. Therefore, additional research is needed to better understand the relationship between neonatal vitamin D, potential genetic variations affecting vitamin D metabolism and risk of schizophrenia.

According to one systematic review of 26 animal studies and 10 human studies, animal studies suggested that low prenatal vitamin D levels negatively impacted brain development and subsequent functionality and behavior, but evidence from human studies indicated that low prenatal vitamin D status was inconclusively associated with only mild cognitive and psychological impairments in children [80]. A subsequent study in India found no association between prenatal vitamin D levels and cognitive function as measured by the Kaufman Assessment of Battery for Children-II and Wechsler Intelligence Scale for Children-III (that underwent extensive

adaptation to the local cultural context and validation) in children (9–10 years) and adolescents (13–14 years) [81]. However, authors concluded that the evidence was inconclusive due to missing data on maternal vitamin D status (in about 14% of subjects) and lack of information on maternal diet, sunlight exposure, use of vitamin D supplements at time of biomarker testing, and child's vitamin D status. Therefore, additional studies are needed to better understand the role of prenatal vitamin D in children's risk of schizophrenia and cognitive function.

Vitamin D has also been shown to play a role in mental health in children and adolescents. A recent systematic review of 41 studies reported that low levels of vitamin D in childhood and adolescence were associated with psychological symptomology and disorders including depression, ADHD, and autism [82].

In adults, a systematic review and meta-analysis of 26 observational studies and 3 intervention studies (n = 19–9,556) low levels of vitamin D have also been associated with poorer cognition and cognitive decline [83]. However, heterogeneity of the studies including variations in neuropsychological tests and categorizing low (ranging from <25 to <50 nmol/L) and high (ranging from ≥ 50 to ≥1 00 nmol/L) vitamin D are limitations which may affect interpretation of the results. Therefore, additional longitudinal studies with more consistent use of cognitive tests and categorizations of vitamin D level are needed to further evaluate these findings. Low vitamin D levels have been shown to correlate with depression, anxiety, and other psychological disorders, and vitamin D deficiency is found more commonly in adults with mental illness [84–87]. A cross-sectional Dutch study found that Vitamin D deficiency was 4.7 times more common among patients with bipolar disorder, schizophrenia, or schizoaffective disorder than among the Dutch general population [88]. Furthermore, one study of suicide attempters (n = 59), non-suicidal depressed patients (n = 17), and healthy controls (n = 14) found that low levels of vitamin D have also been associated with increased suicide risk as assessed by a structured interview by a psychiatrist [89]. However, the small sample size and homogeneous population limit generalizability. Therefore, additional studies with larger and more heterogeneous groups are needed.

Conversely, adequate vitamin D levels may decrease the risk of depression and anxiety. In a large cross-sectional study of Finnish men and women ages 30–79 years (n = 5371; 354 with depressive disorder and 222 with anxiety disorder), those with a biomarker (25(OH)D (calcidiol); prehormone of vitamin D) indicating higher serum concentrations of vitamin D showed a reduced risk of depression even after adjustment for a large number of sociodemographic, lifestyle, and metabolic factors [90]. Although findings are mixed regarding the benefit of vitamin D supplementation exclusively [91, 92], two separate meta-analyses reported that similar to folate and B12, vitamin D may be effective as adjunctive therapy for depression [9, 91].

In summary, preliminary evidence indicates that low or high prenatal vitamin D levels may be associated with an increased risk of schizophrenia in children, but additional studies are needed to confirm these findings. The effects of prenatal vitamin D supplementation on cognition in children are inconclusive. In some children and adolescents, low vitamin D levels seem to be associated with increased risk for psychiatric disorders including depression, ADHD, and ASD. Low vitamin D levels may also play a role in cognitive performance and decline and psychological disorders in adults. Furthermore, low vitamin D levels may increase the risk of suicidal ideation. Given the above evidence of the association between low vitamin D levels or deficiency and depression and mental illness, additional research should be a priority, especially in suicidal ideation.

Iron is essential for proper development of oligodendrocytes (brain cells that produce myelin) and is a cofactor for several enzymes that synthesize neurotransmitters [93]. Foods rich in iron include lean meat, seafood, poultry, beans, and fortified cereals, breads, green vegetables, and other foods [94]. Iron deficiency is one of the most common nutritional deficiencies in the world, particularly in developing countries [95].

Very low prenatal iron levels may result in permanent alterations in the myelination of neurons and dopamine metabolism [24, 96]. Observational studies have found positive associations between prenatal iron status and cognitive function [97]. A large prospective cohort study (n = 11,656) based on data from the Northern Finnish Birth Cohort Study conducted in 1966, reported that compared to offspring of prenatally anemic mothers, 14- and 16-year-old children of non-anemic mothers had higher school performance scores, as measured by school scores taken at the ages of 14 (self-reported questionnaires) and 16 (school reports) and higher levels of education at the age of 31 [98]. After adjusting for multiple confounders including sex, birth weight, birth month, and a wide range of maternal factors (parity, smoking, mental status, whether pregnancy was wanted or not, education, social class, and marital status), but not maternal intelligence, home environment, or child's iron status, only maternal iron levels in the ninth month of pregnancy were significantly associated with the offspring's school performance. However, use of self-reported questionnaires and school scores alone in the absence of objective measures of academic achievement and consideration of other sociocultural variables limit generalizability of these findings. Another later prospective population-based study of Vietnamese infants found that children of anemic mothers scored lower on the Bayley Scales of Infant Development (BSID) composite score at 6 months than infants of non-anemic mothers [99].

Iron deficiency in infancy and childhood negatively impacts cognitive function, but the timing of the deficiency results in different outcomes. Deficiency during 6–12 months of age is associated with long-term deleterious effects on cognition that are likely irreversible even when iron levels normalize [100, 101]. Deficiency in early infancy affects executive control and has been associated with increased risk of behavioral problems and poor academic performance in adolescence and adulthood [100, 101]. Children (ages 6–12 years) with iron deficiency anemia (IDA) also show lower total IQ scores that increased 4.8 points [assessed by the Wechsler Intelligence Scale for Children-Revised (WISC-R) intelligence test] after 4–6 months of iron plus multivitamin supplementation [102].

Iron may also benefit cognition and IQ even in children and adolescents with normal iron levels. A systematic review and meta-analysis of 14 studies (n = 1,900) concluded that iron supplementation improved attention and concentration in adolescents with normal iron levels. Iron supplementation also improved IQ in children/adolescents who were previously anemic [103]. A subsequent systematic review and meta-analysis evaluating 32 studies in children ages 5–12 years, reported that iron supplementation improved global cognitive scores and measures of attention and concentration in non-anemic children. Additionally, iron supplementation improved IQ in anemic children [104].

Iron deficiencies also affect cognition in adults. A recent systematic review and meta-analysis of iron supplements and the effects of iron deficiency in women of childbearing age (13–45 years) found an improvement in cognition after iron treatment in seven out of ten studies [105]. However, a cross-sectional study by Cook et al. [106] examined women ages 18–35 and found that iron deficiency anemia (IDA), but not iron deficiency (ID), was associated with reduced attention as assessed by a continuous performance task.

In addition to cognition, iron may also play a role in symptoms of depression. A recent meta-analysis of three studies indicated an inverse relationship between iron intake and depression in adults [107]. However, additional studies are needed to validate these findings.

In summary, these findings suggest that iron levels play an important role in cognition throughout the lifespan, but the timing and severity of deficiency influence its effects, and there may be a dose effect. Additionally, adequate iron levels may reduce the risk of depression. Given that iron deficiency is one of the most common nutritional deficiencies in the world, additional research regarding the benefit of iron supplementation should be a priority.

Iodine is a trace element which is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Thyroid

hormones are necessary for proper central nervous system development in fetuses [108]. Therefore, iodine is essential for normal brain development and deficiency may have deleterious effects on cognition. Iodine deficiency is the leading cause worldwide of preventable intellectual disability and may also lead to milder cognitive deficits on tests of intellect effects including intellectual impairment [109–111]. Iodized salt is the most common food source; other foods high in iodine include seaweed, cod, yogurt, and milk [66]. Inadequate iodine at the end of the first trimester and the early second trimester may increase the risk of impaired intellectual ability and result in potentially irreversible abnormalities in brain development [110–112]. Additionally, low levels of prenatal iodine have been associated with impaired executive functioning [113], and Bath et al. [114] found negative effects on child IQ at age 8 years of age and on reading ability at age 9 years. A longitudinal follow-up (at 9 years) of the Gestational Iodine Cohort study found that children whose mothers had mild-to-moderate iodine deficiency prenatally had reductions in spelling, grammar, and English literacy performance (based on Australian national curriculum and Tasmanian state curriculum educational assessment data) compared with children whose mothers' had adequate iodine levels. Associations remained significant after adjustment for a range of biological factors (maternal age at birth of child, gestational length at time of birth, gestational age at time of urinary iodine collection, birth weight, and sex). Differences in spelling also remained significant after further adjustment for socioeconomic factors (maternal occupation and education) [112]. These findings indicate that prenatal iodine deficiency can have detrimental effects on children's neurocognition, including intellectual disability which is not reversible by iodine supplementation during childhood [115]. However, in a subsequent trial of mothers with normal iodine levels, prenatal iodine supplementation did not show any benefit to neurodevelopment (assessed by Bayley Scales of Infant and Toddler Development (Bayley-III) compared to the placebo group) [116].

In summary, severe prenatal iodine deficiency, common in underdeveloped regions, is the number one cause of preventable intellectual disability. Evidence suggests that even mild-to-moderate deficiency during pregnancy can result in adverse effects on children's cognition, but prenatal iodine supplementation in women with normal iodine levels may not have any beneficial effects. Given its significant impact, more efforts to prevent severe deficiencies should be a public health priority. Additional studies are needed to determine the true effects of mild-to-moderate prenatal iodine deficiency children's cognition, however.

Zinc is involved in numerous aspects of cellular metabolism, DNA synthesis [117], and cell division [118]. Food sources of zinc include beans, legumes, oysters, meat, chicken, nutritional yeast, and fortified cereals that include nuts, seeds, oats, and wheat germ [119]. One prenatal study (n = 539) found that higher zinc levels during the first trimester and in cord blood were associated with lower scores on language abilities (measured by BSID) in offspring at one year of age [120]. A systematic review and meta-analysis [18 studies, 12 of which were randomized controlled trials; 11 in children and 1 in adults; and 6 observational] evaluated zinc intake and cognition in children and adults. Nine of the 18 studies reported a positive association between zinc intake or status with one or more measures of cognitive function. A meta-analysis of data from the six RCTs conducted in children revealed that there was no significant overall effect of zinc intake on any indices of cognitive function: intelligence, executive function, and motor skills. There were some small indicators of improvement on aspects of executive function and motor development following zinc supplementation in children. However, heterogeneity of study design was reported as a major limitation [121]. Three randomized controlled studies found that adjunctive zinc supplementation was statistically significant in treatment for depression [122–124]. A meta-analysis of 17 studies (n = 1643 depressed and 804 control subjects) by Swardfager et al. [125] found lower zinc levels in depressed patients (ages 25–65, mean

age 37.7 years) and a linear association between low plasma concentration of zinc and depression severity. A more recent meta-analysis of 9 studies of older individuals without dementia also reported an inverse relationship between zinc intake and risk of depression [107].

In summary, evidence indicates that high prenatal zinc levels may negatively affect language abilities in offspring. In children and adults, findings are inconclusive regarding zinc status and effects on cognition. However, in children, supplements may have a slight benefit on cognition. In older adults, both levels and intake potentially play a role in depression. Additionally, zinc supplementation potentially augments effectiveness of antidepressants, but further research is needed before implementing in practice.

Multivitamins (MVIs)

Since nutrients act synergistically and may be interdependent for proper absorption and effectiveness, prenatal multivitamins are routinely recommended. In a population-based case–control study (n = 707), a group of young children (24–60 months old) with autism had mothers who were less likely than mothers of typically developing children to report having taken prenatal vitamins during the three months before pregnancy and/or the first month of pregnancy. Significant effects were found for maternal MTHFR 677 TT genotypes that showed greater risk for autism if prenatal vitamins were not used [126]. However, MTHFR 677 TT requires l-methylfolate versus regular folic acid in the MVI; therefore, this raises a question regarding the genetic predisposition and potential need for other nutrients in pregnant women with MTHFR mutations and their effects on children's psychological health and/or risk of autism.

In adults, some evidence indicates that MVIs may improve cognition and psychological health. A systematic review and meta-analysis of 10 studies (N = 3,200) of individuals aged found that MVIs taken $\geq$1 month enhanced immediate free recall memory as measured by measures of immediate recall, but not other cognitive domains such as delayed free recall memory or verbal fluency [127]. However, a subsequent randomized, double-blind, placebo-controlled trial (n = 5947) of long-term MVI supplementation and cognitive function in male physicians ($\geq$65 years) found no benefits on global cognition as measured by (1) Telephone Interview for Cognitive Status (TICS), a telephone adaptation of the Mini-Mental State Examination; (2) immediate and (3) delayed recalls of the East Boston Memory Test (EBMT), to assess verbal memory; (4) the delayed recall of a 10-word list in the TICS to test verbal memory; and (5) a category fluency task. The primary prespecified outcome of the cognitive sub-study was a composite score of global cognition [128]. A double-blind randomized placebo-controlled trial examined the effects of an MVI on symptoms of ADHD and depression in adults (n = 80) and found that MVI supplementation for 8 weeks improved symptoms of adult ADHD (based on clinician-rated ADHD scales) and improved mood (assessed by the Montgomery–Asberg Depression Rating Scale) in those with moderate to severe depression [129]. A subsequent follow-up study (n = 72) approximately one year later reported that benefits were maintained in those who remained on MVIs [130].

In summary, preliminary evidence indicates that prenatal MVIs may prevent autism in offspring. MVIs may potentially improve immediate free recall and symptoms of ADHD and depression in adults. Future research is also needed to further investigate the role of MTHFR polymorphisms, prenatal folate (l-methylfolate) supplementation, and other nutrients in neurodevelopment and mental health in children.

Fats

Prenatal

In addition to vitamins and minerals, fats, particularly long-chain polyunsaturated fatty acids (LC-PUFAs) play a crucial role in brain development. Therefore, it is important to consider the

type of fats women consume during pregnancy. LC-PUFAs are omega-3 (n – 3; including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)), and omega-6 fatty acids (n – 6; including Linoleic acid (LA) and arachidonic acid (AA)). ALA is present in plant oils, such as flaxseed, soybean, and canola oils. DHA and EPA are found in various seeds, walnuts, Brussels sprouts, fish, fish oils, and krill oils [131]. AA is found in phytoplankton and algae, seeds, nuts, legumes, meat, and poultry. The critical role of (DHA) and (AA) in brain and central nervous system development is well established [132]. Higher levels of prenatal DHA and AA are associated with improved neurodevelopmental outcomes until at least 18 months of age, and possibly benefit neurocognition and mental health in children [133, 134]. However, a systematic review and a separate meta-analysis of randomized controlled studies of prenatal LC-PUFA supplementation found no beneficial effects on neurodevelopment [135, 136]. More recent evidence suggested that n – 3 and n – 6 LC-PUFAs may have a beneficial effect on IQ [137, 138]. Also, in a randomized controlled trial, Ramakrishnan et al. [139] found that DHA (n – 3) supplementation in the second half of pregnancy in Mexican women has the potential to improve sustained attention in children from infancy through 5 years of age (n = 797) as assessed by the Conners' Kiddie Continuous Performance Test (K-CPT).

Another study by Bernard et al. [137] found excess LA (n-6) in colostrum (the first secretion from the mammary glands after giving birth) was negatively associated with motor and global cognition scores at 2 and 3 years of age when using parent-reported questionnaires for motor and language at 2 years of age and global cognition measures at 3 years. Cognitive scores were similar to infants who were never breastfed. In a related study (n = 1090) using the French Etude des Déterminants pré- et postnatals précoces du développement et de la santé de l'Enfant (EDEN) mother–child cohort, any breastfeeding duration was associated with full scale and verbal IQ score increases as assessed by the Wechsler Preschool and Primary Scale of Intelligence-III. Colostrum LA levels were negatively associated with Verbal IQ and children exposed to colostrum high in LA and low in docosahexaenoic acid (DHA) had lower IQs than those exposed to colostrum high in DHA and those exposed to colostrum low in LA and DHA. Finally, the association between breastfeeding duration and child IQ was stronger when LA levels were high [138]. However, to our knowledge, this is a new finding and contradictory to other evidence. Therefore, additional studies are needed to replicate and validate this finding.

In a population-based cohort study, Steenwag de Graffe and colleagues found that the ratio of n – 3 to n – 6 is an important consideration because higher maternal DHA (n – 3) and n – 3 to n – 6 ratios are associated with fewer emotional problems in children at 6 years of age as assessed by the parent-administered Diagnostic Interview Schedule for Children-Young Child version [DISC-Y], teacher report form, and combined parent/teacher report and scores [35]. A recent animal study also reported effects on mood and behavior: excess intake of n – 6 compared to n – 3 LC-PUFAs, or an increased ratio of n – 6 to n – 3, in mice during pregnancy contributed to impaired or altered neocortical genesis in offspring and anxiety-related behavior problems later in adulthood. The anxiety-related behaviors persisted even after balancing their dietary ratio of n – 3 to n – 6 PUFAs [140]. Other animal studies that have induced n-3 fatty acid deficiency reported neural activity and habituation patterns found in ADHD [141, 142]. In a human study, utilizing a subset (n = 70) of a sample enrolled in a previous randomized, double-blind, controlled clinical trial of the effects of prenatal DHA supplementation on pregnancy and gestation [143] maternal DHA levels were inversely correlated with children's distractibility in infancy and toddlerhood [144].

Fish is an excellent source of LC-PUFAs and numerous epidemiological studies have found beneficial effects of fish intake (and seafood) during pregnancy on children's neurocognition [145–149]. Although there have been reported concerns about potential mercury neurotoxicity,

a recent systematic review concluded that the benefits of neurodevelopment outweigh the potential detriments [150]. Furthermore, Dietary Guidelines for America (2015–2020) recommend that women who are pregnant or breastfeeding should consume a variety of seafood (from sources that are lower in methyl mercury) per week, for healthy brain development [151]. Also, the American Academy of Pediatrics (AAP) recommends consuming one to two servings of fish per week during pregnancy to guarantee a sufficient amount of DHA in breast milk [152]. However, due to the pressure on fish species and increasing demand for EPA and DHA, algae oils are being investigated as a possible sustainable LC-PUFA [153].

While an adequate amount of healthy (unsaturated) fat is necessary and beneficial to brain development, increased consumption of unhealthy (saturated) fats during pregnancy has been shown to play a role in inflammatory processes, negatively impacting neurodevelopment [154, 155]. Additionally, higher levels of fat intake increase the potential for excessive prenatal weight gain and obesity which has been correlated with adverse effects on neurodevelopment and mental health including cerebral palsy, cognitive impairment, autism spectrum disorders, attention deficit hyperactivity disorder, anxiety, depression, schizophrenia, and eating disorders [156, 157]. The relationship between body weight and body mass index (BMI) during pregnancy will be discussed further in another section (*Diet Quality and BMI*).

Childhood and Adolescence

Since the brain continues to grow and develop during infancy, LC-PUFA's remain essential. Breast milk (rich in LC-PUFA's) is considered the gold standard for infant nutrition and has been shown to have superior effects on neurodevelopment compared to commercial infant formula [158–161], especially in preterm infants [162]. However, a systematic review of 84 studies reported that many of the cognitive benefits of breastfeeding were due to confounders including maternal cognitive and socioeconomic effects [163].

In children and adolescents, omega-3 supplementation may reduce symptoms of ADHD. A recent systematic review and meta-analysis (n = 2,024) of clinical trials and biological studies reported that data suggests that children and adolescents with ADHD have deficiencies in n-3 PUFA levels and omega-3 supplementation improves cognitive function and ADHD symptoms [164]. However, additional studies are needed to further examine these findings and determine appropriate dosing before supplementation can be implemented in practice.

Adults

A meta-analysis of six studies reported that omega-3 fatty acids (taken for 3–40 months) statistically decreased the rate of cognitive decline as assessed by the Mini-Mental State Exam and may help to prevent cognitive decline in older adults [165]. An important factor noted by the authors is that it may be necessary to introduce omega-3's earlier, before the onset of any cognitive decline. A comprehensive dose–response meta-analysis of 21 studies of individuals with mild cognitive impairment, cognitive decline, dementia, Alzheimer disease, and Parkinson disease reported that a one serving per week increment of fish was associated with lower risks of dementia and Alzheimer disease [166]. These findings suggest that marine sources of PUFAs are associated with lower risk of cognitive impairment associated with aging and related diseases.

Gumpricht et al. [167] proposed that research using a combination of omega-3 fatty acids and vitamin E supplementation should be further investigated as an option to reduce symptomology of neurodevelopmental disorders such as autism, ADHD, and apraxia. They theorized that omega-3's and vitamin E may reduce the increased oxidative stress, neuroinflammation, and altered antioxidant defenses associated with

these disorders. Furthermore, omega-3 supplementation has been associated with lower vitamin E levels; therefore, vitamin E supplementation may be needed to ensure that lower vitamin E levels do not interfere with or inhibit the beneficial effects of the omega-3. A recent update on a Cochrane review of vitamin E supplementation for MCI and AD concluded that vitamin E does not improve cognitive function in MCI or dementia, but may slow functional decline in AD. Although these findings are based on only two trials, authors note that the quality of the two trials was good [168].

A systematic review of 20 articles by Pompili et al. [169] found that individuals with psychiatric conditions have lower levels of n-3 PUFAs compared to control groups. Furthermore, decreased n-3 PUFA levels were shown to contribute to suicide risk. However, these findings are not consistent with large epidemiological studies that found no significant difference in reduction of n-3 PUFA levels between those with psychiatric conditions and/or suicide risk [170]. Prenatal depression (PND) has also been associated with lower levels of total n-3 (DHA and EPA) and a higher n-6/n-3 PUFA ratio. Additionally, the duration of PND was associated with lower levels of n-3 PUFAs, including DHA and EPA [171].

Meta-analyses investigating the effectiveness of n-3 PUFAs treatment for depression report mixed results, but some studies have shown that supplements with a high EPA to DHA ratio might be as effective as adjunctive therapy to antidepressants [9, 172]. One systematic review and two meta-analyses have specifically revealed possible benefits of n-3 PUFAs adjunctive supplementation for unipolar and bipolar depression [173–175]. Additionally, a recent meta-analysis of 26 studies reported that higher fish consumption may reduce the risk of depression [176]. Although an abridged Cochrane review from 2016 concluded that there is not sufficient evidence regarding the use of n-3 PUFAs for treatment of major depressive disorders [177]. However, for patients with poor impulse control, mood, or psychotic disorders, The American Psychology Association (APA) Task Force on Complementary and Alternative Medicine recommends one gram of omega-3's (EPA + DHA) daily [174].

Omega-3 fats may also play a role in schizophrenia risk and symptomology. In a randomized placebo-controlled study, 41 individuals designated as at ultra-high risk for schizophrenia were given omega-3 fatty acids compared to 40 control subjects. At 1 year, only two individuals who received omega-3's developed schizophrenia compared to 11 in the control group, with a highly significant difference in both symptoms and functions [178].

A recent systematic review and meta-analysis (n = 2,240) from 11 countries reported that improvement in symptoms of anxiety was associated with omega-3 fatty acid treatment compared with controls in both placebo-controlled and non-placebo-controlled trials. However, the association of treatment with reduced anxiety symptoms was significantly greater in individuals with clinical diagnoses than in those without clinical diagnoses. Additionally, symptom reduction was significantly better than that of controls, only with higher dosages (at least 2000 mg/d) and not with lower dosages (<2000 mg/d) [179].

In summary, findings indicate that LC-PUFAs during pregnancy can have a beneficial effect on children's IQ. Evidence is mixed on their effects on other aspects of neurodevelopment; however, the American Dietary Guidelines for America (2015–2020) recommend seafood/fish (high in omega-3/n-3 fats) intake during pregnancy to promote healthy brain development. A higher ratio of n-3 to n-6 fats is potentially beneficial for cognition in children, whereas higher n-6 may be detrimental. Type and amount of fat intake during pregnancy in an important consideration as it influences weight gain and BMI and excessive weight gain and/or BMI can potentially negatively affect cognition and psychological health of children. Evidence suggests that LC-PUFAs remain important in infancy for healthy neurodevelopment, but some data is contradictory. In children and adolescents, omega-3 supplementation may improve cognition and symptoms of ADHD. In adults, evidence suggests that

omega-3's benefit cognitive health in aging and related disorders and in psychiatric disorders including depression, bipolar disorder, schizophrenia, anxiety, and they may also be associated with suicide risk. Similarly, fish (high in omega-3's) intake has been shown to reduce the risk of both cognitive decline and depression. Additional studies examining intake of omega-3 fats earlier in life/adulthood to prevent cognitive decline and potentially dementia and AD later in life seem warranted. Omega-3's may act synergistically with vitamin E and enhance their effectiveness; this is especially significant as omega-3 supplementation may increase vitamin E requirements.

Other Dietary Considerations

Diet Quality

In addition to specific vitamins, minerals, and fats, the overall quality of diet during pregnancy also affects neurodevelopmental outcomes. Prenatal diets consisting of fish, fruit, and monounsaturated fat are associated with improved neurocognition and mental health in children [180, 181]. Conversely, unhealthy prenatal diets (high in saturated fat, starch, and sugar) have been linked to emotional and behavioral dysregulation in childhood and adolescence [31, 180, 182, 183]. Furthermore, maternal diet and nutritional status may influence children's food preferences, appetite, and intake later in life [184–186], which may subsequently affect their cognition and psychological health throughout the remainder of their lifecycle.

A systematic review of 18 studies reported that a better quality maternal diet had a small positive association with neurodevelopment and cognition (language, communication skills, IQ). Better quality diets had greater intakes of vegetables, fish, legumes, whole grains, and vegetable oils; unhealthy diets had greater intake of processed foods (fried foods, French fries, meats) confectionary foods (cakes, candy, sugary drinks), refined cereals, and salty snacks. However, the author's note that future studies that control for the quality of the children's diet are also needed [181]. Subsequently, a large cohort study (n = 12,195) found that pregnant women who ate more fruits and vegetables had children with the highest mean IQ at 8 years of age compared to women who ate more meat and potatoes and white bread and coffee [187]. Findings remained after adjusting for multiple well-known confounders, including maternal education.

Overall quality of diet also affects cognition and psychological health in children and adolescents. In support of this, other research has found an increased risk of mental health problems with unhealthy eating patterns (high intake of sugar, saturated fats, and processed foods) independent of other health factors (smoking and exercise) and environmental factors (socioeconomic status, family conflict, poor family functioning and social support, and adolescent dieting) [188–190]. In a cross-sectional study of 428 children aged 6–8 years (216 boys and 212 girls), poor diet quality was associated with worse cognition (nonverbal fluid intelligence/abstract reasoning) as assessed by Raven's Colored Progressive Matrices and the effect was stronger in boys [191]. A systematic review of 12 epidemiological studies reported an association between an unhealthy diet and poor mental health in children and adolescents [182]. A subsequent prospective study of adolescents aged 14–17 reported that consumption of the Western diet (high in refined grains, processed meat foods or snacks, and high-sugar and high-fat foods) at 14 years of age was positively associated with higher externalizing behavior scores as measured by the Youth Self-Report externalizing/internalizing T-scores and clinically concerning externalizing behaviors at 17 years of age [192]. However, authors note several important points: (1) it is possible that the relationship between diet and mental health is bidirectional, and causality cannot be established in the current analysis. That is, adolescents experiencing emotional distress may turn to foods that are high in fat, sugar, and salt as a coping mechanism for psychological symptoms or as a result of appetite change;

(2) Findings in females only may relate to females in this sample having significantly greater externalizing T-scores and clinically concerning externalizing T-scores at 14 and 17 years; and (3) Hormonal influences may account for these gender differences. Notably, other studies have also observed gender differences in the diet–mental health relationship. Therefore, it is important that gender differences are examined when conducting further research in this area. This also raises a question about the potential timing of nutritional needs at different stages of development in males and females. Future research should examine males at a more comparable stage of physical development.

In adults, a meta-analysis of 13 studies reported that a healthy diet (high fruits, vegetables, whole grains, and fish) may be associated with reduced odds of depression. However, there was not a significant association between a Western diet (higher intake of meat and dairy) and depression [193]. A larger more recent systematic review and meta-analysis including 21 studies confirmed an inverse relationship between diets higher in fruit, vegetables, whole grains, fish, olive oil, and low-fat dairy and the risk of depression, and a positive correlation between diets high in red and/or processed meat, refined grains, sweets, and high-fat dairy products and increased risk of depression [194].

Specific Diets (DASH, Mediterranean, MIND, and Few Foods)

The Dietary Approaches to Stop Hypertension (DASH), Mediterranean, and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets have been shown to play a role in cognitive health. The DASH diet is based on five dietary factors: (i) $\geq$400 g of fruits and vegetables, (ii) $\geq$28 g of fish, (iii) $\geq$28 g equivalent servings of fiber-rich grains ($\geq$1.1 g of fiber/10 g of carbohydrate), (iv) <1500 mg Na, and (v) $\leq$145 ml of soft drinks. A recent cross-sectional study demonstrated that higher diet quality for adolescents (aged 12.5–17.5) and ideal diet score (based on five dietary factors above, consistent with the DASH diet), were associated with a higher attention capacity as measured by the d2 Test of Attention. In contrast, the Mediterranean diet (high intake of fruit, vegetables, legumes, whole grain products and fish, a low to moderate consumption of meat, dairy products, and alcohol (in particular red wine) and olive oil as the main source of fat) score or macronutrient/fiber intake were not associated with attention capacity in this study [195]. Yet, other research has found that the Mediterranean diet may be beneficial for cognition and depression in adults. A meta-analysis examining the effects of the Mediterranean diet on cognition (8 studies; N = 16,719) and depression (9 studies; N = 8,291) reported a reduced risk of cognitive impairment and depression with moderate to high adherence to a Mediterranean diet. Regarding depression, with high adherence to the diet, the protective effects were significant and were independent of age. However, with only moderate adherence, the beneficial effects lessened as age advanced [196]. This suggests that higher levels of nutrients from stronger adherence to the diet may be necessary to provide continued benefits with increasing age. Additional studies are needed to further examine this, however. In a subsequent systematic review of 16 studies that compared the effects of a healthy/traditional diet, Mediterranean diet, and Western diet on depression, both the healthy/traditional and Mediterranean diets yielded possible protection against depression. Conversely, there was a positive association between a Western diet and depression [197].

The DASH diet may also support cognition in adulthood. Berendensen et al. [198] found that greater long-term adherence to the DASH diet was associated with mildly better global cognition and verbal memory in women over 70 years of age. The authors reported that the difference in cognitive function equated to a benefit of being one year younger. These results are consistent

with other results highlighting the benefits of the DASH diet for cognition [199].

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is a combination of the Mediterranean and DASH diet. Adherence to the MIND diet is rated as a MIND diet score (0–15; 0 = no adherence at all, 15 = perfect adherence) [200], and analyzes 15 dietary components that are beneficial for brain health (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five that are detrimental to brain health (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food) [201]. Higher MIND diet scores have been shown to reduce the risk of cognitive decline in older adults. In a study by Morris et al. [202], higher MIND diet scores were positively associated with slower decline in global cognitive score and with each of five cognitive domains including perceptual organization, working memory, and particularly for episodic memory, semantic memory, and perceptual speed. Authors reported that the difference in decline rates for attaining to the top tertile of MIND diet scores versus the lowest tertile was equivalent to being 7.5 years younger in age. Also, potential confounding factors including obesity, education, age, and physical activity had no impact on the estimated MIND diet effect.

In children and adolescents, a Few Foods elimination diet has been shown to improve symptoms of ADHD. A Few Foods diet (FFD) is a restricted (or "few foods") diet [typically two meats (often lamb and turkey), two carbohydrate sources (rice and potato), two fruits (often banana and pear), a range of root and green vegetables, bottled water, sunflower oil, and milk-free margarine] followed for a period of three to four weeks [203, 204]. A recent systematic review and meta-analysis of Double-Blind Placebo-Controlled Trials Evaluating the Efficacy of Diet Interventions on the Behavior of Children with ADHD reported a medium to large effect size (0.80) for a Few Foods diet [205]. However, compliance with this diet may be difficult and requires highly motivated families. Additional research should focus on elucidating the underlying physiological mechanisms involved in the potential benefits of ADHD symptomology.

In summary, findings suggest that a healthy, high-quality diet benefits cognition and psychological health beginning in the prenatal stages of development. Unhealthy diets seem to negatively impact cognition and mental health throughout the lifespan. Evidence suggests that the Mediterranean diet protects against cognitive decline and depression and the DASH and MIND diets potentially help to prevent cognitive decline associated with aging. Because diet quality affects BMI in pregnancy, childhood, adolescence, and adulthood, and BMI affects cognition and psychological health, diet quality may be a critical dietary consideration that deserves further research and public health attention.

Diet Quality and BMI

Diet quality also affects prenatal weight, BMI, and rate of weight gain. High maternal BMI and/or excessive weight gain during pregnancy may negatively influence aspects of cognition such as language, communication, and IQ, as well as mental health in offspring [206]. Pugh et al. [207] reported that children (10 years old) of women with a pregravid BMI $\geq$25 kg/m^2 had a low average IQ ($\leq$89) (assessed by the Stanford Binet Intelligence Scale-4th edition and children of mothers with higher gestational weight gain (GWG)) and performed slower on an executive function task (assessed by the number of perseverative errors on the Wisconsin Card Sorting Test and time to complete Part B on the Trail Making Test). Similarly, a systematic review by Veena et al. [32] reported that maternal obesity was associated with lower cognitive function in children. A recent meta-analysis by Li et al. [208] found that obese women were 47% more likely to have a child with ASD compared to normal-weight women. However, there was significant heterogeneity among the studies and some studies did not control for variables such as maternal age and psychiatric illness.

Conversely, low BMI (of <19.9 kg/m^2) or maternal malnutrition has been associated with increased risk of psychological disorders [209]. Additionally, evidence indicates that children of mothers with low BMI's have significantly higher risk of delayed mental development, lower IQ scores, and mild intellectual disability [210, 211]. Underweight mothers might have nutritional deficiencies that negatively impact development of brain structure and neurotransmitter and/or neuroendocrine systems [212, 213] resulting in impaired cognitive function [32], but further work in this area is needed to determine the potential underlying mechanisms. Animal studies have demonstrated that prenatal protein–calorie malnutrition specifically is associated with neurological alterations similar to those with schizophrenia in humans [214, 215].

In children and adolescents (ages 3–21), a systematic review of sixty-seven studies found a negative relationship between obesity and executive functioning, visuospatial performance, and motor skill and mixed effects on general cognitive functioning, language, learning, memory, and academic achievement [216]. A more recent study of 843 adolescents (14–17 years old) found that higher BMIs were associated with depression (assessed by the BECK Depression Inventory) and Internalizing and Externalizing Behavioral Problems (assessed by Child Behavior Check List Youth Self-Report) [217–219].

Evidence suggests that BMI also plays a role in cognition and mental health in adults. Benito-Leon Joverweight, et al. [220] conducted a population-based cross-sectional study [the Neurological Diseases in Central Spain study (NEDICES)] in adults (n = 1,949) aged $\geq$ 65 and found that overweight (BMI 25–29.9 kg/m [2]) and obese adults (BMI $\geq$ 25 kg/m^2) was associated with the lowest quartiles of the 37-MMSE, Trail Making Test-A (more errors), verbal fluency, delayed free recall, immediate logical memory, and premorbid intelligence. Results remained after adjusting for confounders including age, gender, educational category, intake of medications that potentially affect cognition function, diabetes mellitus, hypertension, dementia, ever smoker, ever drinker, and waist circumference. A recent systematic review and meta-regression analysis of 19 studies (n = 589,649; ages 35–65 years) found that obesity (BMI $\geq$ 30) but not overweight (25 < BMI < 30) was associated with dementia in late life. Additionally, data indicated that the association between underweight (BMI $\leq$ 18.5) and dementia is inconclusive [221]. Higher BMIs have also been shown to potentially increase the risk of depression [222, 223].

In summary, quality of overall diet plays an important role in cognition and mental health beginning in the prenatal stages of development. Diet quality also impacts weight and BMI, and evidence suggests that both low and high prenatal BMIs may be associated with impaired cognition and psychological disorders in children. Higher BMIs in children, adolescents, and adults have been associated with negative effects on cognitive health and an increased risk of depression.

Limitations and Future Research

There are multiple overlapping methodological and content-based limitations in the studies reviewed. Methodologically, many of the studies reviewed relied on self-reports of diet recall or Food Frequency Questionnaires (FFQs) [31, 35, 60, 107, 134, 166, 180, 182, 183, 186, 188–202, 224], which affect the accuracy of assessing actual intake of certain foods or nutrients. Future studies need more accurate methods of assessing actual food/nutrient intake. For example, using FFQs in addition to diet recall and/or 24 h food records in combination with biomarker testing would provide more robust assessments of nutritional values. In addition, micronutrients work in concert and their metabolism is often interdependent with other nutrients or nutritional factors, so that is a potential limitation to studying micronutrients in isolation as was attempted in several of the studies reviewed. Future studies could study interdependent nutrients and/or utilize baseline biomarker testing more consistently to ensure vitamin or nutrient status is normal

before intervention. Also, studies lacked consistency in dose, composition, and/or duration of nutrient intake or supplementation, which would improve accuracy and replicability of findings. The timing of biomarker testing (especially prenatally) was another variant in the studies reviewed here [35, 36, 54, 55, 69, 225]. Some studies included subjects with normal levels of vitamins while others included subjects with low levels; this can impact the effectiveness of the intervention in ways that are not fully understood, and potentially skews outcomes and results. Other studies were limited by lack of generalizability [59, 61, 68, 88, 138, 139, 220].

In addition, while some studies used objective measures to assess cognitive functions and emotional findings, several relied on self-report measures in isolation which limits the robustness of the findings. There were also inconsistencies between studies using cognitive assessments in which some used single or selective cognitive domains while ignoring others, while other studies focused on global cognitive assessments alone. This thwarts the understanding of a more nuanced impact of various nutrients on cognitive and emotional functioning. Also lacking in the literature reviewed was the use of brain imaging techniques in conjunction with neuropsychological measures to examine the impact of nutrition. While some studies used interventions and randomized controlled trials, more well-controlled studies are needed that attempt to control for the role of important mediating and moderating factors such as socioeconomic status, BMI, maternal IQ, and education. Additionally, several studies were cross-sectional and there is a need for more longitudinal studies to better evaluate long-term versus short-term nutritional effects.

Regarding content of this literature, there is inherent complexity in determining nutritional metabolism mechanism and interrelated physiological pathways as well as deciphering the precise impact of lifestyle and other sociocultural influences on nutritional status. Furthermore, there is a relative lack of research in the area of infant and toddler nutrition and short- and long-term impact on cognition and psychological health. Given some of the existing evidence related to prenatal and adult l-methylfolate, future research also needs to examine the effects of l-methylfolate in children and adolescents, as this has the potential to significantly impact cognitive and psychological health on a more global level. Future studies are also needed to further examine pregnant women with MTHFR gene mutations as this will not only potentially impact their own mental health, but potentially their children's via epigenetics. More research needs to focus on children and adolescents with MTHFR polymorphisms and individualized forms of folate (l-methylfolate) and B12. Given the severity and burden of the diseases, examining the impact of prenatal nutrition (choline, vitamin D, and malnutrition) and childhood and adolescent nutrition on the risk of severe neuropsychiatric and neurodevelopmental disorders such as schizophrenia and autism should be a priority. Studies are also needed to further examine the negative effects of excessive intake and/or high serum levels of various vitamins and nutrients. Investigations of the physiological mechanisms responsible for nutritional interactions can also provide additional clues to direct future research.

Summary

The evidence reviewed some highlights of the suggested links between nutrition and neurocognition and psychological health throughout the lifecycle. These links offer vast potential for nutrition to serve as an important modifiable risk factor for cognitive impairment and mental illness and deserves more attention and consideration. Despite inconclusive or mixed findings regarding some nutritional factors and their role in neurocognition and psychological health, certain factors show more consistency. One of the more consistent findings is the potential benefit of an overall healthy diet (high in fruits, vegetables, fiber, and low in saturated fats and sugars) throughout the lifespan. Diet quality is lacking in both developed and developing countries, albeit for different reasons. Therefore, public health

efforts need to focus on promoting and instilling healthy eating habits beginning as early in life as possible, since it is more difficult to change eating habits later in life. Additionally, prenatal nutrition should be a priority as it not only has the potential to impact cognitive and psychological health later in life, but may also influence lifelong dietary choices with subsequent effects. Furthermore, unhealthy diets prenatally and throughout the lifespan contribute to excessive weight gain and a higher BMI, which negatively impact cognition and mental health. Current findings suggest that efforts to support nutritional education and healthy nutrition may be cost-effective with pros outweighing the cons. While it is difficult to define a healthy diet across different cultures, studies of diets are consistent in finding that natural foods such as fruits, vegetables, nuts, olive oil (other mono/polyunsaturated oils), whole grains, seafood, and low-fat protein should be encouraged. In contrast, although not specifically reviewed here, more processed and artificial foods often contain artificial ingredients and chemicals which could potentially negatively impact the brain and neurological functioning, further contributing to neurocognitive and/or neuropsychiatric problems.

In addition to overall diet, certain micronutrients (vitamin D, choline, folate, and iron) and fats (omega-3's) show more consistent evidence suggesting a beneficial role in cognition and mental health throughout the lifespan. These factors deserve prioritized attention as the potential benefits of their implementation may outweigh the detriments of delaying their implementation. Based on the widespread deficiency and inadequacy of vitamin D and its potential associations with mental illness, suicidal ideation, and impaired cognition, public health policy-makers need to evaluate the cost versus benefit of implementing screening and/or testing guidelines (for such populations).

Folate or FAS may play an important role in prenatal, child, adolescent, and potentially adult cognition and mental health and deserves further attention. Since evidence indicates that individuals with MTHFR gene mutations have an increased genetic predisposition to depression, bipolar disorder, and schizophrenia [39], and possibly ADHD [226], more research is needed regarding appropriate folic acid intake and supplementation (l-methylfolate), as this could significantly impact the quality of life for such individuals.

Iron has been shown to be necessary for brain development and beneficial for cognition and psychological health in childhood, and adolescence (throughout the lifespan). Therefore, public health policy-makers need to evaluate the cost versus benefit of more routine screening for iron deficiency anemia (IDA), particularly for high--risk populations and/or in individuals experiencing impaired cognition or psychological symptoms.

The potential benefit of omega-3 fatty acids throughout the lifecycle is an important area of focus. They may be particularly important prenatally for healthy brain development and subsequent functionality. Research suggests that omega-3's are also beneficial for mental health in childhood, adolescence, and adulthood. Additionally, excessive ratio of omega-6 (n-6) to omega-3 (n-3) fats may negatively affect cognition and mental health. The excessive ratio of n-6 to n-3 fats reflects most current diets and should therefore be addressed. Public health efforts are warranted to help increase awareness of this and encourage more consumption of fish and seafood or nonmeat sources for omega-3 supplementation, thereby decreasing the ratio of n-6 to n-3 fats.

It is important to consider that certain populations may be inherently at a higher risk for nutritional deficiencies including vegetarians/vegans, pregnant women, infants, children, and older adults. Globally, pregnant women and their children under 5 years at the highest risk for micronutrient deficiencies (MNDs); iron, iodine, folate, vitamin A, and zinc are the most widespread MNDs [227]. Older adults are at a higher risk of vitamin deficiencies due to changes in their metabolism, gut bacteria, and subsequent ability to absorb nutrients. Another important consideration is the role of psychological conditions that are known to affect food intake such as depression, anorexia and bulimia nervosa, autism, and ADHD (typically secondary to

decreased appetite from medication), as poor nutritional status may induce or exacerbate psychiatric symptoms. Also, some medications [i.e., antiepileptic and antidiabetic; for an extensive list, see [228]] increase the need for specific nutrients such as vitamin D and zinc. Therefore, specific nutrient supplementation or an MVI is typically necessary for such populations, but patients should be further evaluated by a medical doctor or registered dietitian. Conversely, given some of the evidence regarding negative effects of excessive vitamin or nutrient intake on cognition, particularly during pregnancy, women need to be better educated and informed about the appropriate type and dose of prenatal vitamins and supplements.

Public health policy-makers and organizations worldwide could consider reevaluating current dietary guidelines, focusing on neurocognition and mental health. It would also be beneficial to focus on foods provided by daycare centers, schools, and long-term care facilities, to improve overall diet quality. Public health initiatives could are needed to encourage and promote healthier eating via advertising, social media, technology, and other avenues.

Future research is still needed before recommendations and interventions can be implemented, however. Given the potential substantial impact on public health, it is urgent to make such research a priority. Analogous to folic acid and the prevention of neural tube defects, other nutritional interventions have the potential to impact neurocognition and mental health worldwide. Although more conclusive evidence is necessary, consideration of the findings to date may prove useful for future research.

Conclusion

The various evidence regarding the relationship between nutrition and neurocognitive and psychological disorders are encouraging with ample opportunities to positively impact the tremendous health burden posed by these disorders. Therefore, it is essential to continue to enhance the quality of research to further investigate nutritional factors and interventions that can be implemented to aid in their prevention, mitigation, and/or treatment. In the interim, public health policy-makers need to prioritize evaluating the cost versus benefit of implementing more consistent findings related to overall quality of diet and omega-3 fatty acids. Support and initiatives from public health policy-makers and organizations worldwide are essential to improve nutritional status and subsequent cognitive and psychological health throughout the lifespan.

References

1. Barker DJP. Mothers, babies, and health in later life. 2nd ed. Edinburgh: Churchill Livingstone; 1998.
2. Harding JE. The nutritional basis of the fetal origins of adult disease. Int J Epidemiol. 2001;30(1):15–23.
3. Heindel JJ, Vandenberg LN. Developmental origins of health and disease: a paradigm for understanding disease cause and prevention. Curr Opin Pediatr. 2015;27(2):248–53.
4. Bani-Fatemi A, Howe AS, De Luca V. Epigenetic studies of suicidal behavior. Neurocase. 2015;21 (2):134–43.
5. Bani-Fatemi A, Zai C, De Luca V. Early onset schizophrenia: Gender analysis of genome-wide potential methylation. Clin Chim Acta. 2015;449:63–7.
6. Gómez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci. 2008;9 (7):568–78.
7. Tyagi E, Zhuang Y, Agrawal R, Ying Z, Gomez--Pinilla F. Interactive actions of Bdnf methylation and cell metabolism for building neural resilience under the influence of diet. Neurobiol Dis. 2015;73:307–18.
8. Dauncey MJ. Nutrition, the brain and cognitive decline: insights from epigenetics. Eur J Clin Nutr. 2014;68(11):1179–85.
9. Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, et al. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. Am J Psychiatry. 2016;173(6):575–87.
10. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanza-Martinez V, Freeman MP, et al. Nutritional medicine as mainstream in psychiatry. Lancet Psychiatry. 2015;2(3):271–4.
11. Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015;18(4):231–45.

12. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev. 2014;72(4):267–84.
13. Anjos T, Altmae S, Emmett P, Tiemeier H, Closa-Monasterolo R, Luque V, et al. Nutrition and neurodevelopment in children: focus on NUTRIMENTHE project. Eur J Nutr. 2013;52 (8):1825–42.
14. Douglas SSU. Mental and Nervous Disorders Associated with Pellagra. Archives of Internal Medicine, 1915:121.
15. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944-1945. Arch Gen Psychiatry. 1992;49(12):983–8.
16. de Rooij SR, Wouters H, Yonker JE, Painter RC, Roseboom TJ. Prenatal undernutrition and cognitive function in late adulthood. Proc Natl Acad Sci U S A. 2010;107(39):16881–6.
17. Stein Z, Susser M, Saenger G, Marolla F. Nutrition and mental performance. Science. 1972;178 (4062):708–13.
18. Logan AC, Jacka FN. Nutritional psychiatry research: an emerging discipline and its intersection with global urbanization, environmental challenges and the evolutionary mismatch. J Physiol Anthropol. 2014;33:22.
19. The world health report. Primary health care now more than ever. Geneva: World Health Organization; 2008.
20. Mathers CD LD. Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods and results. Geneva; 2005.
21. Ferri CPPM, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Alzheimer's Disease International Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112–7.
22. WHO AsDIa. Dementia: a public health priority 2012.
23. Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? Arch Dis Child. 2012;97(3):260–5.
24. Benton D, a.i.s.b.l IE. Micronutrient status, cognition and behavioral problems in childhood. Eur J Nutr. 2008;47 Suppl 3:38–50.
25. Georgieff MK. The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. Biochem Soc Trans. 2008;36(Pt 6):1267–71.
26. Zhang X, Yuan X, Chen L, Wei H, Chen J, Li T. The change in retinoic acid receptor signaling induced by prenatal marginal vitamin A deficiency and its effects on learning and memory. J Nutr Biochem. 2017;47:75–85.
27. Ali H, Hamadani J, Mehra S, Tofail F, Hasan MI, Shaikh S, et al. Effect of maternal antenatal and newborn supplementation with vitamin A on cognitive development of school-aged children in rural Bangladesh: a follow-up of a placebo-controlled, randomized trial. Am J Clin Nutr. 2017;106(1):77–87.
28. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5(11):949–60.
29. Health USDoHHSNIo. https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ on March 5 2018.
30. Valera-Gran D, Navarrete-Muñoz EM, Garcia de la Hera M, Fernández-Somoano A, Tardón A, Ibarluzea J, et al. Effect of maternal high dosages of folic acid supplements on neurocognitive development in children at 4–5 year of age: the prospective birth cohort Infancia y Medio Ambiente (INMA) study. Am J Clin Nutr. 2017;106(3):878–87.
31. Steenweg-de Graaff J, Tiemeier H, Steegers-Theunissen RP, Hofman A, Jaddoe VW, Verhulst FC, et al. Maternal dietary patterns during pregnancy and child internalising and externalising problems. The Generation R Study. Clin Nutr. 2014;33(1):115–21
32. Gale CR, Krishnaveni GV, Kehoe SH, Srinivasan K, Fall CH. Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. BMC Pregnancy Childbirth. 2016;16:220.
33. Gao Y, Sheng C, Xie RH, Sun W, Asztalos E, Moddemann D, et al. New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring Children - A Systematic Review. PLoS ONE. 2016;11 (11):e0165626.
34. Roza SJ, van Batenburg-Eddes T, Steegers EA, Jaddoe VW, Mackenbach JP, Hofman A, et al. Maternal folic acid supplement use in early pregnancy and child behavioural problems: The Generation R Study. Br J Nutr. 2010;103(3):445–52.
35. Steenweg-de Graaff JC, Tiemeier H, Basten MG, Rijlaarsdam J, Demmelmair H, Koletzko B, et al. Maternal LC-PUFA status during pregnancy and child problem behavior: the Generation R Study. Pediatr Res. 2015;77(3):489–97.
36. Steenweg-de Graaff J, Ghassabian A, Jaddoe VW, Tiemeier H, Roza SJ. Folate concentrations during pregnancy and autistic traits in the offspring. The Generation R Study. Eur J Public Health. 2015;25 (3):431–3.
37. Mech AW, Farah A. Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2016;77(5):668–71.
38. Pilsner JR, Hu H, Wright RO, Kordas K, Ettinger AS, Sanchez BN, et al. Maternal MTHFR genotype and haplotype predict deficits in early cognitive development in a lead-exposed birth cohort in Mexico City. Am J Clin Nutr. 2010;92(1): 226–34.

39. Peerbooms OL, van Os J, Drukker M, Kenis G, Hoogveld L, de Hert M, et al. Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability? Brain Behav Immun. 2011;25(8):1530–43.
40. Lewis SJ, Lawlor DA, Davey Smith G, Araya R, Timpson N, Day IN, et al. The thermolabile variant of MTHFR is associated with depression in the British Women's Heart and Health Study and a meta-analysis. Mol Psychiatry. 2006;11(4):352–60.
41. Jha S, Kumar P, Kumar R, Das A. Effectiveness of add-on l-methylfolate therapy in a complex psychiatric illness with MTHFR C677 T genetic polymorphism. Asian J Psychiatr. 2016;22:74–5.
42. Petridou ET, Kousoulis AA, Michelakos T, Papathoma P, Dessypris N, Papadopoulos FC, et al. Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. Aging Ment Health. 2016;20(9):965–73.
43. Bender A, Hagan KE, Kingston N. The association of folate and depression: A meta-analysis. J Psychiatr Res. 2017;95:9–18.
44. Papakostas GI, Shelton RC, Zajecka JM, Bottiglieri T, Roffman J, Cassiello C, et al. Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized clinical trial. J Clin Psychiatry. 2014;75(8):855–63.
45. Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry. 2012;169(12):1267–74.
46. Nishio K, Goto Y, Kondo T, Ito S, Ishida Y, Kawai S, et al. Serum folate and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism adjusted for folate intake. J Epidemiol. 2008;18(3):125–31.
47. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/ on March 5 2018.
48. Herbert VDK. Vitamin B12 in modern nutrition in health and disease. 8th ed. Baltimore: Williams and Wilkins; 1994.
49. Herbert V. Vitamin B12 in present knowledge in nutrition. 17th ed. Washington: International Life Sciences Institute Press; 1996.
50. Combs G. Vitamin B12 in The vitamins. New York: Academic; 1992.
51. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. Semin Hematol. 1999;36(1):35–46.
52. IoMFaN Board. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington: National Academy; 1998.
53. Lim SY, Kim EJ, Kim A, Lee HJ, Choi HJ, Yang SJ. Nutritional Factors Affecting Mental Health. Clin Nutr Res. 2016;5(3):143–52.
54. Bhate V, Deshpande S, Bhat D, Joshi N, Ladkat R, Watve S, et al. Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children. Food Nutr Bull. 2008;29(4):249–54.
55. del Rio Garcia C, Torres-Sanchez L, Chen J, Schnaas L, Hernandez C, Osorio E, et al. Maternal MTHFR 677C > T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment. Nutr Neurosci. 2009;12(1):13–20.
56. Eilander A, Muthayya S, van der Knaap H, Srinivasan K, Thomas T, Kok FJ, et al. Undernutrition, fatty acid and micronutrient status in relation to cognitive performance in Indian school children: a cross-sectional study. Br J Nutr. 2010;103(7):1056–64.
57. Louwman MW, van Dusseldorp M, van de Vijver FJ, Thomas CM, Schneede J, Ueland PM, et al. Signs of impaired cognitive function in adolescents with marginal cobalamin status. Am J Clin Nutr. 2000;72(3):762–9.
58. Duong MC, Mora-Plazas M, Marín C, Villamor E. Vitamin B-12 deficiency in children is associated with grade repetition and school absenteeism, independent of folate, iron, zinc, or vitamin a status biomarkers. J Nutr. 2015;145(7):1541–8.
59. Kvestad I, Hysing M, Shrestha M, Ulak M, Thorne-Lyman AL, Henjum S, et al. Vitamin B-12 status in infancy is positively associated with development and cognitive functioning 5 y later in Nepalese children. Am J Clin Nutr. 2017;105(5):1122–31.
60. Venkatramanan S, Armata IE, Strupp BJ, Finkelstein JL. Vitamin B-12 and Cognition in Children. Adv Nutr. 2016;7(5):879–88.
61. Kvestad I, Taneja S, Kumar T, Hysing M, Refsum H, Yajnik CS, et al. Vitamin B12 and folic acid improve gross motor and problem-solving skills in young north indian children: a randomized placebo-controlled trial. PLoS ONE. 2015;10(6):e0129915.
62. Moore E, Mander A, Ames D, Carne R, Sanders K, Watters D. Cognitive impairment and vitamin B12: a review. Int Psychogeriatr. 2012;24(4):541–56.
63. Zeisel SH CK. Choline In: Erdman JW MI, Zeisel SH, editors. Present Knowledge in Nutrition, 10th ed. Washington, DC: Wiley-Blackwell; 2012:405–18.
64. IoMaFaN Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington: National Academy; 1998.
65. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. Annu Rev Nutr. 2006;26:229–50.

66. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/Choline-HealthProfessional/ on March 5, 2018.
67. Corbin KD, Zeisel SH. The nutrigenetics and nutrigenomics of the dietary requirement for choline. Prog Mol Biol Transl Sci. 2012;108:159–77.
68. Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. FASEB J. 2018:fj201700692RR.
69. Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E. Choline intake during pregnancy and child cognition at age 7 years. Am J Epidemiol. 2013;177(12):1338–47.
70. Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry. 2013;170(3):290–8.
71. Freedman R, Ross RG. Prenatal choline and the development of schizophrenia. Shanghai Arch Psychiatry. 2015;27(2):90–102.
72. Liu Y, Zhang H, Ju G, Zhang X, Xu Q, Liu S, et al. A study of the PEMT gene in schizophrenia. Neurosci Lett. 2007;424(3):203–6.
73. McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J. 2008;22(4):982–1001.
74. MF H. Vitamin D. modern nutrition in health and disease, 10th ed. Philadelphia Lippincott Williams and Wilkins; 2006.
75. Norman AW HH. Vitamin D. In: Bowman BA RR, editors. Present knowledge in nutrition, 9th ed. Washington DC: ILSI Press; 2006.
76. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/ on March 5 2018.
77. Annweiler C, Maby E, Meyerber M, Beauchet O. Hypovitaminosis D and executive dysfunction in older adults with memory complaint: a memory clinic-based study. Dement Geriatr Cogn Disord. 2014;37(5–6):286–93.
78. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351(9105):805–6.
79. McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, Burne TH, et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Arch Gen Psychiatry. 2010;67(9):889–94.
80. Pet MA, Brouwer-Brolsma EM. The impact of maternal vitamin d status on offspring brain development and function: A systematic review. Adv Nutr. 2016;7(4):665–78.
81. Veena SR, Krishnaveni GV, Srinivasan K, Thajna KP, Hegde BG, Gale CR, et al. Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence. Asia Pac J Clin Nutr. 2017;26(3):438–49.
82. Föcker M, Antel J, Ring S, Hahn D, Kanal Ö, Öztürk D, et al. Vitamin D and mental health in children and adolescents. Eur Child Adolesc Psychiatry. 2017;26(9):1043–66.
83. Goodwill AM, Szoeke C. A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition. J Am Geriatr Soc. 2017;65(10):2161–8.
84. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013;202:100–7.
85. Bičíková M, Dušková M, Vítků J, Kalvachová B, Řípová D, Mohr P, et al. Vitamin D in anxiety and affective disorders. Physiol Res. 2015;64(Suppl 2):S101–3.
86. Imai CM, Halldorsson TI, Eiriksdottir G, Cotch MF, Steingrimsdottir L, Thorsdottir I, et al. Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes—AGES--Reykjavik Study. J Nutr Sci. 2015;4:e37.
87. Khoraminya N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayery A. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Aust N Z J Psychiatry. 2013;47(3):271–5.
88. Boerman R, Cohen D, Schulte PF, Nugter A. Prevalence of Vitamin D deficiency in adult outpatients with bipolar disorder or schizophrenia. J Clin Psychopharmacol. 2016;36(6):588–92.
89. Grudet C, Malm J, Westrin A, Brundin L. Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. Psychoneuroendocrinology. 2014;50:210–9.
90. Jääskeläinen T, Knekt P, Suvisaari J, Männistö S, Partonen T, Sääksjärvi K, et al. Higher serum 25-hydroxyvitamin D concentrations are related to a reduced risk of depression. Br J Nutr. 2015;113(9):1418–26.
91. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. Psychosom Med. 2014;76(3):190–6.
92. Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J Clin Psychopharmacol. 2013;33(3):378–85.
93. Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Oligodendrocytes and myelination: the role of iron. Glia. 2009;57(5):467–78.
94. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/ on March 5 2018.

95. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. Public Health Nutr. 2009;12 (4):444–54.
96. Lozoff B. Iron deficiency and child development. Food Nutr Bull. 2007;28(4 Suppl):S560–71.
97. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr. 2001;131(2S–2):649S–66S; discussion 66S–68S.
98. Fararouei M, Robertson C, Whittaker J, Sovio U, Ruokonen A, Pouta A, et al. Maternal Hb during pregnancy and offspring's educational achievement: a prospective cohort study over 30 years. Br J Nutr. 2010;104(9):1363–8.
99. Tran TD, Biggs BA, Tran T, Simpson JA, Hanieh S, Dwyer T, et al. Impact on infants' cognitive development of antenatal exposure to iron deficiency disorder and common mental disorders. PLoS ONE. 2013;8(9):e74876.
100. Beard JL. Why iron deficiency is important in infant development. J Nutr. 2008;138(12):2534–6.
101. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000;105(4):E51.
102. Agaoglu L, Torun O, Unuvar E, Sefil Y, Demir D. Effects of iron deficiency anemia on cognitive function in children. Arzneimittelforschung. 2007;57(6A):426–30.
103. Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L. The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J. 2010;9:4.
104. Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. CMAJ. 2013;185(17):E791–802.
105. Greig AJ, Patterson AJ, Collins CE, Chalmers KA. Iron deficiency, cognition, mental health and fatigue in women of childbearing age: a systematic review. J Nutr Sci. 2013;2:e14.
106. Cook RL, O'Dwyer NJ, Parker HM, Donges CE, Cheng HL, Steinbeck KS, et al. Iron deficiency anemia, not iron deficiency, is associated with reduced attention in healthy young women. Nutr. 2017;9(11).
107. Li Z, Li B, Song X, Zhang D. Dietary zinc and iron intake and risk of depression: A meta-analysis. Psychiatry Res. 2017;251:41–7.
108. National Research Council CtAtHIoPI. Health implications of perchlorate ingestion Washington. DC: The National Academies; 2005.
109. JT D. Modern nutrition in health and disease In: Shils ME SM, Ross AC, Caballero B, Cousins RJ, editors. Baltimore: Lippincott, 10th ed. Williams and Wilkins; 2006:300–11.
110. Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken JW. Nutrients for cognitive development in school-aged children. Nutr Rev. 2004;62(8):295–306.
111. Zimmermann M, Delange F. Iodine supplementation of pregnant women in Europe: a review and recommendations. Eur J Clin Nutr. 2004;58 (7):979–84.
112. Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. J Clin Endocrinol Metab. 2013;98(5):1954–62.
113. van Mil NH, Tiemeier H, Bongers-Schokking JJ, Ghassabian A, Hofman A, Hooijkaas H, et al. Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. J Nutr. 2012;142(12):2167–74.
114. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the avon longitudinal study of parents and children (ALSPAC). Lancet. 2013;382 (9889):331–7.
115. de Escobar GM, Obregón MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutr. 2007;10 (12A):1554–70.
116. Zhou SJ, Skeaff SA, Ryan P, Doyle LW, Anderson PJ, Kornman L, et al. The effect of iodine supplementation in pregnancy on early childhood neurodevelopment and clinical outcomes: results of an aborted randomised placebo-controlled trial. Trials. 2015;16:563.
117. Prasad AS. Zinc: an overview. Nutrition. 1995;11(1 Suppl):93–9.
118. Institute of Medicine FaNB. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc Washington. DC: National Academy Press; 2001.
119. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/Choline-HealthProfessional/ on March 5, 2018.
120. Polanska K, Hanke W, Krol A, Gromadzinska J, Kuras R, Janasik B, et al. Micronutrients during pregnancy and child psychomotor development: Opposite effects of Zinc and Selenium. Environ Res. 2017;158:583–9.
121. Warthon-Medina M, Moran VH, Stammers AL, Dillon S, Qualter P, Nissensohn M, et al. Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis. Eur J Clin Nutr. 2015;69(6):649–61.
122. Nowak G, Siwek M, Dudek D, Zieba A, Pilc A. Effect of zinc supplementation on antidepressant therapy in

unipolar depression: a preliminary placebo-controlled study. Pol J Pharmacol. 2003;55(6):1143–7.
123. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zieba A, Popik P, et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: a double blind, placebo-controlled study. J Affect Disord. 2009;118(1–3):187–95.
124. Ranjbar E, Kasaei MS, Mohammad-Shirazi M, Nasrollahzadeh J, Rashidkhani B, Shams J, et al. Effects of zinc supplementation in patients with major depression: a randomized clinical trial. Iran J Psychiatry. 2013;8(2):73–9.
125. Swardfager W, Herrmann N, Mazereeuw G, Goldberger K, Harimoto T, Lanctôt KL. Zinc in depression: a meta-analysis. Biol Psychiatry. 2013;74(12):872–8.
126. Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tancredi DJ, et al. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology. 2011;22(4):476–85.
127. Grima NA, Pase MP, Macpherson H, Pipingas A. The effects of multivitamins on cognitive performance: a systematic review and meta-analysis. J Alzheimers Dis. 2012;29(3):561–9.
128. Grodstein F, O'Brien J, Kang JH, Dushkes R, Cook NR, Okereke O, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. Ann Intern Med. 2013;159(12):806–14.
129. Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. Br J Psychiatry. 2014;204:306–15.
130. Rucklidge JJ, Frampton CM, Gorman B, Boggis A. Vitamin-Mineral Treatment of ADHD in Adults. J Atten Disord. 2017;21(6):522–32.
131. Health USDoHHSNIo https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/ on March 5 2018.
132. Luchtman DW, Song C. Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. Neuropharmacology. 2013;64:550–65.
133. Hadders-Algra M, Bouwstra H, van Goor SA, Dijck-Brouwer DA, Muskiet FA. Prenatal and early postnatal fatty acid status and neurodevelopmental outcome. J Perinat Med. 2007;35(Suppl 1):S28–34.
134. Campoy C, Escolano-Margarit MV, Ramos R, Parrilla-Roure M, Csabi G, Beyer J, et al. Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age. Am J Clin Nutr. 2011;94(6 Suppl):1880S–8S.
135. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2013;97(3):531–44.
136. Dziechciarz P, Horvath A, Szajewska H. Effects of n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on neurodevelopment and visual function in children: a systematic review of randomized controlled trials. J Am Coll Nutr. 2010;29(5):443–54.
137. Bernard JY, Armand M, Garcia C, Forhan A, De Agostini M, Charles MA, et al. The association between linoleic acid levels in colostrum and child cognition at 2 and 3 y in the EDEN cohort. Pediatr Res. 2015;77(6):829–35.
138. Bernard JY, Armand M, Peyre H, Garcia C, Forhan A, De Agostini M, et al. Breastfeeding, Polyunsaturated Fatty Acid Levels in Colostrum and Child Intelligence Quotient at Age 5-6 Years. J Pediatr. 2017;183:43–50.e3.
139. Ramakrishnan U, Gonzalez-Casanova I, Schnaas L, DiGirolamo A, Quezada AD, Pallo BC, et al. Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial. Am J Clin Nutr. 2016;104(4):1075–82.
140. Sakayori N, Kikkawa T, Tokuda H, Kiryu E, Yoshizaki K, Kawashima H, et al. Maternal dietary imbalance between omega-6 and omega-3 polyunsaturated fatty acids impairs neocortical development via epoxy metabolites. Stem Cells. 2016;34(2):470–82.
141. Vancassel S, Blondeau C, Lallemand S, Cador M, Linard A, Lavialle M, et al. Hyperactivity in the rat is associated with spontaneous low level of n-3 polyunsaturated fatty acids in the frontal cortex. Behav Brain Res. 2007;180(2):119–26.
142. Levant B, Zarcone TJ, Fowler SC. Developmental effects of dietary n-3 fatty acids on activity and response to novelty. Physiol Behav. 2010;101(1):176–83.
143. Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol. 2003;101(3):469–79.
144. Colombo J, Kannass KN, Shaddy DJ, Kundurthi S, Maikranz JM, Anderson CJ, et al. Maternal DHA and the development of attention in infancy and toddlerhood. Child Dev. 2004;75(4):1254–67.
145. Daniels JL, Longnecker MP, Rowland AS, Golding J, Health ASTUoBIoC. Fish intake during pregnancy and early cognitive development of offspring. Epidemiology. 2004;15(4):394–402.
146. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet. 2007;369(9561):578–85.
147. Jacobson JL, Jacobson SW, Muckle G, Kaplan-Estrin M, Ayotte P, Dewailly E. Beneficial effects of a polyunsaturated fatty acid on infant development:

evidence from the inuit of arctic Quebec. J Pediatr. 2008;152(3):356–64.
148. Oken E, Østerdal ML, Gillman MW, Knudsen VK, Halldorsson TI, Strøm M, et al. Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. Am J Clin Nutr. 2008;88(3):789–96.
149. Boucher O, Burden MJ, Muckle G, Saint-Amour D, Ayotte P, Dewailly E, et al. Neurophysiologic and neurobehavioral evidence of beneficial effects of prenatal omega-3 fatty acid intake on memory function at school age. Am J Clin Nutr. 2011;93(5):1025–37.
150. Starling P, Charlton K, McMahon AT, Lucas C. Fish intake during pregnancy and foetal neurodevelopment–a systematic review of the evidence. Nutrients. 2015;7(3):2001–14.
151. Agriculture USDoHaHSaUSDo. 2015–2020 Dietary Guidelines for Americans 8th ed.
152. So Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–41.
153. Lenihan-Geels G, Bishop KS, Ferguson LR. Alternative sources of omega-3 fats: can we find a sustainable substitute for fish? Nutrients. 2013;5(4):1301–15.
154. Niculescu MD, Lupu DS. High fat diet-induced maternal obesity alters fetal hippocampal development. Int J Dev Neurosci. 2009;27(7):627–33.
155. Sullivan EL, Nousen EK, Chamlou KA. Maternal high fat diet consumption during the perinatal period programs offspring behavior. Physiol Behav. 2014;123:236–42.
156. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn. 2017;37(1):95–110.
157. Lyall K, Munger KL, O'Reilly É, Santangelo SL, Ascherio A. Maternal dietary fat intake in association with autism spectrum disorders. Am J Epidemiol. 2013;178(2):209–20.
158. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry. 2008;65(5):578–84.
159. Smithers LG, Kramer MS, Lynch JW. Effects of breastfeeding on obesity and intelligence: causal insights from different study designs. JAMA Pediatr. 2015;169(8):707–8.
160. Belfort MB, Rifas-Shiman SL, Kleinman KP, Guthrie LB, Bellinger DC, Taveras EM, et al. Infant feeding and childhood cognition at ages 3 and 7 years: Effects of breastfeeding duration and exclusivity. JAMA Pediatr. 2013;167(9):836–44.
161. Brown Belfort M. The Science of Breastfeeding and Brain Development. Breastfeed Med. 2017;12(8):459–61.
162. Schneider N, Garcia-Rodenas CL. Early nutritional interventions for brain and cognitive development in preterm infants: a review of the literature. Nutrients. 2017;9(3).
163. Walfisch A, Sermer C, Cressman A, Koren G. Breast milk and cognitive development–the role of confounders: a systematic review. BMJ Open. 2013;3(8):e003259.
164. Chang JP, Su KP, Mondelli V, Pariante CM. Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: A systematic review and meta-analysis of clinical trials and biological studies. Neuropsychopharmacology. 2018;43(3):534–45.
165. Zhang XW, Hou WS, Li M, Tang ZY. Omega-3 fatty acids and risk of cognitive decline in the elderly: a meta-analysis of randomized controlled trials. Aging Clin Exp Res. 2016;28(1):165–6.
166. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016;103(2):330–40.
167. Gumpricht E, Rockway S. Can ω-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders? Nutrition. 2014;30(7–8):733–8.
168. Farina N LD, Isaac M, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. 2017.
169. Pompili M, Longo L, Dominici G, Serafini G, Lamis DA, Sarris J, et al. Polyunsaturated fatty acids and suicide risk in mood disorders: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2017;74:43–56.
170. Tsai AC, Lucas M, Okereke OI, O'Reilly EJ, Mirzaei F, Kawachi I, et al. Suicide mortality in relation to dietary intake of n-3 and n-6 polyunsaturated fatty acids and fish: equivocal findings from 3 large US cohort studies. Am J Epidemiol. 2014;179(12):1458–66.
171. Chang JP, Lin CY, Lin PY, Shih YH, Chiu TH, Ho M, et al. Polyunsaturated fatty acids and inflammatory markers in major depressive episodes during pregnancy. Prog Neuropsychopharmacol Biol Psychiatry. 2018;80(Pt C):273–8.
172. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. J Clin Psychiatry. 2011;72(12):1577–84.
173. Sarris J, Mischoulon D, Schweitzer I. Adjunctive nutraceuticals with standard pharmacotherapies in bipolar disorder: a systematic review of clinical trials. Bipolar Disord. 2011;13(5–6):454–65.
174. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry. 2012;73(1):81–6.

175. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS ONE. 2014;9(5):e96905.
176. Li F, Liu X, Zhang D. Fish consumption and risk of depression: a meta-analysis. J Epidemiol Community Health. 2016;70(3):299–304.
177. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. ω-3 Fatty acids for major depressive disorder in adults: an abridged Cochrane review. BMJ Open. 2016;6(3):e010172.
178. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long--chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010;67(2):146–54.
179. Su KP, Tseng, P.T., Lin, P.Y. Okubo, R. Chen, T.Y. Chen, Y.W., & Matsuoka, Y.J.. Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms a systematic review and meta-analysis. JAMA Netw Open. 2018;1(5):1–16.
180. Jacka FN, Ystrom E, Brantsaeter AL, Karevold E, Roth C, Haugen M, et al. Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. J Am Acad Child Adolesc Psychiatry. 2013;52(10):1038–47.
181. Borge TC, Aase H, Brantsæter AL, Biele G. The importance of maternal diet quality during pregnancy on cognitive and behavioural outcomes in children: a systematic review and meta-analysis. BMJ Open. 2017;7(9):e016777.
182. O'Neil A, Quirk SE, Housden S, Brennan SL, Williams LJ, Pasco JA, et al. Relationship between diet and mental health in children and adolescents: a systematic review. Am J Public Health. 2014;104 (10):e31–42.
183. Pina-Camacho L, Jensen SK, Gaysina D, Barker ED. Maternal depression symptoms, unhealthy diet and child emotional-behavioural dysregulation. Psychol Med. 2015;45(9):1851–60.
184. de Lauzon-Guillain B, Jones L, Oliveira A, Moschonis G, Betoko A, Lopes C, et al. The influence of early feeding practices on fruit and vegetable intake among preschool children in 4 European birth cohorts. Am J Clin Nutr. 2013;98 (3):804–12.
185. Jones L, Moschonis G, Oliveira A, de Lauzon-Guillain B, Manios Y, Xepapadaki P, et al. The influence of early feeding practices on healthy diet variety score among pre-school children in four European birth cohorts. Public Health Nutr. 2015;18(10):1774–84.
186. Emmett PM, Jones LR, Golding J. Pregnancy diet and associated outcomes in the avon longitudinal study of parents and children. Nutr Rev. 2015;73 (Suppl 3):154–74.
187. Freitas-Vilela AA, Pearson RM, Emmett P, Heron J, Smith AD, Emond A, et al. Maternal dietary patterns during pregnancy and intelligence quotients in the offspring at 8 years of age: Findings from the ALSPAC cohort. Matern Child Nutr. 2017.
188. Jacka FN, Kremer PJ, Leslie ER, Berk M, Patton GC, Toumbourou JW, et al. Associations between diet quality and depressed mood in adolescents: results from the Australian healthy neighbourhoods study. Aust N Z J Psychiatry. 2010;44(5):435–42.
189. Jacka FN, Kremer PJ, Berk M, de Silva-Sanigorski AM, Moodie M, Leslie ER, et al. A prospective study of diet quality and mental health in adolescents. PLoS ONE. 2011;6(9):e24805.
190. Jacka FN, Rothon C, Taylor S, Berk M, Stansfeld SA. Diet quality and mental health problems in adolescents from East London: a prospective study. Soc Psychiatry Psychiatr Epidemiol. 2013;48 (8):1297–306.
191. Haapala EA, Eloranta AM, Venäläinen T, Schwab U, Lindi V, Lakka TA. Associations of diet quality with cognition in children - the Physical Activity and Nutrition in Children Study. Br J Nutr. 2015;114(7):1080–7.
192. Trapp GS, Allen KL, Black LJ, Ambrosini GL, Jacoby P, Byrne S, et al. A prospective investigation of dietary patterns and internalizing and externalizing mental health problems in adolescents. Food Sci Nutr. 2016;4(6):888–96.
193. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr. 2014;99 (1):181–97.
194. Li Y, Lv MR, Wei YJ, Sun L, Zhang JX, Zhang HG, et al. Dietary patterns and depression risk: A meta-analysis. Psychiatry Res. 2017;253:373–82.
195. Henriksson P, Cuenca-García M, Labayen I, Esteban-Cornejo I, Henriksson H, Kersting M, et al. Diet quality and attention capacity in European adolescents: the healthy lifestyle in Europe by nutrition in adolescence (HELENA) study. Br J Nutr. 2017;117(11):1587–95.
196. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol. 2013;74 (4):580–91.
197. Rahe C, Unrath M, Berger K. Dietary patterns and the risk of depression in adults: a systematic review of observational studies. Eur J Nutr. 2014;53 (4):997–1013.
198. Berendsen AAM, Kang JH, van de Rest O, Feskens EJM, de Groot LCPG, Grodstein F. The dietary approaches to stop hypertension diet, cognitive function, and cognitive decline in american older women. J Am Med Dir Assoc. 2017;18 (5):427–32.

199. Tangney CC. DASH and mediterranean-type dietary patterns to maintain cognitive health. Curr Nutr Rep. 2014;3(1):51–61.
200. Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the MedDietScore. Prev Med. 2007;44(4):335–40.
201. McEvoy CT, Guyer H, Langa KM, Yaffe K. Neuroprotective diets are associated with better cognitive function: the health and retirement study. J Am Geriatr Soc. 2017;65(8):1857–62.
202. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. 2015;11(9):1015–22.
203. Carter CM, Egger J, Soothill JF. A dietary management of severe childhood migraine. Hum Nutr Appl Nutr. 1985;39(4):294–303.
204. Carter CM, Urbanowicz M, Hemsley R, Mantilla L, Strobel S, Graham PJ, et al. Effects of a few food diet in attention deficit disorder. Arch Dis Child. 1993;69(5):564–8.
205. Pelsser LM, Frankena K, Toorman J, Rodrigues Pereira R. Diet and ADHD, reviewing the evidence: A systematic review of meta-analyses of double-blind placebo-controlled trials evaluating the efficacy of diet interventions on the behavior of children with ADHD. PLoS ONE. 2017;12(1): e0169277.
206. Casas M, Chatzi L, Carsin AE, Amiano P, Guxens M, Kogevinas M, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: Two southern european birth cohort studies. Int J Epidemiol. 2013;42(2):506–17.
207. Pugh SJ, Richardson GA, Hutcheon JA, Himes KP, Brooks MM, Day NL, et al. Maternal obesity and excessive gestational weight gain are associated with components of child cognition. J Nutr. 2015;145(11):2562–9.
208. Li YM, Ou JJ, Liu L, Zhang D, Zhao JP, Tang SY. Association between maternal obesity and autism spectrum disorder in offspring: A meta-analysis. J Autism Dev Disord. 2016;46(1):95–102.
209. Wahlbeck K, Forsén T, Osmond C, Barker DJ, Eriksson JG. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. Arch Gen Psychiatry. 2001;58(1):48–52.
210. Heikura U, Taanila A, Hartikainen AL, Olsen P, Linna SL, von Wendt L, et al. Variations in prenatal sociodemographic factors associated with intellectual disability: a study of the 20-year interval between two birth cohorts in northern Finland. Am J Epidemiol. 2008;167(2):169–77.
211. Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes (Lond). 2012;36(10):1312–9.
212. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr. 2007;85(2):614S–20S.
213. Schlotz W, Phillips DI. Fetal origins of mental health: evidence and mechanisms. Brain Behav Immun. 2009;23(7):905–16.
214. Palmer AA, Printz DJ, Butler PD, Dulawa SC, Printz MP. Prenatal protein deprivation in rats induces changes in prepulse inhibition and NMDA receptor binding. Brain Res. 2004;996(2):193–201.
215. Meyer U, Feldon J. Epidemiology-driven neurodevelopmental animal models of schizophrenia. Prog Neurobiol. 2010;90(3):285–326.
216. Liang J, Matheson BE, Kaye WH, Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes (Lond). 2014;38(4):494–506.
217. Chojnacki MR, Raine LB, Drollette ES, Scudder MR, Kramer AF, Hillman CH, et al. The negative influence of adiposity extends to intraindividual variability in cognitive control among preadolescent children. Obesity (Silver Spring). 2018;26(2):405–11.
218. Baumgartner NW, Walk AM, Edwards CG, Covello AR, Chojnacki MR, Reeser GE, et al. Relationship between physical activity, adiposity, and attentional inhibition. J Phys Act Health. 2018;15(3):191–6.
219. Oddy WH, Allen KL, Trapp GSA, Ambrosini GL, Black LJ, Huang RC, et al. Dietary patterns, body mass index and inflammation: Pathways to depression and mental health problems in adolescents. Brain Behav Immun. 2018;69:428–39.
220. Benito-León J, Mitchell AJ, Hernández-Gallego J, Bermejo-Pareja F. Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES). Eur J Neurol. 2013;20(6):899–906, e76–7.
221. Albanese E, Launer LJ, Egger M, Prince MJ, Giannakopoulos P, Wolters FJ, et al. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589, 649 men and women followed in longitudinal studies. Alzheimers Dement (Amst). 2017;8:165–78.
222. Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ. Are the obese at greater risk for depression? Am J Epidemiol. 2000;152(2):163–70.
223. Carpenter KM, Hasin DS, Allison DB, Faith MS. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. Am J Public Health. 2000;90(2):251–7.
224. Rivas-García TE, Marcelo-Pons M, Martínez-Arnau F, Serra-Catalá N, Santamaría-Carrillo Y, Cauli O. Blood zinc levels and cognitive and functional evaluation in non-demented older patients. Exp Gerontol. 2018.

225. Steenweg-de Graaff J, Roza SJ, Steegers EA, Hofman A, Verhulst FC, Jaddoe VW, et al. Maternal folate status in early pregnancy and child emotional and behavioral problems: the Generation R Study. Am J Clin Nutr. 2012;95(6):1413–21.
226. Gokcen C, Kocak N, Pekgor A. Methylenetetrahydrofolate reductase gene polymorphisms in children with attention deficit hyperactivity disorder. Int J Med Sci. 2011;8(7):523–8.
227. Bailey RL, West KP, Black RE. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab. 2015;66(Suppl 2):22–33.
228. Youdim AaG, David S. 2018. https://www.merckmanuals.com/professional/nutritional-disorders/nutrition-general-considerations/nutrient-drug-interactions on September 7 2018.

Chapter 29

Hepatic Encephalopathy

Jasmohan S. Bajaj and Kevin D. Mullen

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease [1]. HE is primarily divided into two components: overt HE (OHE) and minimal HE (MHE). OHE is the specific type of HE that can be diagnosed clinically through a constellation of signs and symptoms while MHE cannot be diagnosed clinically. It has been estimated that OHE is present in 30–45% of patients with cirrhosis with an annual risk of development in 20% of patient with cirrhosis [2]. There is a uniformly poor survival after development of OHE. MHE is manifested by impairment in specialized testing and is considered by most to be a pre-clinical stage of OHE [1]. MHE has been diagnosed in up to 60–80% of patients with cirrhosis and is associated with increased progression to OHE, poor quality of life, and a high risk of traffic violations and accidents [3].

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There is an immense societal cost of OHE and MHE. A recent report showed that although there is a reduction in hospital stay for patients with OHE, the costs are likely to increase over the coming years. Although the exact cost of MHE has not been calculated to date, it is immense in terms of the non-medical societal burden caused by lost productivity and higher traffic accidents [4].

Neurocognitive and Neuroscience Theory and Background

Essentially, the search for the mechanisms responsible for the mediation of hepatic encephalopathy has existed ever since the first description of this syndrome as we know it today [5, 6]. Gabuzda and colleagues in the 1950s suggested ammonia may play a significant role in HE [7]. This ammonia theory of HE continued for some time, but correlation of ammonia levels and the severity of HE was noted to be poor in multiple studies. This poor correlation was more likely related to unreliable ammonia assays since more recent studies show good correlations [8–10]. During the era of some disenchantment with ammonia as the sole toxin responsible for HE, a series of alternative hypotheses were developed (Table 29.1). Merely describing all of these concepts can be a too lengthy discussion for this review. We will make selected comments on some of the hypotheses before focusing on the widely accepted newest proposal for the case of HE.

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Table 29.1 Hypothesis of pathogenesis of HE

• Ammonia neurotoxicity
• Ammonia with other neurotoxins
• False neurotransmitter/plasma amino acid imbalance
• Gamma-aminobutyric acid (GABA)
• Endogenous benzodiazepines
• Histamine
• Cerebral edema
• Ammonia, cerebral edema, and cytokines

Table 29.2 Causes of astrocyte swelling

- Ammonia entry → Glutamine accumulation
- Benzodiazepines (active on peripheral-type binding site)
- Hyponatremia
- Cytokines
- Glutamate

First and foremost despite some poor correlation studies over the years, there is as noted above once again good data showing a correlation between the severity of HE and the level of blood ammonia [11]. This on its own does not prove ammonia causes HE, but other new data describe a very real link between excess ammonia entering the brain and molecular events known to be occurring in the brain. We will return to this issue later.

The gamma-aminobutyric acid (GABA) benzodiazepine hypothesis of HE was an off shot of the original GABA hypothesis developed by Schafer et al. [12]. Rather than simple over activity of the GABAergic system due to excess GABA, the newer hypothesis proposed that endogenous benzodiazepines were accumulating in the brain in liver failure. These compounds were isolated and partially identified and behaved like most sedative-type benzodiazepines [13]. Reversal of HE in humans supported this hypothesis when over 30% of patients with severe HE were immediately aroused by the benzodiazepine antagonist flumazenil [14]. These observations have not been followed up but are still worthy of investigation.

Perhaps one of the most divisive issues on the study of the mechanisms of HE was the extraordinary discrepancies between different animal models of HE used by different laboratory teams [15]. Over time reasonable good evidence for endogenous opiates, histamine, and other compounds was published [16]. However, all of these somewhat separate concepts began to by overtaken by a new cerebral edema hypothesis of HE [17].

Formerly thought to be only present in acute liver failure cerebral edema was eventually noted to be present in virtually all animal models of HE as well as in human HE in chronic liver disease [18]. These unifying observations were partially due to a result of noting specific neurochemical findings on nuclear magnetic spectroscopy of the brain in liver failure. Depletion of myoinositol was interpreted to be due to osmotic shifts in the brain in liver failure [19, 20]. The underlying mechanism seems to involve primarily ammonia uptake into perivascular astrocytes. This ammonia binds to glutamate to form the osmotically active compound glutamine. This increase in intracellular glutamine causes cell swelling which is thought to lead to a cascade of events resulting in HE. Upregulation of specific types of peripheral benzodiazepine receptors occurs in this process which leads to increased production of potent neurosteroids which may affect neural function by GABA-mediated pathways [17]. Since benzodiazepine compounds and other agents can aggravate or cause astrocyte swelling (Table 29.2), we now have a unifying hypothesis of HE which includes particular roles for cytokines and products of oxidative stress (Table 29.2). The role of inflammatory cytokines in the pathogenesis of HE has been the most recent concept to be developed [21]. It potentially explains the severity of HE in sepsis but a clearer role may be seen when artificially raising blood ammonia levels are used as provocation for HE. Quite high ammonia levels can be tolerated after an oral glutamine challenge in cirrhotic patients [22]. However, if inflammatory markers are elevated in the blood at the time of challenge then neurocognitive decline is reliably seen [23].

The pathogenesis of HE has evolved quite a bit over the last five to six decades. To a significant extent the clues taken to unlock the cause of this enigmatic syndrome are empirical clinic observations. A great deal of evidence points to the gut as the origin for the factor or factors causing HE. Ammonia is still a key toxin thought to play a role in HE primarily by inducing cerebral edema by its excessive entry into the brain. Other co-factors as well as ammonia are now targets for developing new therapies for HE.

Review of the Attempts to Identify the Most Specific Neuropsychological Assessment for Diagnosis

Altered Mental Status in Patients with Cirrhosis; It Is Not All HE

Although HE is present in most cirrhotic patients with altered mental status, it is definitely not the only reason for change in mentation in these patients [24]. There are several other differential diagnoses for the development of cognitive dysfunction in cirrhotics, especially intra-cranial events, electrolyte abnormalities, and sepsis. Therefore the overall susceptibility of the brain toward alteration of higher mental function is present in cirrhosis and HE should only be diagnosed after exclusion of other potential causes.

Physical Examination

Physical exam in MHE by definition should not unearth any focal or lateralizing neurologic deficits. The physical exam in OHE should initially concentrate on assessing mental status using the West Haven Criteria [24].

A detailed evaluation of the vitals and airway should be performed at the outset and those should be managed first and foremost. Once those pressing issues have been managed, it is then important to perform a detailed neurological examination [4].

Motor Exam

In most cases the presence of a previously unknown focal motor deficit is not typical of OHE, which tends to be a global rather than a focal process.

Patients with OHE have hyper-reflexia, positive Babinski's sign and in grade 2 and 3 have asterixis [24]. Asterixis is defined as a flapping tremor caused by the disturbance in the oscillatory networks in the brain. It can be demonstrated in the tongue and the upper and lower extremities. In patients who are too obtunded to raise their hands up "as they are stopping traffic," they should be instructed to grip the examiner's hands. The grip in patients with asterixis is never constant and oscillates between tight and loose.

Care should be taken not to confuse asterixis with tremulousness associated with alcohol abuse or withdrawal. Asterixis is not specific for HE and can also be seen in carbon dioxide intoxication and uremia [4].

Motor exam in HE patients can also demonstrate Parkinsonian symptoms with the attendant rigidity and tremors. In a small subgroup, spinal cord involvement with spastic paraparesis, resulting from hepatic myelopathy can also occur, but this syndrome is distinct from HE [25].

Neuropsychological Examination and Psychometric Testing

MHE has a specific deficit profile on psychometric testing while the manifestations of OHE can range from mild difficulty in concentration to frank coma. The West Haven Criteria are used most frequently to grade HE from stages 0–4, of which 4 is coma. Stage 0 is no overt HE therefore stage 0 with psychometric or neurophysiological abnormalities is MHE [24]. Stage 1 and higher are in the realm of OHE (Table 29.3). Only low-grade HE, i.e., pre-coma grade 1 and 2 in the West Haven criteria, and MHE are the components of HE that require a detailed neuropsychological evaluation. The rest can be diagnosed clinically [26].

The major neuropsychological abnormalities in HE are attention deficits [27]. The attentional hierarchy as described by Posner is impaired at all levels of vigilance, orienting and executive functions [28]. Attention deficits also result in learning impairment and difficulty in working memory. There is also a defect in visuo-motor coordination and construction ability and in speed of mental processing. Underlying most of these deficits is the impairment of response inhibition [27].

Neuropsychometric testing for HE concentrates on the evaluation of these specific spheres. There are several batteries for the diagnosis of HE which have

Table 29.3 West Haven criteria of altered mental status in hepatic encephalopathy

Stage	Consciousness	Intellect and behavior	Neurologic findings
0	Normal	Normal	Normal examination; impaired psychomotor testing
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behavior	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behavior	Muscular rigidity and clonus; hyper-reflexia
4	Coma	Coma	Decerebrate posturing

been studied, all of which are based on detecting attention deficits and processing speed [27].

The PSE syndrome test used by Weissenborn et al. has been validated for the diagnosis of MHE in non-alcoholic cirrhotics in Germany, Italy, and Spain [27, 29, 30]. It consists of number connection test-A (NCT-A), number connection test-B (NCT-B), line drawing test errors and time, serial dotting test, and digit symbol test (DST). Test results within the ±1 SD range are score 0, between 1 and 2 SD are –1 point, between 2 and 3 SD –2 points, and beyond 3 SD is scored –3. Results better than the mean plus 1 SD are given 1 point; therefore +6 to –18 points is the range of scores. The cutoff between normal and pathological results was found to be −4 points which resulted in a sensitivity of 96 and 100% specificity. This testing strategy has been validated in Spain, where there are population norms available (www.redeh.org), and in Italy. There is variation in the use of the subscores for line drawing test. This battery has also been recommended by the Working Group on Hepatic Encephalopathy. However, validation of this in the USA has not been performed to date.

The Working Group also recommended that if the PSE syndrome test was not available, a combination of two of the following four tests, NCT-A, NCT-B, DST, or BDT. The convention typically used is impairment in at least two of these tests 2 standard deviations beyond age and education-matched healthy controls [1].

A recent consensus statement (yet unpublished) but discussed in the 13th ISHEN meeting recommended the use of repeated battery for assessment of neuropsychological status (RBANS) or PSE syndrome test. RBANS has been used for the evaluation of Alzheimer's disease, schizophrenia, traumatic brain injury, and in a selected population of patients with cirrhosis awaiting liver transplantation. However, it has not been specifically validated in HE [31]. RBANS is a copyrighted set of tests consisting of five domains. It is divided into cortical and subcortical domains as well and as expected, HE patients predominantly perform worse with the subcortical than the cortical component testing [32].

Neurophysiologic Testing

Another type of tests used in HE are neurophysiological tests which are offered under the supervision of a neurologist. These range from a simple electroencephalogram (EEG) to sophisticated techniques of automated evoked potentials. Spectral EEG, mean dominant frequency, and peak power frequency of EEG have been studied but have demonstrated subjectivity. Spectral and bispectral EEG are easier to interpret but have poor reliability.

Evoked potentials are the mainstay of the neurophysiological testing armamentarium. Evoked potentials studied in HE are auditory, visual, and somatosensory. Latency between administration and signal and latency between peaks are the most sensitive parameters. Somatosensory evoked potentials showed 48% with abnormal inter-peak latencies N20-N65 but no correlation with psychometric tests. Event-related evoked potentials studied were both visual and auditory P300 latencies. Visual P300 was found to be abnormal in 78% compared to psychometric abnormalities in only 41% in one study. Another study found abnormal auditory P300 present in 25% vs. 20% NCT-A abnormalities which could also predict progression to OHE. Most studies with

evoked potentials included early OHE along with MHE [33].

Limitations of Currently Available Psychometric and Neurophysiologic Tests

These psychometric and neurophysiologic tests, although available, require specialized personnel for administration and interpretation. This becomes difficult to apply in a regular clinic setting although they are ideal for research settings [34]. Therefore recent studies have been performed for tests that can be applied in the clinic settings by personnel other than psychologists. These tests are the critical flicker frequency (neurophysiological test) and two computerized psychometric test systems, the Cognitive Drug Research (CDRS) and the inhibitory control tests, which will be explained in detail in Section "State-of-the-Art Diagnostic, Open Access, and Treatments".

Additional Helpful Information About the Diagnostic Question

MHE and early HE can be difficult to diagnose in the specialist hepatology clinic and even more so in the primary care setting. The initial diagnosis needs a high index of suspicion for selectively testing patients or referring them to the hepatologist or the psychologist.

Population to Be Tested

Patients with cirrhosis who do not have overt hepatic encephalopathy (which is a clinical diagnosis) and those who are not on psychoactive medications should be tested for MHE. Ortiz et al. and Stewart et al. recommend restricting this testing to cirrhotic patients who are working full time, driving, and those operating heavy machinery [26, 35]. Consensus statements regarding diagnosis of cognitive dysfunction and the timing of this testing are debatable.

We would recommend testing for MHE as soon as the patient is diagnosed with cirrhosis or when the patient has some cognitive complaint using psychometric or neurophysiological testing depending on local expertise.

The diagnosis of early HE is a combination of psychometric and clinical diagnosis according to West Haven criteria; separating early HE versus MHE may not be always possible or even necessary. This is because cognitive dysfunction is a continuous problem and may need treatment regardless of stage. However, when the patient reaches the later stages of HE there is no psychometric testing required and a clinical diagnosis is sufficient.

Timing of testing in patients who do not have MHE is every 6 months to 1 year or after events that can precipitate OHE. However, the natural history of MHE has not been completely elucidated at this time. The consensus is that initial testing should be offered if available, the other alternative being to treat without testing since the prevalence is approximately 80% of patients tested [4].

State-of-the-Art Diagnostic, Open Access, and Treatments

State of the Art and Open Access Diagnostic Strategies

Diagnostic strategies for MHE have been a constant source of investigation and discussion but a compromise between tests that are adequately descriptive versus tests that can be rapidly offered in clinic needs to be achieved. This is due to the relative importance of MHE and early HE both from the standpoint of an individual and the public health relevance because of MHE's bearing on driving ability.

Critical flicker frequency (CFF) tests the ability of a patient to perceive flickering which has a direct correlation with psychometric abnormalities [36]. During this test, the patient is asked to indicate the maximum frequency at which they can still perceive the light as flickering while changing the frequency over time. Light is controlled by a 3-mm artificial

pupil and at least 10 trials are counted. Studies have shown that a CFF threshold of 38–39 Hz could differentiate between manifest HE (i.e., early stages of OHE) and no HE and it was less sensitive in differentiating MHE from manifest HE. This test has been tested in Spain and India as well with good results [30, 37]. Encouragingly, it can be performed by clinic personnel without the need for a psychologist within a short period of time and apart from the equipment, has minor costs. CFF has, however, not been validated for the US population.

The CDR consists of five psychometric subsets that test attention power, attention continuity, speed of memory, and quality of episodic and working memory. This battery has been developed by Cognitive Drug Research (CDR) Ltd (Goring-on-Thames, UK). These tests have 50 parallel forms and have population norms for the UK. A recent study compared the CDR to the PHES and showed improvement after liver transplantation and worsening after a nitrogen challenge. In this study, MHE patients were impaired in all subsets and there was worsening of the quality of working and episodic memory after a nitrogen challenge. CDR will be available in 2009 from the UK at an assessment cost of 30 pounds sterling [38].

Inhibitory control test (ICT) is a computerized variant of the continuous performance test, which assesses sustained attention and response inhibition [39]. It has been used in the description of traumatic brain injury, schizophrenia, and attention deficit disorder. ICT consists of 1728 stimuli, 40 lures and 212 targets that are presented within 13 minutes after a training run. A higher lure and lower target rate represent worse psychometric performance. ICT has been validated in the US population with 88% sensitivity for the diagnosis of MHE when a patient had >5 lures using a standard psychometric battery as the gold standard. ICT also predicted the development of OHE and changed appropriately with the clinical state of the patients, i.e., improved after therapy and worsened after shunting procedures. Clinic personnel were also able to administer ICT with minimal training and it was found to be cheaper than psychometric test administration. It is appropriate for MHE testing at the clinic level in a US population and will be available in a freely downloadable form [40, 41].

Treatments for HE

Therapy for MHE and HE is targeted toward the gut in most cases due to the ammoniagenic potential of gut contents that have been hypothesized to cause HE. Lactulose and lactitol are non-absorbable disaccharides which result in acidification of stool contents, expulsion of stool bacteria, and laxative action. They have been useful in the therapy of acute OHE, especially those in the later stages, along with specialized intensive unit care for respiratory and metabolic monitoring and reversal of possible precipitating factors [42]. Chronic HE therapy, including treatment of MHE is in a flux. Lactulose does not meet the standard criteria for efficacy according to a Cochrane Database but is still extensively used as the first-line therapy for HE due to its low cost [43]. It is associated with several adverse effects and adherence tends to be low in the general OHE population. In MHE, however, lactulose has been tested in several randomized controlled trials. A recent trial demonstrated enhancement in quality of life parameters as well as psychometric improvement [44].

Rifaximin is a non-absorbable antibiotic that has been used for the therapy of OHE in Europe and the USA. It is not associated with compliance issues but is expensive compared to lactulose [45]. The use of rifaximin in MHE has not been studied to date.

Other therapies for OHE include zinc supplementation, metronidazole, flumazenil, and neomycin, all of which have currently fallen out of favor due to their adverse effect profile or low efficacy. *N*-Acetylcarnitine and acarbose have demonstrated some efficacy as therapy for OHE in trials either limited to few patients or to one center and these require validation in other centers before they can be included in OHE treatment clinically [42].

Specific therapies studied for MHE apart from the above are synbiotics, probiotics, and probiotic yogurt [46, 47]. Probiotic therapy, across several small trials,

has consistently demonstrated MHE reversal [48–52]. Liu et al. showed that treatment with fiber or fiber with probiotics equally reversed MHE and in most cases also improved the overall liver disease [46]. Other trials with probiotics and probiotic yogurt again point toward the primary gut-related pathogenesis of MHE and HE as a whole [52]. The exact mechanism of action for probiotic action is not defined but gut bacterial population replacement and metabolic changes induced by probiotics have been proposed.

A Brief Section on Relevant Family or Social Issues

HE as a whole severely affects the ability of the individual as well as the family to function in daily life. OHE, especially in the later stages, represents the manifestation of end-stage liver disease and has a profound adverse effect on mortality [53]. Although OHE currently is not an indication for transplantation, it is associated with worse liver disease and requires immediate attention from a medical standpoint [54].

MHE and early OHE without treatment are associated with worse quality of life, increased progression to OHE and death, and impaired driving ability [33]. Quality of life is an essential component of the clinical exam which is often ignored in our busy daily practice.

Repeated studies have underlined the immense negative effect of MHE in all spheres of daily living, except communication skills [44]. Importantly quality of life improves after successful MHE therapy [44]. Since MHE disproportionately affects attention and visuo-motor coordination, its effect on working capability is greater on "blue-collar" rather than "white-collar" workers and can result in an unfavorable socio-economic influence [55].

Driving capability is an important topic in the USA since it symbolizes freedom to move, which in smaller cities is the lifeline for most people. However, driving also consists of a series of intricate and complex sensory motor actions, which not only affects the individual but also the persons they are sharing the road with. MHE has been shown to affect not only driving ability but also navigation in road tests and on a driving simulator [56, 57]. Importantly this is also associated with a higher risk of traffic accidents and violations [58]. The role of family and society is central in the evaluation of driving since not only both are affected in the case of an untreated, impaired driver, they also have to accommodate for the needs of the patient in case the driving privileges are revoked [57]. Physicians who suspect driving impairment should involve the families and state driving agencies since patients with MHE have poor insight into their driving skills.

The association of other psychiatric and mood disorders along with MHE needs to be investigated with a possible psychological interview. The role of continuing alcohol abuse in this population cannot be over-stressed. In both these cases, the involvement of the family is paramount in confirming the statements of the patients and in ensuring adherence with therapy and alcohol abstinence. The family members play a central role in the psychosocial assessment of these patients who are often candidates for liver transplant and remain a necessary resource for clinicians to rely on as members of the patient care team [59].

Summary

During the last 10 years or so there has been a shift in the emphasis in HE. Formerly, it was felt appropriate to only include patients with severe HE (West Haven Scale – Stage 3–4) in clinical treatment trials. This was partly driven by the FDA demand for "significant" HE. It was also because low grades of HE were considered to be quite difficult to detect and assess. Recently there has been a major resurgence in interest in low-grade HE which includes subclinical or minimal HE and Stage 1 and 2 HE by the West Haven Scale (Table 29.3). The interest stems from our ability now to detect and quantify low-grade HE. Perhaps more importantly most patients with low-grade HE have less severe liver disease than those with severe overt HE. Consequently numerous confounding factors are not issues in patients with low-grade HE and largely compensated liver disease. Therefore definitive test results of clinical treatment trials can be achieved in this relatively stable population of cirrhotic patients.

Precisely what measurement tools will win out in the rush to quantify degrees of minimal or low-grade HE remains to be seen? At the very least the Amodio proposals to improve the West Haven Scale should be adopted. A very easy to use scale called CHESS – Clinical Hepatic Encephalopathy Staging Scale [60] may come into more widespread use also. More notable will be the RBANS and inhibitory control tests in the USA. The next 5–10 years will see many clinical studies employing these new diagnostic tools. In time these types of studies will produce treatments that will be used for the entire spectrum of HE.

References

1. Ferenci P, Lockwood A, Mullen K, Terter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716–21.
2. Poordad FF. Review article: the burden of hepatic encephalopathy. Alim Pharmacol Ther. 2007;25 (Suppl 1):3–9.
3. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol. 2001;16:531–5.
4. Mullen K, Ferenci P, Bass NM, Leevy CB, Keeffee EK. An algorithm for the management of hepatic encephalopathy. Seminars in Liver Disease. 2007;27:32–48.
5. Adams RD, Foley JM. The neurological changes in the more common types of severe liver disease. Trans Am Neurolog Ass. 1949;74:217–9.
6. Adams RD, Foley JM. The neurological disorder associated with liver disease. Proc Assoc Res Nerv Ment Dis. 1953;32:198–237.
7. Gabuzda GJ, Phillips GB, Davidson CS. Reversible toxic manifestations in patients with cirrhosis of the liver given cation exchange resins. New Eng J Med. 1952;246:124–30.
8. Sorensen M, Keiding S. New findings on cerebral ammonia uptake in HE using functional (13) N-ammonia PET. Metab Brain Dis. 2007;22:277–84.
9. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga ASC, Mullen KD. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med. 2003;114:188–93.
10. Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, Madl C. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology. 2000;31:30–4.
11. Riggio O, Masini A, Efrati C, Nicolae F, Angeloni S, Salvatori FM, Bezzi M, Attili AF, Merli M. Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study. J Hepatol. 2005;42:674–9.
12. Schafer DF, Jones EA. Hepatic encephalopathy and the gamma-aminobutyric-acid neurotransmitter system. Lancet. 1982;1:18–20.
13. Ferenci P, Schafer DF, Kleinberger G, Hoofnagle JH, Jones EA. Serum levels of gamma-aminobutyric-acid-like activity in acute and chronic hepatocellular disease. Lancet. 1983;2:811–4.
14. Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Bellomo G, Belloni G, Grisorio B, Annese M, Bacca D, Francavilla R, Barbarini G. Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicenter double-blind, placebo-controlled, cross-over study. Hepatology. 1998;28:374–8.
15. Jones EA, Skolnick P, Gammal SH, Basile AS, Mullen KD. NIH conference. The gamma-aminobutyric acid A (GABAA) receptor complex and hepatic encephalopathy. Some recent advances. Ann Intern Med. 1989;11:532–46.
16. Lozeva V, Tuomisto L, Sola D, Plumed C, Hippelainen M, Butterworth R. Increased density of brain histamine (H)1 receptors in rats with portacaval anastomosis and in chronic patients with chronic hepatic encephalopathy. Hepatology. 2001;33:1370–6.
17. Vaquero J, Butterworth RF. Mechanisms of brain edema in acute liver failure and impact of novel therapeutic interventions. Neurol Res. 2007;29:683–90.
18. Cordoba J, Alonso J, Rovira A, Jacas C, Sanpedro F, Castells L, Vargas V, Margarit C, Kulisewsky J, Esteban R, Guardia J. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of (1) H-magnetic resonance abnormalities after liver transplantation. J Hepatol. 2001;35:598–604.
19. Norenberg MD, Jayakumar AR, Rama Rao KV, Panickar KS. New concepts in the mechanism of ammonia-induced astrocyte swelling. Metab Brain Dis. 2007;22:219–34.
20. Haussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. Hepatology. 2006;43:1187–90.
21. Shawcross DL, Wright G, Olde Damink SW, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. Metab Brain Dis. 2007;22:125–38.
22. Romero-Gomez M, Grande L, Camacho I, Benitez S, Irles JA, Castro M. Altered response to oral glutamine challenge as prognostic factor for overt episode in patients with minimal hepatic encephalopathy. J Hepatol. 2002;37:781–7.
23. Haussinger D, Schliess F. Pathogenetic mechanisms of hepatic encephalopathy. Gut. 2008;57:1156–65.
24. Blei AT, Cordoba J. Hepatic Encephalopathy. Am J Gastroentero. 2001;96:1968–76.

25. Weissenborn K, Tietge UJ, Bokemeyer M, Mohammadi B, Bode U, Manns MP, Caselitz M. Liver transplantation improves hepatic myelopathy: evidence by three cases. Gastroenterology. 2003;124:346–51.
26. Ortiz M, Jacas C, Cordoba J. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. J Hepatol. 2005;42(Suppl):S45–53.
27. Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. J Hepatol. 2001;34:768–73.
28. Weissenborn K, Heidenreich S, Ennen J, Ruckert N, Hecker H. Attention deficits in minimal hepatic encephalopathy. Metab Brain Dis. 2001;6:13–9.
29. Amodio P, Campagna F, Olianas S, Iannizzi P, Mapelli D, Penzo M, Angeli P, Gatta A. Detection of minimal hepatic encephalopathy: normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. J Hepatol. 2008;9:346–53.
30. Romero-Gomez M, Cordoba J, Jover R, del Olmo JA, Ramirez J, Reyk R, de Madaria MC, Nunez D, Flavia M, Company L, Rodrigo JM, Felipo V. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology. 2007;45:879–85.
31. Iduru S, Mullen KD. The demise of the pencil? New computer-assisted tests for minimal hepatic encephalopathy. Gastroenterology. 2008;135:1455–6.
32. Mooney S, Hassanein TI, Hilsabeck RC, Ziegler EA, Carlson M, Maron LM, Perry W. Utility of the repeatable battery for the assessment of neuropsychological status (RBANS) in patients with end-stage liver disease awaiting liver transplant. Arch Clin Neuropsychol. 2007;22:175–86.
33. Bajaj JS. Minimal hepatic encephalopathy matters in daily life. World J Gastroenterol. 2008;14:3609–15.
34. Bajaj JS, Etemadian A, Hafeezullah M, Saeian K. Testing for minimal hepatic encephalopathy in the United States: an AASLD survey. Hepatology. 2007;45:833–4.
35. Stewart CA, Smith GE. Minimal hepatic encephalopathy. Nat Clin Pract Gastroenterology Hepatol. 2007;4:677–85.
36. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology. 2002;35:357–66.
37. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. J Hepatol. 2007;47:67–73.
38. Mardini H, Saxby BK, Record CO. Computerized psychometric testing in minimal encephalopathy and modulation by nitrogen challenge and liver transplant. Gastroenterology. 2008;135:1582–90.
39. Garavan J, Ross TJ, Stein EA. Right hemispheric dominancy of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci USA. 1999;96:8301–6.
40. Bajaj JS, Hafeezullah M, Franco J, Varma RR, Hoffmann RG, Knox JF, Hischke D, Hammeke TA, Pinkerton SD, Sacian K. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. Gastroenterology. 2008;135:1591–600.
41. Baja JS, Saeian K, Verber MD, Hischke D, Hoffmann RG, France J, Varma RR, Rao SM. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. Am J Gastroenterol. 2007;102:754–60.
42. Mullen KD, Amodio P, Morgan MY. Therapeutic studies in hepatic encephalopathy. Metab Brain Dis. 2007;22:407–23.
43. Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. Lancet. 2005;365:431–3.
44. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology. 2007;45:549–59.
45. Bass NM. Review article: the current pharmacological therapies for hepatic encephalopathy. Alim Pharmacol Ther. 2007;25(Suppl 1):23–31.
46. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtoic J, Riordan SM. Synbiotic modulation of gut flora; effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology. 2004;39:1441–9.
47. Sharma P, Sharma BV, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2008;20:506–11.
48. Loguercio C, Abbiati R, Rinaldi M, Romano A, Del Vecchio Blanco C, Coltorti M. Long-term effects of *Enterococcus faecium* SF68 versus lactulose in the treatment of patients with cirrhosis and grade 1–2 hepatic encephalopathy. J Hepatol. 1995;23:39–46.
49. Loguercio C, Del Vecchio Blanco C, Coltorti M. Enterococcus lactic acid bacteria strain SF68 and lactulose in hepatic encephalopathy: a controlled study. J Int Med Res. 1987;15:335–43.
50. Macbeth WA, Kass EH, McDermott WV Jr. Treatment of hepatic encephalopathy by alteration of intestinal flora with *Lactobacillus acidophilus*. Lancet. 1965;191:399–403.
51. Malaguarnera M, Greco F, Barone G, Gargante MP, Malaguarnera M, Toscano MA. *Bifidobacterium longum* with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. Dig Dis Sci. 2007;52:3259–65.
52. Bajaj JS, Saeian K, Christensen KM, Hafeezullah M, Varma RR, Franco J, Pleuss JA, Krakower G, Hoffman RG, Binion DG. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. Am J Gastroenterol. 2008;103:1707–5.

53. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodes J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999;30:890–5.
54. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver Transpl. 2007;13:1366–71.
55. Groeneweg M, Quero JC, DeBruijn I, Hartmann IJ, Essink-bot ML, Hop WC, Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. Hepatology. 1998;28:45–9.
56. Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. Hepatology. 2004;39:739–45.
57. Bajaj JS, Hafeezullah M, Hoffmann RG, Varma RR, Franco J, Binion DG, Hammeke TA, Saeian K. Navigation skill impairment: another dimension of the driving difficulties in minimal hepatic encephalopathy. Hepatology. 2008;47:596–604.
58. Bajaj JS, Hafeezullah M, Hoffmann RG, Saeian K. Minimal hepatic encephalopathy: a vehicle for accidents and traffic violations. Am J Gastroenterol. 2007;102:1903–9.
59. Bajaj JS, Saeian K, Hafeezullah M, Hoffmann RG, Hammeke TA. Patients with minimal hepatic encephalopathy have poor insight into their driving skills. Clin Gastroenterol Hepatol. 2008;6:1135–9, quiz 1065.
60. Ortiz M, Cordova J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. Alim Pharmacol Ther. 2007;26:859–67.

Chapter 30

Toxic Disorders and Encephalopathy

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The purpose of the present chapter is to selectively review the literature on the neuroanatomical, neuropsychological, and emotional/behavioral effects of exposure to four different substances: organic solvents, lead, manganese (Mn), and carbon monoxide (CO). A discussion of all toxins is beyond the scope of this chapter. Rather, we chose to focus on the most common, the best researched, and, in our opinion, the most interesting. Recent research regarding each of these substances has provided a window into the mechanisms for changes in behavior and cognition. There are far too many substances known to affect the central nervous system to review them all here. In addition, the volume of literature on each of the substances we discuss is too large for comprehensive review. Rather, our goal is to provide clinicians with a theoretical background of the changes in behavior/emotions and cognition commonly observed with exposure to these substances, and to provide guidance for assessing exposed individuals. In this updated chapter, we have added a discussion of manganese, as there is a rapidly expanding literature on cognitive dysfunction with strong neuroimaging studies. We have also updated the other substances with some worthwhile additions to the literature. We will start with a general conceptualization of the cognitive neuroscience of toxic exposure before addressing each of the four substances. For each substance, we will review the particulars of exposure and symptom expression, the neurobehavioral symptoms, the neuroimaging changes, and the relationship among these. Based upon these findings, where possible, we will recommend areas to focus on and hypotheses to explore when evaluating patients with such exposures. We will address general themes for the assessment of patients with a history of toxic exposure, including measurement of exposure, determination of effort in medical–legal cases, and collaboration with occupational medicine specialists. Finally, we will comment where the field should focus on going forward.

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Cognitive Neuroscience of Exposure to Neurotoxins

It has long been known that certain chemicals are toxic to the central nervous system (CNS), and this toxicity is often expressed through changes

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in behavior. For example, an awareness of the effect of heavy metals such as lead and mercury on the brain and behavior goes back centuries [1]. The term "mad as a hatter" originates from the exposure to mercury that hat makers experienced. The known effects of lead on the developing CNS in turn led to the reduction of leaded gasoline and lead-based paints. It is clear that exposure to toxins that affect the CNS impacts both cognition and emotions/behavior. However, despite some theorizing with individual toxins, there is not an overriding cognitive neuroscience-based conceptualization of toxic exposure. The lack of an overarching theme is in part a function of different toxins impacting different systems of the brain (e.g., Parkinsonism with Mn exposure has led to exploration of the basal ganglia). However, in many cases, there is only observational reporting of deficits and the brain systems affected as inferred from neuropsychological data or based on neuroimaging. At the end of the chapter, we will discuss systems we believe would be ripe for hypothesis-based exploration in toxic exposure.

Organic Solvents

Organic solvents are used in a variety of industries, both in the manufacturing process and in cleanup operations. In addition, solvents can be a substance of abuse (i.e., inhalant abuse or "huffing"), although our discussion will focus on work-related exposure. Exposure can occur through inhalation, absorption through the skin, or ingestion. The route of exposure can be a combination of means, such as inhaling fumes while using solvents on a rag to clean up paint, absorbing the solvent on the rag through the skin, and then eating without washing up. Organic solvents are known to be lipophilic and are thus thought to have an affinity for the white matter of the brain because of myelin's high-fat content. It is not surprising then that for a number of years, there have been reports of solvents affecting human behavior and cognition. Acute symptoms, including dizziness, headache, or feelings of intoxication, can occur, but most of the research has focused on the effects of chronic exposure. The level of exposure that is required for symptoms to result has not been precisely determined. A thorough understanding of the intensity, duration, and symptoms of exposure is needed to attach causation, and this is most often best accomplished by an occupational medicine specialist. In addition, exposure typically occurs to multiple substances or mixtures of solvents and there is not a known biological marker, such as blood levels, to document exposure.

A classification of exposure-related symptoms has been proposed [2]. Type 1 is mild, brief intoxication that is reversible. Type 2 classification is of moderate severity, but permanence has not been established. Type 2A focuses on emotional changes, while type 2B is related to intellectual changes. Type 3 is a global, severe, and permanent dementia. We do not find this classification clinically useful, and it is also not typically used in research. The current DSM-5 conceptualization of mild and major neurocognitive disorders would fit with Type 2 and Type 3, respectively. While mild neurocognitive disorder is alternatively conceptualized as mild cognitive impairment and a precursor for dementia, there is limited evidence that there is a progression to dementia in most solvent cases if the individual is removed from the exposure. More recently, there has been a focus on detecting solvent encephalopathy based on screening those at risk based on occupation [3] and developing decision rules for diagnosis [4].

There are a number of very thorough reviews of a wide range of studies examining the neurobehavioral effects of exposure to solvents [5–11]. Here, we will focus on studies that highlight specific issues that relate to symptom expression and outcome, and address the primary nature of the cognitive dysfunction that occurs following exposure to organic solvents.

Cognitive Changes

A wide range of cognitive deficits has been observed following exposure to organic solvents.

The reader is referred to prior reviews for more in-depth coverage of individual studies (e.g., [7, 11]). A meta-analysis [12] of cognitive deficits in 53 occupational solvent-exposed groups from studies comparing performance to nonexposed control subjects revealed significant effect sizes for measures of memory, motor performance, visual construction, and particularly attention. Cognitive processing speed, response alternation, and inhibition were found to be the most sensitive measures for detecting differences. Thus, tests such as the Stroop Color-Word Test, Trail Making Test, and Digit Symbol/Coding have been widely used in studies of solvent exposure. Other researchers have also found utility in visual perceptual and constructional measures (see [11]), including the block design subtest and embedded figures test. However, these tests of attention and perception should by no means be considered marker tests of cognitive dysfunction related to solvent exposure. The European consensus statement was published in 2012 on neuropsychological characteristics, assessment, and guidelines for diagnostics of solvent-induced cognitive changes, or "solvent-induced encephalopathy" as it is often referred to in the literature [13]. The following domains are typically impaired, and thus the consensus recommend these areas should be examined: attention (processing speed and complex attention), memory (immediate, delayed, and recognition), fine motor speed and dexterity, construction, and verbal and visual concept formation/reasoning.

We want to comment specifically on a twin cohort study that examined 21 monozygotic twins discordant for solvent exposure [14]. Twin studies are particularly potent for demonstrating deficits; the use of discordant twins controls for more of the variance than the use of healthy control subjects and thus provides support for the effects of solvents on cognition. In this study, deficits were present in the exposed twin group in perceptual organization, attention, and associative learning. We highlight this study as compelling evidence of the cognitive deficits that can occur following work-related exposure to organic solvents. In addition, the deficits observed are fairly typical of deficits reported in many studies of cognitive change associated with solvent exposure.

There is some evidence to suggest that the primary deficits observed following solvent exposure are related to attention, working memory, and/or frontal/executive dysfunction [10]. Indeed, a few studies have found specific deficits in complex attention and working memory [15–17]. This would certainly be consistent with the recent neuroimaging literature cited below. However, deficits have been reported in a variety of areas and, as Morrow et al. [18] point out, differences in methodology, measures, and populations make it difficult to conclude that a specific pattern of deficits exists. Therefore, from a clinical perspective with individual patients, a comprehensive battery assessing the typical domains (i.e., motor, sensory, visual perceptual, language, attention/processing, memory, and executive skills) appears prudent.

A number of findings may affect clinical practice and are worth further comment. First, although not universally found, there is some evidence of a dose–response effect, i.e., greater intensity of exposure or longer duration of exposure leads to more cognitive symptoms (e.g., [19]). In addition, it appears that the deficits are reversible in some individuals (e.g., [19]), but become permanent in other individuals at some undefined point in time. The factors that lead to permanent deficits have yet to be determined. However, there has been suggestion that the presence of psychiatric symptoms along with cognitive deficits may signal the likelihood of developing permanent deficits (e.g., [20]). This finding of psychiatric symptoms affecting neurological recovery has precedence in what is known about recovery from concussion. Finally, there is some emerging evidence that the cognitive deficits may be exacerbated by aging, particularly with heavier exposure [21, 22]. However, overall there is no evidence at the present time that changes in cognition associated with solvent exposure are progressive, and in

some cases cognition improves after individuals are removed from exposure [23].

Emotional/Behavioral Changes

Solvent exposure has also been associated with psychiatric symptoms and behavior change, primarily mood disturbance, and anxiety. This has been documented with personality assessment and diagnostic interviewing with different populations of solvent-exposed individuals [24–28]. These psychiatric symptoms do not appear to be responsible for or to account for the cognitive deficits that patients also experience (e.g., [29]). In addition, it is not clear to date if the increased rates of diagnosed depression and anxiety share the same neurobiological pathways as cognitive changes [30].

Neuroimaging

There have been few well-designed studies that have utilized neuroimaging following exposure to organic solvents. Early studies were mainly the case reports of voluntary solvent exposure/inhalant abuse (e.g., "huffing" gasoline). These cases focused on changes in the white matter of the brain [31–33]. More recently, there was a study that utilized magnetic resonance spectroscopy (MRS) to examine the brain metabolites in thalamic, basal ganglia, and parietal white matter regions of 49 shoemakers exposed to glues and degreasers [34]. It reported a higher ratio of choline to creatine, which suggests demyelination, in exposed workers compared to controls. The ratio of N-acetylaspartate to creatine, which is indicative of neuronal, not axonal, health did not differ between groups. This suggests that solvent exposure leads to changes in cerebral white matter and not gray matter, at least in the regions studied by these authors. It is also important to note that the MRS findings correlated with the duration of exposure, such that longer duration of exposure was associated with higher choline/creatine ratios in basal ganglia. The authors suggest that MRS, in addition to standard magnetic resonance imaging (MRI) and neuropsychiatric evaluation, may be useful in determining the degree of cerebral involvement in solvent-exposed workers. No measures of cognitive function were administered, and while each subject underwent a psychiatric examination, no objective measures of behavior or emotional status were reported. Further work relating MRS findings to cognitive and psychiatric symptoms following solvent exposure is needed to determine whether MRS will have any direct clinical utility.

We have also published a study that highlights changes in cerebral white matter in workers with a history of exposure to solvents [25]. We used MRI to measure the volume of the corpus callosum, the largest white matter bundle in the brain. Thirty-one railroad workers with at least 10 years of exposure to solvents were compared to 31 age-, education-, and intelligence-matched healthy control subjects. The volume of the corpus callosum was smaller in the railroad workers, and this was not a product of health status or psychiatric symptoms. The area of difference was restricted to the genu of the corpus callosum, and not the body or the splenium. In addition, smaller corpus callosum volume was associated with a greater degree of exposure to solvents. Finally, the volume of the corpus callosum correlated with cognitive measures of frontal lobe function, such that smaller volume of the genu was associated with worse performance.

These two structural imaging studies have shown an association between work-related exposure to solvents and differences in the brain's white matter. This is consistent with the hypothesis that solvents selectively affect cerebral white matter due to their lipophilic nature. However, this does not rule out changes in gray matter following solvent exposure, as this has not been well studied to date. For example, there have been no imaging studies to date reporting solvent-related changes in the hippocampus. In fact, one might hypothesize that the changes in white matter would lead to gray matter degeneration, but this remains to be empirically tested. One could also argue that gray matter changes have led to the degradation of the white matter.

Finally, although the Haut et al. [25] study suggests that frontal lobe functions are affected by the difference in the white matter of the genu, this does not rule out effects that solvents may have on other regions of cerebral white or gray matter.

Consistent with the hypothesis that solvents affect frontal lobe functions, there is a small pilot functional imaging study that demonstrated differences in frontal lobe activation during working memory [35]. Specifically, on two different tasks of working memory, six individuals with a history of solvent exposure were studied with O^{15} water positron emission tomography. Although they performed the tasks at the same level as controls, exposed subjects activated different areas in the frontal cortex on both tasks. The findings were interpreted as indicating that since the frontal cortex was dysfunctional, solvent-exposed subjects had to compensate by recruiting additional cortex to complete the working memory tasks. This is certainly consistent with Haut et al. [25], who demonstrated a relationship between differences in the genu of the corpus callosum and frontal lobe functions. Another functional imaging study supports this conclusion. Tang et al. [36] used fMRI to examine the brain activation associated with working memory performance on an *n*-back task. Individuals with a history of solvent exposure performed worse on the task and had lower levels of activation in the typical areas of working memory (cingulate, frontal, and parietal cortex). There was a correlation between lifetime solvent exposure and activation, such that increased exposure was associated with decreased activation. Thus, there is increasing evidence that solvent exposure affects frontal/executive systems. However, the findings from these studies should be considered preliminary, and replication with different solvent-exposed populations and different methods is necessary before the results can be fully confirmed.

However, not all studies fully support these findings. One study used a combination of imaging modalities to examine the effects of solvent exposure [28]. The authors were specifically testing whether solvent exposure affected frontal/subcortical circuits and used diffusion tensor imaging (DTI) to assess white matter, MRS to assess gray and white matter metabolites, and single-photon emission computerized tomography (SPECT) to assess dopamine binding in the basal ganglia. Although the sample was small (N = 10 for individuals with exposure and N = 11 for normal controls), differences in dopamine binding using SPECT, as well as changes in frontal gray matter using MRS, were observed. Correlations with cognitive performance were present. White matter differences were not found. This points to the need for ongoing study of the neuroanatomical substrates of solvent-related cognitive, emotional, and behavioral changes.

In summary, exposure to organic solvents can lead to changes in cognition and result in depression and anxiety. These symptoms are not experienced by all who are exposed, and symptoms can remit for some if exposure ends. Some individuals will experience permanent deficits, which could potentially be exacerbated by age, but further research is needed. There is emerging evidence from neuroimaging that solvents affect the white matter of the brain and that the frontal lobes may be particularly affected. In addition, the cognitive deficits associated with solvent exposure may have a primary frontal focus. However, further research is needed to replicate, clarify, and extend these findings.

Lead

Exposure to lead can be occupational, via the use of lead in a variety of industries, or environmental, from exposure to lead waste. In addition, despite regulation, exposure to lead-based paint occurs environmentally and occupationally. For example, here in West Virginia, we have evaluated workers who were working on old bridges coated with lead paint. During the work, the bridges were contained so as not to allow the lead to escape into the environment. The workers wore protective gear and their blood levels were monitored, but some nonetheless become acutely ill and symptomatic.

Exposure to lead occurs through inhalation and ingestion. Lead accumulates in soft bone, and thus previous cumulative exposure can be determined from bone studies with some reliability. More recent exposure is typically estimated via blood lead levels. Symptoms can also be acute or chronic, including neurological symptoms such as ataxia and peripheral neuropathy. Treatment of course involves removing the individual from exposure and in some cases, chelation is used to remove the lead from the body. Anecdotally, we have conducted evaluations of the lead-exposed bridge workers noted above, before and after chelation, and did not observe much in the way of improvement in cognitive symptoms.

For the purposes of this chapter, we will focus on adult exposure to lead and will not address the neurodevelopmental effects of lead on the cognitive and emotional functioning of children. In addition, we will not exhaustively review the studies on the effects of lead on cognition and emotion, as a comprehensive review of the literature pertaining to adult cumulative lead exposure was recently published [37]. For earlier reviews, the reader is referred to [38–40]. We should also note that most of the data on the effects of lead exposure comes from chronic, long-term exposure.

Cognitive Function

Only recently have the long-term cognitive effects of past lead exposure been recognized in adults [41]. Shih and colleagues [37] conducted a systematic search of studies published between 1996 and 2006 that examined the relationship between biological markers of recent (i.e., blood) and cumulative (i.e., bone) lead dose and cognitive function. The 21 studies included used cross-sectional or longitudinal approaches to evaluate three population groups: environmentally exposed individuals, individuals with current occupational exposure, and individuals with former occupational exposure. Briefly, the review concluded that environmental or occupational lead exposure was consistently associated with dysfunction in numerous cognitive domains, including verbal and visual memory, visuospatial skills, motor and psychomotor speed, attention, executive function, dexterity, and peripheral motor strength.

The cumulative effect of lead on cognitive function has been longitudinally studied in three independent groups of individuals: former U.S. organic lead and tetraethyl lead (TEL) exposed manufacturing workers, current and former Korean inorganic lead workers, and 50–70-year-old residents of Baltimore with environmental lead exposure [41]. For the former U.S. lead workers, higher bone lead level was a significant predictor of decline on tests of cognitive function, which included verbal memory and learning, visual memory, executive ability, and manual dexterity. The change in function was observed over a two-year time period, suggesting that changes in brain function due to prior lead exposure do not merely persist, but appear to progress. The study of Korean inorganic lead workers allowed the authors to evaluate the effects of recent versus past lead exposure over three visits. Results revealed associations of blood lead and cognitive function at baseline, and association of bone lead levels with declines over time in executive abilities, and manual dexterity. Thus, there was an acute effect of recent exposure and a long-term effect of cumulative exposure on cognitive function. Among environmentally exposed individuals, bone lead level was associated with worse cognitive function across domains, while blood lead level was not associated with cognitive performance. There may be persistent effects of cumulative lead dose from previous environmental exposure that is independent of recent lead exposure. Longitudinal analysis showed a weaker association between bone lead and cognitive decline over time, suggesting that in this population, the deficits may persist, but do not necessarily progress.

Another study is very interesting and timely as it incorporates the theory of cognitive reserve (CR, [42]). Currently employed smelter workers with equivalent levels of chronic lead exposure were stratified into low and high CR groups

using reading level. Results revealed a dose–response relationship in the low CR group, but not the high CR group, for measures of attention and processing speed. Notably, there was a dose–response relationship in both groups for motor dexterity, a domain less likely to be influenced by CR. This suggests that CR modifies symptom expression, and may be protective against the cognitive effects associated with exposure to lead.

Finally, Khalil et al. [43] examined current cognitive functioning in a group of lead-exposed workers who had been previously examined 22 years before. Bone lead levels assessed in 1982 and reassessed 22 years later found the latter levels to predict current cognitive dysfunction as well as cognitive decline over the 22 years of the study. In addition, in older workers (age 55 and over), bone lead levels were predictive of worse cognitive performance that the authors suggest indicates the vulnerability of older workers to cumulative burden of lead.

In summary, chronic exposure to either organic or inorganic lead results in changes in cognition. It is not known whether there are differential effects on cognitive function of exposure to organic versus inorganic lead. The cognitive changes observed are broad and can involve a number of different domains, including memory, attention, visual–spatial ability, executive function, and motor skills. There appears to be an effect of past environmental and occupational lead exposure on brain function that is persistent and in some populations may progress. In addition, CR may influence the deficits.

Emotional Functioning

In addition to cognitive changes, exposure to lead leads to changes in emotional functioning, including depression, anxiety, and anger control. Such symptoms are observed in individuals with current and previous occupational exposure, as well as those with environmental exposure (see [37]). Lindgren et al. [44] examined mood disturbance in current and former lead smelter workers. They found that current and cumulative lead exposure was related to self-reported anger, confusion, depression, fatigue, and tension. Similarly, in a community sample of middle-aged to elderly men, cumulative lead measured by bone lead level was associated with anxiety and depression [45]. Thus, lead exposure is often associated with changes in emotional functioning, particularly anxiety and depression symptoms. Although it has been suggested that the emotional symptoms are only observed following higher levels of exposure [37], psychiatric symptoms following modest exposure levels have also been reported (e.g., [45]).

Neuroimaging

There is growing evidence to support the notion that adult exposure to lead has a persistent effect on brain structure, as measured by MRI [46] and MRS [47, 48]. In addition, these structural changes have been associated with cognitive function [49, 50].

Differences in brain structure were correlated with past organic lead exposure in a large cohort (n = 532) of occupationally exposed individuals [46]. Higher bone lead levels were associated with greater number and severity of white matter lesions and lower total brain volume. Higher lead levels were also associated with smaller volumes of the parietal white and gray matter, temporal white matter, cingulate gyrus, and insula. In addition, poorer cognitive performance was correlated with smaller total brain volume, as well as smaller volumes of total gray matter, parietal gray matter, and temporal gray and white matter [50]. Further, using a path analysis to infer cause and effect, brain volume was shown to mediate the effect of cumulative lead level on cognitive function in the domains of visual construction, executive function, and eye–hand coordination [51].

The cumulative effects of lead exposure have also been associated with differences in brain metabolite ratios using MRS [47, 48]. Among community-dwelling individuals without occupational exposure, a higher bone lead level was associated with a higher myoinositol-to-creatine

ratio, proposed to represent an increase in glial cells, in the hippocampus [47]. The findings suggest that lead exposure is associated with changes in a brain structure vital to memory functioning, although cognition was not assessed in this study. Using MRS and measures of cognitive performance, Weisskopf et al. [48] studied the cumulative effect of chronic occupational organic lead exposure in monozygotic twins (J.G. and E.G.) who were retired painters. Results revealed that the bone lead levels were 5–10 times higher in the twins than in the general population, and were 2.5 times higher in J.G. compared to E.G. MRS results showed that J.G. had a decrease of 10–30% in the N-acetylaspartate to creatine ratio, thought to represent neuronal loss, measured in the hippocampus and frontal lobes. In addition, although both patients showed cognitive impairment suggestive of frontal lobe dysfunction, J.G. had significantly poorer short-term memory performance than E.G.

Finally, a recent study of executive functions of lead-exposed workers using fMRI sheds light on the effects of lead on cortical networks [52, 53]. In a moderately sized, occupationally lead-exposed sample of all adult female lead battery factory workers, compared with healthy controls, the investigation teams examined brain activation during performance on two versions of the Wisconsin Card Sorting Task. They reported less activation in the left dorsolateral prefrontal cortex with the more complex version of the task in the workers with lead exposure relative to the controls. In addition, activation was inversely related to lead concentrations such that increased lead in the blood was associated with less activation.

In sum, the changes in cognition observed following exposure to lead appear to have a structural basis. There is compelling MRI evidence of lead exposure leading to changes in brain volume. However, a specific pattern of either cognitive deficits or structural brain changes has yet to emerge. While the large sample size of the above studies is to be applauded, investigations taking a more theoretical approach to studying changes in brain structure may help elucidate the changes in brain function, including cognition and emotion, that are associated with lead exposure.

Manganese

Manganese (Mn) is a trace element that is necessary for good health but is toxic at elevated levels, and can be toxic at low occupational levels. Mn is without smell or taste and usually comes in a gray–white powder that can be absorbed into the body by inhalation if in aerosol form or by ingestion [54]. The mechanism of poisoning is frequently by acute exposure or by long-term lower exposure in industries such as mining, welding, farming, and manufacturing, particularly the steel industry [55]. Occupationally, welders are particularly vulnerable as welding fume aerosols are often small enough to reach the alveolar compartment of the lungs. The aerosols are then absorbed via the pulmonary route and enter the blood circulation directly to the brain without passing through the homeostatic control of the liver [56]. Mn can also cause increased susceptibility to bronchitis and pneumonitis, and animal tests show that Mn possibly causes toxicity to reproduction or development [54, 56]. As Mn is a naturally occurring substance that is present in our bodies and is often expelled though feces within a few days, it can be difficult to detect after a period of time. However, MRI can be helpful in detecting increased amounts in the brain in conjunction with elevated levels in blood [57]. It is also possible for individuals to have increased Mn blood levels and increased T1 MRI signals in the globus pallidus while not displaying any clinical symptoms [58].

Cognitive Symptoms

Cognitive deficits are common after Mn exposure, particularly in those with prolonged or higher level exposure as there appears to be a dose-dependent relationship between Mn

exposure and neuropsychological deficits. In a series of well-known studies of welders working on the San Francisco/Oakland Bay Bridge, Bowler and her colleges [59–62] found that the 43 workers who worked in confined spaces without protection and poor ventilation had worse neuropsychological function as compared to published norms, and the relationship was dose-dependent. Specifically, they were found to have deficits on motor tasks, executive function, sustained concentration and sequencing, verbal learning, and working and immediate memory. A Japanese study also found an association between the number of years of Mn exposure and motor functioning and reaction time in attention tests [63]. They also found statistically lower sustained attention on the Continuous Performance Test in welders, even with lower exposure levels. Greiffenstein and Lees-Haley [64] cautioned, however, that studies of Mn-exposed groups often use participants with lower baseline demographics such as education and cognitive ability as compared to normal controls, and that the neuropsychological measures used are often nonspecific to Mn exposure. These potentially important factors should be considered before drawing conclusions. Other studies have also shown temporary deficits in individuals after they were removed from Mn exposure [65], and no difference in symptom complaints between the Mn exposure group and a control group [66].

While a strong link has been established between prolonged and high Mn exposure and its deleterious effects on neurocognitive functioning in adults, research has also suggested that children and adolescents are at risk following Mn exposure. Lucchini et al. [67] studied 311 Italian adolescents ages 11–14 living in a region with a ferroalloy plant that had emissions of Mn. Results indicated that the group had significant impairment in motor coordination, hand dexterity, and odor identification. There was also a positive association between tremor intensity and Mn level detected in blood and hair. Thus, there are deleterious effects on adolescents with Mn exposure that occurs outside of the workplace. This natural exposure effect on adults has also been reported [55].

Emotional Symptoms

Neuropsychiatric symptoms following Mn exposure are often one of the first signs of central nervous system impact. Common psychiatric symptoms and behavior changes include mood changes (i.e., depression, irritability, and apathy), anxiety, and acute psychosis in some patients. Indeed, *Locura manganica* or "manganese madness" has been described in exposed miners as the initial symptoms of manganism (clinical signs and symptoms that looks like Parkinson's disease but are not caused by that disease, [68]) in Chile, Australia, and Taiwan [69]. Such psychosis is characterized by "compulsive or violent behaviours, emotional instability, disorientation, and hallucinations" [70].

The long-term impact on psychiatric functioning from Mn exposure can unfortunately linger years or decades after exposure. Verhoeven and colleagues [71] describe a case of a 49-year-old metal worker who started exhibiting mood and behavior changes and increased apathy before developing "paranoid ideation, thoughts of reference, sleep disturbances and bizarre behaviors" about two years later (p. 2). He had no prior history of physical or psychiatric illness. MRI showed T1 signal intensity of the globus pallidus bilaterally. While his psychosis was successfully treated with an antipsychotic medication, he continued to have neurobehavioral and cognitive changes consistent with Mn exposure and became disabled.

Neurological Changes

Manganese can have an irreversible effect on both the peripheral and the central nervous systems [55]. One of the most commonly seen neurological consequences of Mn neurotoxicity is the effect on the basal ganglia, particularly the

globus pallidus, which results in "motor, cognitive, and mood dysfunction" [72], causing manganism, a parkinsonian syndrome [62]. As noted above, Bowler and her colleagues studied welders who had prolonged exposure to Mn while working on the San Francisco/Oakland Bay Bridge. Using the Unified Parkinson Disease Rating Scale (UPDRS), they found the workers had tremor, bradykinesia, postural instability, micrographia or changes in handwriting, and other changes such as abnormalities involving face, voice, and gait [61]. A follow-up study by the same authors found that despite the absence from confined space welding for more than three years, only neuropsychological functioning improved over time, while olfactory, extrapyramidal, and mood disturbances remained constant or increased [73], suggesting a degenerative process.

Neuroimaging

MRI is used to detect the presence of abnormal levels of Mn in the brain. T1-weighted imaging of the basal ganglia using intensity [74] and/or T1 relaxation rates [57] are now widely accepted [75]. In addition, T1 relaxation rates correlate with cognitive dysfunction [76] and can be observed after short-term exposure [77]. The relationship between T1 relaxation rate and hours worked has been found to be nonlinear, suggesting there is a critical level of exposure before MRI can detect an effect [78]. Interestingly, comparing groups with different means and degree of exposure can be differentiated by MRI. Long et al. [79] examined welders, smelters, and unexposed factory workers. Although the smelters were exposed to higher air levels of Mn and had been exposed for a longer duration, the welders had greater brain impact as determined by greater T1 hyperintensity in the hippocampus and thalamus. In addition to T1 intensity and relaxation differences, T1 volumetrics are lower in welders in the basal ganglia and thalamus, and these brain volume differences correlate with cognitive and motor performance [80]. There is also evidence of white matter disturbance following Mn exposure using DTI. Kim et al. [74] reported reduced fractional anisotropy (FA) in the corpus callosum and frontal white matter in welders. Increases in radial diffusivity were suggested to implicate demyelination. Importantly, changes in white matter integrity correlated with motor and cognitive performance. Decreased FA in the basal ganglia has also been reported [78].

MRS has been used to examine the chemical composition of brain tissue after Mn exposure, with inconsistent results. Casjens et al. [81] failed to find differences in brain metabolites levels between exposed welders and controls. There was no correlation between airborne or blood levels of Mn and GABA concentrations. They attributed the lack of correlation to the low levels of exposure. Consistent with this, Ma et al. [82] reported an increased level of thalamic GABA as well as a correlation between thalamic GABA levels and motor dysfunction in exposed welders. There was a dose–response effect, with welders with lower exposure not showing a difference in GABA relative to controls.

Finally, there is a series of studies examining brain activation patterns in welders with Mn exposure using fMRI. Chang reported that when performing motor and working memory tasks, Mn-exposed welders showed increased compensatory activation to complete the tasks [83, 84]. Cognitively, the Mn-exposed group showed statistically lower performance in the areas of verbal delayed recall and recognition, visuoconstruction, visual immediate and delayed recall, basic auditory attention span and divided attention, and general cognitive efficiency (Stroop) even when controlling for demographic variables.

In summary, Mn exposure results in cognitive and emotional changes. MRI can indicate the level of Mn exposure by T1 relaxation rates, which correlate with cognitive performance. A variety of neuroimaging techniques (e.g., fMRI, DTI) implicate the basal ganglia, consistent with the Parkinsonism seen with these patients. There is also evidence of changes in brain volume in the basal ganglia, but differences in brain activation (increases and decreases) in

the frontal cortex should not be ignored. Finally, there is a correlation between brain imaging findings and cognitive performance and also a dose–response effect, which gives support to a causal link between Mn exposure and CNS toxicity.

Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless, tasteless gas produced by incomplete combustion of carbon-based fuels [85]. CO is the second most common cause of non-medicinal poisoning in the US, with an average of 438 deaths annually [86]. The mechanism of poisoning is frequently accidental, via faulty heating systems. There thus is an upsurge in cases in the fall and winter months [85, 87]. Intentional poisoning from suicide attempt, often via exposure to automobile exhaust, is also common. Diagnosis may be complicated or initially delayed by the nonspecific and flu-like nature of the symptoms of CO exposure, including headache, nausea, irritability, confusion, dizziness, and visual disturbances [88]. Individuals in different areas of the same house with excess CO may have different degrees of exposure; conversely, similar levels of exposure can result in different clinical presentations [89]. In addition, there may be complicating factors of substance intoxication in both accidental exposure and suicide attempts.

CO has a high affinity for hemoglobin, greater than that of oxygen [90], and combines with hemoglobin to form carboxyhemoglobin (COHb). This decreases the oxygen content of blood, resulting in tissue hypoxia [88]. Because of its high oxygen utilization, the CNS is highly susceptible to the effects of CO [88]. Toxic effects of CO appear to be related to both tissue hypoxia and CO-related cellular damage [91]. Measurement of COHb level in blood may be used for diagnosis and to estimate severity of exposure. However, the overall ability of COHb to predict death, neurologic and cognitive sequelae, or response to treatment is poor [88, 90, 92–94]. Treatment involves administration of oxygen, often hyperbaric oxygen therapy, to increase the rate of elimination of CO from the body [90]. It is unclear whether hyperbaric treatment decreases the incidence of sequelae, as the literature is conflicting [95], although a recent review suggested reduced short- and long-term mortality with hyperbaric treatment [96]. When not fatal, which is often the case, CO poisoning leads to a host of cognitive, behavioral, and neurologic symptoms (see [91] for a comprehensive review). The majority of the literature regarding CO poisoning is based on acute, rather than chronic, exposure as acute poisoning more often comes to clinical attention and is thus more readily diagnosed. Effects of chronic, low-level exposure may be misdiagnosed or go unrecognized [91]. The clinical relevance of such exposure is thus less often examined and less well-understood. Unless otherwise stated, the cognitive and behavioral effects and neuroimaging findings discussed below refer to acute CO poisoning.

Cognitive Symptoms

Cognitive symptoms are common following CO poisoning. Rates of cognitive impairment range from 30% in consecutive patient series [97] to 93% of patients with moderate to severe poisoning [98]. The cognitive symptoms that have been observed following CO poisoning vary widely and range in severity (see [91]). Most often, CO poisoning is associated with impairment in memory, as well as attention, processing speed, visual–spatial skills, executive functions, and intellect [89, 91, 93, 97–99]. Case reports of chronic exposure have described similar deficits, including impaired executive function, conceptualization, visual construction and visuospatial judgment, psychomotor speed and attention, and memory [89, 100]. In some cases of acute exposure, a pure amnesic syndrome has been reported (e.g., [99, 101]). One series of 21 patients one year after CO poisoning described that 76% of the sample had impaired memory, 75% had executive dysfunction, 57% had slowed mental processing, and 45% had impaired

attention [98]. However, a consistent neuropsychological pattern has not been found, as there is a high degree of individual variability. Variability has even been reported in cases resulting from the same CO accident, with the same level of CO exposure [92, 102]. The persistence of deficits varies as well, as some individuals experience improvement of cognitive symptoms over time, while others experience continued cognitive impairment [93–95, 103]. Some studies have found an increase in dementia risk following CO exposure. For instance, Lai et al. [104] found a 1.6-fold increase in dementia in those with CO exposure as compared to nonexposed patients. Similarly, Wong et al. [105] studied 14,590 patients with CO poisoning and a 58,360 age-, sex-, and index date-matched comparison cohort over nine years. Results showed significant risk of dementia in a long-term follow-up after adjustment for age, sex, and comorbidity such as diabetes, stroke, cancer, hypertension, and hyperlipidemia.

Emotional Symptoms

Behavioral and emotional symptoms are also commonly observed following CO poisoning. Depression, anxiety, and emotional lability are most frequently described, both following acute poisoning and chronic, low-level exposure [92, 100], although there have been rare case reports of OCD and Kluver-Bucy syndrome symptoms [91]. Of 21 patients examined one year after acute CO exposure [98], 20 had clinically significant self-reported affective disturbance. In a prospective series of 127 CO-poisoned individuals, depression and anxiety were present in 45% of patients at 6 weeks and in 43% at 12 months after exposure [106]. Some emotional symptoms are premorbid, e.g., depression in individuals who are exposed to CO from suicide attempt. Jasper et al. [106] noted higher rates of depression and anxiety 6 weeks after CO exposure in individuals with poisoning via suicide attempt as compared to those with accidental exposure. However, mood disturbance may be observed following accidental poisoning as well. Indeed, in the series described by Jasper et al. [106], at 6 and 12 months post-exposure, depression and anxiety were as common in individuals with accidental as those with intentional CO poisoning. Such behavioral symptoms may affect the cognitive sequelae as well, but do not fully account for these deficits (e.g., [93, 94]).

Neurological Changes

Neurologically, movement disorders or parkinsonian syndromes have been reported acutely following CO exposure [91]. For a subset of patients, the cognitive and neurologic symptoms are delayed. That is, these patients appear to have fully recovered from the acute symptoms within minutes or hours of exposure, only to have an encephalopathy emerge weeks to months after the initial exposure. Parkinsonian symptoms predominate, including bradykinesia, masked facies, and gait disturbance. The delayed syndrome is estimated to occur in .06–40% of CO-exposed individuals [91], but the structural neuroimaging findings and clinical symptoms may resolve [102, 107, 108]. There is some indication of increased risk of the delayed syndrome with increasing age, longer duration of coma, and prolonged anoxia [108, 109]. In general, delayed onset of symptoms is associated with worse cognitive and imaging outcome (e.g., [110–112]).

Neuroimaging

Although the specific pathophysiology is not fully understood, structural brain changes can be observed on neuroimaging of individual cases as well as in group studies. Hypoxic-ischemic insult affecting gray matter, basal ganglia necrosis, diffuse atrophy due to apoptosis, and demyelination have all been described. Due to the variety of pathophysiologic mechanisms, varied neuroimaging patterns are observed [113]. Neuroimaging changes are frequently associated with cognitive performance, although impaired cognitive functioning has been described in acutely

and chronically exposed individuals for whom neuroimaging is normal [89, 97].

Atrophy has been described affecting whole brain, fornix, hippocampus, and corpus callosum [93, 94, 98]. Using quantitative MRI, Porter et al. [94] found that atrophic change in the corpus callosum had occurred in 80% of CO exposure cases within 6 months. Although the patients were cognitively impaired, no relationship was found between callosal atrophy and neuropsychological performance. More recently, using more sensitive diffusion-weighted measures, corpus callosum changes have been associated with decreased processing speed [114]. In addition, differences in the volume of the fornix have been reported after CO exposure and these correlate with memory dysfunction [93]. Cortically, there appears to be a predilection for the temporal lobe, although this is relatively uncommon [115]. Bilateral hippocampal infarcts, associated with amnestic syndromes, have also been described [101, 116]. Diffuse volume loss beyond the basal ganglia and limbic structures has also been reported using voxel-based morphometry [110], with smaller volume correlating with worse cognitive performance.

Basal ganglia lesions, particularly affecting the globus pallidus, have long been widely identified using MRI [102, 113, 115] and MRS [89]. However, these lesions are not universally found, even in the presence of parkinsonian symptoms [89, 102]. Interestingly, palladal lesions were present in an individual without concomitant parkinsonian symptoms and absent in an individual with such symptoms, following the same exposure [102]. In addition, substances other than carbon monoxide can produce basal ganglia lesions (e.g., [117]). The finding of basal ganglia disruption has primarily been based on case reports or samples of more severely ill patients. More recent prospective studies have indicated that the rate of lesions to the basal ganglia in general, and the globus pallidus in particular, may be lower than originally presumed. However, Pulsipher et al. [118] found that 28% of their prospective series of CO patients had reduced basal ganglia volumes at 6 months post-exposure. This was in the absence of observable basal ganglia lesions in all but one patient.

More commonly, imaging studies have observed white matter lesions, particularly affecting periventricular regions. In a consecutive series of 73 patients following CO poisoning [97], 12% had MRI-identified white matter hyperintensities; these were more often in periventricular regions in comparison to controls. Only one patient had lesions in the globus pallidus. The lesions were stable when patients were reimaged 6 months later.

White matter demyelination may be responsible for the delayed neurological syndrome; delayed cytotoxic edema is hypothesized [103, 113, 119]. In one series of patients with the delayed syndrome, diffusion-weighted imaging showed signal hyperintensities in periventricular white matter, as well as the corpus callosum, internal capsule, and brain stem [119]. Diffusion tensor imaging has also demonstrated the white matter disruption that occurs following CO exposure. Six patients with delayed neurologic syndrome following intentional CO exposure underwent DTI and showed lower fractional anisotropy (FA), a measure of white matter integrity, in the centrum semiovale than controls, both at initial imaging and 3 months later following hyperbaric oxygen treatment [120]. Interestingly, FA improved in patients from pre- to post-treatment. Diffusion-weighted lesions have been shown to predict delayed neurological sequela and to correlate with the degree of cognitive impairment [110, 111]

In summary, CO exposure often leads to changes in cognitive and emotional functioning. A wide variety of cognitive deficits has been observed, including memory and frontal lobe and executive functions. To date, it is difficult to specify a particular pattern of deficits that is observed with CO exposure. This is likely a function of a number of different variables related to the exposure, the presumed mechanism of injury, as well as individual differences. A severe exposure with accompanying anoxia is likely to produce severe memory deficits. At lower levels, a more subcortical, frontal/executive pattern may emerge. Finally, whether the individual had

premorbid depression and the exposure is the result of a suicide attempt also may interact to produce a different pattern of impairment. The results of neuroimaging studies have demonstrated a variety of structural deficits, and these correlate with cognitive changes. One of the most important findings is that basal ganglia lesions, while they do occur, are not as prevalent as initially thought and are clearly not the only brain region affected by CO exposure. Other regions affected include periventricular white matter, and less commonly the hippocampus, fornix, corpus callosum, and general brain volume.

Additional Issues in the Assessment of Toxic Exposure

When clinically evaluating a patient with reported exposure to toxins, we recommend having a focus on the battery based upon the literature, but also to broadly assess each individual patient. Most of the research studies on toxic exposure have used limited batteries. This may be for the sake of convenience, to encourage subjects to participate in the study without burdening them, or to have a short, focused battery when assessing a large number of subjects. The observation of focal deficits may be a consequence of the more limited batteries utilized in research studies. We suggest that any clinical assessment include a range of measures that at minimum screen the major cognitive domains (i.e., motor, cortical sensory, visual–spatial and construction, language, attention and processing, memory, and frontal and executive functions), as well as test hypotheses based upon the literature and the specific complaints of the patient. For example, a thorough assessment of memory and frontal and executive functions should occur with any patient with CO exposure, but additional focus on spatial and perceptual processes may be necessary if there is a parkinsonian presentation.

Each case of toxic exposure requires an assessment of the exposure. This is a highly specialized assessment and requires a good working knowledge of the literature regarding exposure variables that influence deficits and outcomes. This is particularly true if one is going to draw conclusions about cause and effect, such as that an individual's cognitive and emotional symptoms are the result of their exposure to a specific substance. In most instances, unless the neuropsychologist has extensive experience with toxins, we recommend deferring the exposure assessment to a specialist. In many cases, this is a physician with board certification in occupational medicine. We were very fortunate at West Virginia University to have a strong occupational medicine department and are very comfortable with these physicians' assessment of whether an individual has been exposed to a substance at a level that has the potential to produce cognitive deficits and psychiatric symptoms. For solvents, it is rarely the case that an individual is exposed to a single agent, as mixtures are commonly used. Whereas in lead, Mn, and CO exposure, blood and/or bone levels may be available, it is rare to have a biological marker or level for solvent exposure (e.g., [121]). MRI can also document Mn exposure, whereas there is no MRI or PET signature for solvent exposure. In addition, the use of retrospective patient report has inherent limitations, particularly in individuals with cognitive symptoms. These factors highlight the complexities of exposure assessments.

Many cases of toxic exposure also involve civil litigation, a workers' compensation claim, or an application for Social Security disability. Thus, clinical assessment of secondary gain is warranted and should include measurement of symptom validity. There are reports of malingering in cases of exposure to toxins [122–125] and care should be taken to consider effort when assessing the effects of exposure on cognition and emotion. Reduced effort on neuropsychological evaluation does not necessarily correlate with the prevalence of a psychiatric diagnosis [28], but it is recommended in clinical cases as well as research studies to include measures of effort/symptom validity [13].

Treatment and Family Impact

There have been some attempts at rehabilitation of toxic encephalopathy with some positive but also mixed outcomes [44, 123]. There is also evidence of the effects of toxic encephalopathy on marital and family functioning [126]. Loss of wages and disability for this population have the biggest impact on life and family functioning. In addition, in the most severe cases that result in dementia, there are other caregiver issues to consider. Such issues include the need for spouses to stop working to care for their loved one, loss of social support for the patient and their spouse, and increased caregiving burden overall with concurrent aging playing an additive effect on their pre-existing toxic encephalopathy.

Future Considerations

In neuropsychology, there has long been an attempt to factor out the effects of emotions on cognition. In other words, do the cognitive deficits observed following toxic exposure go beyond any reactionary emotional changes to the exposure, be it traumatic from the exposure or depressive from loss of functioning? While there is a practical element to this venture, it also has the potential to remove variance that is indicative of brain dysfunction. Rather than a knee jerk response to remove the variance associated with behavioral/emotional symptoms, we should work to understand how depression, anxiety, or disinhibition are expressions of the effects of the exposure on the brain's integrity and functions. This has been explored with HIV [127] and is worth pursuing with toxic exposure, as history suggests that changes in emotions, behavior, and cognition are inextricably linked and an expression of brain dysfunction. There is, however, little attempt to link the overlap of cognition and emotion to neuroanatomy. For example, CO exposure is known to affect both the basal ganglia and the limbic system. Is there a relationship between the degree of symptoms of anxiety post-exposure, changes in memory and the degree of changes observed in the hippocampus and/or fornix? Likewise, do changes in the basal ganglia predict changes in mood that represent changes in the reward circuitry? How are the cognitive and neuroimaging symptoms from Mn exposure similar and different from other basal ganglia diseases? We have found one study that compared Mn-exposed individuals to patients with Parkinson's disease [81]. Future studies comparing different types of exposure patients with other well-characterized clinical samples may further develop cognitive neuroscience-based theories to explain the impact of toxic exposure on cognitive and emotional functioning. For example, neuropsychologists such as Nelson Butters assisted in the conceptualizations of various dementias and amnesia based on comparisons of different clinical groups (e.g., [128])

In conclusion, cognitive and emotional changes following exposure to organic solvents, lead, manganese, and carbon monoxide are well-documented. Recent advances using neuroimaging have begun to elucidate the structural underpinnings of the cognitive and behavioral changes. Evidence is mounting that cerebral white matter may be particularly vulnerable and may account for many of the cognitive symptoms. However, gray matter also plays a significant role. For each of these toxins, there is a high degree of variability in symptom expression among individual patients. More research is needed to clarify the variance in the cognitive and emotional symptoms for each of these conditions. Recent studies have highlighted the effect that aging and cognitive reserve may play in the expression of deficits. Future studies that prospectively attempt to understand the variance in symptom expression by integrating cognitive, emotional, and neuroimaging measures will further advance the care we provide to toxin-exposed patients and their families. A focus on comparisons with other well-delineated clinical groups may lead to some insights as well as work to understand the overlap in cognitive and emotional symptoms rather than dissociating them.

References

1. Needleman H. Lead poisoning. Annu Rev Med. 2004;55:209–22.
2. Baker EL, Fine LJ. Solvent neurotoxicity: the current evidence. J Occup Med. 1986;28(2):126–9.
3. Furu H, Sainio M, Hyvarinen HK, et al. Detecting chronic solvent encephalopathy in occupations at risk. Neurotoxicology. 2012;33(4):734–41.
4. Verberk MM, van der Hoek JA, van Valen E, et al. Decision rules for assessment of chronic solvent-induced encephalopathy: Results in 2370 patients. Neurotoxicology. 2012;33(4):742–52.
5. Baker EL. A review of recent research on health effects of human occupational exposure to organic solvents. A Crit Rev J Occup Med. 1994;36(10): 1079–92.
6. Hartman D. Neuropsychological toxicology: identification and assessment of human neurotoxic syndromes. 2nd ed. New York: Springer; 1995.
7. Jin CF, Haut M, Ducatman A. Industrial solvents and psychological effects. Clin Occup Environ Med. 2004;4(4):597–620, v.
8. Mikkelsen S. Epidemiological update on solvent neurotoxicity. Environ Res. 1997;73(1–2):101–12.
9. Sainio MA Sr. Neurotoxicity of solvents. Handb Clin Neurol. 2015;131:93–110.
10. White RPS. Solvent encephalopathy. Oxford: Oxford University Press; 1993.
11. Morrow LMS, Sandstrom DJ. Neuropsychological sequelae associted with occupational and environmental exposure to chemicals. New York: Kluwer Academic/Plenum Oublishers; 2001.
12. Meyer-Baron M, Blaszkewicz M, Henke H, et al. The impact of solvent mixtures on neurobehavioral performance: conclusions from epidemiological data. Neurotoxicology. 2008;29(3):349–60.
13. van Valen E, van Thriel C, Akila R, et al. Chronic solvent-induced encephalopathy: European consensus of neuropsychological characteristics, assessment, and guidelines for diagnostics. Neurotoxicology. 2012;33(4):710–26.
14. Hanninen H, Antti-Poika M, Juntunen J, Koskenvuo M. Exposure to organic solvents and neuropsychological dysfunction: a study on monozygotic twins. Br J Ind Med. 1991;48(1):18–25.
15. Akila R, Muller K, Kaukiainen A, Sainio M. Memory performance profile in occupational chronic solvent encephalopathy suggests working memory dysfunction. J Clin Exp Neuropsychol. 2006;28(8):1307–26.
16. Morrow LA. Cuing attention: Disruptions following organic solvent exposure. Neuropsychology. 1994;8 (3):471–6.
17. Morrow LA, Robin N, Hodgson MJ, Kamis H. Assessment of Attention and Memory Efficiency in Persons with Solvent Neurotoxicity. Neuropsychologia. 1992;30(10):911–22.
18. Morrow LA MS, Sandstrom DJ. Neuropsychological sequelae associated with occupational and environmental exposure to chemicals. 2001.
19. Morrow LA, Steinhauer SR, Condray R, Hodgson M. Neuropsychological performance of journeymen painters under acute solvent exposure and exposure-free conditions. J Int Neuropsychol Soc: JINS. 1997;3(3):269–75.
20. Morrow LA, Ryan CM, Hodgson MJ, Robin N. Risk-Factors Associated with Persistence of Neuropsychological Deficits in Persons with Organic-Solvent Exposure. J Nerv Ment Disease. 1991;179(9):540–5.
21. Nilson LN, Backman L, Sallsten G, Hagberg S, Barregard L. Dose-related cognitive deficits among floor layers with previous heavy exposure to solvents. Arch Environ Health. 2003;58(4):208–17.
22. Nilson LN, Sallsten G, Hagberg S, Backman L, Barregard L. Influence of solvent exposure and aging on cognitive functioning: an 18 year follow up of formerly exposed floor layers and their controls. Occup Environ Med. 2002;59(1):49–57.
23. van Valen E, Wekking E, van der Laan G, Sprangers M, van Dijk F. The course of chronic solvent induced encephalopathy: a systematic review. Neurotoxicology. 2009;30(6):1172–86.
24. Condray R, Morrow LA, Steinhauer SR, Hodgson M, Kelley M. Mood and behavioral symptoms in individuals with chronic solvent exposure. Psychiatry Res. 2000;97(2–3):191–206.
25. Haut MW, Kuwabara H, Ducatman AM, et al. Corpus callosum volume in railroad workers with chronic exposure to solvents. J Occup Environ Med. 2006;48(6):615–24.
26. Morrow LA, Ryan CM, Goldstein G, Hodgson MJ. A distinct pattern of personality disturbance following exposure to mixtures of organic solvents. J Occup Med. 1989;31(9):743–6.
27. Morrow LA, Gibson C, Bagovich GR, Stein L, Condray R, Scott A. Increased incidence of anxiety and depressive disorders in persons with organic solvent exposure. Psychosom Med. 2000;62 (6):746–50.
28. Visser I, Lavini C, Booij J, et al. Cerebral impairment in chronic solvent-induced encephalopathy. Ann Neurol. 2008;63(5):572–80.
29. Morrow LA, Stein L, Bagovich GR, Condray R, Scott A. Neuropsychological assessment, depression, and past exposure to organic solvents. Appl Neuropsychol. 2001;8(2):65–73.
30. Visser I, Wekking EM, de Boer AG, et al. Prevalence of psychiatric disorders in patients with chronic solvent induced encephalopathy (CSE). Neurotoxicology. 2011;32(6):916–22.
31. Aydin K, Sencer S, Demir T, Ogel K, Tunaci A, Minareci O. Cranial MR findings in chronic toluene abuse by inhalation. AJNR Am J Neuroradiol. 2002;23(7):1173–9.

32. Rosenberg NL, Kleinschmidt-DeMasters BK, Davis KA, Dreisbach JN, Hormes JT, Filley CM. Toluene abuse causes diffuse central nervous system white matter changes. Ann Neurol. 1988;23 (6):611–4.
33. Unger E, Alexander A, Fritz T, Rosenberg N, Dreisbach J. Toluene abuse: physical basis for hypointensity of the basal ganglia on T2-weighted MR images. Radiology. 1994;193(2):473–6.
34. Alkan A, Kutlu R, Hallac T, et al. Occupational prolonged organic solvent exposure in shoemakers: brain MR spectroscopy findings. Magn Reson Imaging. 2004;22(5):707–13.
35. Haut MW, Leach S, Kuwabara H, et al. Verbal working memory and solvent exposure: a positron emission tomography study. Neuropsychology. 2000;14(4):551–8.
36. Tang CY, Carpenter DM, Eaves EL, et al. Occupational solvent exposure and brain function: an fMRI study. Environ Health Perspect. 2011;119 (7):908–13.
37. Shih RA, Hu H, Weisskopf MG, Schwartz BS. Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead. Environ Health Perspect. 2007;115(3):483–92.
38. Balbus-Kornfeld JM, Stewart W, Bolla KI, Schwartz BS. Cumulative exposure to inorganic lead and neurobehavioural test performance in adults: an epidemiological review. Occup Environ Med. 1995;52(1):2–12.
39. Goodman M, LaVerda N, Clarke C, Foster ED, Iannuzzi J, Mandel J. Neurobehavioural testing in workers occupationally exposed to lead: systematic review and meta-analysis of publications. Occup Environ Med. 2002;59(4):217–23.
40. Meyer-Baron M, Seeber A. A meta-analysis for neurobehavioural results due to occupational lead exposure with blood lead concentrations < 70 microg/100 ml. Arch Toxicol. 2000;73(10–11): 510–8.
41. Stewart WF, Schwartz BS. Effects of lead on the adult brain: a 15-year exploration. Am J Ind Med. 2007;50(10):729–39.
42. Bleecker ML, Ford DP, Celio MA, Vaughan CG, Lindgren KN. Impact of cognitive reserve on the relationship of lead exposure and neurobehavioral performance. Neurology. 2007;69(5):470–6.
43. Khalil N, Morrow LA, Needleman H, Talbott EO, Wilson JW, Cauley JA. Association of cumulative lead and neurocognitive function in an occupational cohort. Neuropsychology. 2009;23(1):10–9.
44. Lindgren KN, Masten VL, Tiburzi MJ, Ford DP, Bleecker ML. The factor structure of the Profile of Mood States (POMS) and its relationship to occupational lead exposure. J Occup Environ Med. 1999;41(1):3–10.
45. Rhodes D, Spiro A 3rd, Aro A, Hu H. Relationship of bone and blood lead levels to psychiatric symptoms: the normative aging study. J Occup Environ Med. 2003;45(11):1144–51.
46. Stewart WF, Schwartz BS, Davatzikos C, et al. Past adult lead exposure is linked to neurodegeneration measured by brain MRI. Neurology. 2006;66 (10):1476–84.
47. Weisskopf MG, Hu H, Sparrow D, Lenkinski RE, Wright RO. Proton magnetic resonance spectroscopic evidence of glial effects of cumulative lead exposure in the adult human hippocampus. Environ Health Perspect. 2007;115(4):519–23.
48. Weisskopf MG, Hu H, Mulkern RV, et al. Cognitive deficits and magnetic resonance spectroscopy in adult monozygotic twins with lead poisoning. Environ Health Perspect. 2004;112(5):620–5.
49. Caffo B, Chen S, Stewart W, et al. Are Brain Volumes based on Magnetic Resonance Imaging Mediators of the Associations of Cumulative Lead Dose with Cognitive Function? Am J Epidemiol. 2007.
50. Schwartz BS, Chen S, Caffo B, et al. Relations of brain volumes with cognitive function in males 45 years and older with past lead exposure. NeuroImage. 2007;37(2):633–41.
51. Caffo B, Chen S, Stewart W, et al. Are brain volumes based on magnetic resonance imaging mediators of the associations of cumulative lead dose with cognitive function? Am J Epidemiol. 2008;167(4):429–37.
52. Seo J, Chang Y, Jang KE, et al. Altered executive function in the welders: A functional magnetic resonance imaging study. Neurotoxicology Teratol. 2016;56:26–34.
53. Seo J, Lee BK, Jin SU, et al. Altered executive function in the lead-exposed brain: A functional magnetic resonance imaging study. Neurotoxicology. 2015;50:1–9.
54. (ATSDR) AfTSaDR. 2012 https://www.atsdr.cdc.gov/phs/phs.asp?id=100&tid=23. Accessed 10/16/2017, 2017.
55. Bowler RM, Beseler CL, Gocheva VV, et al. Environmental exposure to manganese in air: Associations with tremor and motor function. Sci Total Environ. 2016;541:646–54.
56. Roels HA, Bowler RM, Kim Y, et al. Manganese exposure and cognitive deficits: a growing concern for manganese neurotoxicity. Neurotoxicology. 2012;33(4):872–80.
57. Dorman DC, Struve MF, Wong BA, Dye JA, Robertson ID. Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. Toxicol Sci: Off J Soc Toxicology. 2006;92(1):219–27.
58. Chang Y, Woo ST, Kim Y, et al. Pallidal index measured with three-dimensional T1-weighted gradient echo sequence is a good predictor of manganese exposure in welders. J Magn Reson Imaging: JMRI. 2010;31(4):1020–6.

59. Bowler RM, Mergler D, Sassine MP, Larribe F, Hudnell K. Neuropsychiatric effects of manganese on mood. Neurotoxicology. 1999;20(2–3):367–78.
60. Bowler RM, Gysens S, Diamond E, Booty A, Hartney C, Roels HA. Neuropsychological sequelae of exposure to welding fumes in a group of occupationally exposed men. Int J Hyg Environ Health. 2003;206(6):517–29.
61. Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. Manganese exposure: neuropsychological and neurological symptoms and effects in welders. Neurotoxicology. 2006;27(3): 315–26.
62. Bowler RM, Nakagawa S, Drezgic M, et al. Sequelae of fume exposure in confined space welding: a neurological and neuropsychological case series. Neurotoxicology. 2007;28(2):298–311.
63. Laohaudomchok W, Lin X, Herrick RF, et al. Neuropsychological effects of low-level manganese exposure in welders. Neurotoxicology. 2011;32 (2):171–9.
64. Greiffenstein MF, Lees-Haley PR. Neuropsychological correlates of manganese exposure: a meta-analysis. J Clin Exp Neuropsychol. 2007;29 (2):113–26.
65. Bleich S, Degner D, Sprung R, Riegel A, Poser W, Ruther E. Chronic manganism: fourteen years of follow-up. J Neuropsychiatry Clin Neurosci. 1999;11(1):117.
66. Roels HA, Ghyselen P, Buchet JP, Ceulemans E, Lauwerys RR. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med. 1992;49 (1):25–34.
67. Lucchini RG, Guazzetti S, Zoni S, et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. Neurotoxicology. 2012;33(4):687–96.
68. O'Neal SL, Zheng W. Manganese Toxicity Upon Overexposure: a Decade in Review. Curr Environ Health Rep. 2015;2(3):315–28.
69. Finkelstein Y, Milatovic D, Aschner M. Modulation of cholinergic systems by manganese. Neurotoxicology. 2007;28(5):1003–14.
70. Halliwell B GJ. Free radicals and biology and medicine. Oxford University Press; 2005.
71. Verhoeven WM, Egger JI, Kuijpers HJ. Manganese and acute paranoid psychosis: a case report. J Med Case Rep. 2011;5:146.
72. Lezak MDHD. Bigler ED. Neuropsychological Assessment: Tranel D; 2012.
73. Bowler RM, Gocheva V, Harris M, et al. Prospective study on neurotoxic effects in manganese-exposed bridge construction welders. Neurotoxicology. 2011;32(5):596–605.
74. Kim Y, Jeong KS, Song HJ, et al. Altered white matter microstructural integrity revealed by voxel-wise analysis of diffusion tensor imaging in welders with manganese exposure. Neurotoxicology. 2011;32(1):100–9.
75. Fitsanakis VA, Zhang N, Avison MJ, Gore JC, Aschner JL, Aschner M. The use of magnetic resonance imaging (MRI) in the study of manganese neurotoxicity. Neurotoxicology. 2006;27 (5):798–806.
76. Bowler RM, Yeh CL, Adams SW, et al. Association of MRI T1 relaxation time with neuropsychological test performance in manganese- exposed welders. Neurotoxicology. 2017.
77. Lewis MM, Flynn MR, Lee EY, et al. Longitudinal T1 relaxation rate (R1) captures changes in short-term Mn exposure in welders. Neurotoxicology. 2016;57:39–44.
78. Lee EY, Flynn MR, Du G, et al. Editor's Highlight: Lower Fractional Anisotropy in the Globus Pallidus of Asymptomatic Welders, a Marker for Long-Term Welding Exposure. Toxicol Sci: Off J Soc Toxicology. 2016;153(1):165–73.
79. Long Z, Jiang YM, Li XR, et al. Vulnerability of welders to manganese exposure–a neuroimaging study. Neurotoxicology. 2014;45:285–92.
80. Chang Y, Jin SU, Kim Y, et al. Decreased brain volumes in manganese-exposed welders. Neurotoxicology. 2013;37:182–9.
81. Casjens S, Dydak U, Dharmadhikari S, et al. Association of exposure to manganese and iron with striatal and thalamic GABA and other neurometabolites - Neuroimaging results from the WELDOX II study. Neurotoxicology. 2017.
82. Ma RE, Ward EJ, Yeh CL, et al. Thalamic GABA levels and occupational manganese neurotoxicity: Association with exposure levels and brain MRI. Neurotoxicology. 2017.
83. Chang Y, Kim Y, Woo ST, et al. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. Neurotoxicology. 2009;30(4):555–63.
84. Chang Y, Lee JJ, Seo JH, et al. Altered working memory process in the manganese-exposed brain. NeuroImage. 2010;53(4):1279–85.
85. Centers for Disease C, Prevention. Unintentional non-fire-related carbon monoxide exposures–United States, 2001–2003. MMWR Morb Mortal Wkly Rep. 2005;54(2):36–39.
86. Sircar K, Clower J, Shin MK, Bailey C, King M, Yip F. Carbon monoxide poisoning deaths in the United States, 1999 to 2012. Am J Emerg Med. 2015;33(9):1140–5.
87. Centers for Disease C, Prevention. Carbon monoxide–related deaths–United States, 1999–2004. MMWR Morb Mortal Wkly Rep. 2007;56(50): 1309–1312.
88. Gale SD, Hopkins RO, Weaver LK, Bigler ED, Booth EJ, Blatter DD. MRI, quantitative MRI, SPECT, and neuropsychological findings following

carbon monoxide poisoning. Brain Inj. 1999;13(4): 229–43.
89. Prockop LD. Carbon monoxide brain toxicity: clinical, magnetic resonance imaging, magnetic resonance spectroscopy, and neuropsychological effects in 9 people. J Neuroimaging: Off J Am Soc Neuroimaging. 2005;15(2):144–9.
90. Wolf SJ, Lavonas EJ, Sloan EP, Jagoda AS, American College of Emergency P. Clinical policy: Critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. Ann Emerg Med. 2008;51(2):138–152.
91. Hopkins RO, Woon FL. Neuroimaging, cognitive, and neurobehavioral outcomes following carbon monoxide poisoning. Behav Cogn Neurosci Rev. 2006;5(3):141–55.
92. Dunham MD, Johnstone B. Variability of neuropsychological deficits associated with carbon monoxide poisoning: four case reports. Brain Inj. 1999;13(11):917–25.
93. Kesler SR, Hopkins RO, Weaver LK, Blatter DD, Edge-Booth H, Bigler ED. Verbal memory deficits associated with fornix atrophy in carbon monoxide poisoning. J Int Neuropsychol Soc: JINS. 2001;7 (5):640–6.
94. Porter SS, Hopkins RO, Weaver LK, Bigler ED, Blatter DD. Corpus callosum atrophy and neuropsychological outcome following carbon monoxide poisoning. Arch Clin Neuropsychol: Off J Natl Acad Neuropsychologists. 2002;17(2):195–204.
95. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002;347(14):1057–67.
96. Huang CC HC, Chen YC, Lin HJ, Hsu CC, Wang JJ, Su SB, Guo HR. Hyperbaric oxygen therapy is associated with lower short- and long-term mortality in patients with carbon monoxide poisoning. Chest. 2017.
97. Parkinson RB, Hopkins RO, Cleavinger HB, et al. White matter hyperintensities and neuropsychological outcome following carbon monoxide poisoning. Neurology. 2002;58(10):1525–32.
98. Gale SD, Hopkins RO, Weaver LK, Bigler ED, Booth EJ, Blatter DD. MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. Brain Inj. 1999;13(4): 229–43.
99. Wilson BA. Cognitive functioning of adult survivors of cerebral hypoxia. Brain Inj. 1996;10(12): 863–74.
100. Myers RA, DeFazio A, Kelly MP. Chronic carbon monoxide exposure: a clinical syndrome detected by neuropsychological tests. J Clin Psychol. 1998;54(5):555–67.
101. Bourgeois JA. Amnesia after carbon monoxide poisoning. Am J Psychiatry. 2000;157(11):1884–5.
102. Sohn YH, Jeong Y, Kim HS, Im JH, Kim JS. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. Arch Neurol. 2000;57(8):1214–8.
103. Cocito L, Biagioli M, Fontana P, et al. Cognitive recovery after delayed carbon monoxide encephalopathy. Clin Neurol Neurosurg. 2005;107 (4):347–50.
104. Lai CY, Huang YW, Tseng CH, Lin CL, Sung FC, Kao CH. Patients With Carbon Monoxide Poisoning and Subsequent Dementia: A Population-Based Cohort Study. Medicine. 2016;95(1): e2418.
105. Wong CS, Lin YC, Hong LY, et al. Increased Long-Term Risk of Dementia in Patients With Carbon Monoxide Poisoning: A Population-Based Study. Medicine. 2016;95(3):e2549.
106. Jasper BW, Hopkins RO, Duker HV, Weaver LK. Affective outcome following carbon monoxide poisoning: a prospective longitudinal study. Cogn Behav Neurol: Off J Soc Behav Cogn Neurology. 2005;18(2):127–34.
107. Choi IS. Parkinsonism after carbon monoxide poisoning. Eur Neurol. 2002;48(1):30–3.
108. Min SK. A brain syndrome associated with delayed neuropsychiatric sequelae following acute carbon monoxide intoxication. Acta Psychiatr Scand. 1986;73(1):80–6.
109. Kuroda H, Fujihara K, Mugikura S, Takahashi S, Kushimoto S, Aoki M. Altered white matter metabolism in delayed neurologic sequelae after carbon monoxide poisoning: A proton magnetic resonance spectroscopic study. J Neurol Sci. 2016;360:161–9.
110. Chen NC, Huang CW, Lui CC, et al. Diffusion-weighted imaging improves prediction in cognitive outcome and clinical phases in patients with carbon monoxide intoxication. Neuroradiology. 2013;55(1):107–15.
111. Kim YS, Cha YS, Kim MS, et al. The usefulness of diffusion-weighted magnetic resonance imaging performed in the acute phase as an early predictor of delayed neuropsychiatric sequelae in acute carbon monoxide poisoning. Hum Exp Toxicol. 2017:960327117722821.
112. Yeh ZT, Tsai CF, Yip PK, et al. Neuropsychological performance in patients with carbon monoxide poisoning. Appl Neuropsychol Adult. 2014;21 (4):278–87.
113. Lo CP, Chen SY, Lee KW, et al. Brain injury after acute carbon monoxide poisoning: early and late complications. AJR Am J Roentgenol. 2007;189(4): W205–11.
114. Chen PC, Chen MH, Chen HL, et al. Callosal damage and cognitive deficits in chronic carbon monoxide intoxication: A diffusion tensor imaging study. J Neurol Sci. 2015;355(1–2):101–7.
115. O'Donnell P, Buxton PJ, Pitkin A, Jarvis LJ. The magnetic resonance imaging appearances of the brain in acute carbon monoxide poisoning. Clin Radiol. 2000;55(4):273–80.

116. Gottfried JA, Chatterjee A. Carbon monoxide-mediated hippocampal injury. Neurology. 2001;57 (1):17.
117. Yarid NA, Harruff RC. Globus Pallidus Necrosis Unrelated to Carbon Monoxide Poisoning: Retrospective Analysis of 27 Cases of Basal Ganglia Necrosis. J Forensic Sci. 2015;60(6):1484–7.
118. Pulsipher DT, Hopkins RO, Weaver LK. Basal ganglia volumes following CO poisoning: A prospective longitudinal study. Undersea Hyperb Med. 2006;33(4):245–56.
119. Chu K, Jung KH, Kim HJ, Jeong SW, Kang DW, Roh JK. Diffusion-weighted MRI and 99mTc-HMPAO SPECT in delayed relapsing type of carbon monoxide poisoning: evidence of delayed cytotoxic edema. Eur Neurol. 2004;51(2):98–103.
120. Lo CP, Chen SY, Chou MC, et al. Diffusion-tensor MR imaging for evaluation of the efficacy of hyperbaric oxygen therapy in patients with delayed neuropsychiatric syndrome caused by carbon monoxide inhalation. Eur J Neurol. 2007;14(7): 777–82.
121. Jang JY, Lee SY, Kim JI, Park JB, Lee KJ, Chung HK. Application of biological monitoring to the quantitative exposure assessment for neuropsychological effect by chronic exposure to organic solvents. Int Arch Occup Environ Health. 1999; 72(2):107–14.
122. Bianchini KJ, Houston RJ, Greve KW, et al. Malingered neurocognitive dysfunction in neurotoxic exposure: an application of the Slick criteria. J Occup Environ Med. 2003;45(10):1087–99.
123. van Hout MS, Schmand B, Wekking EM, Hageman G, Deelman BG. Suboptimal performance on neuropsychological tests in patients with suspected chronic toxic encephalopathy. Neurotoxicology. 2003;24(4–5):547–51.
124. Greve KW, Bianchini KJ, Black FW, et al. The prevalence of cognitive malingering in persons reporting exposure to occupational and environmental substances. Neurotoxicology. 2006;27(6):940–50.
125. Greve KW, Bianchini KJ, Black FW, et al. Classification accuracy of the Test of Memory Malingering in persons reporting exposure to environmental and industrial toxins: Results of a known-groups analysis. Arch Clin Neuropsychol: Off J Natl Acad Neuropsychologists. 2006;21(5): 439–48.
126. Abjornsson G, Palsson B, Karlson B, Orbaek P, Osterberg K. Psychological distress and coping in women married to men with a diagnosis of solvent-induced chronic toxic encephalopathy. Brain Inj. 2005;19(6):417–23.
127. Castellon SA, Hardy DJ, Hinkin CH, et al. Components of depression in HIV-1 infection: their differential relationship to neurocognitive performance. J Clin Exp Neuropsychol. 2006;28(3): 420–37.
128. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. J Neurosci: Off J Soc Neuroscience. 1989;9(2):582–7.

Chapter 31

Neurocognition in Mitochondrial Disorders

Kevin M. Antshel

Background

A mitochondrion (plural *mitochondria*) is a specialized cellular subunit found in most living cells. Mitochondria generate most of a cell's supply of adenosine triphosphate (ATP) and supply the cell with energy primarily derived from oxidation of carbohydrates and fatty acids in the mitochondria. A mitochondrion has its own DNA and its own transcription and translation processes. The mitochondrial DNA encodes only 13 polypeptides which are located in the inner mitochondrial membrane as subunits of the respiratory chain complexes.

A clinically heterogeneous group of disorders, mitochondrial disorders, are a result of mitochondrial respiratory chain dysfunction. Biochemically, mitochondrial disorders are associated with respiratory chain dysfunction because all 13 subunits encoded by mitochondrial DNA are subunits of respiratory chain complexes. Caused by an abnormality in the terminal component of aerobic energy metabolism – oxidative phosphorylation (OXPHOS) – mitochondrial disorders can be a result of either mutations of nuclear DNA (contained in the chromosomes) or mitochondrial DNA (contained in organellar nucleoids) [1]. Nuclear DNA mutations generally present in early to middle childhood and mitochondrial DNA mutations present later (late childhood and beyond). Because OXPHOS is necessary for nearly all cells, most mitochondrial disorders affect multiple organ systems [2, 3].

The mitochondrial genome is inherited matrilineally. Depending upon the cell and the specific energy requirements of a tissue, there may be hundreds to even thousands of mitochondria within each cell; each mitochondrion will contain several mitochondrial DNA copies. Thus each cell will contain hundreds and possibly thousands of mitochondrial DNA copies. Spontaneous mitochondrial DNA mutations can occur, often in the context of DNA replication. Once a mutation occurs, the cell is considered heteroplasmic (e.g., coexistence of two different mitochondrial DNA genotypes). If the mutation is contained in the female germ line, this mutation can be passed on to offspring [2, 3]. As a function of ongoing mitochondrial and cellular division, the mitochondrial DNA mutation burden evolves across time. A threshold level for each mutation is thought to exist, which is a percentage of the total mutant mitochondrial DNA copy number beyond which the cell (and therefore tissue) will manifest pathology [4].

Classification of mitochondrial disorders is difficult, yet broadly can be grouped into primary mitochondrial DNA disorders and nuclear mitochondrial genetic disorders. Primary mitochondrial disorders are either maternally inherited or occur de novo. Primary mitochondrial disorders consist of DNA rearrangements (large-scale partial deletions and duplications) such as Kearns–Sayre syndrome

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(KSS), point mutations such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), and Leigh syndrome (LS). The nuclear mitochondrial genetic disorders are generally inherited in an autosomal recessive pattern. (Barth syndrome, a nuclear mitochondrial disorder of cardiolipin, is transmitted in an X-linked recessive fashion.) The nuclear mitochondrial genetic disorders can be grouped into primary disorders of the respiratory chain, disorders of mitochondrial protein import, and disorders of RNA metabolism, among others.

There are multiple distinct mitochondrial disorders including MELAS, MERRF, KSS, LS, Leber hereditary optic neuropathy (LHON), and neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP). Mitochondrial disorders have considerable clinical heterogeneity and most individuals with a mitochondrial disorder are not easily categorized into one discrete syndrome. Given the wide range of presentations and symptoms, it is not surprising that mitochondrial disorders collectively are one of the most common forms of inborn errors of metabolism, with a prevalence of roughly 1:8,500 live births [5, 6].

The Process of Diagnosing a Mitochondrial Disorder

The diagnosis of a mitochondrial disorder generally begins with a clinical evaluation. The organs most often affected in mitochondrial disorders are highly energy-demanding tissues, such as the central nervous system (CNS), skeletal and cardiac muscle, pancreatic islets, liver, and kidney. As shown in Table 31.1, relatively common clinical features of mitochondrial disorders include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, renal tubular acidosis, liver dysfunction, optic atrophy, pigmentary retinopathy, and diabetes mellitus. Neurological symptoms can include fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. A laboratory evaluation is included in the diagnostic evaluation for suspected mitochondrial disorders. Elevated plasma alanine on amino acid analysis or elevation of lactate, pyruvate, or Kreb's cycle intermediates on urine organic acid analysis is pathognomic and requires follow-up.

Table 31.1 Common mitochondrial disorders symptoms

System	Common symptoms
Central nervous system	Myoclonus, sensorineural deafness, external ophthalmoplegia, optic atrophy, pigmentary retinopathy, dementia, stroke-like episodes, seizures, ataxia
Peripheral nervous system	Axonal neuropathy
Muscle	Hypotonia, exercise intolerance, ptosis, external ophthalmoparesis
Heart	Cardiac dysrhythmia, hypertrophic cardiomyopathy
Endocrine	Diabetes, short stature, hypoparathyroidism

Elevated lactate is a non-specific finding, is highly subject to the conditions of the sample, and alone does not differentiate between mitochondrial disorders and secondary lactic acidosis caused by conditions of the draw (e.g., tourniquet or excess crying) or poor sample preparation (e.g., failure to ice the sample or process immediately). Plasma lactate levels alone are not reliable markers of mitochondrial disease, and when performed with a tourniquet can result in a label of "lactic acidosis" inappropriately and subject a child to unnecessary invasive testing. Thus, evaluation for suspected mitochondrial disease should include plasma amino acids (looking for elevated alanine), urine organic acids (looking for Kreb's cycle intermediates or elevated lactate/pyruvate), and consideration of other non-metabolic causes of neurological or developmental abnormalities (for example, profound hypotonia secondary to Prader–Willi Syndrome, peroxisomal disease, or chromosomal abnormalities). If indicated, blood studies for mitochondrial mutations or muscle biopsy may be indicated. However, muscle biopsy findings are often normal in children with obvious mitochondrial disease.

Neuroimaging studies can also prove helpful toward diagnosing a mitochondrial disorder. Basal ganglia calcification and/or atrophy, cerebellar atrophy, or high-signal occipital cortex change on

T2-weighted images are relatively common neuroimaging findings in mitochondrial disorders [7, 8], but are not specific to mitochondrial disorders.

After a mitochondrial disorder has been diagnosed, the treatment is largely supportive. Coenzyme Q, an electron carrier that may improve respiratory chain function, helps some individuals with mitochondrial disorders. Others may show some improvement on vitamin "cocktails" that also have antioxidant or alternative electron carrier properties, such as riboflavin, vitamin E, vitamin K, biotin, lipoic acid, and others, carnitine or creatine. Management of comorbid diabetes and cardiac issues is also central to ongoing management.

The clinical heterogeneity both within and between mitochondrial disorders is well documented. Thus, rather than discussing the mitochondrial disorders as a whole, specific mitochondrial disorders will be discussed. Within each specific mitochondrial disorder, characteristic symptoms, pathophysiological mechanisms, neuropsychological findings, and (when applicable) psychiatric phenotypes will be discussed.

Biological Underpinnings of Mitochondrial Disorders

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes (MELAS)

Symptoms. MELAS generally has an onset of symptoms between ages 2 and 20 years. An A→G mutation in the transfer $RNA^{Leu(UUR)}$ gene at position 3,243 of the mitochondrial DNA accounts for the majority of MELAS cases. The initial symptoms are often some combination of stroke-like episodes, encephalopathy characterized by generalized tonic–clonic seizures, lactic acidosis, ragged-red fibers (an accumulation of abnormal mitochondria in muscle fibers), recurrent headaches, exercise intolerance, proximal limb weakness, and/or recurrent vomiting [9]. The generalized tonic–clonic seizures are associated with stroke-like episodes of transient hemiparesis. The cumulative residual effects of these stroke-like episodes gradually impair motor abilities (via basal ganglia calcifications), vision, and cognition (especially memory), often by adolescence or young adulthood. Sensorineural hearing loss also commonly occurs in MELAS [10]. The mean survival from disease onset to death in MELAS is 6.5 years [11].

Neuroimaging. Multifocal infarct-like lesions in the occipital, parietal, and temporal cortices associated with neuronal loss and gliosis are the most common neuroimaging finding in MELAS. Volumetric loss is also commonly reported in the basal ganglia, thalamus, and cerebellum [12–14].

Increased MRI T2 signal in the posterior cerebrum is commonly observed during stroke-like episodes. Focal or diffuse atrophy, focal or diffuse hyperintensities (periventricularly, in the deep white matter, subcortically, or cortically), cystic lesions predominantly in the parieto-temporal region are also commonly reported [15, 16]. Reduced *N*-acetylaspartate (NAA), choline, creatine peaks, and/or an increased lactate peak are also commonly observed MRS findings in MELAS [17, 18].

A slow progression of stroke-like lesions from temporal to parietal and occipital regions occurs during the course of the disease [15, 19]. Unlike ischemic strokes, however, an increased apparent diffusion coefficient (ADC) is observed in MELAS [20]. (The ADC is a quantitative measure of the degree of bioenergetic compromise in the ischemic lesion. The probability of tissue infarction is inversely proportional to the ADC; the lower the tissue ADC, the greater the degree of compromise and the more likely tissue is to infarct [21].) Also divergent from ischemic strokes, the MELAS lesion distribution does not follow vascular territories and there is often no associated vascular pathology [22]. Similarly, in MELAS, following a stroke-like episode, there is an increase in water diffusion. In ischemic stroke, however, water diffusion decreases [23]. This increase in water diffusion has been hypothesized to be a result of cellular swelling due to mitochondrial dysfunction [20].

Deficits on tests of executive functioning have also been commonly reported [24], despite the relative preservation of the frontal lobes in MELAS [25]. The frontal lobe, however, has deep and reciprocal

connections to the more posterior regions of the brain [26]. If the posterior regions are anomalous, the inputs received by the frontal lobe will be disrupted.

Pathophysiology. The MELAS pathogenesis is largely unknown. However, several hypotheses have been forwarded that attempt to explain the stroke-like episodes which are the MELAS hallmark. One theory posits that mitochondrial neuronopathy is the cause and neuronal vulnerability/hyperexcitability is the basis for the seizures and stroke-like episodes [27]. With increased capillary permeability and neuronal vulnerability, episodic neuronal hyperexcitability develops causing prolonged seizures and leading to the progressive spread of stroke-like lesions. This theory further asserts that neuronal hyperexcitability results from energy-dependent ion transport failure in the context of an oxidative phosphorylation defect. This ion transport failure results in increased extracellular potassium or glutamate, leading to neuronal hyperexcitability.

An alternative theory attempts to connect blood vessel disease and the development of stroke-like episodes, based on hypocitrullinemia (low levels of plasma citrulline, an intermediate in the urea cycle for excreting ammonia) commonly observed in MELAS. Nitric oxide production/catabolism dysfunction may be a mechanism underlying both MELAS blood vessel disease and stroke-like episodes. In an ATP-dependent process, small intestine enterocytes synthesize the majority of citrulline. In MELAS, reduced availability of ATP for citrulline production may lower plasma citrulline levels. In response to this dysfunctional mitochondrial protein synthesis, the cell attempts to compensate for the overall respiratory chain deficiency and as a result expands the mitochondrial mass, typically observed as ragged-red fibers. Cytochrome c oxidase (COX) activity thus becomes increased beyond normal levels.

Nitric oxide plays a role in controlling smooth muscle tone and mediating vasodilation and cerebral perfusion. Nitric oxide binds to COX, displacing oxygen, yet due to elevated COX levels a relative shortage of nitric oxide develops. It is this nitric oxide shortage that is thought to propel the MELAS endothelial dysfunction and contributes to the stroke-like episodes due to aberrant autoregulation. Support for this theory comes from data suggesting that individuals with normal (or deficient COX activity as in MERRF) have normal vasodilation and do not have stroke-like episodes.

Neuropsychology. Unlike most other mitochondrial disorders, dementia is a common clinical finding in MELAS. For example, in one of the largest MELAS studies, Hirano reported that 54 of 60 individuals (90%) with MELAS met clinical criteria for dementia [10]. Hearing impairments characterized by progressive sensorineural hearing loss are another common (~75%) clinical finding in MELAS [10].

In one of the first neuropsychological studies of individuals with mitochondrial disorders, Kartsounis [28] compared individuals with MELAS (n = 3) to individuals with various other mitochondrial disorders. While general cognitive dysfunction was observed in the majority (61%) of the 36 patients, the individuals with MELAS demonstrated greater cognitive deterioration.

The largest study of neuropsychological functioning in MELAS included 91 adults with MELAS [29] and compared neuroimaging and neuropsychological results to 15 age-matched adults with MERRF. Individuals with MELAS performed less well than individuals with MERRF on multiple neuropsychological tests including tests of abstract reasoning, verbal memory, visual memory, language (consisting of naming and fluency), executive function, attention, and visual–spatial abilities [29]. A linear relationship was reported between the neuropsychological mean score and MRS ventricular lactate values with $r = -0.439$ ($p < 0.001$); the higher the lactate value the less well the individual performed on the neuropsychological tests. These authors hypothesized that it is the lactic acidosis which imparts the considerable neurocognitive sequelae by means of neuronal swelling death [30] due to the relatively higher cell membrane permeability of lactic acid [31]. This lactic acidosis then prevents normalization of cortical energy metabolism [32].

Case studies have similarly described rapid cognitive deterioration in MELAS. For example, Sartor et al. [33] reported on a 37-year-old male who began experiencing cognitive deterioration at age 14. By age 28, psychosis, epileptic seizures, and stroke-like

episodes had developed. In his early 30s, dementia was diagnosed [33].

The general finding from mitochondrial neuropsychological research suggests that individuals with MELAS have more generalized and significant cognitive deficits than other types of mitochondrial disorders.

Psychiatric. Adults with MELAS are also susceptible to encephalopathic psychosis [33–36]; with the progression of dementia, psychosis and psychotic episodes become increasingly frequent in MELAS [37–39]. Likewise, in samples ascertained for psychosis, MELAS has been reported [40]. Depression and panic disorders have also been reported in adults with MELAS [41].

Myoclonic Epilepsy with Ragged-Red Fibers (MERRF)

Symptoms. Myoclonus is generally the first symptom of MERRF. This brief, involuntary muscular twitching is then often followed by generalized seizures, ataxia, weakness, and dementia [42]. The onset of symptoms is most often in childhood, usually after a period of typical development. Sensorineural hearing loss, short stature, and optic atrophy also occur. Ragged-red fibers in the muscle biopsy are a defining feature of MERRF.

Neuroimaging. As with most of the mitochondrial disorders, basal ganglia calcification is a common MERRF neuroimaging finding [42]. Degeneration of cerebellar cortex cells, Clarke's nuclei and dorsal root ganglia as well as subcortical gray matter loss, especially in the inferior medullary olives are also frequently reported [12–14].

Pathophysiology. MERRF is caused by a heteroplasmic mutation at nucleotide 8,344 (A8344G) of the tRNA(Lys) gene of mitochondrial DNA. This mutation impairs mitochondrial protein synthesis and causes a respiratory chain dysfunction [43]. Higher levels of mutated mitochondrial DNA correlate with decreased protein synthesis, decreased oxygen consumption, and COX [43, 44].

Neuropsychology. Kaufmann [29] studied 15 adults with MERRF, comparing results to adults with MELAS. Relative to adults with MELAS, adults with MERRF had lower MRS ventricular lactate levels and did better on neuropsychological tests.

Kearns–Sayre Syndrome (*KSS*)

Symptoms. KSS is typically diagnosed during childhood often as a function of ptosis and/or ophthalmoplegia. KSS affects primarily the CNS, skeletal muscle, and heart and is typically fatal in young adulthood. CNS involvement typically consists of cerebellar ataxia, mental retardation, dementia, and sensorineural hearing loss. Unlike other mitochondrial disorders (e.g., MELAS, MERRF), strokes and seizures are uncommon in KSS.

The mitochondrial DNA in KSS is heteroplasmic, meaning that there is a mixture of wild type and mutated mitochondrial DNA within a single cell. In KSS, a deletion (between positions 8,469 and 13,147) in the mitochondrial DNS sporadically occurs. The most common deletion is a 4.9 kb deletion, occurring in about 1/3 of KSS cases [45]. An identical deletion also occurs in Pearson syndrome and chronic progressive external ophthalmoplegia (CPEO). In KSS, neither the size nor the location of the deletion predicts clinical phenotype. Rather, the KSS clinical phenotype is predicted by the ratio of deleted and wild-type mitochondrial DNA. Very high levels of deleted mitochondrial DNA in all tissues are likely to cause Pearson syndrome; lower levels of deleted mitochondrial DNA cause KSS. In CPEO, deleted mitochondrial DNA may be detected only in muscle tissue.

Neuroimaging. Cortical and white matter atrophy, cerebral and cerebellar white matter hypodensity, basal ganglia calcification, increased lactate/creatinine, and decreased *N*-acetylaspartate/creatinine ratios are the most common KSS neuroimaging findings [45, 46]. It has been suggested that a disconnection of Purkinje cells at the dentate nucleus may play a role in the pathogenesis of KSS cerebellar ataxia.

Neuropsychology. Bosbach et al. [47] assessed six individuals with KSS on a neuropsychological battery. Results indicated that verbal memory functions and general intellectual functioning were largely in

the average range; however, despite adequate visual acuity, focal cognitive impairments in visuospatial, executive, and attention skills were reported. The extent of cognitive impairment, defined as mild, moderate, or severe on the basis of the number of abnormal test results, did not correlate with the age of onset of symptoms or disease duration [47].

Leigh Syndrome (LS) and Neurogenic Muscle Weakness, Ataxia, Retinitis Pigmentosa (NARP)

Symptoms. LS and NARP are both progressive neurodegenerative disorders caused by abnormalities of mitochondrial energy generation. Both syndromes have been associated to 8993T>G/C mutations in the subunit 6 of the ATP synthase. Heteroplasmy level higher that 90% of the mutant mitochondrial DNA typically results in LS; less than 90% heteroplasmic levels generally results in NARP.

LS has an earlier onset, often after a viral infection, and occurs in roughly 1:35,000 live births [48]. Decompensation (often with lactic acidosis) during an intercurrent illness is typically associated with psychomotor retardation or regression. Hypotonia, spasticity, cerebellar ataxia, and peripheral neuropathy are common.

NARP is also very rare and is characterized by proximal neurogenic muscle weakness with sensory neuropathy, ataxia, and pigmentary retinopathy. Onset of symptoms, particularly ataxia and global developmental delays, is often in early childhood [49]. Individuals with NARP can be relatively stable for many years, but may suffer episodic deterioration, often in association with viral illnesses.

Neuroimaging. Bilateral symmetrical hypodensities in the basal ganglia and bilateral symmetrical hyperintense T2 signal abnormalities in the brain stem and basal ganglia are characteristic LS neuroimaging findings [50, 51].

Neuropsychology. No studies have reported neuropsychological data on individuals with LS or NARP. Several case reports have described clinical neurological findings in LS. Psychomotor retardation and general weakness are the most common finding [52]; ataxia and optic anomalies such as nystagmus and ophthalmoparesis are also common. Several case reports have indicated that mental retardation is common in NARP [53, 54]

Leber Hereditary Optic Neuropathy (LHON)

Symptoms. LHON is a common cause of maternally inherited visual failure. The typical clinical presentation of LHON is painless loss of vision in one eye during young adulthood with symptoms developing in the other eye 6–12 weeks later [55]. Peripheral neuropathy and cardiac conduction defects can also occur.

Neuroimaging. Clinical CNS manifestations are highly variable yet often include medulla and cerebellum white matter lesions. These CNS features develop approximately 4 years after the onset of the visual decline [56].

A hypothesis for the LHON white matter lesions includes the roles of inflammation and energetic metabolism dysfunction [56]. LHON mutations lead to a chronic increase of oxidative stress which in turn leads to retinal ganglion and optic nerve axonal degeneration [57]. LHON neuroimaging studies have documented lesions compatible with chronic multiple sclerosis [56, 58, 59].

Neuropsychology. No data have been reported on neuropsychological functioning in individuals with LHON. The characteristic LHON visual field defect is a centrocecal scotoma (horizontal oval defect in the field of vision situated between and embracing both the point of fixation and the blind spot). Clinically, in addition to visual loss, neurological abnormalities such as postural tremor, peripheral neuropathy, and movement disorders have been reported to be more common in LHON compared to controls [60].

Barth Syndrome

Symptoms. Barth syndrome has a characteristic phenotype which includes skeletal and cardiac myopathy, cyclic neutropenia, and excretion of

3-methylglutaconic acid (a derivative of leucine) in urine. Barth syndrome is caused by point, deletion, and splice-junction mutations in the tafazzin (*TAZ*) gene, located on Xq28.12 [61]. Males with Barth syndrome are generally short in stature relative to peers during childhood yet catch and may surpass peers during adolescence [62].

Neuropsychology. A relatively consistent Barth Syndrome cognitive phenotype includes diminished visual–spatial and math skills yet reading skills comparable to same-age peers [63].

Non-syndromic Mitochondrial Disease

Symptoms. Many individuals are diagnosed with mitochondrial disease that does not fit neatly into one diagnostic entity (e.g., MELAS, LHON). Clinically, these individuals are often diagnosed with an encephalomyopathy.

Neuropsychology. Neuropsychological research on encephalomyopathy has generally consisted of chart reviews and case studies. For example, Nissenkorn et al. [64] reported that 60% (22 of 37) of their pediatric encephalomyopathy population had cognitive or developmental delays. Hypotonia, microcephaly, and seizures were the three most common clinical findings in this diverse group of children with encephalomyopathy. Similarly, Scaglia et al. [65] reported that cognitive or developmental delays occur in 68% (77 of 113) of their sample of pediatric patients with encephalomyopathy.

Given the high prevalence of developmental and cognitive disorders in the mitochondrial disease population, mitochondrial studies should be considered in children with developmental delay, seizures, and hypotonia [66]. Similarly, elevated plasma concentration of lactate has been frequently noted in autism [67]. A population-based study of 69 children with autism found that 7.2% of their sample had a confirmed mitochondrial disorder [68]. If replicated, mitochondrial disorders may represent a large etiologic subgroup of autism.

Treatment

Treatment for mitochondrial disorders most often includes a mitochondrial "cocktail" of coenzyme-Q10, L-carnitine, niacin, thiamin, vitamin B complexes, vitamin E, and creatine [69, 70]. Coenzyme-Q10 has an important function in electron transport and is a gene regulator, upregulating some genes and down regulating others [71]. Vitamin E is located in the outer mitochondrial membrane and helps to regulate mitochondrial superoxide generation and supports mitochondrial integrity. Research on efficacy of mitochondrial "cocktails" varies [72, 73] yet these remain the primary treatment for mitochondrial disorders. Cognitive outcomes are not currently being used in clinical trials. Rather, MRS and clinical findings are the most frequent dependent variables.

Neurological Similarities Among Mitochondrial Disorders

Basal Ganglia Calcification

Despite considerable heterogeneity in age of onset, presenting symptoms, disease course, pathophysiology, and clinical outcomes, basal ganglia calcification is a rather common neurological finding in the mitochondrial disorders. The basal ganglia consist of the caudate and putamen (striatum), as well as the globus pallidus. The basal ganglia receive glutamatergic excitatory inputs from all areas of the cerebral cortex in a somatotopic fashion, and most of the intrinsic gamma-amino butyric acid (GABA)nergic inhibitory output from the basal ganglia is from the globus pallidus to the thalamus and cerebral cortex. The striatum is composed of medium spiny neurons with large dendritic trees, resulting in similar large convergence of divergent "fields" from many different neuronal regions.

Calcification of the basal ganglia results from excess calcium deposits which harden and

subsequently are toxic to neurons. In idiopathic basal ganglia calcification, the globus pallidus is the structure most often calcified [74]. No data have reported which areas of the basal ganglia are calcified in mitochondrial disorders. In mitochondrial disorders, basal ganglia calcification has been hypothesized to be a function of hypoparathyroidism [75] which ultimately leads to basal ganglia calcification. For example, defective energy production as occurs in mitochondrial disorders may particularly affect glutamatergic neuron receptors. Decreased levels of intracellular ATP leads to membrane depolarization and a persistent increase in the influx of calcium ions into the cells. Excessive calcium ion influx activates a host of calcium ion-dependent signaling pathways and stimulates nitric oxide production. Nitric oxide can then react with superoxide anions to form peroxynitrite. Peroxynitrite in turn disintegrates into toxic hydroxyl free radicals that can further disturb cellular mitochondrial function and energy production [76, 77]. The net result of this process is basal ganglia cell loss.

White Matter Anomalies

Brainstem/cerebellum myelin gliosis as well as cerebrum dysmyelination or demyelination are commonly reported neurological outcomes in mitochondrial disorders. (Dysmyelination refers to myelin which is biochemically abnormal or the oligodendrocytes having a molecular abnormality that affects either the formation or the maintenance of myelin. Demyelination refers to the destruction of already formed myelin, usually via an inflammatory and immune-mediated process.)

The myelin anomalies produce a variety of clinical symptoms and are thought to contribute to the visual (due to lesions of the optic nerve) and motor (due to lesions of the corticospinal tracts) disturbances that are very prevalent in mitochondrial disorders.

Neuropsychological Assessment in Mitochondrial Disorders

Given the progressive nature of many mitochondrial disorders, serial neuropsychological assessment can be very useful. Through repeat testing, assessment can be conceptualized in the form of assessment of the *process of growth* rather than assessment of growth at a particular point of time. Assessing the process of growth means that evaluations would take place serially, assessing the process of change intra-individually based on baseline evaluation and on serial outcome measurements. Ongoing follow-up evaluations would allow for the creation of a personal growth curve for each individual that would record growth, regression, or stagnations in the cognitive developmental process.

There is no one psychological test which has been demonstrated to be more specific or sensitive to the mitochondrial disorders' neuropsychological profile of strengths/vulnerabilities. Nonetheless, as detailed in Table 31.2, several psychological tests make conceptual sense to include in any mitochondrial disorder testing battery. Because of the commonly observed basal ganglia and myelin abnormalities, particularly important domains to assess include memory, visuospatial, motor, and executive functions.

Table 31.2 Psychological tests recommended for assessing mitochondrial disorders

Domain	Psychological test
IQ	WISC-IV, WAIS-IV, SB-5
Memory	CMS, WMS-IV, CVLT-II, Rey–Osterrieth complex figure
Attention	Conners CPT, Gordon diagnostic system
Visuospatial	Rey–Osterrieth complex figure
Executive function	WCST, TOL, DKEFS, Stroop Color Word Test
Motor	Grooved pegboard

In addition to psychological tests conducted in the clinic, it is also important to include measures of real-world functioning such as adaptive behavior checklists (completed by a parent, care provider, or spouse) as well as psychiatric assessments including self-and other-report checklists such as the BASC-2 for children and SCL-90-R or ABCL for adults. While more removed as a neurological surrogate than objective neuropsychological data, these measures of real-world functioning provide information that can assist in gauging the ecological validity of the neuropsychological test results. For example, a young adult who performs capably on psychological tests in the clinic yet is failing several classes in college is informative.

Fatigue is a concern in any neuropsychological assessment, yet is particularly likely in the mitochondrial disorder population. Thus, rather than one 4-h assessment or even two 2-h assessments, testing should occur in smaller time blocks.

Conclusions/Future Directions

"Any age, any symptom, any organ" [78] has been used to describe mitochondrial disorders and the vast heterogeneity of symptoms that characterizes the spectrum of mitochondrial disorders. While chronic in nature, mitochondrial disorders appear to either have a stable course and preserved function or a progressive course and greatly decreased functioning [79]. Neuropsychological assessment can play a role in monitoring the trajectory of the mitochondrial disorder and its functional impacts. The most common neurological abnormalities in mitochondrial disorders are basal ganglia calcification and myelin anomalies. Given the deep and reciprocal connections of the basal ganglia to the frontal lobe, neuropsychological assessment should include measures of executive functioning.

Future mitochondrial research should continue to integrate magnetic resonance spectroscopy (MRS) with neurological and neuropsychological assessments. While MRS has been around for 20+ years, this in vivo localized measurement tool has not been well integrated into mitochondrial disorder research. Metabolites, such as NAA, creatine, and choline, are easily assessed via MRS and are relevant to the study of mitochondrial disorders.

Future mitochondrial research should also include more longitudinal assessment of cognition. Dynamic assessment of functioning, rather than static measurement, will permit individual growth curve modeling and allows providers to more reliably and validly assess the disease course.

Finally, the paucity of neuropsychological studies, both cross-sectional and longitudinal, likely reflects that neuropsychologists are not routinely involved in care for individuals with mitochondrial disorders. This is unfortunate as neuropsychologists have a great deal to offer individuals with mitochondrial disorders and their families. For example, neuropsychological assessment may play a role in determining the efficacy of various treatments in mitochondrial disorders. Similarly, following children with mitochondrial disorders into adolescence and adulthood may provide important information regarding the impact of these insults on the developing brain. Mitochondrial disorders offer a unique opportunity to trace the path from gene to brain to behavior. While much has been discovered in terms of gene to brain in mitochondrial disorder, unfortunately, to date, the link to behavior has not received as much research focus.

References

1. Schapira AH. Mitochondrial disease. Lancet. 2006;368(9529):70–82.
2. Leonard JV, Schapira AH. Mitochondrial respiratory chain disorders I: mitochondrial DNA defects. Lancet. 2000;355(9200):299–304.
3. Leonard JV, Schapira AH. Mitochondrial respiratory chain disorders II: neurodegenerative disorders and nuclear gene defects. Lancet. 2000;355(9201):389–94.
4. Schon EA, Bonilla E, DiMauro S. Mitochondrial DNA mutations and pathogenesis. J Bioenerg Biomembr. 1997;29(2):131–49.
5. Arpa J, Cruz-Martinez A, Campos Y, et al. Prevalence and progression of mitochondrial diseases: a study of 50 patients. Muscle Nerve. 2003;28(6):690–5.
6. Majamaa K, Moilanen JS, Uimonen S, et al. Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population. Am J Hum Genet. 1998;63(2):447–54.
7. Barragan-Campos HM, Vallee JN, Lo D, et al. Brain magnetic resonance imaging findings in patients with

mitochondrial cytopathies. Arch Neurol. 2005;62 (5):737–42.
8. Scaglia F, Wong LJ, Vladutiu GD, Hunter JV. Predominant cerebellar volume loss as a neuroradiologic feature of pediatric respiratory chain defects. AJNR Am J Neuroradiol. 2005;26(7):1675–80.
9. Hirano M, Ricci E, Koenigsberger MR, et al. Melas: an original case and clinical criteria for diagnosis. Neuromuscul Disord. 1992;2(2):125–35.
10. Hirano M, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts. J Child Neurol. 1994;9(1):4–13.
11. Sano M, Polanco Y, De Vivo DC. Comparative analysis of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes and myoclonus epilepsy and ragged red fibers. Ann Neurol. 1998;44:576–677.
12. Sparaco M, Bonilla E, DiMauro S, Powers JM. Neuropathology of mitochondrial encephalomyopathies due to mitochondrial DNA defects. J Neuropathol Exp Neurol. 1993;52(1):1–10.
13. Tanji K, Kunimatsu T, Vu TH, Bonilla E. Neuropathological features of mitochondrial disorders. Semin Cell Dev Biol. 2001;12(6):429–39.
14. Betts J, Lightowlers RN, Turnbull DM. Neuropathological aspects of mitochondrial DNA disease. Neurochem Res. 2004;29(3):505–11.
15. Finsterer J, Jarius C, Baumgartner M. Parkinson's disease associated with impaired oxidative phosphorylation. Neuroradiology. 2001;43(11):997–1000.
16. Grunwald F, Zierz S, Broich K, Schumacher S, Bockisch A, Biersack HJ. HMPAO-SPECT imaging resembling Alzheimer-type dementia in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS). J Nucl Med. 1990;31 (10):1740–42.
17. Abe K, Yoshimura H, Tanaka H, Fujita N, Hikita T, Sakoda S. Comparison of conventional and diffusion-weighted MRI and proton MR spectroscopy in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like events. Neuroradiology. 2004;46(2):113–17.
18. Moller HE, Kurlemann G, Putzler M, Wiedermann D, Hilbich T, Fiedler B. Magnetic resonance spectroscopy in patients with MELAS. J Neurol Sci. 2005;15(229–230):131–39.
19. Iizuka T, Sakai F, Kan S, Suzuki N. Slowly progressive spread of the stroke-like lesions in MELAS. Neurology. 2003;61(9):1238–44.
20. Kolb SJ, Costello F, Lee AG, et al. Distinguishing ischemic stroke from the stroke-like lesions of MELAS using apparent diffusion coefficient mapping. J Neurol Sci. 2003;216(1):11–15.
21. Fiehler J, Knudsen K, Kucinski T, et al. Predictors of apparent diffusion coefficient normalization in stroke patients. Stroke. 2004;35(2):514–19.
22. Oppenheim C, Galanaud D, Samson Y, et al. Can diffusion weighted magnetic resonance imaging help differentiate stroke from stroke-like events in MELAS? J Neurol Neurosurg Psychiatry. 2000;69 (2):248–50.
23. Beauchamp NJ Jr, Barker PB, Wang PY, vanZijl PC. Imaging of acute cerebral ischemia. Radiology. 1999;212(2):307–24.
24. Neargarder SA, Murtagh MP, Wong B, Hill EK. The neuropsychologic deficits of MELAS: evidence of global impairment. Cogn Behav Neurol. 2007;20 (2):83–92.
25. Allard JC, Tilak S, Carter AP. CT and MR of MELAS syndrome. AJNR Am J Neuroradiol. 1988;9 (6):1234–38.
26. Selemon LD, Goldman-Rakic PS. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci. 1988;8 (11):4049–68.
27. Iizuka T, Sakai F, Ide T, Miyakawa S, Sato M, Yoshii S. Regional cerebral blood flow and cerebrovascular reactivity during chronic stage of stroke-like episodes in MELAS – implication of neurovascular cellular mechanism. J Neurol Sci. 2007;257(1–2):126–38.
28. Kartsounis LD, Troung DD, Morgan-Hughes JA, Harding AE. The neuropsychological features of mitochondrial myopathies and encephalomyopathies. Arch Neurol. 1992;49(2):158–60.
29. Kaufmann P, Shungu DC, Sano MC, et al. Cerebral lactic acidosis correlates with neurological impairment in MELAS. Neurology. 2004;62(8):1297–302.
30. Staub F, Mackert B, Kempski O, Peters J, Baethmann A. Swelling and death of neuronal cells by lactic acid. J Neurol Sci. 1993;119(1):79–84.
31. Nedergaard M, Goldman SA, Desai S, Pulsinelli WA. Acid-induced death in neurons and glia. J Neurosci. 1991;11(8):2489–97.
32. Rehncrona S, Rosen I, Siesjo BK. Brain lactic acidosis and ischemic cell damage: 1. Biochemistry and neurophysiology. J Cereb Blood Flow Metab. 1981;1(3):297–311.
33. Sartor H, Loose R, Tucha O, Klein HE, Lange KW. MELAS: a neuropsychological and radiological follow-up study. Mitochondrial encephalomyopathy, lactic acidosis and stroke. Acta Neurol Scand. 2002;106(5):309–13.
34. Sharfstein SR, Gordon MF, Libman RB, Malkin ES. Adultonset MELAS presenting as herpes encephalitis. Arch Neurol. 1999;56(2):241–43.
35. Amemiya S, Hamamoto M, Goto Y, et al. Psychosis and progressing dementia: presenting features of a mitochondriopathy. Neurology. 2000;55(4):600–1.
36. Suzuki T, Koizumi J, Shiraishi H, et al. Mitochondrial encephalomyopathy (MELAS) with mental

disorder. CT, MRI and SPECT findings. Neuroradiology. 1990;32(1):74–76.
37. Thambisetty M, Newman NJ. Diagnosis and management of MELAS. Expert Rev Mol Diagn. 2004;4 (5):631–44.
38. Kazuno AA, Munakata K, Mori K, et al. Mitochondrial DNA sequence analysis of patients with 'atypical psychosis'. Psychiatry Clin Neurosci. 2005;59 (4):497–503.
39. Kato T. The other, forgotten genome: mitochondrial DNA and mental disorders. Mol Psychiatry. 2001;6:625–33.
40. Munakata K, Iwamoto K, Bundo M, Kato T. Mitochondrial DNA 3243A>G mutation and increased expression of LARS2 gene in the brains of patients with bipolar disorder and schizophrenia. Biol Psychiatry. 2005;57(5):525–32.
41. Miyaoka H, Suzuki Y, Taniyama M, et al. Mental disorders in diabetic patients with mitochondrial transfer RNA(Leu) (UUR) mutation at position 3243. Biol Psychiatry. 1997;42(6):524–6.
42. Hirano M, DiMauro S. Clinical features of mitochondrial myopathies and encephalomyopathies. In: Lane R, editor. Handbook of muscle disease, vol. 1. New York, NY: Marcel Dekker Inc; 1996. p. 479–504.
43. Chomyn A, Meola G, Bresolin N, Lai ST, Scarlato G, Attardi G. In vitro genetic transfer of protein synthesis and respiration defects to mitochondrial DNA-less cells with myopathy-patient mitochondria. Mol Cell Biol. 1991;11(4):2236–44.
44. Masucci JP, Davidson M, Koga Y, Schon EA, King MP. In vitro analysis of mutations causing myoclonus epilepsy with ragged-red fibers in the mitochondrial tRNA(Lys)gene: two genotypes produce similar phenotypes. Mol Cell Biol. 1995;15 (5):2872–81.
45. Degoul F, Nelson I, Lestienne P, et al. Deletions of mitochondrial DNA in Kearns-Sayre syndrome and ocular myopathies: genetic, biochemical and morphological studies. J Neurol Sci. 1991;101(2):168–77.
46. Lestienne P, Ponsot G. Kearns-Sayre syndrome with muscle mitochondrial DNA deletion. Lancet. 1988;1 (8590):885.
47. Bosbach S, Kornblum C, Schroder R, Wagner M. Executive and visuospatial deficits in patients with chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome. Brain. 2003;126(Pt 5):1231–40.
48. Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol. 2001;49(3):377–83.
49. Holt IJ, Harding AE, Petty RK, Morgan-Hughes JA. A new mitochondrial disease associated with mitochondrial DNA heteroplasmy. Am J Hum Genet. 1990;46(3):428–33.
50. Rossi A, Biancheri R, Bruno C, et al. Leigh Syndrome with COX deficiency and SURF1 gene mutations: MR imaging findings. AJNR Am J Neuroradiol. 2003;24(6):1188–91.
51. Arii J, Tanabe Y. Leigh syndrome: serial MR imaging and clinical follow-up. AJNR Am J Neuroradiol. 2000;21(8):1502–09.
52. Yang YL, Sun F, Zhang Y, et al. Clinical and laboratory survey of 65 Chinese patients with Leigh syndrome. Chin Med J (Engl). 2006;119(5):373–77.
53. Lopez-Gallardo E, Solano A, Herrero-Martin MD, et al. NARP syndrome in a patient harbouring an insertion in the MT-ATP6 gene that results in a truncated protein. J Med Genet. 2009;46(1):64–67.
54. Sperl W, Jesina P, Zeman J, et al. Deficiency of mitochondrial ATP synthase of nuclear genetic origin. Neuromuscul Disord. 2006;16(12):821–29.
55. Man PY, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. J Med Genet. 2002;39 (3):162–69.
56. Perez F, Anne O, Debruxelles S, et al. Leber's optic neuropathy associated with disseminated white matter disease: a case report and review. Clin Neurol Neurosurg. 2009;111(1):83–86.
57. Howell N. Leber hereditary optic neuropathy: respiratory chain dysfunction and degeneration of the optic nerve. Vision Res. 1998;38(10):1495–504.
58. Harding AE, Sweeney MG, Miller DH, et al. Occurrence of a multiple sclerosis-like illness in women who have a Leber's hereditary optic neuropathy mitochondrial DNA mutation. Brain. 1992;115(Pt 4):979–89.
59. Jansen PH, van der Knaap MS, de Coo IF. Leber's hereditary optic neuropathy with the 11 778 mtDNA mutation and white matter disease resembling multiple sclerosis: clinical, MRI and MRS findings. J Neurol Sci. 1996;135(2):176–80.
60. Nikoskelainen EK, Marttila RJ, Huoponen K, et al. Leber's "plus": neurological abnormalities in patients with Leber's hereditary optic neuropathy. J Neurol Neurosurg Psychiatry. 1995;59(2):160–64.
61. Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nat Genet. 1996;12(4):385–89.
62. Kelley RI, Cheatham JP, Clark BJ, et al. X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. J Pediatr. 1991;119(5):738–47.
63. Mazzocco MM, Kelley RI. Preliminary evidence for a cognitive phenotype in Barth syndrome. Am J Med Genet. 2001;102(4):372–78.
64. Nissenkorn A, Zeharia A, Lev D, et al. Multiple presentation of mitochondrial disorders. Arch Dis Child. 1999;81(3):209–14.
65. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. Pediatrics. 2004;114(4):925–31.
66. Uusimaa J, Remes AM, Rantala H, et al. Childhood encephalopathies and myopathies: a prospective

study in a defined population to assess the frequency of mitochondrial disorders. Pediatrics. 2000;105(3 Pt 1):598–603.
67. Coleman M. Advances in autism research. Dev Med Child Neurol. 2005;47(3):148.
68. Oliveira G, Diogo L, Grazina M, et al. Mitochondrial dysfunction in autism spectrum disorders: a population-based study. Dev Med Child Neurol. 2005;47(3):185–89.
69. Chow CK. Vitamin E regulation of mitochondrial superoxide generation. Biol Signals Recept. 2001;10 (1–2):112–24.
70. Komura K, Hobbiebrunken E, Wilichowski EK, Hanefeld FA. Effectiveness of creatine monohydrate in mitochondrial encephalomyopathies. Pediatr Neurol. 2003;28(1):53–58.
71. Geromel V, Darin N, Chretien D, et al. Coenzyme Q (10) and idebenone in the therapy of respiratory chain diseases: rationale and comparative benefits. Mol Genet Metab. 2002;77(1–2):21–30.
72. Matthews PM, Ford B, Dandurand RJ, et al. Coenzyme Q10 with multiple vitamins is generally ineffective in treatment of mitochondrial disease. Neurology. 1993;43(5):884–90.
73. Berbel-Garcia A, Barbera-Farre JR, Etessam JP, et al. Coenzyme Q 10 improves lactic acidosis, strokelike episodes, and epilepsy in a patient with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes). Clin Neuropharmacol. 2004;27(4):187–91.
74. Gomille T, Meyer RA, Falkai P, Gaebel W, Konigshausen T, Christ F. Prevalence and clinical significance of computerized tomography verified idiopathic calcinosis of the basal ganglia. Radiologe. 2001;41(2):205–10.
75. Harvey JN, Barnett D. Endocrine dysfunction in Kearns-Sayre syndrome. Clin Endocrinol (Oxf). 1992;37(1):97–103.
76. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. Nat Rev Drug Discov. 2004;3(3):205–14.
77. Duchen MR. Mitochondria and calcium: from cell signalling to cell death. J Physiol. 2000;529(1):57–68.
78. Munnich A, Rotig A, Chretien D, Saudubray JM, Cormier V, Rustin P. Clinical presentations and laboratory investigations in respiratory chain deficiency. Eur J Pediatr. 1996;155(4):262–74.
79. Debray FG, Lambert M, Chevalier I, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases. Pediatrics. 2007;119(4):722–33.

Part VIII
Substance Abuse

Chapter 32

Substance Use Disorders: Cognitive Sequelae, Behavioral Manifestations, Neuroimaging Correlates, and Novel Interventions

James J. Mahoney III, Kirk R. Bryant, and Marc W. Haut

The United States is currently in the midst of a substance abuse crisis. According to the 2016 National Survey on Drug Use and Health (NSDUH), approximately 20.1 million people had a substance use disorder (SUD) in 2016 [1]. Specifically, 15.1 million people met criteria for alcohol use disorder and 7.4 million people met criteria for an illicit SUD, the most common being for marijuana (4.0 million people) and opioids (2.1 million people). Unfortunately, the number of individuals with SUD far exceeds the number of patients receiving substance use treatment. Specifically, of the 20.1 million people with SUD, only 3.8 million people received any form of substance use treatment with only 2.2 million receiving treatment at a specialty facility [1]. Further complicating matters is the high comorbidity between SUD and other psychiatric disorders. In 2016, an estimated 8.2 million adults (3.4 percent of all adults) had both mental illness and SUDs in the past year, and 2.6 million adults (1.1 percent of all adults) had co-occurring *serious* mental illness and SUDs. About half of those with co-occurring mental illness and a SUD did not receive either mental health care or specialty substance use treatment, and approximately one-third of those with co-occurring *serious* mental illness and a SUD did not receive either type of care [1]. Another factor impeding on SUD is the lack of medication-assisted treatments (MAT) for SUDs, other than MAT for alcohol and opioids, especially given the rise of other substances of abuse such as methamphetamine.

The current conceptualization regarding the immediate and long-term neural effects of substance use focuses on dopamine (DA), and the nucleus accumbens (NAc), which is the center in the reward circuitry [2–6]. The NAc maintains direct and indirect involvement in several brain regions associated with emotions, self-regulation, disinhibition, insight, craving, and habit forming, which include the dorsal striatum, amygdala, hippocampus, and prefrontal cortex [3].

The acute effects of substance use result in a surge of DA throughout the reward circuitry. Given the reinforcing effects of this surge of DA, the probability of continued and future substance use is subsequently increased. Chronic substance use eventually leads to a suppression of DA availability over time secondary to the persistent release of dopamine caused by substance use. As a

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result, when using substances but also reacting to cues associated with use, a surge of DA is triggered, bringing individuals closer to their baseline, pre-substance using DA level. Substance use is highly reinforcing because of the depleted DA system and individuals attempt to return to a state of "homeostasis", i.e., prior levels of dopamine. In other words, actual substance use or even cues associated with substance use increases dopamine and substance seeking behavior is subsequently a reinforced response to the need to restore DA. Also, moderating these behaviors, is the lack of top-down control. The prefrontal cortex is hypoactive, due to a lack of dopamine in the system, causing an individual to be less likely to inhibit impulsive behaviors, including substance use. The insula and anterior cingulate cortex are also critical as they are associated with insight and self-monitoring, and when both or either is hypoactive secondary to chronic suppression of DA, the individual is unaware of cyclical, impulsive drug seeking/taking behaviors. A recent meta-analysis of functional imaging studies supported this reward processing network conceptualization of addiction [7].

The goal of this chapter is to discuss the most common drugs of abuse, including the cognitive sequelae related to substance use, behavioral manifestations associated with use of substances, and structural/functional neuroimaging findings associated with substance use, with a focus on structural measures of brain volume or cortical thickness, white matter status measured by diffusion-weighted imaging, and resting state functional connectivity. Substance abuse disorders that will be reviewed are (1) opioids, (2) alcohol, (3) stimulants (cocaine, methamphetamine, MDMA), (4) cannabis, (5) synthetic substances (cannabinoids, cathinones), (6), benzodiazepines, (7) hallucinogens, and (8) prescription substances of abuse (for Parkinson's and antiepileptic medications). This last area is a newer topic that we will not review exhaustively, but rather introduce the topic with some specific examples.

We will then broadly discuss confounding variables and risk factors possibility impacting or further exacerbating substance-related cognitive deficits, and finally, pharmacological treatments (e.g., cognitive-enhancing agents) and non-pharmacological techniques (e.g., neuromodulation) being studied for the treatment of SUDs.

Cognitive Deficits Associated with SUDs

Cognitive sequelae related to substance use are well documented in the literature and deficits have been found across several cognitive domains [8–16]. While substance use has been associated with diffuse cognitive deficits, established theories have posited that addiction is associated with impairments related to top-down cognitive control of behavior (executive functions), subsequently impacting key stages of the addictive cycle and interfering with psychosocial and treatment outcomes [17–19]. In addition, the commonly impaired executive functions in substance users are critical for successful goal-directed behavior change needed to succeed in treatment [20, 21].

Accounting for cognitive impairment is of critical importance given that these deficits are a risk factor for poor treatment outcomes in those with SUDs, including cocaine [22–24], alcohol [25, 26], and marijuana use disorder [27, 28]. By accounting for cognitive deficits, treatment plans can be modified accordingly and tailored specifically to the individual patient in order to maximize the potential for successful outcomes. For example, individuals with memory retrieval problems can receive cues to enhance their recall of new coping strategies. Likewise, those with executive deficits such as decreased cognitive flexibility/problem-solving can be taught how to apply specific coping strategies in specific situations. In addition to cognitive functioning, the integration of neurobiological evidence with psychological and psychosocial factors has provided better explanations of addictive behaviors [3].

The following sections of this chapter will detail the cognitive deficits, along with behavioral and structural and some functional correlates (e.g., neuroimaging), which are typically characteristic of individuals with SUD, specifically

related to opioids, alcohol, stimulants, marijuana, synthetics, hallucinogens, and less typically thought of substances of abuse. However, many of the studies described on cognitive deficits in substance use and the imaging correlates of those deficits are cross-sectional and not prospective. Thus, an unresolved issue is whether the cognitive deficits reported, compared to a control (no substance use) or comparison group (minimal substance use), are a result of the substance use, a predisposition to substance use, or a combination of the two. We will describe some studies that show a difference in some individuals relative to controls before substance use starts, indicating there can preexisting/predisposing structural and functional brain changes associated with substance use.

Another qualifying issue in this literature is the emerging evidence of differential effects of substance use on the brain of adolescents versus adults. There is some strong evidence that substance use impacts adolescent's brains differently, given ongoing development, than adult brains and that these changes can negatively impact future development going forward. The evidence is not yet present for each substance of abuse we review, but it will likely be in the near future, possibly by the time this chapter is published. Finally, emotional/behavioral factors associated with SUDs are often intertwined with cognition as the same neural circuits are shared. In addition, impaired emotions further impair cognition, which further reduces adherence. Thus, the emotional factors associated with SUDs are important not only for quality of life, but also for their direct and indirect impacts on outcome

Opioids

Opioids include both illicit substances (e.g., heroin) as well as analgesic agents prescribed in clinical practice. Opioids act in both the central and peripheral nervous system most often upon three G-protein-coupled receptors (mu, delta, and kappa), which activate cellular responses [29]. Opioids can be divided into naturally occurring opioids (e.g., morphine, codeine, papaverine, and thebaine), semi-synthetic (e.g., diamorphine, dihydrocodeine, buprenorphine, nalbuphine, naloxone, and oxycodone), and synthetic (e.g., methadone, fentanyl, sufentanil [29]. While opioids are effective in pain management, they also pose high abuse liability and are subject to misuse. The primary routes of opioid administration include ingestion (e.g., swallowing or chewing), insufflation (e.g., snorting), inhalation (e.g., smoking or inhaling), and injection (intravenous, intramuscular/subcutaneous). According to the 2016 NSDUH, an estimated 11.8 million adolescent and adult Americans aged 12 (the beginning of adolescence per NSDUH) or older reported misusing opioids in the past year with approximately 2.1 of this estimate meeting criteria for opioid use disorder (OUD) [1]. Opioids were involved in 42,249 deaths in 2016, and opioid overdose deaths were five times higher in 2016 than in 1999 [30].

Cognitive Deficits Associated with Opioid Use

Acute and chronic opioid use has been associated with deficits across several cognitive domains, including attention, concentration, memory, visuospatial skills, and psychomotor speed [31]. Long-term cognitive effects of opioid use appear to have the greatest impact on executive functions, including the ability to shift cognitive set and inhibit responses [31]; however, there is evidence that opioid-related deficits may lessen with sustained abstinence. For example, one study in individuals with opioid use disorder (OUD) with varying lengths of abstinence (3 days to 24 months) found that longer periods of abstinence was correlated with better performance on a decision-making task, and those who were abstinent from opioids for 24 months performed comparable to controls [32]. Regarding the impact of medication-assisted treatment (MAT) on cognition, while results have shown that patients prescribed buprenorphine tend to

perform better than those prescribed methadone [33–35]. While studies have shown that individuals receiving MAT demonstrate greater cognitive impairment when compared to healthy controls [36], it has not been proven that the impairment would be specifically related to their opioid substitution drugs [36–38], but possibly secondary to their prior substance use and other comorbid diagnoses. For example, adults with opioid use disorders are at elevated risk for infectious diseases such as HIV and hepatitis C [39–41], both of which are also associated with cognitive sequelae related to the progression of the disease course.

Behavioral, Emotional, and Psychiatric Symptoms Associated with Opioid Use

As mentioned previously, approximately 50% of those with SUD have a comorbid psychiatric diagnosis, possibly leading to an exacerbation of cognitive deficits exceeding those which are caused by either the SUD or psychiatric diagnosis alone. For example, prior studies indicate that individuals with comorbid major depressive disorder and opioid use disorder have more prominent cognitive deficits and also reduced treatment adherence [42]. Depression, in the absence of other comorbid psychiatric diagnoses, including SUD, has been associated with cognitive dysfunction across several domains including attention, executive functions, memory, and psychomotor speed [43]. In support of this, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) incorporate criteria specific to cognition when diagnosing major depressive disorder: "the diminished ability to think or concentrate, or indecisiveness" [44]. Executive functioning may be particularly impaired in individuals with depression, subsequently contributing to deficits across other domains, such as memory, attention, and problem-solving, as they also involve executive and prefrontal function [45, 46].

It is also well described in the literature that individuals with OUD experience emotional dysregulation, though the literature conflicts regarding whether users have over or under responses. For example, on an emotion recognition test, opioid users had difficulties decoding facial emotional expressions in comparison to controls [47]. In addition, active and abstinent former heroin users evidenced reduced subjective arousal responses to both pleasant and unpleasant images compared to healthy controls [48, 49]. Conversely, active opioid users had higher arousal response to negative, unpleasant images, and both current and abstinent opioid users had increased arousal response to neutral images when compared to healthy controls [50].

Neuroimaging Abnormalities Associated with Opioid Use

Chronic opioid use has been linked to various structural brain abnormalities, with evidence of gray matter volume loss [51–53] as well as effects on white matter [54–56]. Although abnormalities are present throughout the brain, they are most prominent in the frontal [52, 53] and temporal lobes [51] and cingulate cortex [51, 57]; however, these findings are not consistent. For example, Reid et al. (2008) [58] used voxel-based morphometry to examine the brain structure of individuals with opioid use disorder compared to healthy controls and found a significant decrease only in the thalamic gray matter volume. Furthermore, some studies that examined gray matter in patients with opioid use disorder found no difference between the group of individuals with OUD and a group of healthy controls [59, 60]. This may in part be due to differences in the samples, but also the methodology used to detect the cortical gray matter, which are almost exclusively measures of volume and density. Cortical thickness, as opposed to volume and density measures, may be more appropriate when assessing morphologic abnormalities in brain structure given the potential increase in sensitivity to smaller changes [61–63]. The link between cortical thickness and opiate use is not widely studied. A single study by Li et al. [61] employed cortical thickness

measures and reported several areas of cortical thinning in heroin-dependent individuals relative to healthy controls, (bilateral superior frontal, left caudal middle frontal, right insular, and right superior temporal regions). Duration of heroin use was associated with decreased cortical thickness in the right superior frontal and right insular cortices. Future studies measuring cortical thickness may provide additional information on the complex neuropathophysiology of opiate use disorders.

Multiple studies have utilized diffusion tensor imaging (DTI) to examine the white matter (WM) in the context of opioid use disorders. One of the more prominent findings has been decreased WM integrity, measured as fractional anisotropy (FA), in frontal regions and the cingulate gyrus of those with long-term opiate use [57, 64–66]. Furthermore, decreased WM integrity has been associated with higher instances of relapse [56], suggesting the strength of WM connections is related to maintaining recovery after treatment. Additional studies in heroin-dependent individuals have found significantly decreased FA within the frontal, temporal, and cingulate regions [54] as well as the corpus callosum, thalamocortical radiations, and inferior longitudinal fasciculus [64]. We are not aware of a study that has combined measures of cortical thickness and WM integrity in a single sample of opiate users, nor with resting state measures of connectivity. Importantly, there is some data to suggest that treatment (e.g., methadone) may have a negative effect on brain structure over time [56].

Using resting state (rs) rsfMRI to examine blood-oxygen-level dependent (BOLD) signal, Copersino et al. found an improvement in the default mode network integration early in the course of abstinence from opioid dependence, based on blood-oxygen-level-dependent findings [67]. Ma et al. utilized rsfMRI and DTI in 14 individuals with heroin dependence and 14 health controls. They found reductions in the functional connectivity of the posterior cingulate cortex and precuneus and the parahippocampal gyrus and the medial prefrontal cortex, as well as decreased structural connectivity (FA) [68].

Alcohol

Alcohol is a psychotropic depressant of the CNS that involves different neurotransmitters, including the stimulation of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the CNS, and the inhibition of glutamate, the main central excitatory neurotransmitter [69]. According to the 2016 NSDUH, an estimated 135.7 million of Americans aged 12 or older were current (past month) alcohol users with approximately 65.3 million reporting binge use (greater than 4 or 5 drinks on the same occasion for males and females, respectively) and 16.3 million reporting heavy alcohol use (binge drinking on 5 or more occasions in the past month) [1].

Cognitive Deficits Associated with Alcohol Use

Individuals with alcohol use disorder demonstrate cognitive impairment that often involves impairments in memory, visuoperception, and frontal functions including deficits in attention, working memory, episodic learning and memory, and executive functions [70–73]. Standardized measures have revealed executive impairments on tasks related to response inhibition, problem-solving, cognitive flexibility, set-shifting, and impulsivity [71]. While the literature strongly supports an association between chronic alcohol use and cognitive impairment, there is considerable variability in the pattern and extent of cognitive deficits among individuals with alcohol use disorder [74].

Abstinence from alcohol can result in improvement in cognitive functioning that suggests spontaneous recovery from functional impairment, and/or through the development of compensatory mechanisms. For example, when compared to individuals with alcohol use disorder with shorter durations of alcohol abstinence, those with a longer durations of non-use demonstrated less impairment on tasks related to attention [75, 76], working memory [75, 77], disinhibition, and cognitive abstraction/flexibility

[75, 76, 78]. However, other studies demonstrate persistent impairment, even following months or years of alcohol abstinence, in executive functioning including deficits related to decision-making [79–82].

Long-term, excessive alcohol use is an associated risk factor in the development of alcohol-related dementia (ARD), which is one of the most common types of dementia [83–85]. Given that the primary affected regions include the frontal cortex, hypothalamus, and cerebellum, the clinical features are suggestive of a frontal or subcortical dementia [86]. Wernicke–Korsakoff syndrome (WKS) occurs when alcohol replaces food and results in thiamine deficiency, which causes neurological and cognitive impairments. WKS is common in those with alcohol use disorder and presents as significant memory deficit that is amnestic in nature. While WKS is generally specific to significant memory deficits, rather than the global impairment found with ARD, there is some evidence that ARD may be on the same continuum as WKS [87]. Mild cognitive disorder secondary to alcohol use can be reversed, to some extent, with sustained abstinence; however, once the course progresses to ARD, irreversible damage may persist even with continued abstinence.

Behavioral, Emotional, and Psychiatric Symptoms Associated with Alcohol Use

The comorbidity of depression and alcohol use disorder ranges from 25.7% to 70% [88, 89] and those with alcohol use disorder are nearly 5 times more likely to meet criteria for an affective disorder than those without alcohol use disorder [90]. While it is well known that both alcohol and depression can contribute to cognitive dysfunction independently, the literature regarding whether co-occurring depression exacerbates cognitive deficits in those with alcohol use disorder is mixed. For example, in a meta-analytic review of the literature related to comorbid alcohol use and depression, the comorbid groups did not differ significantly from those with depression only or alcohol use only in the majority of reports [91]. In those cases where differences in neuropsychological performances were found between groups, it was not consistently identified across studies.

Neuroimaging Abnormalities Associated with Alcohol Use

Neuroimaging deficits associated with chronic alcohol use have been widely and long studied. Results include a range of gray matter structures and white matter pathways. In particular, there are volume reductions in frontal grey and white matter as well as the cerebellum [92]. These structural brain changes are at least partially reversible with abstinence, and are associated with improvements in cognitive function [73]. Importantly, there is evidence of preexisting, genetically predisposed structural brain deficits in some individuals with alcohol use disorder [93]. Use of alcohol during adolescence, when the brain is still developing and vulnerable to insult, may have particularly negative outcomes on brain structure [94]. Because of the pre-use differences noted in brain structure, prospective studies are particularly important in differentiating the impact of alcohol use versus predisposing difference in brain structures. For example, a prospective study reported declines in white matter integrity in adolescents who used both alcohol and cannabis, but not in those who used alcohol alone [95]. Results from a large prospective sample demonstrated adolescents who began heavy drinking showed an accelerated decline in frontal grey matter relative to controls that was not substantially moderated by cannabis use [96].

Functional imaging studies in alcohol users are numerous and there are existing reviews of many areas, such as cue-based reactivity (“or the psychological and physiological responses elicited by exposure to alcohol-related stimuli”), where studies have identified many brain areas in which alcohol cues elicit activation [97].

Specifically, alcohol cues elicited robust activation of limbic and prefrontal regions, including ventral striatum, anterior cingulate, and ventromedial prefrontal cortex, as well as activation of parietal and temporal regions, including posterior cingulate, precuneus, and superior temporal gyrus [97]. One recent study of heavy male drinkers, utilizing fMRI to measure functional connectivity, examined motor, cognitive and mood measures 90 min after administration alcohol or placebo. The authors found disruptions of functional connectivity that were associated with the mood, motor, and cognitive effects of acute and chronic alcohol use [98]. Adolescents prior to the initiation of alcohol use showed a different pattern of brain activation than nondrinkers and, following initiation of heavy episodic use of alcohol, showed decreased efficiency of information processing [99]. Models that include demographic factors with cognitive data and neuroimaging data provide the best predictors of future alcohol use [100].

Stimulants (Cocaine, Methamphetamine, MDMA)

Cocaine acts by inhibiting the reuptake of serotonin, norepinephrine, and dopamine [101]. Cocaine can be administered orally, nasally, intravenously, or by inhaled smoke. Crack cocaine is a lower purity form of cocaine that is produced by neutralization of cocaine hydrochloride with a solution of baking soda and then smoked producing an immediate "high." According to the 2016 NSDUH, an estimated 1.9 million Americans aged 12 or older were current (past month) cocaine users (432,000 reported using crack cocaine); approximately half of this estimate met criteria for cocaine use disorder [1]. A stimulant with a different mechanism of action, methamphetamine, causes the release of the neurotransmitters dopamine, norepinephrine, and serotonin, and results in increased heart rate and blood pressure. Acute behavioral effects of methamphetamine typically include feelings of euphoria, alertness, wakefulness, increased energy, and suppression of appetite. According to the 2016 NSDUH, an estimated 684,000 Americans aged 12 or older met criteria for methamphetamine use disorder (MUD) [1].

Cognitive Deficits Associated with Stimulant Use

There is a wealth of literature describing cognitive impairment in individuals with cocaine use disorder [9, 10, 102, 103]. In a recent meta-analytic review of 46 studies that included 1452 chronic cocaine users and 1411 controls, cocaine users evidenced deficits related to attention, episodic memory, and working memory with effect sizes of moderate or greater magnitude [104], findings that are consistent with previous meta-analyses [9, 10]. More specifically, findings revealed moderate impairment in these domains during intermediate abstinence (<12 weeks), milder impairment noted during short-term abstinence (<5 days), and smaller effect-size estimates following long-term abstinence (>20 weeks). While deficits related to attention, episodic memory, and working memory are most prominent, individuals with cocaine use disorder also demonstrate executive dysfunction, including reduced insight, judgment, and decision-making, as well as impulsivity and disinhibition. Impairments related to visuoperception, psychomotor speed, and manual dexterity are also common [105–109].

Although the prevalence of cognitive impairment related to MUD has been a source of debate [110], the presence of cognitive deficits in a subset of individuals who engaged in long-term, high-dose methamphetamine use has been consistent [8, 111–113]. Specifically, deficits are prominent in attention/information processing speed, learning and memory, and frontal lobe functioning, and these cognitive abnormalities have been linked to deficits in presynaptic dopamine (DA) neuronal markers [114–117]. Partial recovery of neuropsychological functioning and improvement in affective distress can be achieved after a period of sustained abstinence from methamphetamine use [118]. Sustained

abstinence from methamphetamine has been associated with improved performance on tests of mental flexibility, attention, processing speed, verbal memory, fine motor functioning, and verbal fluency [118]. However, more than 40% of individuals with prior MUD still experienced cognitive impairments even after prolonged abstinence from methamphetamine [111]. Another closely related psychostimulant, methylenedioxymethamphetamine (MDMA), has also been associated with deficits related to memory and executive functions [119, 120], though some studies report minimal differences between MDMA users and controls [121].

Behavioral, Emotional, and Psychiatric Symptoms Associated with Stimulant Use

Another factor possibly modulating cognition are emotional symptoms such as depression as 41.6% of adults with amphetamine use disorders and 35.7% of those with cocaine use disorders have a lifetime history of the disorder, assessed via structured, clinical interview assessing lifetime prevalence of DSM-IV diagnostic criteria [122]. This is especially relevant given that comorbid depression is a known risk factor for relapse in patients receiving treatment for cocaine use [123]. Cocaine and methamphetamine can cause mood disturbances and psychosis during active use and withdrawal, and symptoms can persist in early abstinence [124–126]. One particular study found that, when compared to healthy controls, cocaine users reported significantly more symptoms of depression as evidenced by higher scores on the Beck Depression Inventory – 2nd Edition [127]. Interestingly though, none of the individuals with cocaine use disorder met DSM-V diagnostic criteria for any depressive or affective disorder, yet yielded higher scores than controls. These findings may have treatment implications because individuals with lower rates of depression were more likely to remain cocaine abstinent after treatment [128]. Given the relationship between depression and cognition, one possibility is that those with elevated depression and subsequently reduced cognition may have had greater difficulty practicing the techniques provided during treatment, such as relapse prevention strategies, making these individuals more susceptible to relapse.

Methamphetamine use often results in irritability, agitation, and numerous other forms of psychiatric distress possibly related to the myriad of interpersonal problems experienced by these individuals [124]. In one particular study, depressive symptoms declined significantly during treatment, with the greatest effect for those who achieved abstinence from methamphetamine. In addition, major depression was associated with poorer outcomes and impairment across multiple domains of functioning [129].

Neuroimaging Abnormalities Associated with Stimulant Use

Cocaine use is associated with changes in both gray and white matter structure. Prefrontal gray matter volume increases were reported in the left inferior frontal gyrus and bilateral ventromedial prefrontal cortex in 19 long-term users after abstinence/time, as compared to no changes in healthy controls [130]. A recent meta-analysis showed overlap in grey matter changed between cocaine and methamphetamine users, but greater declines in the right insula and superior frontal lobe [131]. Differences in prefrontal and striatal grey matter moderates readiness for treatment in cocaine use disorder as a function of the presence of cluster C personality disorder [132]. Specifically, cocaine users with Cluster C traits showed a positive correlation between gyrus rectus gray matter volume and readiness for change, but cocaine users without Cluster C symptoms showed a negative correlation between gray volume of the rostral cingulate and readiness for

change. There are some reports of nicotine dependence, as well as depression and impulsivity, influencing prefrontal grey matter changes in cocaine users, but some studies have not found a relationship [133]. White matter changes in cocaine users have been reported in frontal, limbic, striatal, and cingulate areas with negative associations with duration of use and positive associations with duration of abstinence [134]. There is preliminary longitudinal data to suggest improvement over time with positive treatment outcome [135].

A case-controlled study examined 50 biological sibling pairs (one stimulant-dependent subjects and their stimulant-naive sibling) as well as 50 healthy controls matched for age and IQ. Stimulant dependent subjects used cocaine (94%) or amphetamine (6%); other neurological and psychiatric histories were exclusionary factors. The stop-signal reaction time procedures were used to measure inhibitory control, because of its known neural circuitry that is associated with the brain systems known to be compromised in stimulant drug dependence. The sibling pairs were found to have the same abnormalities in frontostriatal brain circuits relative to controls [136]. This suggests that some of the structural brain abnormalities attributed to stimulant use may predate use. However, this does not mean that stimulant use is not without an impact on brain structure, as demonstrated by the studies reporting changes in regional neural volumes after abstinence. For example, a prospective study of 188 MDMA-naive users who had a high likelihood of future use as determined by their self-reported intention to "probably" or "certainly" use ecstasy for the first time in near future and/or having one or more friends who already use ecstasy. The investigators examined serotonin transporters with single-photon emission computed tomography (SPECT), and used perfusion-weighted imaging (PWI) to study regional blood volume. They also used magnetic resonance spectroscopy to examine brain metabolites, and DTI to measure white matter brain structure [137]. After beginning use, changes were present in blood flow to the globus pallidus and putamen, and in white matter integrity using fractional anisotropy in the frontoparietal white matter and thalamus. No changes were observed with the serotonin transporter densities using SPECT to search throughout the brain. There were also no changes observed in brain metabolites. The changes in brain structure and function using DTI and PWI occurred after an average of six tablets of MDMA. A recent study of resting state networks in methamphetamine dependent individuals with and without psychosis [138] found disruption of default mode networks in both groups with improvement in networks noted with increasing response to treatment for the psychosis and abstinence.

Cannabis

Cannabis, also known as marijuana, is a psychoactive drug intended for medical or recreational use. The main psychoactive part of cannabis is tetrahydrocannabinol (THC) which exerts its most prominent effects via its actions on G-protein-coupled receptors, specifically two types of cannabinoid receptors, the CB1 receptor and the CB2 receptor [139, 140]. By CB1 receptor activation, THC indirectly increases dopamine release and produces psychotropic effects [141]. According to the 2016 NSDUH, an estimated 24 million of Americans aged 12 or older were current (past month) cannabis users with approximately 4 million of this estimate meeting criteria for cannabis use disorder [1].

Cognitive Deficits Associated with Cannabis Use

Acute and chronic cannabis use are risk factors for reduced performances on cognitive measures of attention, information processing speeding, learning and memory, and executive/frontal function [12, 142–148]. Results from

meta-analyses found that non-intoxicated cannabis users perform worse on measures of global neuropsychological function when compared with nonusers [149]. Notwithstanding, a number of studies have shown that chronic, high-dose cannabis use may only affect a small subset of individuals with higher use [143, 144], but long-term effects, if they exist, are generally subtle and not clinically disabling [150, 151]. In a recent review that suggested that cannabis use leads to neuropsychological decline, the associations were modest, were present only for the group with the heaviest cannabis use, and were often attenuated (or no longer significant) after controlling for potential confounding variables [152].

The literature is mixed on the long-term cognitive sequelae related to cannabis use, but evidence suggests that the degree of neuropsychological impairment and following successful abstinence may depend on the frequency and duration of cannabis use, length of abstinence, and age at onset of use. [12, 142, 143, 149]. Although not without its detractors [153, 154], a longitudinal study by Meier et al. [145] may provide the strongest evidence of widespread loss of cognitive function with heavy cannabis use. With the increase in the number of states who allow for medical cannabis as well as recreational use, further prospective longitudinal studies are needed to clarify the issue.

Behavioral, Emotional, and Psychiatric Symptoms Associated with Cannabis Use

In a meta-analysis, cannabis use, especially chronic use, results indicated that cannabis may be associated with an increased risk for developing depressive disorders. There is a need for further longitudinal exploration of the association between cannabis use and developing depression, particularly taking into account cumulative exposure to cannabis and potentially significant confounding factors [155]. One report has noted a longitudinal relationship between reductions in cannabis use and improvements in anxiety, depression, and sleep quality [156].

Neuroimaging Abnormalities Associated with Cannabis Use

Changes in the prefrontal cortex, subcortical striatal structures, and the limbic system have been reported in cannabis users [157–160]. Dose-response data is unclear with some studies finding a relationship and others not [157, 161]. However, one study examined memory performance in adolescents who were abstinent for at least six months and correlated their performance with hippocampal volume [162]. The performance was lower in users compared to controls, and was associated with smaller right hippocampal volume. The correlation between brain structure and function links cannabis related learning and memory deficits to the hippocampus, but does not determine cause and effect. There is also is a relationship between cannabis use and reduced medial orbital frontal volume and decision-making deficits in adolescents [162]. Smith and colleagues [159] found differences in striatal and thalamic shape using large-deformation high-dimensional brain mapping with MRI among a small group of current cannabis users that was related to working memory deficits. Analysis of the shape of the subcortical structures was used in addition to surface area as shape may be a more sensitive measure of subtle changes in subcortical structures. Shollenbarger et al. [163] found reduced frontal gyrification was related to reduced working memory. Shollenbarger et al. [164] noted changes in white matter integrity in the frontal-limbic connections that correlated with apathy. Thus, structural deficits are tied to function (cognition and behavior) in a number of studies.

Functional imaging studies have reported a variety of changes associated with cannabis use. In particular, cannabis use is associated with

changes to functional connectivity that impacts the effort required for working memory [161] and also disruptions the networks associated with awareness [165]. Cues for use also show a differential activity of the reward circuitry in cannabis users versus nonusers [166]. However, as with cognitive studies, there are some negative results [167] suggesting the full effects of cannabis are not yet clear.

Synthetic Substances (Cannabinoids, Cathinones)

Synthetic cannabinoids are a relatively recent phenomenon beginning with their development as potential therapeutic agents in the 1960 s. John William Hoffman, a chemistry professor at Clemson University, developed many of these compounds, such as d-lysergic acid (LSD), in an ongoing effort to find new therapeutic agents. To his dismay, in the early 2000s the substances began being used recreationally as users sought a legal alternative to marijuana. Often called "spice" or "K2", the compounds are sprayed on herbs and often marketed as incense sometimes with the label, "not for human consumption" [168]. These compounds are functionally similar to delta-9-tetrahydrocannabinol (THC); however, there are some key differences when comparing synthetic cannabinoids to marijuana that likely contribute to more adverse and unpredictable effects. Analyses of chemical composition have shown that approximately one-third of these products contain more than one compound, which adds to the unpredictability of their effects [168]. They have a greater binding affinity for the CB1 receptor and are a full agonist rather than a partial agonist like THC, which contributes to greater potency than marijuana according to in vivo and animal studies [168]. Furthermore, unlike THC, several synthetic cannabinoid metabolites bind and exhibit greater effects on CB1 and CB2 receptors [169]. In addition to the greater affinity for CB1 and CB2 receptors, synthetic cannabinoids do not contain the same cannabinoids and flavonoids as marijuana, some of which are thought to mitigate adverse symptoms. For example, the absence of anticonvulsant phytocannabinoids could be one of the mechanisms contributing to convulsions in synthetic users [170]. Others speculate that the cannabinoids and flavonoids contained in the marijuana plant, exhibit anti-anxiety and antipsychotic effects and their absence from synthetic compounds, may contribute to psychotic symptoms associated with synthetic cannabinoid use reported in some case reports [171]. For example, cannabidiol (CBD), is one of these compounds contained in marijuana, that is absent from synthetics, has been shown to have anxiolytic and antipsychotic properties [171]. Reported adverse effects of synthetic compounds include nausea and vomiting, shortness of breath or depressed breathing, hypertension, tachycardia, chest pain, muscle twitches, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment [170]. The unpredictable nature of synthetics cannabinoids, along with their greater intensity and higher toxicity has resulted in Emergency Department visits and hospitalizations [172].

Cognitive Deficits Associated with Synthetic Substance Use

The literature on long-term synthetic cannabinoid use and cognitive deficits is sparse given that public use of synthetic compounds is a relatively recent phenomenon and has, therefore, not been studied to the extent as marijuana's effect on cognition. There are no controlled studies; in fact, most information has been derived from case studies and animal models [173]. A review of literature involving animal models of synthetic cannabinoid exposure is provided by Castaneto and colleagues [168] who reported that chronic exposure in adolescent rats impaired short-term and working memory but chronic exposure in adult rates caused no lasting effects [168]. Others have found discrimination deficits in adult rats with continuous exposure since puberty [174].

Research with human subjects is complicated by comorbidities, concurrent substance use, and

other confounds. Some of these confounds have been illustrated in a recent study comparing marijuana users vs synthetic cannabinoid users [173]. Synthetic cannabinoid users performed significantly worse on measures of executive functioning. However, these individuals were recruited from inpatient psychiatric facilities and "open wards" and had significantly more anxiety and depression and were less educated, muddying the comparison.

Behavioral, Emotional, and Psychiatric Symptoms Associated with Synthetic Substance Use

Typically, psychotic symptoms (hallucinations, paranoia, disorganized thought) dissipate within several hours after use of synthetic substances; however, there have been case reports involving more protracted symptoms lasting days to months [171]. These effects have been documented in persons without a history of psychosis but are more often present as exacerbations of a preexisting psychiatric condition [175, 176]. In a case series during a four-month period, 13% of admissions to a psychiatric hospital involved the use of synthetic cannabinoids. It was the first hospitalization for 4/17 patients. Of the remaining 13 patients, 9 had exacerbations of previously documented conditions, while 4 presented with new onset psychotic symptoms. Additionally, length of stay was longer as compared to those with psychotic symptoms that were independent of synthetic cannabinoid use [176]. Clinically, these psychotic symptoms appear to respond best to time and not medication.

Neuroimaging Findings and Synthetics

There are no published systematic group studies of brain structure and/or function in individuals with long-term use of synthetic cannabinoids. There are case reports of adverse events temporally related to synthetic use including adrenoleukodystrophy [177] and ischemia/stroke [178, 179].

Benzodiazepines

Benzodiazepines are a commonly prescribed drug for anxiety disorder, epilepsy, and insomnia. They primarily influence the major inhibitory neurotransmitter, GABA and have a dampening effect on the neurological system, which leads to both positive therapeutic effects and negative side effects [180]. Olfson, King, and Schoenbaum [181] retrospectively reviewed data from 2008 and reported that the percentage of adults who filled at least one prescription for benzodiazepine during the 2008 calendar year increased with age (2.6% (18–35 years), 5.4% (36–50 years), 7.4% (51–64 years), 8.7% (65–80 years)). The prevalence for women was twice that of men. The potential for overdose death resulting from benzodiazepine use alone is almost nonexistent; however, the deaths related to benzodiazepine use combined with other substances has increased by fourfold since 2002 resulting in 8791 deaths in 2015, including 75% involving opioids (according to data from the National Institute on Drug Abuse (NIDA)) [182]. Motor vehicle accidents and falls have also been associated with benzodiazepine use [182].

Cognitive Deficits Associated with Benzodiazepine Use

The acute cognitive effects of benzodiazepine use include increased sedation, and decreased processing speed, attention, explicit memory, and priming [183]. Encoding information appears most impaired during peak plasma concentrations [183], with information learned prior to administration remaining intact [184]. The elderly can be particularly susceptible to cognitive side effects [185].

The findings for long-term benzodiazepine use have been mixed and are complicated by methodological differences and inherent

comorbidities [186]. For example, one study [187] highlighted the potential negative effects of anxiety on cognition, independent of benzodiazepine dose or use duration. With this caveat, Barker and colleagues [186], conducted a meta-analysis of 13 studies that included subjects who used benzodiazepine for at least one year, objective measures of cognition, and control groups or within subjects design. They found moderate to large effect sizes for all cognitive domains compared to controls, indicating a diffuse effect on cognition, although some domains, notably processing speed, nonverbal memory, and speed were affected to a greater degree.

When considering the risk for dementia, it can be challenging and important to control for potential confounds (e.g., psychiatric history, comorbid substance use, age, and gender). Lagnaouia and colleagues found a significantly increased risk for dementia in individuals who had used benzodiazepines at least once before the interview date, after controlling for age, gender, education level, living alone, wine consumption, psychiatric history, and depressive symptomatology [188]. In a large case-control population study of individuals > 66 years of age, Billioti de Gage and colleagues found that prior benzodiazepine use for at least five years was associated with Alzheimer's disease with an adjusted odds ratio of 1.51 that continued to persist after adjustment for anxiety, depression, and insomnia (OR = 1.43) [189]. Dose has also been shown to impact risk for dementia. For example, Billioti de Gage and colleagues also found increased odds ratios for increased exposure density (1.32 odds ratio for three to six months of prescribed daily doses, and 1.84 odds ratio for more than six months of prescribed daily doses), and for long versus short half-life benzodiazepine (1.70 vs. 1.43) [189]. This difference in risk between long and short half-life benzodiazepines was also supported by Shash and colleagues in a large prospective cohort community study involving 3 cities in France [190]. At the 8-year follow-up, users of benzodiazepines at baseline had a 10% increased risk of dementia; users of long half-life benzodiazepine were at greater risk than those using short half-life benzodiazepine. A key factor that could influence the association between benzodiazepine use and dementia is that benzodiazepine may be used to treat prodromal symptoms of a neurodegenerative condition such as anxiety; thereby creating a coincidental association rather than causation [191].

Neuroimaging Abnormalities Associated with Benzodiazepine Use

There is limited data on the effects of long-term benzodiazepine use on brain structure. One study used ratings by three neuroradiologists of atrophy on computed tomography scans for 20 long-term users compared with 36 age and sex-matched radiology patient controls who were expected to have normal scans and with substance use and medical comorbid disorders ruled out. Blinded raters measured cerebral atrophy (scale from 1-5), size of ventricles, sulci, and folia. They reported no differences between the long-term users and controls [192]. There is an additional study that examined the impact of long-term benzodiazepine use on brain volume in individuals with schizophrenia that noted higher dose was associated with smaller volumes of the caudate nucleus [193].

Hallucinogens

Hallucinogens have long been used in societies for various reasons including spiritual rituals and increase feelings of transcendence. Potential therapeutic effects have also been explored, including the more recent trend of microdosing [194]. Conversely, there is concern that hallucinogens can increase psychological distress and lead to persistent effects [195, 196]. Hallucinogens include phenylalkylamines (e.g., mescaline), 2,5-dimethoxy-4-methylamphetamine (DOM), indoleamines (e.g., (þ)-lysergic acid diethylamide (LSD), and psilocybin [197]. These substances

have a substantial impact on the serotonergic system. The two major classes of psychedelic hallucinogens, the indoleamines (e.g., LSD) and the phenethylamines (e.g., mescaline), are both partial agonists at the 5-HT2A receptors in the central nervous system, and the noradrenergic locus coeruleus and cerebral cortex are among the regions of prominent effects through these receptors. [198].

As reported by NIDA (https://www.drugabuse.gov/drugs-abuse/hallucinogens), the prevalence of hallucinogen use differs by age, and individuals 18–25 years of age have the highest yearly (6.9%) and lifetime (17.2%) use. In contrast, individuals 12 to 17 years of age have a 1.8% yearly and 2.7% lifetime use, and individuals 26 years of age and older have a 1% yearly use and 16.6% lifetime use.

Cognitive Deficits Associated with Hallucinogen Use

The acute effects of hallucinogens on consciousness have been described as entropy of the mind, a hypothesis that brain activity and associated psychology are less predictable in the psychedelic state. [199]. Acute effects can include hallucinations, distortions of time, feeling of transcendence, and distorted perception. Carter and colleagues [200] hypothesized that impaired attentional processes may reflect an inability to filter and suppress stimuli. No strong evidence for long-term neuropsychological deficits has been found, but this will be important to explore this further in large prospective studies [201].

Behavioral, Emotional, and Psychiatric Symptoms Associated with Hallucinogen Use

The psychological impact of hallucinogens can vary based on the context of consumption. When used in the context of religious or spiritual rituals, negative effects are rare. For example, 115 Brazilian syncretic (blending of native and Christian belief systems) churchgoers with regular use of the hallucinogen ayahuasca as part of religious ceremonies, outperformed controls on a wide variety of neuropsychological tests (Stroop test, Wisconsin Card Sorting Test, and Letter-Number Sequencing from the WAIS-III), had better scores on the Frontal Systems Behavior Scale, and reported less psychopathology [195]. The controls were also involved in religion, and were matched to ayahuasca users on age, education, IQ, and other demographic variables. Similarly, when a group of Native Americans who regularly used peyote in a religious context was compared to controls, there were no differences in cognitive performance or psychological measures [202].

Hallucinogens have also been explored as therapeutic agents. Some studies have reported mystical and meaningful experiences that extend beyond the acute duration of the effect, and others have indicated reduced fear and increased empathy and prosocial behavior [203]. The more recent trend of microdosing, particularly since the publication of Fadiman's (2011) book entitled *The psychedelic explorer's guide: Safe, therapeutic, and sacred journeys* [204], involves taking small amounts of a hallucinogen at regular intervals with the aim of improving functioning and mood without intoxicating effects [194]. The literature presently lacks the controlled study of microdosing; however, there are accumulating anecdotal reports. Johnstad conducted structured interviews of individuals who engaged in the practice. He reported that the most common substances were psilocybin and LSD, and these were often taken in 1/10 doses several times a week as discussed in Fadiman's book. The most common reported therapeutic effects include improved mood, increased concentration, and alleviation from medical symptoms such as migraines [187]. Conversely, the most common negative side effects were insomnia and greater than the desired intoxication. Several participants noted that these inadvertent intoxication events occurred at inopportune times such as at work. Microdosing has also been described in recent popular publications. For example, in an article in Wired [205], Solon described individuals who

had experienced cognitive and creative enhancement that provided an advantage in competitive work environments such as Silicon Valley. Ayelet Waldman, a novelist and former public defender, detailed the mood stabilizing effects of microdosing and corresponding benefits for her marriage [206, 207].

In contrast to reported therapeutic effects, hallucinogen use has also been associated with negative effects such as "bad trips" or prolonged psychotic symptoms. Users can also acutely experience panic attacks, fear, and anxiety [195], and there are case studies that report longer lasting symptoms such as flashbacks [196]. Again the question of predisposition is unanswered, and it is difficult to determine if individuals who experience prolonged symptoms are predisposed to psychotic symptoms or happen to have an emerging thought disorder that is unveiled following use or onset coincidentally coincides with exposure.

Neuroimaging Abnormalities Associated with Hallucinogen Use

There have been few systematic studies on changes in brain structure and function associated with hallucinogen use. Differences in neuroimaging outcomes in long-term users have been reported, with the caveat that it is difficult to control for potential confounds (e.g., comorbid substance use). For example, the study of ayahuasca [195] reported that users had a thinner posterior cingulate cortex relative to controls who were matched for age, sex, years of education, verbal IQ, and fluid IQ, without association with the cognitive tests. The PCC is an area implicated in attention, self-referential thought, and internal mentation [208]. Thinning of the PCC was inversely correlated with duration and intensity of use. In addition, case reports suggest unusual adverse events including demyelination [209] and posterior reversible encephalopathy syndrome [209, 210].

Less Commonly Thought of Prescription Substances of Abuse (AEDs, DRTs)

Some less commonly thought of prescription medications outside the realm of stimulants, opioids, and benzodiazepines, have abuse potential and are especially relevant to neuropsychologists due to their use to treat neurological disorders. This section will focus on two groups of medications associated with abuse potential, which include medications used in dopamine replacement therapy (DRTs) for Parkinson's disease (PD) and gabapentinoids, such as gabapentin and pregabalin, which are classified as antiepileptic drugs (AEDs).

Dopamine Replacement Therapy (DRT)

DRT typically involves treatment with a dopamine precursor, Levodopa, that can cross the blood–brain barrier, or dopamine agonists (e.g., pramipexole, ropinirole) [211]. There are cases described in the literature of patients increasing their levodopa intake well beyond the level needed for optimal treatment of their motor symptoms [212]. The prevalence is estimated at 3–4% of those being treated with DRT [213]. DRT abuse is more common in persons of male gender, young onset PD, prior history of substance abuse, and history of affective disorder [214].

Cognitive Deficits Associated with DRT

Consistent with abuse potential, DRT can result in dopaminergic changes to the mesocorticolimbic system that results in decreased ability to learn from negative consequences and increased reward seeking [215]. In a large cross-sectional study of over 3000 PD patients, treatment of PD

with dopamine agonists is associated with a 2–3.5 fold increase of having an impulse control disorder [216]. Also, the acute cognitive and behavioral effects of DRT abuse can mimic hypomanic symptoms (e.g., flight of ideas, disorganized thought patterns, distractibility, and impulsivity) [217].

Behavioral, Emotional, and Psychiatric Symptoms Associated with DRT Use

Spigset and Scheele [212] described two patients who independently increased their levodopa dosage to 1500–2000 mg/day to obtain sustained euphoria despite side effects such as hyperkinesias, anorexia, and hallucinations. This dosage was well above the 400–800 mg/day needed to mitigate their motor symptoms. Attempts to reduce the dose can be met with extreme opposition and a reduced dose is often accompanied by severe dysphoria. For example, one patient shot himself six days following an attempt to reduce his dose from 1200 to 800 [212].

Antiepileptic Drugs (AEDs)

Another less commonly thought of medication with abuse potential is the class of antiepileptic drugs (AEDs). One class of these drugs with abuse potential is gabapentinoids such as gabapentin and pregabalin. We focus on these particular AEDs due to abuse potential and the more recently recognized phenomenon of using them to augment the effects of other substances [218]. Pregabalin is similar to gabapentin but is six times more potent [218]. These drugs are GABA analogs used to treat conditions including seizures, neurogenic pain, and occasionally alcohol abuse [218]. Even though it is a GABA analog, it does not bind to GABA receptors, rather, it blocks voltage-dependent calcium channels, resulting in an inhibitory effect on the nervous system [219]. Some believe gabapentin also has an impact on the dopaminergic system [220]. A survey involving 1500 respondents in the United Kingdom indicated that the gabapentinoid misuse prevalence in the general population was around 2.5% (1.1% gabapentin, 0.5% pregabalin, 1.3% baclofen) with approximately 63% of these persons abusing at least once monthly [221]. The potential for gabapentinoid abuse appears to be primarily limited to persons with comorbid substance abuse history and case reports often involving co-occurring alcohol, opioid, or cocaine use [222].

Cognitive Deficits Associated with AED Use

There is a wealth of literature on the cognitive effects of AEDs in normal or patient groups taking the medication as prescribed, a full review of this literature is beyond the scope of this article. Rather we will introduce the topic by focusing on gabapentinoids as they appear to have been forefront with the current opioid epidemic. Studying the cognitive effects of AED abuse, including gabapentinoid abuse, is problematic and confounded by the extremely high rate of polysubstance abuse. In persons taking AEDs for treatment of medical conditions, cognitive effects are modest and include attention and processing speed, which may also be impacted by the treated medical condition (e.g., seizures). The cognitive effects of AEDs have been studied in healthy participants. Salinsky and colleagues [223] found the cognitive impact of gabapentin to be minimal in healthy volunteers over a 12-week period of slow titration, although participants reported an increase in cognitive inefficiency. The cognitive effects of gabapentin have been found to be less than that of other AEDs such as carbamazepine [224] and topiramate [225].

Behavioral, Emotional, and Psychiatric Symptoms Associated with AED Use

In a qualitative review, Shifano [218] detailed acute effects of gabapentin abuse, which included euphoria, improved sociability, marijuana-like high and relaxation, zombie-like effects, a

sedative or opiate buzz and occasional psychedelic effects. As noted, the acute effect is often amplification of the effects of co-occurring substance use [222].

Additional Factors Impacting and/or Exacerbating Cognitive Deficits in Substance Users

Given that cognitive impairment is a risk factor for poor treatment outcomes in those with SUD [22–24, 226–228], it is critical to identify factors that may moderate the association between substance use and cognition and/or exacerbate these deficits in substance users. Some of these potential factors include polysubstance use, premorbid intellectual functioning, substance use patterns, and psychosocial factors (including elevated stress and trauma).

Polysubstance Use

Individuals with SUD of one category are significantly likely to abuse other categories of substances as well [229]. Given the cognitive deficits associated with chronic use of a single substance, it is important to consider further decrements caused by use and abuse of multiple substances. For example, in a sample of individuals with opioid use disorder, lifetime comorbid alcohol or cocaine use disorder was associated with greater neurocognitive impairment, particularly in executive functioning [230]. In a recent study, individuals with cocaine use disorder who were moderate users of alcohol and marijuana but did not meet use disorder criteria for the latter two substances, exhibited greater deficits in declarative recall and attention when compared to non-cocaine using, moderate users of marijuana and alcohol. In addition, comorbid cocaine and alcohol use disorders were associated with greater levels of cognitive impairment on measures of executive functioning when compared to those who met criteria for a single SUD, but not both [231]. In four other studies, cocaine users who were not concurrent alcohol users demonstrated greater memory impairment and executive dysfunction when compared to individuals who used both cocaine and alcohol, hypothesized to be due to a heightened cerebrovascular vulnerability of the chronic cocaine abusers [232–235]. Even in the context of these mixed results, exacerbation of deficits related to polysubstance use should be considered when evaluating cognition and developing treatment plans to account for these possibly worsened deficits.

Premorbid Intellectual Functioning (Cognitive Reserve Theory)

Studies of healthy controls have provided useful insights regarding the relationship between premorbid IQ and cognitive functioning as higher IQ has been associated with improved cognitive performance [236, 237]. For example, Diaz-Asper et al. compared the performances of individuals with Above Average (>109), Average [99–109], and Below Average (<90) IQ on tasks of attention, verbal learning and memory, and working memory [236]. Better cognitive performance was found to be a function of IQ classification and, moreover, the magnitude of group differences was greater between the Average and Below Average groups in comparison to differences between the Above Average and Average groups. Consistent with these findings, a recent report in cocaine users demonstrated this association between lower premorbid IQ and reduced cognitive functioning [238]. Theories have been posited to account for this occurrence, one of the most studied being the concept of cognitive reserve [239–242], which states that the brain attempts to compensate for pathology by recruiting alternate, more efficient, neural networks [240, 242, 243]. As such, it has been hypothesized that individuals with higher IQ may demonstrate more effective cognitive compensation in the context of brain pathology [243].

According to cognitive reserve, individuals with higher IQ's may be less susceptible to the detrimental cognitive effects produced by substance use. An alternative possibility is that higher IQ may serve as a protective factor, blunting, reducing, or masking the magnitude of cognitive decline associated with persistent substance use. Given the high rate of relapse early in treatment, accounting for cognitive deficits related to premorbid IQ early in the treatment process is important.

Given the association between cognitive impairment and poor treatment outcomes [22–27], and the known association between lower premorbid IQ and reduced cognition, it is critical to consider modifying treatment approaches based on these factors. For example, it is assumed that people remember what treatment providers tell them (e.g., relapse prevention strategies); however, especially in those with Below Average IQ (e.g., impaired verbal learning and memory and working memory as assessed by the Hopkins Verbal Learning Test and Dual N-Back task), this is clearly not the case based on the findings noted above. By accounting for and evaluating premorbid IQ and, more importantly, the relationship to the individuals' cognitive functioning, the implementation of successful behavioral therapies (i.e., cognitive behavioral therapy) may be increased substantially, leading to better outcomes for those with SUDs. We recommend individuals entering substance use treatment undergo a neuropsychological evaluation. The results obtained from comprehensive neuropsychological evaluations can be of benefit to the treating provider so that treatment plans can be modified accordingly based on the individual's needs and areas of impairment.

Substance Use Characteristics and History (e.g. Years, Recent, Daily Substance Use)

Another important factor to consider is drug use patterns, including duration, frequency, and recency of substance use. In a large meta-analysis of alcohol use and cognitive functioning, "heavy" drinking (3–4 drinks/day) was associated with an increased risk of cognitive impairment; however, "light to moderate" drinking (1–2 drinks/day) was not associated with any cognitive deficits [244]. In addition, when compared to healthy controls, approximately three days of cocaine abstinence was associated with poorer performance on tests of episodic memory, visuospatial skills, and attention/concentration, and deficits remained after two weeks of abstinence [245]. Interestingly, individuals with cocaine use disorder who provided a positive urine toxicology screen at the time of the assessment, suggesting use within the past 3 days, evidenced better performance on measures of attention, executive functioning, and verbal memory as compared to those who were cocaine negative at evaluation. The latter findings suggest the possibility that recent cocaine use may mitigate impairments observed during the early phases of abstinence [246]. Cocaine dose effects are also often apparent; for example, individuals who used greater than two grams of cocaine per week were more likely to experience cognitive impairments in attention, working memory, and processing speed when compared to those who used less than two grams per week [247]. Also, negative correlations have been found between quantity (grams/month) and duration of cocaine use (years) and abstract reasoning and working memory [248].

Neuroimaging Abnormalities Associated with Dose Effects

Neuroimaging findings have demonstrated a negative correlation between lifetime amount of cocaine used and activity in the left inferior parietal lobe extending to the left postcentral gyrus [249]. Related to cognitive measures of attention, working memory, executive control, and vigilance, other neuroimaging findings noted the relationship between cocaine use and parietal dysfunction, specifically lower activation in the right frontoparietal regions [250–252]. In addition, amount of cocaine used (grams/week) was negatively correlated with activation in the left

orbitofrontal cortex, further suggesting that cocaine abusers have persistent functional abnormalities in prefrontal neural networks [253].

Other Predisposing Factors (Stress and Trauma)

Comorbid diagnoses of posttraumatic stress disorder (PTSD) and SUD are significantly elevated as nearly 50% of those meeting criteria for PTSD also met criteria for a SUD [254]. Stress and trauma are also known to contribute to cognitive deficits related to learning and memory, working memory, and visuospatial abilities [255] and are also known to contribute to relapse following treatment for cocaine use disorder [256–259]. In addition, those with cocaine use disorder have reported greater use of cocaine following the occurrence of stressful events [260]. It is possible cocaine use serves as a maladaptive coping mechanism for dealing with distress. In other words, because chronic stress is aversive, an individual may use substances to "self-medicate", which is further supported by the association between increased cocaine craving and increased psychological stress [261]. Further supporting this possibility, elevated lifetime stress has been associated with higher addiction severity in individuals with cocaine use disorder [262]. Given that elevated stress is independently known to contribute to cognitive dysfunction, it is plausible that cognitive deficits produced by elevated levels of stress in combination with substance use, may exceed deficits produced by either stress or substance use alone.

Cognitive-Enhancing Agents and Novel Designs and Techniques for the Treatment of SUD

Cognitive-Enhancing Agents

Given the association between cognitive impairment and poor treatment outcomes in those with SUDs [22–28], remedying these deficits pharmacologically warrants investigations. Many medications with cognitive-enhancing properties have been examined as potential treatments for neuropsychiatric disorders and SUDs [103, 263]. These medications target several neurotransmitter systems, especially dopaminergic and acetylcholinergic systems.

The role of the catecholamine neurotransmitters, norepinephrine, and dopamine, in cognition, motivation, and reward has been recognized for decades [264–267]. Modafinil increases the activity of noradrenergic, dopaminergic, serotonergic, glutamatergic, and hypocretin (orexin) neurotransmitter systems, and decreases γ-aminobutyric acid (GABA) activity, in multiple brain regions. In a double-blind, placebo-controlled, crossover study of 400 mg/day modafinil in 11 nontreatment-seeking subjects who completed the study, with methamphetamine dependence tested sequentially at baseline and after each treatment condition, modafinil improved scores on a working memory task, but only in subjects with low baseline performance (n = 6) [268]. This finding was also found in cocaine users as short-term administration of modafinil improved performances on measures of working memory and sustained attention [269].

The neurotransmitter acetylcholine, through interactions with the dopaminergic reward system in the NAc, prefrontal cortex, and ventral tegmental area, is heavily involved in the cognitive and behavioral processes of SUDs [270]. Cholinesterase inhibitors, such as galantamine and rivastigmine, increase levels of synaptic acetylcholine [270]. These medications have been studied extensively and have been FDA approved for the treatment of mild to moderate Alzheimer's and Parkinson's diseases because of their small effects on dementia-associated cognitive and functional impairments [271, 272]. Given that individuals with addiction display altered cholinergic responses in brain areas relevant to craving, learning, and memory, the cholinergic system may be a promising pharmacological treatment target [273]. In light of known cognitive impairments underlying

addiction, with likely involvement of acetylcholine, substance-dependent individuals appear to be particularly relevant candidates for this research. For example, a recent double-blind, randomized trial of galantamine treatment for 10 days in recently abstinent chronic cocaine abusers (n = 34) demonstrated selective improvement in measures of sustained attention [274]. In addition, acute, low dose administration of rivastigmine improved working memory in cocaine use disorder [275].

Neuromodulation

Noninvasive Brain Stimulation

In addition to pharmacological intervention, nonbehavioral/non-pharmacological approaches for the treatment of SUDs are being developed. For example, given that craving has been a key therapeutic target of numerous experiments over the past decades, investigations have been conducted of noninvasive brain stimulation (NIBS) techniques for reducing substance craving [276, 277]. The principle of NIBS is to target outer brain regions which will then secondarily impact deeper brain structures through connectivity. A meta-analysis of 17 of these studies investigating the effects of NIBS on the dorsolateral prefrontal cortex (DLPFC) suggested stimulation can decrease craving in various SUDs [277]. For example, transcranial direct current stimulation (tDCS) was found to reduce craving in several differences substances [278].

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive, electrophysiological procedure, has shown potential effectiveness in individuals with alcohol, nicotine, and cocaine use disorders in reducing craving and use of these substances [279–281]. The one published study on the use of rTMS for OUD found that a single session of rTMS reduced cue-induced craving in long-term heroin users, with further reduction following five consecutive days of rTMS [282]. The main brain circuitry target for rTMS in the treatment of SUD is the prefrontal cortical network, specifically the DLPFC and the orbitofrontal cortex [281, 283]. These brain regions have important roles in inhibitory control, often impaired in patients with SUDs, and disinhibition associated with relapse susceptibility [284–287]. It is hypothesized that increased activity of the PFC may be a mechanism of action of rTMS in patients with SUD [288]. Other possible mechanisms for the effectiveness of rTMS include the reduction of craving through modulation of the dopaminergic and hypothalamic pituitary adrenal axis, and modulation of executive and decision-making processes, reducing risk-taking behavior [289].

While rTMS appears to have potential efficacy in reducing craving, it also has been associated with improved cognition; a review of the literature revealed 61 reports of performance enhancement associated with rTMS [290]. Dependent on the brain location of the targeted stimulation, improvements were noted on tasks of attention, memory, executive functioning, perceptual discrimination, motor learning, speeded visual search, and language. Given the association of rTMS treatment with improved cognition, and the known cognitive deficits associated with substance use along with their association with treatment drop-out, the potential impact of rTMS warrants development as a treatment adjuvant.

Invasive Brain Stimulation

Deep brain stimulation (DBS) is a surgical procedure in which bipolar electrodes are placed into specific brain regions and stimulated through implanted pulse generators. Stimulation parameters are programmable and depend on targeted brain region, disorder, and patient response. Stimulation induces an electric field up to one cm depending on specific neural tissue density [291]. DBS is currently FDA approved for use in humans for some neurologic conditions (e.g., Parkinson's disease, essential tremor) and is being evaluated for other psychiatric disorders (e.g., treatment-refractory depression and OCD). DBS has not been used extensively in addiction,

but there are preliminary studies. In humans, case studies have reported that stimulation to the ventral striatum/nucleus accumbens reduced the consumption of substances of abuse, such as alcohol, nicotine, and heroin [285]. In one report, an individual who underwent the NAc DBS procedure abstained from drug use during active DBS for the first 2.5 years and remained drug free for 3.5 years following DBS removal with no relapse at a 6-year follow-up. Notable improvements in the subjects' memory, IQ, and emotional status were also observed [292]. In a separate case study, two individuals with treatment-refractory heroin use disorder achieved complete heroin abstinence at 2-year follow-up with the exception of one single incident of heroin consumption in the weeks following surgery. These individuals reported that their isolated use was solely motivated by "mere curiosity" yet was not reinforcing and did not reinstate chronic heroin use [293].

Human case studies of DBS applied to the NAc in heroin users have shown promise and reports of its effectiveness has been demonstrated in other substance using populations as well. For example, in a study of five participants with treatment-resistant alcohol use disorder who received DBS of the NAc, all reported a complete absence of craving for alcohol up to 8 years following DBS implantation; two patients remained abstinent for several years, and three showed a marked reduction of alcohol consumption [294]. Another case study reported that DBS of the NAc reduced symptoms related to OCD, which may serve as additional support given the compulsive nature of some drug-taking behavior [295–299]. Interestingly, one of these studies found that DBS targeting the NAc resulted in an unintended and "effortless" smoking cessation [299].

Conclusion

In conclusion, most substances of abuse are associated with frontal impairments (e.g., attention and executive deficits) and memory dysfunction along with changes to the prefrontal grey matter, striatum and a variety of white matter connecting pathways. Some dose–response data exits, as well as evidence of reversal of changes in brain structure and reversal of cognitive deficits with abstinence. It is important to note that some of the changes observed in individuals with SUDs, both in brain structure and brain function, predate substance use and may predispose individuals to substance use and negatively impact treatment response. Neuroimaging data supports the involvement of the reward circuitry in substance use. Understanding the structural and functional brain changes associated with substance use is important given its impact on treatment outcome.

References

1. Center for Behavioral Health Statistics and Quality. 2016 National Survey on Drug Use and Health: Methodological summary and definitions. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2017.
2. Volkow ND, Wang GJ, Fowler JS, Tomasi D. Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol. 2012;52:321–36.
3. Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. N Engl J Med. 2016;374(4):363–71.
4. Volkow ND, Morales M. The Brain on Drugs: From Reward to Addiction. Cell. 2015;162(4):712–25.
5. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016;3(8):760–73.
6. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res. 2002;137(1–2):75–114.
7. Luijten M, Schellekens AF, Kuhn S, Machielse MW, Sescousse G. Disruption of Reward Processing in Addiction: An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies. JAMA Psychiatry. 2017;74(4):387–98.
8. Dean AC, Groman SM, Morales AM, London ED. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology. 2013;38(2):259–74.
9. Spronk DB, van Wel JH, Ramaekers JG, Verkes RJ. Characterizing the cognitive effects of cocaine: a comprehensive review. Neurosci Biobehav Rev. 2013;37(8):1838–59.

10. Jovanovski D, Erb S, Zakzanis KK. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. J Clin Exp Neuropsychol. 2005;27 (2):189–204.
11. Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, et al. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychol Rev. 2007;17(3):275–97.
12. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. Curr Drug Abuse Rev. 2008;1(1):81–98.
13. Baldacchino A, Balfour DJ, Passetti F, Humphris G, Matthews K. Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. Neurosci Biobehav Rev. 2012;36 (9):2056–68.
14. Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. Addict Biol. 2013;18(2):203–13.
15. Schrimsher GW, Parker JD, Burke RS. Relation between cognitive testing performance and pattern of substance use in males at treatment entry. Clin Neuropsychol. 2007;21(3):498–510.
16. London ED, Berman SM, Voytek B, Simon SL, Mandelkern MA, Monterosso J, et al. Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. Biol Psychiatry. 2005;58(10):770–8.
17. Redish AD, Jensen S, Johnson A. A unified framework for addiction: vulnerabilities in the decision process. Behav Brain Sci. 2008;31(4):415–37; discussion 37-87.
18. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry. 2002;159(10):1642–52.
19. Verdejo-Garcia A, Bechara A. A somatic marker theory of addiction. Neuropharmacology. 2009;56 (Suppl 1):48–62.
20. Blume AW, Marlatt GA. The role of executive cognitive functions in changing substance use: what we know and what we need to know. Ann Behav Med. 2009;37(2):117–25.
21. Loughead J, Wileyto EP, Ruparel K, Falcone M, Hopson R, Gur R, et al. Working memory-related neural activity predicts future smoking relapse. Neuropsychopharmacology. 2015;40(6):1311–20.
22. Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend. 2006;81(3):313–22.
23. Aharonovich E, Nunes E, Hasin D. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. Drug Alcohol Depend. 2003;71(2):207–11.
24. Sofuoglu M. Cognitive enhancement as a pharmacotherapy target for stimulant addiction. Addiction. 2010;105(1):38–48.
25. McKellar J, Kelly J, Harris A, Moos R. Pretreatment and during treatment risk factors for dropout among patients with substance use disorders. Addict Behav. 2006;31(3):450–60.
26. McKellar JD, Harris AH, Moos RH. Predictors of outcome for patients with substance-use disorders five years after treatment dropout. J Stud Alcohol. 2006;67(5):685–93.
27. Aharonovich E, Brooks AC, Nunes EV, Hasin DS. Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. Drug Alcohol Depend. 2008;95(3):279–83.
28. Sofuoglu M, Sugarman DE, Carroll KM. Cognitive function as an emerging treatment target for marijuana addiction. Exp Clin Psychopharmacol. 2010;18(2):109–19.
29. Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012;6(1):11–6.
30. Hedegaard H, Warner M, Minino AM. Drug Overdose Deaths in the United States, 1999-2016. NCHS Data Brief. 2017;294:1–8.
31. Gruber SA, Silveri MM, Yurgelun-Todd DA. Neuropsychological consequences of opiate use. Neuropsychol Rev. 2007;17(3):299–315.
32. Zhang XL, Shi J, Zhao LY, Sun LL, Wang J, Wang GB, et al. Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. Am J Psychiatry. 2011;168(6):610–6.
33. Rapeli P, Fabritius C, Kalska H, Alho H. Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates. BMC Clin Pharmacol. 2011;11:13.
34. Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 2002;67(1):41–51.
35. Rapeli P, Fabritius C, Alho H, Salaspuro M, Wahlbeck K, Kalska H. Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: a naturalistic comparison of cognitive performance relative to healthy controls. BMC Clin Pharmacol. 2007;7:5.
36. Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. Addiction. 2000;95(5):687–95.
37. Prosser J, Cohen LJ, Steinfeld M, Eisenberg D, London ED, Galynker II. Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. Drug Alcohol Depend. 2006;84(3):240–7.
38. Specka M, Finkbeiner T, Lodemann E, Leifert K, Kluwig J, Gastpar M. Cognitive-motor performance of methadone-maintained patients. Eur Addict Res. 2000;6(1):8–19.
39. Meade CS, Bevilacqua LA, Moore ED, Griffin ML, Gardin JG, 2nd, Potter JS, et al. Concurrent substance abuse is associated with sexual risk

behavior among adults seeking treatment for prescription opioid dependence. Am J Addict. 2014;23 (1):27–33.
40. Meade CS, McDonald LJ, Weiss RD. HIV risk behavior in opioid dependent adults seeking detoxification treatment: an exploratory comparison of heroin and oxycodone users. Am J Addict. 2009;18 (4):289–93.
41. Roux P, Fugon L, Jones JD, Comer SD. Hepatitis C infection in non-treatment-seeking heroin users: the burden of cocaine injection. Am J Addict. 2013;22 (6):613–8.
42. Loeber S, Nakovics H, Kniest A, Kiefer F, Mann K, Croissant B. Factors affecting cognitive function of opiate-dependent patients. Drug Alcohol Depend. 2012;120(1–3):81–7.
43. Clark M, DiBenedetti D, Perez V. Cognitive dysfunction and work productivity in major depressive disorder. Expert Rev Pharmacoecon Outcomes Res. 2016;16(4):455–63.
44. Association AP. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
45. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull. 2013;139(1):81–132.
46. Nitschke JB, Heller W, Etienne MA, Miller GA. Prefrontal cortex activity differentiates processes affecting memory in depression. Biol Psychol. 2004;67(1–2):125–43.
47. Kornreich C, Foisy ML, Philippot P, Dan B, Tecco J, Noel X, et al. Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. Psychiatry Res. 2003;119(3):251–60.
48. Aguilar de Arcos F, Verdejo-Garcia A, Peralta-Ramirez MI, Sanchez-Barrera M, Perez-Garcia M. Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. Drug Alcohol Depend. 2005;78(2):159–67.
49. Gerra G, Ceresini S, Esposito A, Zaimovic A, Moi G, Bussandri M, et al. Neuroendocrine and behavioural responses to opioid receptor-antagonist during heroin detoxification: relationship with personality traits. Int Clin Psychopharmacol. 2003;18 (5):261–9.
50. Aguilar de Arcos F, Verdejo-Garcia A, Ceverino A, Montanez-Pareja M, Lopez-Juarez E, Sanchez-Barrera M, et al. Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. Psychopharmacology (Berl). 2008;198(2):159–66.
51. Wang X, Li B, Zhou X, Liao Y, Tang J, Liu T, et al. Changes in brain gray matter in abstinent heroin addicts. Drug Alcohol Depend. 2012;126(3):304–8.
52. Yuan Y, Zhu Z, Shi J, Zou Z, Yuan F, Liu Y, et al. Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals. Brain Cogn. 2009;71 (3):223–8.
53. Liu H, Hao Y, Kaneko Y, Ouyang X, Zhang Y, Xu L, et al. Frontal and cingulate gray matter volume reduction in heroin dependence: optimized voxel-based morphometry. Psychiatry Clin Neurosci. 2009;63(4):563–8.
54. Lin WC, Chou KH, Chen CC, Huang CC, Chen HL, Lu CH, et al. White matter abnormalities correlating with memory and depression in heroin users under methadone maintenance treatment. PLoS ONE. 2012;7(4):e33809.
55. Wang Y, Li W, Li Q, Yang W, Zhu J, Wang W. White matter impairment in heroin addicts undergoing methadone maintenance treatment and prolonged abstinence: a preliminary DTI study. Neurosci Lett. 2011;494(1):49–53.
56. Li W, Zhu J, Li Q, Ye J, Chen J, Liu J, et al. Brain white matter integrity in heroin addicts during methadone maintenance treatment is related to relapse propensity. Brain Behav. 2016;6(2):e00436.
57. Li W, Li Q, Zhu J, Qin Y, Zheng Y, Chang H, et al. White matter impairment in chronic heroin dependence: a quantitative DTI study. Brain Res. 2013;1531:58–64.
58. Reid AG, Daglish MR, Kempton MJ, Williams TM, Watson B, Nutt DJ, et al. Reduced thalamic grey matter volume in opioid dependence is influenced by degree of alcohol use: a voxel-based morphometry study. J Psychopharmacol. 2008;22(1):7–10.
59. Amass L, Nardin R, Mendelson JH, Teoh SK, Woods BT. Quantitative magnetic resonance imaging in heroin- and cocaine-dependent men: a preliminary study. Psychiatry Res. 1992;45(1): 15–23.
60. Rose JS, Branchey M, Buydens-Branchey L, Stapleton JM, Chasten K, Werrell A, et al. Cerebral perfusion in early and late opiate withdrawal: a technetium-99 m-HMPAO SPECT study. Psychiatry Res. 1996;67(1):39–47.
61. Li M, Tian J, Zhang R, Qiu Y, Wen X, Ma X, et al. Abnormal cortical thickness in heroin-dependent individuals. Neuroimage. 2014;88:295–307.
62. Hutton C, Draganski B, Ashburner J, Weiskopf N. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. Neuroimage. 2009;48(2):371–80.
63. Clarkson MJ, Cardoso MJ, Ridgway GR, Modat M, Leung KK, Rohrer JD, et al. A comparison of voxel and surface based cortical thickness estimation methods. Neuroimage. 2011;57(3):856–65.
64. Bora E, Yucel M, Fornito A, Pantelis C, Harrison BJ, Cocchi L, et al. White matter microstructure in opiate addiction. Addict Biol. 2012;17(1):141–8.

65. Qiu Y, Jiang G, Su H, Lv X, Zhang X, Tian J, et al. Progressive white matter microstructure damage in male chronic heroin dependent individuals: a DTI and TBSS study. PLoS ONE. 2013;8(5):e63212.
66. Liu H, Li L, Hao Y, Cao D, Xu L, Rohrbaugh R, et al. Disrupted white matter integrity in heroin dependence: a controlled study utilizing diffusion tensor imaging. Am J Drug Alcohol Abuse. 2008;34(5):562–75.
67. Copersino ML, Price JS, Frost KH, Vitaliano GD, Frederick BD, Lukas SE, et al. Default Mode Network Functional Reorganization During Early Abstinence in Polysubstance-Using Emerging Adults Treated for Opioid Dependence. J Neuropsychiatry Clin Neurosci. 2016:appineuropsych 15090240.
68. Ma X, Qiu Y, Tian J, Wang J, Li S, Zhan W, et al. Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. PLoS ONE. 2015;10(4):e0120861.
69. Costardi JV, Nampo RA, Silva GL, Ribeiro MA, Stella HJ, Stella MB, et al. A review on alcohol: from the central action mechanism to chemical dependency. Rev Assoc Med Bras (1992). 2015;61 (4):381–7.
70. Oscar-Berman M, Valmas MM, Sawyer KS, Ruiz SM, Luhar RB, Gravitz ZR. Profiles of impaired, spared, and recovered neuropsychologic processes in alcoholism. Handb Clin Neurol. 2014;125:183–210.
71. Le Berre AP, Fama R, Sullivan EV. Executive Functions, Memory, and Social Cognitive Deficits and Recovery in Chronic Alcoholism: A Critical Review to Inform Future Research. Alcohol Clin Exp Res. 2017;41(8):1432–43.
72. Fama R, Pfefferbaum A, Sullivan EV. Perceptual learning in detoxified alcoholic men: contributions from explicit memory, executive function, and age. Alcohol Clin Exp Res. 2004;28(11):1657–65.
73. Sullivan EV, Harris RA, Pfefferbaum A. Alcohol's effects on brain and behavior. Alcohol Res Health. 2010;33(1–2):127–43.
74. Fein G, Bachman L, Fisher S, Davenport L. Cognitive impairments in abstinent alcoholics. West J Med. 1990;152(5):531–7.
75. Fein G, Torres J, Price LJ, Di Sclafani V. Cognitive performance in long-term abstinent alcoholic individuals. Alcohol Clin Exp Res. 2006;30(9):1538–44.
76. Loeber S, Duka T, Welzel Marquez H, Nakovics H, Heinz A, Mann K, et al. Effects of repeated withdrawal from alcohol on recovery of cognitive impairment under abstinence and rate of relapse. Alcohol Alcohol. 2010;45(6):541–7.
77. Rosenbloom MJ, Pfefferbaum A, Sullivan EV. Recovery of short-term memory and psychomotor speed but not postural stability with long-term sobriety in alcoholic women. Neuropsychology. 2004;18(3):589–97.
78. Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F. Changes in the episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-month period. Alcohol Clin Exp Res. 2009;33(3):490–8.
79. Munro CA, Saxton J, Butters MA. The neuropsychological consequences of abstinence among older alcoholics: a cross-sectional study. Alcohol Clin Exp Res. 2000;24(10):1510–6.
80. Nowakowska-Domagala K, Jablkowska-Gorecka K, Mokros L, Koprowicz J, Pietras T. Differences in the verbal fluency, working memory and executive functions in alcoholics: Short-term vs. long-term abstainers. Psychiatry Res. 2017;249:1–8.
81. Ando B, Must A, Kurgyis E, Szkaliczki A, Drotos G, Rozsa S, et al. Personality traits and coping compensate for disadvantageous decision-making in long-term alcohol abstinence. Alcohol Alcohol. 2012;47(1):18–24.
82. Fein G, Klein L, Finn P. Impairment on a simulated gambling task in long-term abstinent alcoholics. Alcohol Clin Exp Res. 2004;28(10):1487–91.
83. Cheng C, Huang CL, Tsai CJ, Chou PH, Lin CC, Chang CK. Alcohol-Related Dementia: A Systemic Review of Epidemiological Studies. Psychosomatics. 2017;58(4):331–42.
84. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S4–9.
85. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry. 2003;74(9):1206–9.
86. Harper C. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J Neuropathol Exp Neurol. 1998;57(2):101–10.
87. Zahr NM, Kaufman KL, Harper CG. Clinical and pathological features of alcohol-related brain damage. Nat Rev Neurol. 2011;7(5):284–94.
88. Penick EC, Powell BJ, Liskow BI, Jackson JO, Nickel EJ. The stability of coexisting psychiatric syndromes in alcoholic men after one year. J Stud Alcohol. 1988;49(5):395–405.
89. Conner KR, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol use disorders. J Subst Abuse Treat. 2009;37(2):127–37.
90. Degenhardt L, Hall W, Lynskey M. Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. Addiction. 2001;96(11):1603–14.
91. Hunt SA, Kay-Lambkin FJ, Baker AL, Michie PT. Systematic review of neurocognition in people with co-occurring alcohol misuse and depression. J Affect Disord. 2015;179:51–64.

92. Rosenbloom MJ, Pfefferbaum A. Magnetic resonance imaging of the living brain: evidence for brain degeneration among alcoholics and recovery with abstinence. Alcohol Res Health. 2008;31 (4):362–76.
93. Gierski F, Hubsch B, Stefaniak N, Benzerouk F, Cuervo-Lombard C, Bera-Potelle C, et al. Executive functions in adult offspring of alcohol-dependent probands: toward a cognitive endophenotype? Alcohol Clin Exp Res. 2013;37(Suppl 1):E356–63.
94. Lisdahl KM, Gilbart ER, Wright NE, Shollenbarger S. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. Front Psychiatry. 2013;4:53.
95. Jacobus J, Squeglia LM, Bava S, Tapert SF. White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. Psychiatry Res. 2013;214 (3):374–81.
96. Pfefferbaum A, Kwon D, Brumback T, Thompson WK, Cummins K, Tapert SF, et al. Altered Brain Developmental Trajectories in Adolescents After Initiating Drinking. Am J Psychiatry. 2018;175(4):370–80.
97. Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. Addict Biol. 2013;18(1):121–33.
98. Shokri-Kojori E, Tomasi D, Wiers CE, Wang GJ, Volkow ND. Linking brain connectivity and behavior after acute and chronic alcohol exposure. Mol Psychiatry. 2017;22(8):1079.
99. Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. J Stud Alcohol Drugs. 2012;73(5):749–60.
100. Squeglia LM, Cservenka A. Adolescence and Drug Use Vulnerability: Findings from Neuroimaging. Curr Opin Behav Sci. 2017;13:164–70.
101. Pomara C, Cassano T, D'Errico S, Bello S, Romano AD, Riezzo I, et al. Data available on the extent of cocaine use and dependence: biochemistry, pharmacologic effects and global burden of disease of cocaine abusers. Curr Med Chem. 2012;19(33):5647–57.
102. Bolla KI, Cadet JL. Cocaine. In: Gorp AKWv, ed. Neuropsychology and Substance Use. New York, New York: Taylor and Francis; 2007.
103. Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Cognitive enhancement as a treatment for drug addictions. Neuropharmacology. 2013;64:452–63.
104. Potvin S, Stavro K, Rizkallah E, Pelletier J. Cocaine and cognition: a systematic quantitative review. J Addict Med. 2014;8(5):368–76.
105. Winhusen T, Lewis D, Adinoff B, Brigham G, Kropp F, Donovan DM, et al. Impulsivity is associated with treatment non-completion in cocaine- and methamphetamine-dependent patients but differs in nature as a function of stimulant-dependence diagnosis. J Subst Abuse Treat. 2013;44(5):541–7.
106. Li CS, Milivojevic V, Kemp K, Hong K, Sinha R. Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. Drug Alcohol Depend. 2006;85(3):205–12.
107. Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend. 2002;66(3):265–73.
108. Cadet JL, Bisagno V. Neuropsychological Consequences of Chronic Drug Use: Relevance to Treatment Approaches. Front Psychiatry. 2015;6:189.
109. Fernandez-Serrano MJ, Perales JC, Moreno-Lopez L, Perez-Garcia M, Verdejo-Garcia A. Neuropsychological profiling of impulsivity and compulsivity in cocaine dependent individuals. Psychopharmacology. 2012;219(2):673–83.
110. Hart CL, Marvin CB, Silver R, Smith EE. Is cognitive functioning impaired in methamphetamine users? A critical review. Neuropsychopharmacology. 2012;37(3):586–608.
111. Cherner M, Suarez P, Casey C, Deiss R, Letendre S, Marcotte T, et al. Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. Drug Alcohol Depend. 2010;106(2–3):154–63.
112. Dean AC, Hellemann G, Sugar CA, London ED. Educational attainment is not a good proxy for cognitive function in methamphetamine dependence. Drug Alcohol Depend. 2012;123(1–3):249–54.
113. Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J Neuropsychiatry Clin Neurosci. 2003;15(2):215–20.
114. Johanson CE, Frey KA, Lundahl LH, Keenan P, Lockhart N, Roll J, et al. Cognitive function and nigrostriatal markers in abstinent methamphetamine abusers. Psychopharmacology. 2006;185(3):327–38.
115. Wang GJ, Volkow ND, Chang L, Miller E, Sedler M, Hitzemann R, et al. Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. Am J Psychiatry. 2004;161 (2):242–8.
116. Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry. 2001;158(12): 2015–21.
117. Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry. 2001;158(3):377–82.

118. Iudicello JE, Woods SP, Vigil O, Scott JC, Cherner M, Heaton RK, et al. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. J Clin Exp Neuropsychol. 2010;32(7):704–18.
119. Parrott AC. Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol. 2013;28(4):289–307.
120. Wagner D, Becker B, Koester P, Gouzoulis-Mayfrank E, Daumann J. A prospective study of learning, memory, and executive function in new MDMA users. Addiction. 2013;108(1):136–45.
121. Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope HG Jr. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. Addiction. 2011;106 (4):777–86.
122. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006;67(2):247–57.
123. Poling J, Kosten TR, Sofuoglu M. Treatment outcome predictors for cocaine dependence. Am J Drug Alcohol Abuse. 2007;33(2):191–206.
124. Newton TF, Kalechstein AD, Duran S, Vansluis N, Ling W. Methamphetamine abstinence syndrome: preliminary findings. Am J Addict. 2004;13 (3):248–55.
125. Mahoney JJ, 3rd, Kalechstein AD, De La Garza R, 2nd, Newton TF. Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. Am J Addict. 2008;17(2):83–98.
126. Mahoney JJ, 3rd, Hawkins RY, De La Garza R, 2nd, Kalechstein AD, Newton TF. Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants. Gend Med. 2010;7(5):414–21.
127. Mahoney JJ, 3rd, Thompson-Lake DG, Cooper K, Verrico CD, Newton TF, De La Garza R, 2nd. A comparison of impulsivity, depressive symptoms, lifetime stress and sensation seeking in healthy controls versus participants with cocaine or methamphetamine use disorders. J Psychopharmacol. 2015;29(1):50–6.
128. McKay JR, Van Horn D, Rennert L, Drapkin M, Ivey M, Koppenhaver J. Factors in sustained recovery from cocaine dependence. J Subst Abuse Treat. 2013;45(2):163–72.
129. Glasner-Edwards S, Marinelli-Casey P, Hillhouse M, Ang A, Mooney LJ, Rawson R, et al. Depression among methamphetamine users: association with outcomes from the Methamphetamine Treatment Project at 3-year follow-up. J Nerv Ment Dis. 2009;197(4):225–31.
130. Parvaz MA, Moeller SJ, d'Oleire Uquillas F, Pflumm A, Maloney T, Alia-Klein N, et al. Prefrontal gray matter volume recovery in treatment-seeking cocaine-addicted individuals: a longitudinal study. Addict Biol. 2017;22(5):1391–401.
131. Hall MG, Alhassoon OM, Stern MJ, Wollman SC, Kimmel CL, Perez-Figueroa A, et al. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: a neuroimaging meta-analysis. Am J Drug Alcohol Abuse. 2015;41(4):290–9.
132. Moreno-Lopez L, Albein-Urios N, Martinez-Gonzalez JM, Soriano-Mas C, Verdejo-Garcia A. Prefrontal Gray Matter and Motivation for Treatment in Cocaine-Dependent Individuals with and without Personality Disorders. Front Psychiatry. 2014;5:52.
133. Crunelle CL, Kaag AM, van Wingen G, van den Munkhof HE, Homberg JR, Reneman L, et al. Reduced frontal brain volume in non-treatment-seeking cocaine-dependent individuals: exploring the role of impulsivity, depression, and smoking. Front Hum Neurosci. 2014;8:7.
134. van Son D, Wiers RW, Catena A, Perez-Garcia M, Verdejo-Garcia A. White matter disruptions in male cocaine polysubstance users: Associations with severity of drug use and duration of abstinence. Drug Alcohol Depend. 2016;168:247–54.
135. Ma L, Steinberg JL, Wang Q, Schmitz JM, Boone EL, Narayana PA, et al. A preliminary longitudinal study of white matter alteration in cocaine use disorder subjects. Drug Alcohol Depend. 2017;173:39–46.
136. Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012;335(6068):601–4.
137. de Win MM, Jager G, Booij J, Reneman L, Schilt T, Lavini C, et al. Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. Brain. 2008;131(Pt 11):2936–45.
138. Ipser JC, Uhlmann A, Taylor P, Harvey BH, Wilson D, Stein DJ. Distinct intrinsic functional brain network abnormalities in methamphetamine-dependent patients with and without a history of psychosis. Addict Biol. 2018;23(1):347–58.
139. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5.
140. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346(6284):561–4.
141. Oleson EB, Cheer JF. A brain on cannabinoids: the role of dopamine release in reward seeking. Cold Spring Harb Perspect Med. 2012;2(8).

142. Solowij N, Stephens R, Roffman RA, Babor T. Does marijuana use cause long-term cognitive deficits? JAMA. 2002;287(20):2653–4; author reply 4.
143. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA. 2002;287(9):1123–31.
144. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. Neurology. 2002;59(9):1337–43.
145. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A. 2012;109(40):E2657–64.
146. Pope HG Jr, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. Drug Alcohol Depend. 1995;38(1):25–34.
147. Pope HG Jr, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA. 1996;275(7):521–7.
148. Solowij N. Cannabis and cognitive functioning. New York: Cambridge University Press; 1998.
149. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. 2016;73(3):292–7.
150. Pope HG Jr, Gruber AJ, Yurgelun-Todd D. Residual neuropsychologic effects of cannabis. Curr Psychiatry Rep. 2001;3(6):507–12.
151. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry. 2001;58(10):909–15.
152. Gonzalez R, Pacheco-Colon I, Duperrouzel JC, Hawes SW. Does Cannabis Use Cause Declines in Neuropsychological Functioning? A Review of Longitudinal Studies. J Int Neuropsychol Soc. 2017;23(9–10):893–902.
153. Daly M. Personality may explain the association between cannabis use and neuropsychological impairment. Proc Natl Acad Sci U S A. 2013;110(11):E979.
154. Rogeberg O. Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. Proc Natl Acad Sci U S A. 2013;110(11):4251–4.
155. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med. 2014;44(4):797–810.
156. Hser YI, Mooney LJ, Huang D, Zhu Y, Tomko RL, McClure E, et al. Reductions in cannabis use are associated with improvements in anxiety, depression, and sleep quality, but not quality of life. J Subst Abuse Treat. 2017;81:53–8.
157. Battistella G, Fornari E, Annoni JM, Chtioui H, Dao K, Fabritius M, et al. Long-term effects of cannabis on brain structure. Neuropsychopharmacology. 2014;39(9):2041–8.
158. Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Pazos A, Gutierrez A, et al. Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use. Brain Res. 2010;1317:297–304.
159. Smith MJ, Cobia DJ, Wang L, Alpert KI, Cronenwett WJ, Goldman MB, et al. Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. Schizophr Bull. 2014;40(2):287–99.
160. Yucel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, et al. Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry. 2008;65(6):694–701.
161. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. Neuroimage. 2012;59(4):3845–51.
162. Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, et al. Medial temporal structures and memory functions in adolescents with heavy cannabis use. J Psychiatr Res. 2011;45(8):1055–66.
163. Shollenbarger SG, Price J, Wieser J, Lisdahl K. Impact of cannabis use on prefrontal and parietal cortex gyrification and surface area in adolescents and emerging adults. Dev Cogn Neurosci. 2015;16:46–53.
164. Shollenbarger SG, Price J, Wieser J, Lisdahl K. Poorer frontolimbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults. Neuroimage Clin. 2015;8:117–25.
165. Pujol J, Blanco-Hinojo L, Batalla A, Lopez-Sola M, Harrison BJ, Soriano-Mas C, et al. Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. J Psychiatr Res. 2014;51:68–78.
166. Filbey FM, Dunlop J. Differential reward network functional connectivity in cannabis dependent and non-dependent users. Drug Alcohol Depend. 2014;140:101–11.
167. Cousijn J, Vingerhoets WA, Koenders L, de Haan L, van den Brink W, Wiers RW, et al. Relationship between working-memory network function and substance use: a 3-year longitudinal fMRI study in heavy cannabis users and controls. Addict Biol. 2014;19(2):282–93.
168. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 2014;144:12–41.

169. Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL. Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Delta(9)-THC: mechanism underlying greater toxicity? Life Sci. 2014;97(1):45–54.
170. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol. 2012;8(1):62–4.
171. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. Psychopharmacology. 2013;228(4):525–40.
172. Kronstrand R, Roman M, Andersson M, Eklund A. Toxicological findings of synthetic cannabinoids in recreational users. J Anal Toxicol. 2013;37(8):534–41.
173. Cohen K, Kapitany-Foveny M, Mama Y, Arieli M, Rosca P, Demetrovics Z, et al. The effects of synthetic cannabinoids on executive function. Psychopharmacology. 2017;234(7):1121–34.
174. Schneider M, Schomig E, Leweke FM. Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. Addict Biol. 2008;13(3–4):345–57.
175. Fattore L, Fratta W. Beyond THC: The New Generation of Cannabinoid Designer Drugs. Front Behav Neurosci. 2011;5:60.
176. Glue P, Al-Shaqsi S, Hancock D, Gale C, Strong B, Schep L. Hospitalisation associated with use of the synthetic cannabinoid K2. N Z Med J. 2013;126 (1377):18–23.
177. Fellner A, Benninger F, Djaldetti R. Synthetic cannabinoids revealing adrenoleukodystrophy. J Clin Neurosci. 2016;24:155–6.
178. Bernson-Leung ME, Leung LY, Kumar S. Synthetic cannabis and acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014;23(5):1239–41.
179. Takematsu M, Hoffman RS, Nelson LS, Schechter JM, Moran JH, Wiener SW. A case of acute cerebral ischemia following inhalation of a synthetic cannabinoid. Clin Toxicol (Phila). 2014;52(9):973–5.
180. Olsen RW, Betz H. GABA and glycine. In: Siegel GJ, Albers RW, Brady S, Price DD, editors. Basic Neurochemistry: Molecular. Cellular and Medical Aspects: Elsevier; 2006.
181. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry. 2015;72(2):136–42.
182. Brandt J, Leong C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. 2017;17(4):493–507.
183. Buffett-Jerrott SE, Stewart SH. Cognitive and sedative effects of benzodiazepine use. Curr Pharm Des. 2002;8(1):45–58.
184. Vidailhet P, Danion JM, Kauffmann-Muller F, Grange D, Giersch A, van der Linden M, et al. Lorazepam and diazepam effects on memory acquisition in priming tasks. Psychopharmacology. 1994;115(3):397–406.
185. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. Drug Saf. 1999;21 (2):101–22.
186. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs. 2004;18(1):37–48.
187. Deckersbach T, Moshier SJ, Tuschen-Caffier B, Otto MW. Memory dysfunction in panic disorder: an investigation of the role of chronic benzodiazepine use. Depress Anxiety. 2011;28(11):999–1007.
188. Lagnaoui R, Begaud B, Moore N, Chaslerie A, Fourrier A, Letenneur L, et al. Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol. 2002;55(3):314–8.
189. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ. 2014;349:g5205.
190. Shash D, Kurth T, Bertrand M, Dufouil C, Barberger-Gateau P, Berr C, et al. Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study. Alzheimers Dement. 2016;12(5):604–13.
191. Gray SL, Dublin S, Yu O, Walker R, Anderson M, Hubbard RA, et al. Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. BMJ. 2016;352:i90.
192. Busto UE, Bremner KE, Knight K, terBrugge K, Sellers EM. Long-term benzodiazepine therapy does not result in brain abnormalities. J Clin Psychopharmacol. 2000;20(1):2–6.
193. Huhtaniska S, Jaaskelainen E, Heikka T, Moilanen JS, Lehtiniemi H, Tohka J, et al. Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study. Psychiatry Res. 2017;266:73–82.
194. Johnstad PG. Powerful substances in tiny amounts: An interview study of psychedelic microdosing. Nordic Studies on Alcohol and Drugs. 2018;35(1): 39–51.
195. Bouso JC, Palhano-Fontes F, Rodriguez-Fornells A, Ribeiro S, Sanches R, Crippa JA, et al. Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. Eur Neuropsychopharmacol. 2015;25(4):483–92.
196. Espiard ML, Lecardeur L, Abadie P, Halbecq I, Dollfus S. Hallucinogen persisting perception disorder after psilocybin consumption: a case study. Eur Psychiatry. 2005;20(5–6):458–60.
197. Halberstadt AL, Geyer MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. Neuropharmacology. 2011;61(3): 364–81.

198. Aghajanian GK, Marek GJ. Serotonin and hallucinogens. Neuropsychopharmacology. 1999;21(2 Suppl):16S–23S.
199. Family N, Vinson D, Vigliocco G, Kaelen M, Bolstridge M, Nutt D. Semantic activation in LSD: evidence from picture naming. Language, Cognition, and Neuroscience. 2016;31(10):1320–7.
200. Carter OL, Burr DC, Pettigrew JD, Wallis GM, Hasler F, Vollenweider FX. Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. J Cogn Neurosci. 2005;17(10):1497–508.
201. Halpern JH, Pope HG Jr. Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend. 1999;53(3):247–56.
202. Halpern JH, Sherwood AR, Hudson JI, Yurgelun-Todd D, Pope HG Jr. Psychological and cognitive effects of long-term peyote use among Native Americans. Biol Psychiatry. 2005;58 (8):624–31.
203. Dolder PC, Schmid Y, Muller F, Borgwardt S, Liechti ME. LSD Acutely Impairs Fear Recognition and Enhances Emotional Empathy and Sociality. Neuropsychopharmacology. 2016;41(11):2638–46.
204. Fadiman J. The psychedelic explorer's guide: Safe, therapeutic, and sacred journeys. Toronto, Canada: Park Street Press; 2011.
205. Solon O. Would you take LSD to give you a boost at work? WIRED takes a trip inside the world of microdosing. Wired 2016.
206. Waldman A. A really good day: How microdosing made a mega difference in my mood, my marriage, and my life. New York, New York: Knopf; 2017.
207. Williams A. How LSD saved one woman's marriage. New York: New York Times. New York; 2017.
208. Andrews-Hanna JR. The brain's default network and its adaptive role in internal mentation. Neuroscientist. 2012;18(3):251–70.
209. Spengos K, Schwartz A, Hennerici M. Multifocal cerebral demyelination after magic mushroom abuse. J Neurol. 2000;247(3):224–5.
210. Legriel S, Bruneel F, Spreux-Varoquaux O, Birenbaum A, Chadenat ML, Mignon F, et al. Lysergic acid amide-induced posterior reversible encephalopathy syndrome with status epilepticus. Neurocrit Care. 2008;9(2):247–52.
211. Ambermoon P, Carter A, Hall W, Dissanayaka N, O'Sullivan J. Compulsive use of dopamine replacement therapy: a model for stimulant drug addiction? Addiction. 2012;107(2):241–7.
212. Spigset O, von Scheele C. Levodopa dependence and abuse in Parkinson's disease. Pharmacotherapy. 1997;17(5):1027–30.
213. Pezzella FR, Colosimo C, Vanacore N, Di Rezze S, Chianese M, Fabbrini G, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Mov Disord. 2005;20(1):77–81.
214. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol. 2003;2(10):595–604.
215. Ferrazzoli D, Carter A, Ustun FS, Palamara G, Ortelli P, Maestri R, et al. Dopamine Replacement Therapy, Learning and Reward Prediction in Parkinson's Disease: Implications for Rehabilitation. Front Behav Neurosci. 2016;10:121.
216. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589–95.
217. Maier F, Merkl J, Ellereit AL, Lewis CJ, Eggers C, Pedrosa DJ, et al. Hypomania and mania related to dopamine replacement therapy in Parkinson's disease. Parkinsonism Relat Disord. 2014;20(4):421–7.
218. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28(6):491–6.
219. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6 (1):108–13.
220. Badgaiyan RD. A Novel Perspective on Dopaminergic Processing of Human Addiction. J Alcohol Drug Depend. 2013;1(1).
221. Kapil V, Green JL, Le Lait MC, Wood DM, Dargan PI. Misuse of the gamma-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. Br J Clin Pharmacol. 2014;78(1):190–1.
222. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother. 2016;50(3):229–33.
223. Salinsky MC, Binder LM, Oken BS, Storzbach D, Aron CR, Dodrill CB. Effects of gabapentin and carbamazepine on the EEG and cognition in healthy volunteers. Epilepsia. 2002;43(5):482–90.
224. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Nichols ME, et al. Differential cognitive effects of carbamazepine and gabapentin. Epilepsia. 1999;40(9):1279–85.
225. Martin R, Kuzniecky R, Ho S, Hetherington H, Pan J, Sinclair K, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. Neurology. 1999;52(2):321–7.
226. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. Biol Psychiatry. 2008;64(11):998–1004.
227. Streeter CC, Terhune DB, Whitfield TH, Gruber S, Sarid-Segal O, Silveri MM, et al. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. Neuropsychopharmacology. 2008;33(4):827–36.
228. Turner TH, LaRowe S, Horner MD, Herron J, Malcolm R. Measures of cognitive functioning as

predictors of treatment outcome for cocaine dependence. J Subst Abuse Treat. 2009;37(4):328–34.
229. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry. 1998;55(11):967–72.
230. Arias F, Arnsten JH, Cunningham CO, Coulehan K, Batchelder A, Brisbane M, et al. Neurocognitive, psychiatric, and substance use characteristics in opioid dependent adults. Addict Behav. 2016;60:137–43.
231. Bolla KI, Funderburk FR, Cadet JL. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. Neurology. 2000;54(12):2285–92.
232. Abi-Saab D, Beauvais J, Mehm J, Brody M, Gottschalk C, Kosten TR. The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. Am J Addict. 2005;14(2):166–78.
233. Robinson JE, Heaton RK, O'Malley SS. Neuropsychological functioning in cocaine abusers with and without alcohol dependence. J Int Neuropsychol Soc. 1999;5(1):10–9.
234. Easton C, Bauer LO. Neuropsychological differences between alcohol-dependent and cocaine-dependent patients with or without problematic drinking. Psychiatry Res. 1997;71(2):97–103.
235. Lawton-Craddock A, Nixon SJ, Tivis R. Cognitive efficiency in stimulant abusers with and without alcohol dependence. Alcohol Clin Exp Res. 2003;27(3):457–64.
236. Diaz-Asper CM, Schretlen DJ, Pearlson GD. How well does IQ predict neuropsychological test performance in normal adults? J Int Neuropsychol Soc. 2004;10(1):82–90.
237. Tremont G, Hoffman RG, Scott JG, Adams RL. Effect of intellectual level on neuropsychological test performance: A response to Dodrill (1997). Clinical Neuropsychologist. 1998;12:560–7.
238. Mahoney JJ, Kalechstein AD, De Marco AP, Newton TF, De La Garza R. The relationship between premorbid IQ and neurocognitive functioning in individuals with cocaine use disorders. Neuropsychology. 2017;31(3):311–8.
239. Roldan-Tapia L, Garcia J, Canovas R, Leon I. Cognitive reserve, age, and their relation to attentional and executive functions. Appl Neuropsychol Adult. 2012;19(1):2–8.
240. Satz P, Cole MA, Hardy DJ, Rassovsky Y. Brain and cognitive reserve: mediator(s) and construct validity, a critique. J Clin Exp Neuropsychol. 2011;33(1):121–30.
241. Satz P, Morgenstern H, Miller EN, Selnes OA, McArthur JC, Cohen BA, et al. Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). J Acquir Immune Defic Syndr. 1993;6(5):503–11.
242. Stern Y. Elaborating a hypothetical concept: comments on the special series on cognitive reserve. J Int Neuropsychol Soc. 2011;17(4):639–42.
243. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002;8(3):448–60.
244. Neafsey EJ, Collins MA. Moderate alcohol consumption and cognitive risk. Neuropsychiatr Dis Treat. 2011;7:465–84.
245. Berry J, van Gorp WG, Herzberg DS, Hinkin C, Boone K, Steinman L, et al. Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence. Drug Alcohol Depend. 1993;32(3):231–7.
246. Woicik PA, Moeller SJ, Alia-Klein N, Maloney T, Lukasik TM, Yeliosof O, et al. The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology. 2009;34(5):1112–22.
247. Bolla KI, Rothman R, Cadet JL. Dose-related neurobehavioral effects of chronic cocaine use. J Neuropsychiatry Clin Neurosci. 1999;11(3):361–9.
248. Fernandez-Serrano MJ, Perez-Garcia M, Schmidt Rio-Valle J, Verdejo-Garcia A. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. J Psychopharmacol. 2010;24(9):1317–32.
249. Moreno-Lopez L, Stamatakis EA, Fernandez-Serrano MJ, Gomez-Rio M, Rodriguez-Fernandez A, Perez-Garcia M, et al. Neural correlates of the severity of cocaine, heroin, alcohol, MDMA and cannabis use in polysubstance abusers: a resting-PET brain metabolism study. PLoS ONE. 2012;7(6):e39830.
250. Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, et al. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. Brain Res. 2007;1171:83–92.
251. Barros-Loscertales A, Bustamante JC, Ventura-Campos N, Llopis JJ, Parcet MA, Avila C. Lower activation in the right frontoparietal network during a counting Stroop task in a cocaine-dependent group. Psychiatry Res. 2011;194(2):111–8.
252. Bustamante JC, Barros-Loscertales A, Ventura-Campos N, Sanjuan A, Llopis JJ, Parcet MA, et al. Right parietal hypoactivation in a cocaine-dependent group during a verbal working memory task. Brain Res. 2011;1375:111–9.
253. Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, et al. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage. 2003;19(3):1085–94.
254. Pietrzak RH, Russo AR, Ling Q, Southwick SM. Suicidal ideation in treatment-seeking Veterans of Operations Enduring Freedom and Iraqi Freedom:

the role of coping strategies, resilience, and social support. J Psychiatr Res. 2011;45(6):720–6.
255. Morgan CA 3rd, Doran A, Steffian G, Hazlett G, Southwick SM. Stress-induced deficits in working memory and visuo-constructive abilities in Special Operations soldiers. Biol Psychiatry. 2006;60 (7):722–9.
256. Back S, Dansky BS, Coffey SF, Saladin ME, Sonne S, Brady KT. Cocaine dependence with and without post-traumatic stress disorder: a comparison of substance use, trauma history and psychiatric comorbidity. Am J Addict. 2000;9(1):51–62.
257. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry. 2005;162 (8):1483–93.
258. McMahon RC. Personality, stress, and social support in cocaine relapse prediction. J Subst Abuse Treat. 2001;21(2):77–87.
259. Sinha R. How does stress increase risk of drug abuse and relapse? Psychopharmacology. 2001;158 (4):343–59.
260. Waldrop AE, Back SE, Verduin ML, Brady KT. Triggers for cocaine and alcohol use in the presence and absence of posttraumatic stress disorder. Addict Behav. 2007;32(3):634–9.
261. Sinha R, Fuse T, Aubin LR, O'Malley SS. Psychological stress, drug-related cues and cocaine craving. Psychopharmacology. 2000;152(2):140–8.
262. Mahoney JJ, 3rd, Newton TF, Omar Y, Ross EL, De La Garza R, 2nd. The relationship between lifetime stress and addiction severity in cocaine-dependent participants. Eur Neuropsychopharmacol. 2013;23(5):351–7.
263. Wallace TL, Ballard TM, Pouzet B, Riedel WJ, Wettstein JG. Drug targets for cognitive enhancement in neuropsychiatric disorders. Pharmacol Biochem Behav. 2011;99(2):130–45.
264. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev. 2003;42(1):33–84.
265. Wise RA. Catecholamine theories of reward: a critical review. Brain Res. 1978;152(2):215–47.
266. Wise RA. Rewards wanted: Molecular mechanisms of motivation. Discov Med. 2004;4(22):180–6.
267. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci. 2004;5(6):483–94.
268. Kalechstein AD, De La Garza R, Newton T. Modafinil Administration Improves Working Memory in Methamphetamine-Dependent Individuals Who Demonstrate Baseline Impairment. American Journal on Addictions. 2010;*In Press*.
269. Kalechstein AD, Mahoney JJ, 3rd, Yoon JH, Bennett R, De la Garza R, 2nd. Modafinil, but not escitalopram, improves working memory and sustained attention in long-term, high-dose cocaine users. Neuropharmacology. 2013;64:472–8.
270. Sofuoglu M, Mooney M. Cholinergic functioning in stimulant addiction: implications for medications development. CNS Drugs. 2009;23(11):939–52.
271. Farlow M. A clinical overview of cholinesterase inhibitors in Alzheimer's disease. Int Psychogeriatr. 2002;14(Suppl 1):93–126.
272. Farlow MR. Do cholinesterase inhibitors slow progression of Alzheimer's disease? Int J Clin Pract Suppl. 2002;127:37–44.
273. Adinoff B, Devous MD Sr, Williams MJ, Best SE, Harris TS, Minhajuddin A, et al. Altered neural cholinergic receptor systems in cocaine-addicted subjects. Neuropsychopharmacology. 2010;35 (7):1485–99.
274. Sofuoglu M, Waters AJ, Poling J, Carroll KM. Galantamine improves sustained attention in chronic cocaine users. Exp Clin Psychopharmacol. 2011;19(1):11–9.
275. Mahoney JJ, 3rd, Kalechstein AD, Verrico CD, Arnoudse NM, Shapiro BA, De La Garza R, 2nd. Preliminary findings of the effects of rivastigmine, an acetylcholinesterase inhibitor, on working memory in cocaine-dependent volunteers. Prog Neuropsychopharmacol Biol Psychiatry. 2014;50:137–42.
276. Trojak B, Sauvaget A, Fecteau S, Lalanne L, Chauvet-Gelinier JC, Koch S, et al. Outcome of Non-Invasive Brain Stimulation in Substance Use Disorders: A Review of Randomized Sham-Controlled Clinical Trials. J Neuropsychiatry Clin Neurosci. 2017;29(2):105–18.
277. Jansen JM, Daams JG, Koeter MW, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013;37 (10 Pt 2):2472–80.
278. Coles AS, Kozak K, George TP. A review of brain stimulation methods to treat substance use disorders. Am J Addict. 2018;27(2):71–91.
279. Bellamoli E, Manganotti P, Schwartz RP, Rimondo C, Gomma M, Serpelloni G. rTMS in the treatment of drug addiction: an update about human studies. Behav Neurol. 2014;2014:815215.
280. Sousa AD. Repetitive Transcranial Magnetic Stimulation (rTMS) in the Management of Alcohol Dependence and other Substance Abuse Disorders - Emerging Data and Clinical Relevance. Basic Clin Neurosci. 2013;4(3):271–5.
281. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Ann N Y Acad Sci. 2014;1327:79–93.
282. Shen Y, Cao X, Tan T, Shan C, Wang Y, Pan J, et al. 10-Hz Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex Reduces Heroin Cue Craving in Long-Term Addicts. Biol Psychiatry. 2016;80(3): e13–4.
283. Mishra BR, Praharaj SK, Katshu MZ, Sarkar S, Nizamie SH. Comparison of anticraving efficacy of

right and left repetitive transcranial magnetic stimulation in alcohol dependence: a randomized double-blind study. J Neuropsychiatry Clin Neurosci. 2015;27(1):e54–9.
284. Herremans SC, Van Schuerbeek P, De Raedt R, Matthys F, Buyl R, De Mey J, et al. The Impact of Accelerated Right Prefrontal High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) on Cue-Reactivity: An fMRI Study on Craving in Recently Detoxified Alcohol-Dependent Patients. PLoS ONE. 2015;10(8):e0136182.
285. Kravitz AV, Tomasi D, LeBlanc KH, Baler R, Volkow ND, Bonci A, et al. Cortico-striatal circuits: Novel therapeutic targets for substance use disorders. Brain Res. 2015;1628(Pt A):186–98.
286. Prikryl R, Ustohal L, Kucerova HP, Kasparek T, Jarkovsky J, Hublova V, et al. Repetitive transcranial magnetic stimulation reduces cigarette consumption in schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry. 2014;49:30–5.
287. Protasio MI, da Silva JP, Arias-Carrion O, Nardi AE, Machado S, Cruz MS. Repetitive transcranial magnetic stimulation to treat substance use disorders and compulsive behavior. CNS Neurol Disord: Drug Targets. 2015;14(3):331–40.
288. Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev. 2010;34(4):559–74.
289. Knoch D, Gianotti LR, Pascual-Leone A, Treyer V, Regard M, Hohmann M, et al. Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. J Neurosci. 2006;26(24):6469–72.
290. Luber B, Lisanby SH. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage. 2014;85(Pt 3): 961–70.
291. Hardesty DE, Sackeim HA. Deep brain stimulation in movement and psychiatric disorders. Biol Psychiatry. 2007;61(7):831–5.
292. Zhou H, Xu J, Jiang J. Deep brain stimulation of nucleus accumbens on heroin-seeking behaviors: a case report. Biol Psychiatry. 2011;69(11):e41–2.
293. Kuhn J, Moller M, Treppmann JF, Bartsch C, Lenartz D, Gruendler TO, et al. Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction. Mol Psychiatry. 2014;19(2):145–6.
294. Muller UJ, Sturm V, Voges J, Heinze HJ, Galazky I, Buntjen L, et al. Nucleus Accumbens Deep Brain Stimulation for Alcohol Addiction - Safety and Clinical Long-term Results of a Pilot Trial. Pharmacopsychiatry. 2016;49(4):170–3.
295. Kuhn J, Lenartz D, Mai JK, Huff W, Lee SH, Koulousakis A, et al. Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. J Neurol. 2007;254(7):963–5.
296. Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2010;67(10):1061–8.
297. Grant JE, Odlaug BL, Chamberlain SR. Neurocognitive response to deep brain stimulation for obsessive-compulsive disorder: a case report. Am J Psychiatry. 2011;168(12):1338–9.
298. Sachdev PS, Cannon E, Coyne TJ, Silburn P. Bilateral deep brain stimulation of the nucleus accumbens for comorbid obsessive compulsive disorder and Tourette's syndrome. BMJ Case Rep. 2012; 2012.
299. Mantione M, van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications: case report. Neurosurgery. 2010;66(1):E218; discussion E.

Part IX
Rehabilitation

Chapter 33

Current Approaches to Cognitive Rehabilitation

Sarah A. Raskin

Current Approaches to Rehabilitation

The goal of any rehabilitation application should be to improve the adaptive functioning of people in the setting in which they will be living or working. Accommodation to and for impairments is often a critical variable in the success of rehabilitation efforts. This chapter will review current rehabilitation methods for sensory and motor functioning; cognitive functioning, including deficits in attention, visual–spatial, memory, language, and executive functions; and some recent technical additions to rehabilitation efforts.

Rehabilitation is generally thought of as consisting one of two objectives. The first is interventions that target change at the level of behavior (i.e., "behavioral approaches") and the second is those that target change at the level of restitution (i.e., "restorative approaches") [1]. Behavioral approaches are thought to involve compensating for the function that has been lost. Restitution aims to improve the lost function itself. In more recent years, a third category has been added to include therapies targeting metacognition or self-regulation [2].

Compensatory Approaches

Teaching the use of external compensatory aids to prompt people to complete planned tasks at target times [3] would be an example of a behavioral intervention. A compensation might include a new behavior or substitute skill (such as making lists for shopping; teaching a person with hemiplegia to tie their shoe with their less-affected arm exclusively) and/or an increase in time, effort, or both (such as studying). The injured person may also adapt to a new situation by changing self-expectations, selecting new tasks, or relaxing the criteria for success. Whether people are taught to use the compensation or develop it on their own, they are active participants in its application.

Restorative Approaches

Direct interventions use procedures that aim to improve or restore some underlying ability or cognitive capacity. An example of a restorative or impairment-based cognitive intervention is direct attention training [4], a drill-oriented therapy with hierarchical exercises designed to decrease attention deficits or the administration of functional activities with the more-affected arm to attempt to reestablish pathways affected by the injury.

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Metacognitive Approaches

An example of a metacognitive approach would be training people in the use of strategies or systems that facilitate self-monitoring during task completion [5]. All of these approaches are useful, as appropriate, and are generally used in combination. Throughout this chapter, each of these approaches will be considered within specific domains of rehabilitation. For the most part, both behavioral and restorative approaches can be thought of as cognitive-didactic (bottom-up), whereas metacognitive approaches are functional-experiential (top-down). In cognitive-didactic approaches, underlying cognitive skills such as attention are trained in a focused but hierarchical manner. The classic example is the Attention Process Training program [6]. In functional-experiential models, individuals are trained by doing specific tasks, typically independent living skills [7].

It can also be useful to think of cognitive approaches as internal (within the cognitive processes of the participant, like mental imagery) or external (like a grocery list). Cognitive rehabilitation techniques can also be explicit (direct aids) or implicit (indirect like spaced retrieval) [8].

Perhaps one of the most important requirements for any rehabilitation approach is the need for generalization [9]. One of the first authors to specify an approach to generalization was Gordon [10]. He suggested that the first level of generalization was that gains from rehabilitation should hold true in the same setting with the same materials on separate occasions. The second is that improvement on the training tasks is also observed on a similar but not identical set of tasks. The third level of generalization is that the functions gained in training are shown to transfer to functions in day-to-day living.

Sohlberg and Raskin [11] suggested a set of generalization principles or strategies that could be broadly adopted in both research and clinical practice. These principles, drawn primarily from the applied behavioral literature [12] and from the cognitive psychology literature on transfer or training [13] are (1) actively plan for and program generalization from the beginning of the treatment process, (2) identify reinforcements in the natural environment, (3) program stimuli common to both the training environment and the real world, (4) use sufficient examples when conducting therapy, and (5) select a method for measuring generalization.

These methods are thought to promote generalization through known learning and transfer of training paradigms [14]. The process by which generalization itself occurs, of course, varies according to the treatment approach. Compensation techniques affect generalization by bypassing defective cognitive functions and allowing the person to apply strategies in a large number of settings. Restorative approaches are thought to actually change the cognitive process, thereby allowing the process to be more effective in any setting.

Lessons from Plasticity

Kolb and Whishaw [15] have identified several important principles of plasticity that can be used to inform rehabilitation approaches. The first is that changes in the brain can be shown at many levels, including cellular, synaptic, systems, or in vivo levels. The second is that the brain can be altered by a wide range of experiences, and that experience-dependent changes can be long-lasting. The third is that training studies must be aware of the specific systems being targeted by the training and how these systems react to experience such as the training procedures. The fourth is that experience-dependent changes interact. In addition, of course, some plastic changes reflect compensation while others reflect recovery, and the treatment must specifically be designed with one or the other in mind. In other words, in some cases, the plasticity is one of an intact cortical region taking on the tasks once mediated by the damaged region. In other cases, it is now suggested, damaged regions can actually recover and resume previous functions.

Sensory and Motor Functions

One area of treatment that has shown considerable promise is constraint-induced (CI) therapy [16]. CI therapy is a prescribed, integrated and

systematic therapy designed to induce a patient to use a more-impaired upper extremity for many hours a day for several weeks (depending on the severity of the initial deficit). Some of the important elements are that the therapy requires repetitive, task-oriented training for a significant period of time (several hours a day for 10 or 15 consecutive weekdays). The use of a generalization procedure to transfer gains made in the research laboratory or clinical setting to the patient's real-world environment is essential. Finally, the hallmark of this therapy is constraining the patient to use the more-impaired upper extremity during waking hours over the course of treatment, sometimes by restraining the less-impaired upper extremity in a mitt or cuff. For a review of CI therapy see Morris, Taub, and Mark, 2006 [12].

Another approach to motor deficits is Locomotor Training (LT) [17]. This is an approach to gait rehabilitation that provides truncal support while giving manual sensory signals on a moving treadmill. Participants are supported in a harness over a treadmill. The theoretical basis is that the spinal cord has the capacity to integrate the afferent input and respond with an appropriate motor output through a network of spinal interneurons. In one study the amount of body weight support that was required was reduced from 40 to 0% over a period of weeks [18].

Cognitive Domains

Cognitive training has been studied most extensively in individuals with traumatic brain injury, although recent studies have also demonstrated efficacy in individuals with schizophrenia [19], mild cognitive impairment [20], multiple sclerosis [21] and reading disabilities [22]. For cognitive deficits, treatment seems most effective when a combination of compensatory and restorative approaches are used. Although it seems both simpler and more expedient to use compensation initially, to some extent, the severity of the cognitive impairment is believed to affect the extent to which compensation is spontaneously adopted. Moderately impaired individuals are most likely to compensate, whereas mildly impaired individuals may be unaware of a need to compensate, and severely impaired individuals may lack the skill and insight to implement compensatory behavior without substantial training and support. It is also important to recognize that the use of a particular compensation may have a negative trade-off. Compensatory behaviors should optimize and not hinder utilization of available resources, including the residual capacity of the injured system. Implementation of compensatory behaviors should also consider the consequences for the individual and for others in the individual's environment.

A program specifically designed for individuals with mild to moderate brain injury provides a systematic approach to compensatory strategy training [23]. Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) includes training for managing postconcussion symptoms, prospective memory, attention, learning/memory, and executive functioning. Compensatory strategies include note taking, use of calendars, pacing, relaxation, and self-talk. Improvements have been reported in cognitive performance and self-ratings of quality of life that persist for one year after training, although to date the effect sizes are small. In addition, the program is only designed for those with more mild brain injuries.

Attention

Impairments in attention, concentration, distractibility, and reduced processing speed are among the most commonly reported cognitive impairments. People with neurological disorders may take more time to complete tasks, have difficulty concentrating in noisy or busy environments, experience problems doing more than one thing at once, or forget what they were about to say or do.

Spatial neglect, presumed to be based on an attentional deficit, is one area that has shown the possibility of remediation. The spatial imbalance of stroke patients with unilateral neglect resulting from right ischaemic lesions was reported to be alleviated through the presentation of simple

auditory alerts [24]. The theoretical basis was data suggesting that the nonspatial alertness system is predominantly right-lateralized and receives ascending projections from subcortical systems that are generally still intact in cases of neglect. A similar rationale was used in the development of another training strategy for neglect, known as limb activation training, in which patients with left unilateral neglect are encouraged to make small movements of the left arm [25]. A Cochrane review concluded that while there is evidence for the efficacy of neglect training on the in-session assessments, there is not yet significant evidence that these techniques generalize to daily life [26].

For more complex aspects of attention, one obvious approach to helping people with attention deficits is to make environmental modifications, such as reducing noise or visual distraction, performing only a single task at a time, breaking down tasks into smaller steps, and reducing the impact of stress or fatigue. These suggestions may not only help the person improve their ability to manage the external environment, but may also help their internal emotional state by removing feelings of being overwhelmed.

More controversial, although actually more rigorously investigated are the direct retraining techniques for working with individuals with attentional impairments. Some of the earliest work to demonstrate positive findings in cognitive rehabilitation involved systematic intervention focused on attentional systems [27] and the literature on the rehabilitation of attention is now substantial [28].

The major premise of direct intervention approaches is that attentional abilities can be improved by exercising one or more particular aspects of attention. Treatment has usually engaged patients in a series of repetitive drills or exercises designed to provide opportunities for practice on tasks with increasingly greater attentional demands. Repeated activation and stimulation of attentional systems are hypothesized to facilitate changes in cognitive capacity.

Although a wide variety of treatment tasks have been used in experimental studies of attention training, the Attention Process Training [29] (APT) and APT-II [30] materials developed by Sohlberg et al., have been used in many clinical settings. These materials are hierarchically organized tasks designed to exercise sustained, selective, alternating, and divided attention. Tasks make increasingly greater demands on complex attentional control and working memory. Examples of tasks are listening for descending number sequences, alphabetizing words in a sentence or dividing attention between two simultaneous tasks. A computerized version, APT III has also been designed that presents the materials on the computer and also collects and tracks data. There have been relatively few studies of the newer APT III with one study reporting significant gains in attention but only limited generalization to daily life [31]. A version of the APT for children has also been developed (Pay Attention!) for children with attention deficits [32]. This children's version has shown mild improvements in tests of strategic planning efficiency and on parent and child ratings of ADHD symptoms [33, 34]. A computerized package similar to APT, FORAMENRehab Attention software, has also been used in children with mild traumatic brain injury and partial epilepsy [35]. Other computerized packages for training attention including RehaCom [36] and Cogmed [37]. These programs all have demonstrated improvements in cognitive functioning in a variety of disorders, including multiple sclerosis [38].

A major concern about attention training exercises has been the problem of generalization. For many functions, therapy is clearly most effective when the patient practices skills in the manner and setting in which they will be used. However, merely practicing naturalistic tasks may not be effective in and of itself. Mast naturalistic activities are multidimensional and rely on a variety of different underlying cognitive processes, such as divided attention, memory, and planning. Thus, utilizing a simpler approach that focuses on one process at a time can be beneficial.

A recent study used a qualitative approach to understanding the individual's experience with Attention Process Training [36]. The group that received training reported that in daily life strategies were continuously adjusted as awareness

increased. This suggests that attention process training may lead to improved metacognitive awareness with constant feedback in daily life.

Overall, of all the areas of cognitive processing that have been addressed in the cognitive rehabilitation literature, some of the most compelling findings have been in the realm of improvement of attentional impairments [39]. Improvements have been shown not only on attentional abilities but also in demonstrable functional improvements [40].

Visual–Spatial Functions

Visual field deficits are typically treated with some form of prism glasses [41] or training in visual scanning [42]. Preliminary data from a randomized controlled trial to compare these two types of treatment suggest that visual search training led to significant improvements whereas prism therapy was less effective due to a high number of adverse events (headaches) [43].

One other area that has been investigated is spatial navigation. The primary method for rehabilitating spatial navigation has been with the use of virtual reality platforms, which have been shown to be superior to real-world training studies [44]. In some cases, these virtual reality scenarios are made into computer game platforms to increase engagement [45]. They take the form of either active or passive navigation using verbally guided navigation.

Although most studies of the rehabilitation of alexia have been case studies, one recent group intervention was performed that included nine patients [46]. The individuals being trained were given laptops and asked to use them on their own each day for six weeks, and the usage was recorded by the intervention's software. A brief presentation of a word appeared on the screen simultaneously with a recording of someone reading the word. After the training block, the testing block paired written words and spoken words, some of which matched and some of which did not. Participants were required to determine if they were the same or different. The authors reported small effect sizes but these were supported by changes in connectivity measured with magnetoencephalography.

A systematic review found that most studies to date have been single cases and that few have measured generalization to daily life [47]. Thus while these techniques are promising, more research is needed to determine the best techniques for the rehabilitation of visual–spatial deficits.

Memory

Approaches to remediation of memory and new learning are among the oldest in the cognitive rehabilitation literature. Some approaches are based on techniques that help ordinary individuals remember better, and some are specifically based on what is known following a particular injury or illness. Most recently, approaches from cognitive science and learning theory have been applied to memory rehabilitation, including those attempts to improve memory ability, provide compensatory approaches through externally or internally focused manipulations, and maximize the likelihood of learning and remembering in individuals with memory impairments. The particular approach taken in any one case depends on the nature and severity of the deficit, the degree of insight, the goals of the patient, the environmental demands and expectations, and other factors.

Environmental Modification

Environmental modification may decrease the need for retrieval of specific information from memory. Included in this category are environmental cues, such as large signs posted in the home to remind the person where items are located or how a machine or appliance is operated. These types of modifications can be used in the home, work, or school environment. Modifications can also include removing environmental dangers, such as disabling a stove.

Cues and checklists are a somewhat more active approach. Cues can be specific pieces of

information provided by a family member, or a less specific cue such as an alarm that is set to remind the person when to take a medication. Several sophisticated cuing devices have been created for prospective memory impairments, including Neuropage [48], which uses a central computer and a paging company to page the patient automatically when a task needs to be completed. Neuropage has been demonstrated to significantly improve the ability of people with brain injury to complete tasks [49] and to reduce stress related to careers [3].

Compensatory approaches have focused primarily on the use of datebooks or notebooks [50]. There are many studies that document the efficacy of using external aids for the management of memory disorders [51]. A number of studies emphasized the importance of individualizing the training and the selection of the external aid used and the need to provide direct, systematic instruction in the use of the external aid [52, 53]. In the latter study, the use of external aids was found to be effective when compared to supportive therapy, although the results were not significantly different at follow-up.

Vanishing Cues

There are also several recent techniques designed to maximize learning. Research in both learning theory and cognitive neuroscience has yielded valuable new insights into the best approaches for training new skills in individuals with memory impairments. The method of vanishing cues, for example, was designed to take advantage of spared priming effects in amnesic subjects. Maximum cuing is used initially, and the amount of cuing is slowly reduced over repeated trials, similar to backward chaining techniques. Glisky et al. [54]. have used this technique in several studies in which they have shown improvement in specific functional skills (e.g., operating a computer) and maintenance of skills over time. Despite some transfer of learning to highly similar job contexts, learning continues to be highly task-specific. Huntin and Parkin [55], however, did find an advantage for the method of vanishing cues over rote learning (standard anticipation) in learning computer–related words and their definitions. This result might reflect differences in the subject population and warrants further research.

Errorless Learning

Most strategies to aid memory are based, in part, on repetition and spared procedural learning, particularly in individuals with severe amnesia. One important finding in this area is the demonstration of improved performance with errorless learning [56, 57]. In a series of studies, individuals with severe amnesia learned more quickly and accurately when they were not permitted to make incorrect guesses. Using stem-completion tasks, subjects with severe memory impairments were required to generate words that began with a particular word stem. In an errorless learning condition, the word was given and the subject told to write it down first. On subsequent trials, only correct responses were written down. In the errorful condition, subjects were allowed to generate guesses, including errors. The improved recall was seen in the errorless learning condition, presumably because individuals with amnesia have impaired explicit and episodic memory; errors are thus not recalled as errors, and, by virtue of repetition, are actually primed for later recall. Errorless learning was also shown to be superior on tasks applicable to everyday life, such as recalling names or programming an electronic aid.

One study applied the errorless learning paradigm to a more complex cognitive skill, that of social-problem solving [58]. Sixty individuals with schizophrenia or schizoaffective disorders were randomly assigned to experimental treatment or control groups. The experimental group participated in a social-problem solving training module. This training module included three components. The first was “receiving” skills (identifying problematic social interactions on a videotape), the second was “processing” skills (identification of three basic solutions to the problem), and the third was “sending” skills (practice in applying the solution in a role play). Throughout the training the instructor slowly faded cues to facilitate errorless

learning. The control group received similar content but without errorless conditions. The experimental training group demonstrated significantly better retention of appropriate social-problem solving skills at three months follow-up on the Assessment of Personal Problem-Solving Skills.

While errorless learning has been demonstrated to be effective in cases with severe amnesia, the literature does not support its use universally with other conditions, especially those with more minor deficits or in the early stages of dementia [59]. In fact, in many populations, benefits to performance from retrieval practice with spaced retrieval are greater than in errorless conditions.

Distributed Practice

Another technique of this type used to aid new learning is derived from studies of distributed practice. These studies suggest that learning is facilitated by having review occur over a longer period of time, for example, on hour every day for a week rather than seven hours in one day. This schedule seems to allow time for memory consolidation [60, 61]. There is some evidence to suggest that distributed practice has a greater effect on the cortical network that supports retrieval [62].

Prospective Memory Training

On particularly encouraging approach to direct retraining has been prospective memory training [63]. In a study by Raskin and Sohlberg [64], subjects with traumatic brain injury were required to execute actions at future designated times. As subjects became more proficient, the length of time between task assignment and task execution was systematically increased. Results supported the ability to increase subjects' prospective memory span. In addition, two measures of generalization were used. Subjects improved on both naturalistic probes and performance in daily life (measured with a diary method). A similar spaced-retrieval approach was used by Kurtz et al. [65] to treat attention and prospective memory impairments in individuals with schizophrenia and by Kinsella et al. [66] in individuals with Alzheimer's disease. More recently, visual imagery techniques–focused on visualizing the cue for the information to be remembered–have been useful in people who have primary deficits in prospective memory [67, 68].

Other Memory Techniques

Some direct retraining approaches use repeated exposure and practice to try to facilitate learning. However, there is little evidence to suggest that this approach is helpful for memory remediation [69]. In general, treatments are aimed at problems with encoding, such as elaboration [70] or visual imagery [71]. But there is some evidence that these strategies may actually reduce the cognitive resources available to the individual [72].

Metacognitive strategies to improve learning have been used with some success. These strategies use formal routines to help the person identify and structure material to be learned. For example, Lawson and Rice [73] used executive strategy training in a single case study. This involved identifying the problem, selecting a strategy, using the strategy, and then monitoring the outcome.

Academic Strategies

Academic therapies are focused on aiding in the recall of written material. In the PQRST (preview, question, read, state, test) method the individual is taught to go through a series of stages when reading (preview the material, generate questions, read, state the answers to the questions, test your recall) [74].

TEACH-M is an instructional package designed by Ehlhardt, Sohlberg, Glang, and Albin [75]. The acronym stands for Task analysis, Errorless learning, Assessment, Cumulative Review, High rates of correct practice, and Metacognitive strategy. They demonstrated its efficacy in four individuals with severe memory deficits. These

individuals were able to use these seven steps to successfully learn an email procedure.

Language

Rehabilitation of language deficits generally targets the area of deficit. Thus, therapies are specific to phonological aspects of language, syntactic aspects of language or semantic aspects of language. In addition, treatment can focus on the initiation or elaboration of verbal responses, such as in verbal fluency. Pragmatics is sometimes subsumed under language therapies and has to do with social rules of communication, such as turn-taking.

Treatments aimed at phonology of language are generally used with people who exhibit anomic aphasia. These treatments include semantic feature analysis, semantic cuing, and phonological cuing. Semantic feature analysis aims to activate the semantic network of a particular word. For example, if a person with aphasia is having difficulty retrieving a word, s/he might be asked to describe distinguishing features of the concept that the word represents. The goal is to have spreading activation of the entire semantic network that surrounds the target word, and thus, to activate the target word itself [76]. In semantic cuing treatment, the clinician might provide antonyms, synonyms, categories, or pictures to help guide the person towards the target word, and in phonological cuing the therapist provides cues based on sound, such as rhymes. For a review on the relative efficacy of these therapies see [77].

Treatments aimed at the syntactic level of language include syntax stimulation. The most widely used syntax stimulation treatment is the Helm Elicited Program for Syntax Stimulation (HELPSS) [78]. In this program, the treatment sessions are hierarchically structured and the goal is to elicit verbal productions of specific syntactical structures. The therapist might, for example, read a short story that ends with a question and then a response sentence that follows a particular syntax. The clinician then reads the same passage but now asks the person with aphasia to provide the response sentence.

Some of the oldest therapies have been aimed at treating expressive aphasia by improving the generation of verbal output. Melodic Intonation Therapy [79] puts a focus on the melodic line and rhythm of speech and is based on the theory that this will recruit the non-language hemisphere. Promoting Aphasic's Communicative Effectiveness (PACE) therapy [80] was designed to use the exchange of ideas between the therapist and the person with aphasia. PACE is based on the pragmatic rule of reciprocity whereby the two individuals participate in a conversation as equals. The four principles of PACE are the exchange of new information (typically cards are used and the individual turns over a card and must explain what appears on the card), equal participation, free choice of communicative channels, and functional feedback.

Some recent promising studies have been modeled after constraint-induced therapy [81]. Constraint-Induced Language Therapy (CILT) is designed to eliminate the potential learned nonuse of individuals (the theory that if individuals start to use compensations, to avoid language, the nonuse of language becomes learned) with aphasia [82, 83]. CILT incorporates the principles of repetition, intensity, salience, and specificity of treatment. The idea of constraint, in this case, is the limiting of the person's responses to speech by using visual barriers that prevent any communication through gesture, drawing, facial expression, etc. [84]. The therapy is hierarchically organized so that at first only a single word is required and the full sentences, etc. Results suggested improvements generalized to daily life. Improvements were enhanced when the treatment was distributed rather than intensive [85]. In one study, CILT was demonstrated to be superior to PACE [49].

Dyslexia and Developmental Reading Disorders

There has been a considerable interest of late in behavioral rehabilitation approaches to reading disorders based on the theory that dyslexia arises

from phonological processing deficits. Shaywitz and colleagues [86] examined 77 children identified as poor readers. The children were placed in one of three groups. The first was an experimental intervention that provided 50 min per day of explicit and systematic tutoring about letters, phonemes and letter-sound linkages. This was based on theories that posterior reading systems might be plastic to interventions that are phonologically mediated. The second group received typical school interventions. The third group was a no-intervention control. Compared to pretreatment, those children in the experimental group improved reading accuracy, reading fluency, and reading comprehension. Moreover, they demonstrated increased activation in left hemisphere regions on fMRI.

Richards and Berninger [87] provided children with dyslexia with a three-week instructional program. This program provided explicit instruction and was time-sensitive. Instruction was given in linguistic awareness, grapheme–phoneme associations, decoding and spelling, and a writer's workshop. Children who received training demonstrated improvement in reading and changes in functional connectivity on fMRI such that after training the children with dyslexia were not significantly different than good readers in left inferior frontal gyrus.

A commercial product, Fast ForWord, which uses acoustically modified speech (the speech sounds are digitally generated with selective intensity increases and extended durations), has also been used in studies of rehabilitation of children with dyslexia. This is a computer-based program for rehabilitating reading, with seven training exercises that focus on oral language, discrimination, and listening, as well as phonological processing and listening comprehension. Children with dyslexia have demonstrated improvement in reading accuracy and brain activation changes using this program [88]. In one study [20, 89] children were given this behavioral training in auditory processing and oral language training. These children showed improved reading performance and fMRI demonstrated increases in temporoparietal cortex and left inferior frontal gyrus. However, other studies have failed to find a specific effect of Fast ForWord compared to other behavioral interventions [90] and in a meta-analysis no evidence was found for its effectiveness [91].

Executive Functions

Executive functions are arguably the most difficult cognitive processes to define for the purposes of rehabilitation efforts. In general, rehabilitation efforts involve moving from simple structured activities with significant external cuing and support to more complex, multistep activities in which external support is gradually reduced and internal support or self-direction is required. Unfortunately, these techniques have been evaluated in only a small number of studies.

Compensatory Strategies

Frequently treatment of executive function deficits rely on compensatory strategies, such as posting routines in an obvious spot, restructuring the environment, or teaching task-specific routines. Often these strategies first involve considerable cuing from a therapist but then this is gradually decreased over time.

Behavioral Treatments

Behavioral treatments have been employed both to modify behavioral dyscontrol and to improve initiation and drive. Alderman et al. [92] have demonstrated effective use of a particular behavior modification technique, response cost, in assisting individuals to gain greater inhibitory control over their behavior. In this technique, the patient is given a number of tokens, which as subsequently exchanged for tangible rewards. However, in the interim, the individual is prompted to give the staff one token and state the reason for its loss whenever a target behavior (negative) is observed. The procedure enables

salient feedback to be extracted from the environment, places a minimal load on memory, and increases awareness.

Sohlberg et al. [93], for example, demonstrated that an individual with severe frontal lobe impairment and marked initiation problems responded differentially with different types of cuing. During a group activity, the patient was provided with a cue, at which time he was to ask himself whether he was initiating conversation. He was also provided with some didactic training around the nature of communication and the importance of appearing involved and interested in the activity. His verbal interactions during the group session increased over a baseline period, during which no cues had been given, and following the treatment phase, during with prompts were withdrawn.

There have also been many studies using a compensatory approach to the rehabilitation of executive control. This might include teaching task-specific routines such as grooming and dressing procedures, or preparation of simple meals. Geyer [94] prepared a handout for teaching such task-specific routines for this purpose.

Direct Training

Direct training approaches include structured exercises that provide multiple opportunities for initiating, planning, and carrying out goal-directed activities. The goal of the treatment is for the patient to take on increasing responsibility for carrying out multistep plans and activities. It is important that the treatment be linked to a solid and specific theory of executive functions and known anatomical substrates [95].

Training that targets working memory has shown efficacy in children with attention deficit hyperactivity disorder [96] and training generalized to improved performance on nontrained working memory tasks. Children were given computerized visual–spatial working memory tasks over a period of 14 weeks. Furthermore, after training, brain activity in middle and inferior frontal gyrus was significantly increased [97].

Approaches focused on multitasking, which is related to divided and alternating attention, also have shown some promise. Stablum et al. [98] demonstrated improvements in dual-task performance with practice over five weeks. Generalization was demonstrated by gains noted on the PASAT and a self-report measure.

Metacognitive Strategies

Metacognitive approaches to executive dysfunction focus on increasing insight, self-awareness, and self-regulation. Verbal self-regulation strategies are based on the observation that it is possible to regulate one's own behavior through self-talk. Stuss et al. [99] used a verbal self-regulation approach in an individual with motor impersistence, who could not maintain a simple movement over time. The patient did learn to alter his behavior, although he needed cues to initiate and maintain the self-regulation strategy.

Another kind of intervention at this level involves teaching self-instructional procedures. Cicerone and Wood [100] reported successful treatment with such a procedure of a patient who exhibited planning ability and poor self-control four years after a brain injury. They used as a training task a modified version of the Tower of London. Training involved three distinct phases: overt verbalization, overt self-guidance, and covert internalized self-monitoring. To promote generalization following the program, the client was presented with a structured interpersonal problem and asked to solve it by applying principles learned in the self-instructional training. The results supported the clinical efficacy of verbal mediation training. Additional work with a focus on *greater generalization* has been carried out by Cicerone and Giacino [101] which demonstrated that verbal mediation strategies can lead to improved performance in daily life. As noted by Onsworth, McFarland, and Young [102], such improvements in self-regulatory strategies can lead to an increased awareness of deficits and a more realistic anticipatory awareness of situations where patients may experience difficulty.

Von Cramon, et al. [103] described positive results in a series of patients with frontal lobe dysfunction. Their training procedure enabled patients to reduce the complexity of a multistage problem by breaking it down into more manageable proportions. Problem-solving training incorporated four modules. The first was the generation of goal-directed ideas, the second was systematic and careful comparison of information provided by a problem to be solved, the third consisted of tasks requiring simultaneous analysis of information from multiple sources and the fourth focused on improving abilities to draw inferences. Inferential thinking was operationalized as the ability to predict the goals of another person from an action.

In another study that used the strategy of breaking down a complex problem into smaller portions, Marshall et al. [104] used a formalized modeling of effective problem-solving by a therapist. They reported that the individuals with brain injury, following training, asked more useful questions, adopted new strategies for solving problems that were not presented during training, and showed less random guessing.

The Short-Term Executive Plus (STEP) cognitive rehabilitation program combines attention training and compensatory strategies with group training in problem solving and emotion regulation [105]. This is a 12-week program for 9 h per week. The attention training consisted of the APT-II. Problem solving used a 5-step problem-solving approach that focused on metacognitive awareness of the problem to be solved, picking a plan, and judging if the outcome is acceptable. Regulation of emotion used cognitive behavioral techniques. Generalization was built into the training protocol. A composite executive function measure made up of a number of standardized behavioral measures was used as the primary outcome measure with neuropsychological tests and quality of life as secondary measures. The results suggested that this program was able to significantly reduce executive dysfunction and improve problem-solving in people with brain injury.

A similar series of studies aimed at metacognitive skills fall under the approach of Goal Management Training (GMT) [106]. This technique uses a general purpose algorithm to teach individuals five stages of problem-solving (stop, define the task, list the steps needed, learn the steps, and check your performance). In a controlled study, Levine et al. [62] demonstrated the superiority of GMT to motor skills training when comparing two groups of individuals with brain injury on everyday tasks such as proofreading. This has also been applied to naturalistic tasks such as meal preparation. GMT has been used in a wide variety of populations including aging [107] and traumatic brain injury [108], and has been combined with structured mindfulness training. It has also been combined with Ylvisakers' model that includes self-awareness, goal-setting, planning, self-initiation, self-monitoring, self-inhibition, flexibility, and strategic behavior [109]. A meta-analysis of 21 publications using GMT reported significantly positive small to moderate effect sizes in all cognitive domains measured, except for speed of processing, with gains maintained at follow-up [110].

As with other areas of treatment discussed, the use of metacognitive strategies and self-instructional programs for individuals with acquired frontal injuries is just beginning to be formally evaluated. It is encouraging, however, that positive outcomes have been reported and that there are numerous reports of success with such approaches in a variety of clinical populations. The executive disorders encompass a broad range of cognitive and behavioral difficulties. Effective strategies for such patients require an appreciation for each person's cognitive profile, self-regulation capacity, and level of awareness, so that appropriate specific individual therapies can be designed and generalization can be targeted.

In this vein, Gordon et al. [111] describe a comprehensive day treatment program that is based on specific targets and methods for the treatment of executive dysfunction including cerebral organization, cognitive behavioral theory of problem-solving and learning theory.

Normal Aging

Many authors have pointed out the benefits obtained from providing multimodal approaches to cognitive remediation (e.g., [112]). One example of this is *BrightBrainer,* designed for use in a nursing home setting. It includes exercises for attention, memory recall, executive functioning, and emotional well-being [113]. It has also been used in cases of primary progressive aphasia [114].

One example of this is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) therapies [115]. These therapies apply the principles of cognitive remediation to healthy older adults in an attempt to delay or prevent the development of cognitive disabilities. This program consists of three cognitive training modules that target specific cognitive abilities (memory, reasoning, speed of processing). Large randomized controlled trials have demonstrated that each of the three treatments specifically improves that cognitive domain. More recent studies have also demonstrated delays in the decline of health-related quality of life specifically due to the speed-training intervention [116], and that benefits are maintained for up to five years after training for memory training and up to 10 years after training for reasoning and speed-of-processing training [117].

Neurofeedback Therapy

Neurofeedback therapy has recently been applied to cognitive domains [118]. It has been used to treat individuals with traumatic brain injury [119], attention deficit disorder, dyslexia [120] and stroke. Generally, participants complete a quantitative electroencephalogram (QEEG) baseline assessment. Then a neurotherapeutic bandwidth training objective is determined. For example, the goal may be to reduce theta over P3. Visual feedback is given on a computer screen, for example, the participant might be told to maintain a dot within a red circle. Often participants are rewarded with points for successful bandwidth changes. In individuals with stroke, improvements have been noted in memory, attention, motivation, and language functions [84].

Repetitive Transcranial Magnetic Stimulation

Another technology that has been used recently in hopes of augmenting the effects of cognitive rehabilitation therapy is transcranial magnetic stimulation (TMS) [121]. This technique involves placing a flat coil on the scalp, through which a brief intense pulse of magnetic current is passed from a high-voltage capacitor discharge system. If the frequency of the stimulation is 1 Hz or greater, it is referred to as repetitive TMS (rTMS). rTMS has been reported to lead to cognitive enhancement perhaps through modulation of a cortical network leading to more efficient processing or through disruption of a competing process. rTMS has been used in conjunction with motor and cognitive rehabilitation and some studies have reported that the combined techniques lead to greater improvement than the treatment alone [72]. In a review of non-invasive brain stimulation (NIBS), the authors conclude that cognitive rehabilitation is more effective when combined with NIBS than alone [122].

Virtual Reality

Virtual reality is a computer-generated environment that the user can interact with. There are four types of virtual environments at present. These are head-mounted displays, augmented environment, Fish Tank environment, and projection-based environment. The head-mounted display allows the user to feel completely immersed with all of the external environment blocked from view. However, some users may experience unpleasant side effects, such as motion sickness. In augmented virtual reality systems both the computer-generated images and the rest of the environment is visible. Fish Tank systems have the virtual environment displayed on a computer screen. In

projection-based paradigms a full wall has a projection of the virtual environment. Researchers have described virtual reality as creating complex real-world environments with laboratory control of the variables being displayed.

Virtual reality has been used as a tool to remediate a range of neurologic and psychiatric conditions [123]. These include spatial inattention, attention deficit hyperactivity disorder, posttraumatic stress disorder, arm movements after stroke, traumatic brain injury, and pain. Advantages of virtual reality therapies include increased patient motivation, adaptability, data storage, and reduced medical costs [124].

A review of virtual reality use in the rehabilitation of people with brain injury [125] shows that studies have focused on executive dysfunction, memory impairments, spatial ability impairments, attention deficits, and unilateral visual neglect. For rehabilitation of memory impairments, virtual reality environments have been used to improve procedural learning, which is reported to generalize to real-world performance [126]. A systematic review of 350 studies concluded that virtual reality should be considered a useful tool for cognitive remediation but that further well-controlled studies are needed [127].

Another area of increased interest is the use of virtual reality for children with ADHD [128]. Rizzo and his colleagues have created a Virtual Reality Classroom that has an embedded continuous performance task. In addition, there are simulated and "real-world" auditory and visual distracters [129].

Brain–Computer Interface

There has been considerable popular interest in the idea of a brain–computer interface that can be used for rehabilitation purposes. In a review by Birbaumer and Cohen [130], the majority of these non-invasive brain–computer interfaces (BCIs) have been used for individuals with motor deficits following spinal cord injury or stroke. While there have been some promising studies using invasive procedures with animals in the laboratory, there is still a lack of proven clinical utility. BCIs are typically based on one of several possible neurophysiological rhythms, such as electroencephalographic oscillations. For the most part, noninvasive human studies use biofeedback of EEG oscillations or event-related potentials.

Human rehabilitation studies have demonstrated some limited but promising findings. In individuals who have paralysis from spinal cord lesions, a single case study suggested that the individual was able to activate electrostimulation of arm and hand muscles by controlling EEG readings, but it did not seem to generalize to daily life [131]. Similarly, studies in humans using single motor or parietal neuron spike patterns were not applicable to activities of daily living [132].

Several groups have also tried to restore motor functions following chronic stroke. In a series of studies utilizing MEG, magnetic sensors over the sensorimotor regions of the lesioned hemisphere are used for training. Then a prosthetic hand is attached to the paralyzed hand and the person is trained to use visual feedback to move the hand by increasing sensorimotor rhythms (or mu rhythms) over the lesioned hemisphere [133]. Although positive reports of movement have been given, training often takes a long time and the movement tends to be slow and not naturalistic.

Conclusions

Some of the most exciting new work in the field of rehabilitation is based on models of cortical plasticity. Robertson and Murr [134] have argued that the extent and nature of neural recovery following targeted intervention will depend largely on the severity of the injury. Thus, in the case of a large lesion, there may not be sufficient residual connectivity with which to reestablish a fully functioning network. In these cases, then, treatment should be targeted at the compensatory recruitment of alternative brain regions or the use of compensatory strategies.

In a similar vein, there is some evidence to suggest that patients with brain injury require training that is tailored to their specific level of functioning. For example, an analysis of individual

differences in a study of attention training using the APT training by Sohlberg and colleagues [135] (Sohlberg, McLaughlin, Pavese, Heidrich, and Posner, 2000) indicated differences in treatment efficacy depending on a patient's initial vigilance level. Only individuals who had poor vigilance levels showed improvements in basic attentional skills, and only individuals with better vigilance levels showed improvement on more demanding attentional or working memory tasks. Further work is required to establish predictors of training efficacy and future studies should delineate specific patient profiles in order to determine who is likely to benefit.

The field is also increasingly learning that emotional well-being and emotional regulation need to be factored into cognitive rehabilitation plans. Several recent studies have looked at approaches to reducing anxiety, reducing depression, and improving emotional regulation within a cognitive rehabilitation program (e.g., [136]) especially in individuals with dementia (e.g., [137]).

Research in rehabilitation is increasingly being required to follow evidence-based guidelines, as it has been noted many times that it tends to be limited by the heterogeneity of subjects, methods, and outcome measures. While randomized controlled studies are assumed to provide the best evidence of efficacy, it is also accepted that in clinical practice it might be necessary to combine standard treatment protocols and individualized treatments [138].

As the field of cognitive neuroscience provides more evidence for the specific kinds of practice and experience-dependent learning that lead to most effective cortical plasticity, it should also be possible to target rehabilitation efforts to maximize these potential changes.

References

1. Sohlberg MM. Review article: evidence-based instructional techniques for training procedures and knowledge in persons with severe memory impairment. Revisita de Neuropsicologia. 2006;1(1):14–9.
2. Kennedy M, Coelho C, Turkstra L, Ylvisaker M, Sohlberg MM, Yorkston K, Chiou H, Kahn PF. Intervention for executive functions after traumatic brain injury: a systematic review and meta-analysis. Neuropsychol Rehabil. 2007;iFirst:1–43.
3. Wilson BA, Emslie HC, Quirk K, Evans JJ. Reducing everyday memory and planning problems by means of a paging system: a randomized control crossover study. J Neurol Neurosurg Psychiatry. 2001;70:477–82.
4. Cicerone KD. Remediation of working attention in mild traumatic brain injury. Brain Inj. 2002;16:185–95.
5. Levine B, Stuss D, Milberg W, Alexander M, Schwartz M, Macdonald R. The effects of focal and diffuse brain damage on strategy application: evidence from focal lesions, traumatic brain injury and normal aging. J Int Neuropsychol Soc. 1998;4:247–64.
6. Sohlberg M, Mateer C. Effectiveness of an attentional training program. J Clin Exp Neuropsychol. 1987;9:117–30.
7. Giles G. Cognitive versus functional approaches to rehabilitation after traumatic brain injury: commentary on a randomized controlled trial 2010;64:182–85.
8. Malone ML, Camp CJ. Montessori-based dementia programming®: providing tools for engagement. Dementia. 2007;6:150–7.
9. Raskin S, Gordon W. The impact of different approaches to remediation on generalization. NeuroRehabilitation. 1992;2:38–45.
10. Gordon W. Methodological considerations in cognitive remediation. In: Meier M, Benton A, Diller L, editors. Neuropsychological rehabilitation. Guilford, New York; 1987.
11. Sohlberg MM, Raskin SA. Generalization.
12. Stokes T, Baer D. An implicit technology of generalization. J Appl Behav Anal. 1977;10:349–67.
13. Anderson J. ACT: a simple theory of complex cognition. Am Psychol. 1996;51:355–65.
14. Raskin S, Mateer C. Neuropsychological management of mild traumatic brain injury. New York: Oxford University Press; 2000.
15. Kolb B, Whishaw IQ. Brain plasticity and behavior. Ann Rev Psychol. 1998;49:43–64.
16. Mark VW, Taub E, Morris DM. Neuralplasticity and constraint-induced movement therapy. Eur Medicophys. 2006;42:269–84.
17. Behrman AL, Bowden MG, Nair PM. Neuroplasticity after spinal cord injury and training: an emerging paradigm shift in rehabilitation and walking recovery. Phys Ther. 2006;86:1406–25.
18. Wernig A, Müller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30:229–38.
19. Kurtz MM, Seltzer JC, Fujimoto M, Shagan DS, Wexler BE. Predictors of change in life skills in schizophrenia after cognitive remediation. Schizophr Res. 2009;107:267–74.
20. Kurz A, Pohl C, Ramsenthaler M, Sorg C. Cognitive rehabilitation in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2009;24:163–8.
21. Mitolo M, Venneri A, Wilkinson I, Sharrack B. Cognitive rehabilitation in multiple sclerosis: a systematic review. J Neurol Sci. 2015;15:1–9.
22. Given BK, Wasserman JD, Chari SA, Beattie K, Eden GF. A randomized, controlled study of

computer-based intervention in middle school struggling readers. Brain Lang. 2008;106:83–97.
23. Twamley E, Thomas K, Gregory A, Jak A, Bondi M, Delis D, Lohr J. CogSMART compensatory cognitive training for traumatic brain injury: effects over 1 year. J Head Trauma Rehabil. 2015;30:391–401.
24. Robertson IH, Tegner R, Tham K, Lo A, Nimmo-Smith I. Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. J Clin Exp Psychol. 1995;17:416–30.
25. Robertson IH, McMillan TM, MacLeod E, Edgeworth J, Brock D. Rehabilitation by limb activation training (LAT) reduces impairment in unilateral neglect patients: a single-blind randomised control trial. Neuropsychol Rehabil. 2002;12:439–54.
26. Bowen A, Hazelton C, Pollock A, Lincoln N. Cognitive rehabilitation for spatial neglect following stroke. Cochrane Database Syst Rev. 2013;7:CD003586.
27. Sohlberg MM, Mateer C. Effectiveness of an attention training program. J Clin Exp Neuropsychol. 1987;19:117–30.
28. Rohling M, Faust M, Beverly B, Demakis G. Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Ciceron et al.'s (2000, 2005) systematic reviews. Neuropsychology. 2009;23:20–39.
29. Sohlberg MM, Mateer CA. Attention process training. Association for Neuropsychological Research and Development 1989; Puyallup, WA.
30. Sohlberg MM, et al. Attention process training II: a program to address attentional deficits for persons with mild cognitive dysfunction. Association for Neuropsychological Research and Development 1993; Puyallup, WA.
31. Zickefoose S, Hux K, Brown J, Wulf K. Let the games begin: a preliminary study using attention process training-3 and Lumosity brain games to remediate attention deficits following traumatic brain injury. Brain Inj. 2013;27:707–16.
32. Thomson JB, Kerns KA, Seidenstrang L, Sohlberg MM, Mateer CA. Pay attention! a children's attention process training program. 2001; Wake Forest, NC: Lash & Associates Publishing/Training Inc.
33. Tamm L, Epstein J, Peugh J, Nakonezny P, Hughes C. Preliminary data suggesting the efficacy of attention training for school-aged children with ADHD. Dev Cogn Neurosci. 2013;4:16–28.
34. Kerns K, Eso K, Thomson J. Investigatoin of a direct intervention for improving attention in young children with ADHD. Dev Neuropsychol. 1999;16:273–95.
35. Kaldoja M-L, Saard M, Lange K, Raud T, Ott-Kaarel T, Kolk A. Neuropychological benefits of computer-assisted cognitive rehabilitation (using FORAMENTRehab program) in children with mild traumatic brain injury or partial epilepsy: a pilot study. J Pediatr Rehab Med. 2015;8:2710283.
36. Campbell J, Langdon D, Cercignani M, Rashid W. A randomized controlled trial of efficacy of cognitive rehabilitation in multiple sclerosis: a cognitive behavioural, and MRI study. Neural Plast. 2016;2:11–51.
37. Fuentes A, Kerr E. Maintenance effects of working memory intervention (Cogmed) in children with symptomatic epilepsy. Epilepsy Behav. 2017;67:51–9.
38. Markovic G, Bartfai A, Ekholm J, Nilsson C, Schult M, Lofgren M. Daily management of attention dysfunction two-four years after brain injury and early cognitive rehabilitation with attention process training: a qualitative study. Neuropsychol Rehabil 2018;27.
39. Michel JA, Mateer CA. Attention rehabilitation following stroke and traumatic brain injury. A Rev Eur Medicophys. 2006;42(1):59–67.
40. Ponsford J, Kinsella G. Evaluatin of a remedial programme for attentional deficits following closed head injury. J Clin Exp Neuropsychol. 1988;10: 693–708.
41. Szlyk J, Seiple W, Stelmack J, McMahon T. Use of prisms for navigation and driving in hemianopic patients. Ophthalmic Physiol Opt. 2005;25:128–35.
42. Roth T, Sokolov A, Messias A, Roth P, Weller M, Trauzettal-Kloinski S. Comparing explorative saccades and flicker training in hemianopia. Neurology. 2009;72:324–31.
43. Rowe F, Conroy E, Bedson E, Cwiklinski E, Drummond A, Garcia-Finana M, Howard C, Pollock A, Shipman T, Dodridge C, MacIntosh C, Johnson S, Noonan C, Barton G, Sackley C. A pilot randomized controlled trial comparing effectiveness of prism glasses, visual search training, and standard care in hemianopia. Acta Neurol Scand. 2017;136:310–21.
44. Kober S, Wood G, Hofer D, Kreuzig W, Kiefer M, Neuper C. Virtual reality in neurologic rehabilitation of spatial disorientation. J Neuroeng Rehabil. 2013;10:17.
45. Van der Kuil M, Visser-Meily J, Evers A, van der Ham I. A usability study of a serious game in cognitive rehabilitation: a compensatory navigation training in acquired brain injury patients. Frontiers Psychol. 2018;9:846.
46. Woodhead Z, Penny W, Barnes G, Crewes H, Wise R, Price C, Leff A. Reading therapy strengthens top-down connectivity in patients with pure alexia. Brain 2013;136:2579–591.
47. Hanna K, Hepworth L, Rowe F. The treatment methods for post-stroke visual impairment: a systematic review. Brain Behav. 2017;7:e00682.
48. Teasdale T, Emslie H, Quirk K, Evans J, Fish J, Wilson BA. Alleviation of career strain during the use of the NeuroPage device by people with acquired brain injury. J Neurol Neurosurg Psychiatry. 2009;80:781–3.
49. Wilson BA, Emslie H, Quirk K, Evans J, Watson P. A randomized controlled trial to evaluate a paging system for people with traumatic brain injury. Brain Inj. 2005;19:891–4.
50. Sohlberg MM. External aids: expanding our understanding of the most widely used memory

rehabilitation technique. In: High W, Sander AM, Struchen MA, Hart KA, editors. Rehabilitation for traumatic brain injury. New York: Oxford Press; 2005. p. 47–70.
51. Sohlberg MM, Kennedy MRT, Avery J, Coelho C, Turkstra L, Ylvisaker M, Yorkston K. Practice guidelines for external aids for memory rehabilitation. J Med Speech Lang Pathol 2007;15(1):xv-ii.
52. Hart T, Hawkey K, Whyte J. Use of a portable voice organizer to remember therapy goals in traumatic brain injury rehabilitation: a within-subjects trial. J Head Trauma Rehabil. 2002;17(6):556–70.
53. Schmitter-Edgecombe M, Fahy JF, Whelan JP, Long CJ. Memory remediation after severe closed head injury: notebook training versus supportive therapy. J Clin Consult Psychol. 1995;63(3):484–9.
54. Glisky EL, Schacter DL, Tulving E. Learning and retention of computer-related vocabulary in memory-impaired patients: method of vanishing cues. J Clin Exp Neuropsychol. 1986;8(3):292–312.
55. Hunkin NA, Parkin AJ. The method of vanishing cues: an evaluation of its effectiveness in teaching memory impaired individuals. Neuropsychologia. 1995;33(10):1255–79.
56. Wilson BA, Baddeley A, Evans J, Shiel A. Errorless learning in the rehabilitation of memory impaired people. Neuropsychol Rehabil. 1994;4(3):307–26.
57. Tailby R, Haslam C. An investigation of errorless learning in memory-impaired patients: improve the technique and clarifying the theory. Neuropsychologia. 2003;41:1230–40.
58. Kern RS, Green MF, Mitchell S, Kopelowicz A, Mintz J, Liberman RP. Extensions of errorless learning for social problem-solving deficits in schizophrenia. Am J Psychiatry. 2005;162(3):513–9.
59. Middleton E, Schwartz M. Errorless learning in cognitive rehabilitation: a critical review. Neuropsychol Rehabil. 2012;22(2):138–68.
60. Cherry KE, Simmons SS, Camp CJ. Spaced retrieval enhances memory in older adults with probable Alzheimer's disease. J Clin Geropsychol. 1999;5(3):159–75.
61. Brush J, Camp C. Using spaced retrieval as an intervention during speech-language therapy. Clin Gerontol. 1998;19(1):51–64.
62. Takashim A, Nieuwenhuis I, Rijpkema M, Petersson KM, Jensen O, Fernandez G. Memory trace stabilization leads to large-scale changes in the retrieval network: a functional MRI study on associative memory. Learn Mem. 2007;14:472–9.
63. Raskin S, Sohlberg MM. Prospective memory intervention: a review and evaluation of a pilot restorative intervention. Brain Impair. 2009;10:76–86.
64. Raskin S, Sohlberg M. An investigation of prospective memory training in two individuals with traumatic brain injury. J Head Trauma Rehabil. 1996;11:32–51.
65. Kurtz M, Moberg P, Mozley L, Swanson C, Gur R, Gur R. Effectiveness of an attention- and memory-training program on neuropsychological deficits in schizophrenia. Neurorehabil Neural Repair. 2001;15:75–81.
66. Kinsella G, Ong B, Storey E, Wallace J, Hester R. Elaborated spaced-retrieval and prospective memory in mild Alzheimer's disease. Neuropsychol Rehabil. 2007;17:688–706.
67. Grilli M, McFarland C. Imagine that: self-imagination improves prospective memory in memory-impaired individuals with neurological damage. Neuropsychol Rehabil. 2011;21:847–59.
68. Raskin S, Smith M, Mills G, Pedro C, Zamroziewicz M. Prospective memory intervention using visual imagery in individuals with brain injury. Neuropsychol Rehabil. https://doi.org/10.1080/09602011.2017.1294082.
69. Franzen M, Haut M. The psychological treatment of memory impairment: a review of empirical studies. Neuropsychol Rev. 1991;2:29–63.
70. Goldstein G, et al. Efficacy of memory training: a technological extension and replication. Clin Neuropsychol. 1996;10:66–72.
71. Twum M, Parente R. Role of imagery and verbal labeling in the performance of paired associate tasks by persons with closed head injury. J Clin Exp Neuropsychol. 1994;16:630–9.
72. Komatsu S, Mimura M, Kato M, Wakamatsu N, Kashima H. Errorless and effortful processes involved in the learning of face-name associations by patients with alcoholic Korsakoff's Syndrome. Neuropsychol Rehabil. 2000;10(2):113–32.
73. Lawson M, Rice D. Effects of training in use of executive strategies on a verbal memory problem resulting from closed head injury. J Clin Exp Psychol. 1989;11:842–54.
74. Wilson BA. Rehabilitation of memory. New York: Guilford; 1987.
75. Ehlhardt L, Sohlberg MM, Glang A, Albin R. TEACH-M: a pilot study evaluating an instructional sequence for persons with impaired memory and executive functions. Brain Inj. 2005;19(8):569–83.
76. Coelho CA, Mchugh RE, Boyle M. Semantic feature analysis as a treatment for aphasic dysnomia: a replication. Aphasiology. 2000;14:133–42.
77. Drew RL, Thompson CK. Model-based semantic treatment for naming deficits in aphasia. J Speech Hear Res. 1999;42:972–89.
78. Helm-Estabrooks N, Ramsberger G. Treatment of agrammatism in long-term Broca's aphasia. Br J Commun Disord. 1986;21:39–45.
79. Alberts ML, Sparks RW, Helm NA. Melodic intonation therapy for aphasia. Arch Neurol. 1973;29:130–1.
80. Li EC, Kitselman K, Dusatko D, Spinelli C. The efficacy of PACE in the remediation of naming deficits. J Commun Disord. 1998;21:111–23.
81. Lillie R, Mateer CA. Constraint-based therapies as a proposed model for cognitive rehabilitation. J Head Trauma Rehabil. 2006;21(2):119–30.

82. Pulvermüller F, Neininger B, Elbert T, Mohr B, Rockstroh B, Koebbel P, Taub E. Constraint-induced therapy of chronic aphasia following stroke. Stroke. 2001;32:1621–6.
83. Maher LM, Kendall D, Swearengin JA, Rodriguez A, Leon SA, Pingel K, Holland A, Rothi LJG. A pilot study of use-dependent learning in the context of constraint induced language therapy. J Int Neuropsychol Soc. 2006;12:843–52.
84. Maher LM, Schmadeke S, Swearengin J, Rothi LJG. Intensity variation for constraint induced language therapy for aphasia. The ASHA Leader 2005;166. Convention Program.
85. Dignam J, Copland D, McKinnon E, Burfein P, O'Brien K, Farrell A, Rodriquez A. Intensive versus distributed aphasia therapy: a nonrandomized, parallel-group, dosage-controlled study. Stroke. 2015;46:2206–11.
86. Shaywitz B, Shaywitz S, Blachman B, Pugh K, Fulbright R, Skudlarski P, et al. Development of left occipito-temporal systems for skilled reading in children after a phonologically-based intervention. Biol Psychiatry. 2000;55:926–33.
87. Richards T, Berninger V. Abnormal fMRI connectivity in children with dyslexia during a phoneme task: before but not after treatment 1. J Neurolinguistics. 2008;21:294–304.
88. Temple E, Poldrack R, Protopapas A, Nagarajan S, Salz T, Tallal P, et al. Disruption of the neural response to rapid acoustic stimuli in dyslexia: evidence from functional MRI. Proc Natl Acad Sci USA. 2000;97:13907–12.
89. Temple E, Deutsch G, Poldrack R, Miller S, Tallal P, Merzenich M, et al. Neural deficits in children with dyslexia ameliorated by behavioral remediation: evidence from fMRI. PNAS. 2000;100 (5):2860–5.
90. Gillam R, Loeb D, Hoffman L, Bohman T, Champlin C, Thibodeau L, Widen J, Brandel J, Friel-Patti S. The efficacy of Fast ForWord language intervention in school-age children with language impairment: a randomized controlled trial. J Speech Lang Hear Res. 2008;51:97–119.
91. Strong G, Torgerson C, Torgerson D, Hulme C. A systematic meta-analytic review of evidence for the effectiveness of the "Fast For Word" language intervention program. J Child Psyhcol Psychiatry. 2011;52:224–35.
92. Alderman N, Fry R, Youngson H. Improvement in self-monitoring skills, reduction of behavior disturbance and the dysexecutive syndrome: comparison of response cost and a new programme of self-monitoring training. Neuropsychol Rehabil. 1995;5:193–221.
93. Sohlberg MM, Sprunk H, Metzelaar K. Efficacy of an external cuing system in an individual with severe frontal lobe damage. Cogn Rehabil. 1988;4:36–40.
94. Geyer S. Training executive function skills. Puyallup, WA: Good Samaritan Hospital; 1989.
95. Cicerone K, Levin H, Malec J, Stuss D, Whyte J. Cognitive rehabilitation interventions for executive function: Moving from bench to bedside in patients with traumatic brain injury. J Cogn Neurosci. 2006;18(7):1212–22.
96. Klingberg T, Fernell E, Olesen P, Johnson M, Gustafsson P, Dahlstrom K, et al. Computerized training of working memory in children with ADHD—a randomized controlled trial. J Am Acad Child Adolesc Psych. 2005;44:177–86.
97. Westerg H, Klingberg T. Changes in cortical activity after training of working memory—a single subject analysis. Physiol Behav. 2007;92:186–92.
98. Stablum F, Umiltà C, Mogentale C, Carlan M, Guerrini C. Rehabilitation of executive deficits in closed head injury and anterior communicating artery aneurysm patients. Psychol Res. 2000;63:265–78.
99. Stuss D, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Ann Rev Psychol. 2006;53:401–33.
100. Cicerone K, Wood J. Planning disorder after closed head injury: a case study. Arch Phys Med Rehabil. 1987;68:11–115.
101. Cicerone K, Giacino J. Remediation of executive function deficits after traumatic brain injury. Neuropsychol Rehabil. 1992;2:12–22.
102. Onsworth T, McFarland K, Young R. Self-awareness and psychosocial functioning following traumatic brain injury: an evaluation of a group support programme. Neuropsychol Rehabil. 2000;10:465–84.
103. Von Cramon D, Matthes-Von Cramon G, Mai N. Problem solving deficits in brain injured patients: a therapeutic approach. Neuropsychol Rehabil. 1991;1:45–64.
104. Marshall RC, Karow CM, Morelli CA, Iden KK, Dixon J, Cranfill TB. Effects of interactive strategy modelling training on problem-solving by persons with traumatic brain injury. Aphasiology. 2004;18 (8):659–73.
105. Cantor J, Ashman T, Dams-O'Connor K, Dijkers M, Gordon W, Spielman L, Tsaousides T, Allen H, Nguyen M, Oswald J. Evaluation of the short-term executive plus intervention for executive dysfunction after traumatic brain injury: a randomized controlled trail with minimization. Arch Phys Med Rehabil 2014; 95:1–9.e3.
106. Levine B, Robertson IH, Clare L, Carter G, Hong J, Wilson BA, et al. Rehabilitation of executive functioning: an experimental-clinical validation of goal management training. J Int Neuropsychol Soc. 2000;6:299–312.
107. Levine B, Stuss D, Winocur G, Binns M, Fahy L, et al. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc. 13:143–52.
108. Tornas S, Stubberud J, Solbakk A, Evans J, Schanke A, Lovstad M. Moderators, mediators, and nonspecific outcome after cognitive rehabilitation of executive functions in a randomized controlled trial. Neuropsychol Rehabil. 2017;1:1–22.
109. Effects of a multifaceted treatment program for executive dysfunction after acquired brain injury on indications of executive functioning in daily life. JINS. 2010;16:118–29.

110. Stamenova V, Levine B. Effectiveness of goal management training in improving executive functions: a meta-analysis. Neuropyschol Rehabil. 2018;14:1–31.
111. Gordon WA, Cantor J, Ashman T, Brown M. Treatment of post-TBI executive dysfunction: application of theory to clinical practice. J Head Trauma Rehabil. 2006;156–67.
112. Sohlbert MM, Mateer CA. Cognitive rehabilitation: an integrative neuropsychological approach. New York: Guilford Press; 2001.
113. Burdea G, Polistico K, Krishnamoorthy A, House G, Rethage D, Hundal J, Damiani F, Pollack S. Feasibility study of the *BrightBrainer* integrative cognitive rehabilitation system for elderly with demenia. Disabil Rehabil Assist Technol. 2015;10:421–32.
114. Burdea G, Polistico K, House G, Liu R, Muniz R, Macaro N, Slater L. Int J Neurosci. 2015;125(949):58.
115. Jobe JB, Smith DM, Ball K, Tennstedt SL, Marsiske M, Willis SL, et al. ACTIVE: a cognitive intervention trial to promote independence in older adults. Control Clin Trials. 2001;22:453–79.
116. Wolinsky FD, Unvrezagt FW, Smith DM, Jones R, Wright E, Tennstedt SL. The effects of ACTIVE cognitive training trial on clinically relevant declines in health-related quality of life. J Gerontol Ser B Psychol Soc Sci. 2006;61:S281–7.
117. Rebok G, Ball K, Guey L, Jones R, Kim H, King J, Marsiske M, Morris J, Tennstedt S, Unverzagt F, Willis S. Ten-year effects of the ACTIVE cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc. 2014;62:16–24.
118. Renton T, Tibbles A, Topolovec-Vranic J. Neurofeedback as a form of cognitive rehabilitation therapy following stroke: a systematic review. PLoS ONE. 2017;12:1–17.
119. Duff J. The usefulness of quantitative EEG (QEEG) and neurotherapy in the assessment and treatment of post-concussion syndrome. Clin EEG Neurosci. 2004;35:198–209.
120. Breteler M, Arns M, Peters S, Giepmans I, Verhoeven L. Improvements in spelling after QEEG-based neurofeedback in dyslexia: a randomized controlled treatment study. Appl Psychophysiol Biofeedback. 2010;35:5–11.
121. Luber B, Lisanby S. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage. 2014;85:961–70.
122. Draaisma L, Wessel M, Hummel F. Non-invasive brain stimulation to enhance cognitive rehabilitation after stroke. Neurosci Lett. 2018.
123. Flanagan S, Cantor J, Ashman T. Traumatic brain injury: future assessment tools and treatment prospects. Neuropsychiatr Dis Treat. 2008;5:877–92.
124. Crosbie J, Lennon S, Basford J, McDonough S. Virtual reality in stroke rehabilitation: still more virtual than real. Disabil Rehabil. 2007;29:1139–46.
125. Rose F, Brooks M, Rizzo A. Virtual reality in brain damage rehabilitation: review. Cyberpsychol Behav. 2005;8:241–62.
126. Brooks B, Rose F. The use of virtual reality in memory rehabilitation: current findings and future directions. NeuroRehabilitation. 2003;18:147–57.
127. Shin H, Kim K. Virtual reality for cognitive rehabilitation after brain injury: a systematic review. J Phys Ther Sci. 2015;27:2999–3002.
128. Adams R, Finn P, Moes E, Flannery K, Rizzo A. Distractibility in attention deficit/hyperactivity disorder (ADHD): the virtual reality classroom. Child Neuropsychol. 2009;15:120–35.
129. Parsons T, Bowerly T, Buckwalter J, Rizzo A. A controlled clinical comparison of attention performance in children with ADHD in a virtual reality classroom compared to standard neuropsychological methods. Child Neuropsychol. 2007;13:363–81.
130. Birbaumer N, Cohen L. Brain-computer interfaces: communication and restoration of movement in paralysis. J Physiol. 2007;579:621–36.
131. Pfurtscheller G, Neuper C, Birbaumer N. Human brain-computer interface (BCI). In: Riehle A, Vaadia E, editors. Motor cortex in voluntary movements. A distributed system for distributed functions. Boca Raton: CRC Press; 2005. p. 367–401.
132. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP. Neural ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006;442:164–71.
133. Murase N, Duque J, Mazzocchio R, Cohen L. Influence of interhemispheric. Interactions on motor function in chronic stroke. Ann Neurol. 2004;55:400–9.
134. Robertson IH, Murre JJ. Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychol Bull. 1999;125(5):544–75.
135. Sohlberg MM, McLaughlin KA, Pavese A, Heidrich A, Posner MI. Evaluation of attention process training and brain injury education in persons with acquired brain injury. J Clin Exp Neuropsychol. 2000;22(5):656–76.
136. Howe E, Langlo K, Terjessen H, Roe C, Schanke A, Soberg H, Sveen U, Aas E, et al. Combined cognitive and vocational interventions after mild to moderate traumatic brain injury: study protocol for a randomized controlled trial. Trials. 2017;18:483.
137. Gros A, Bensamoun D, Manera V, Fabre R, Zacconi-Cauvin A-M, Thummler S, Benoit M, Robert P, David R. Recommendations for use of ICT in elderly populations with affective disorders. Front Aging Neurosci 2016;8:269.
138. Cicerone K, Dahlberg C, Kalmer K, et al. Evidence-based cognitive rehabilitation: recommendations for clinical practice. Arch Phys Med Rehabil. 2000;81:1596–615.

Chapter 34

The Role of Mindfulness in Neurorehabilitation: From the Monastery to the Clinic

Colette M. Smart

Introduction

Mindfulness is a broad term that refers to a variety of practices that have their historical origins in the various Buddhist traditions of Asia such as Vipassana, Zen, and Tibetan Buddhism. The purpose of these practices is far reaching, but includes the cultivation of certain faculties of cognition (e.g., attention, awareness) and prosocial emotions (e.g., loving-kindness, compassion), as well as moving individuals toward the experience of "enlightenment", or the realization of the non-solidity of the self. Since the 1970s, mindfulness has entered the West, particularly Western healthcare, in a significant way, and the last two decades, in particular, have seen the scientific investigation of mindfulness come fully into mainstream discourse [1]. This has been made possible by an emergence of more scientifically rigorous studies [2], as well as important advances in neuroscience methods that allow for quantification of both state and trait changes associated with short- and long-term meditation practice. Mindfulness-based interventions (MBIs) have been applied in many different health care settings, with an emerging evidence base supporting their application for various mental health and physical illness conditions [3–6]. The current chapter has four main aims:

(1) To review the cognitive neuroscience literature on mindfulness in healthy populations, in order to provide a theoretical rationale for applying mindfulness in a rehabilitation context;
(2) To examine the current state of the evidence for MBIs in neurological populations and prodrome conditions, and whether a relevant theory has been used to inform the application of those interventions;
(3) To examine the critical methodological issues in mindfulness research;
(4) To provide the reader with practical recommendations and case examples of how to provide mindfulness-based treatment to individual patients within a neurorehabilitation context.

What is Mindfulness?

Before addressing the main aims of this chapter, it is useful to consider what we mean when we use the term "mindfulness". Much confusion exists even amongst researchers about how mindfulness is defined. Before examining the theory and evidence for mindfulness in a neurorehabilitation context, one must be clear about

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what mindfulness is, how relevant outcomes are ascertained, and what the purported mechanisms of action are. The reader is introduced to these three points as a context and foundation for interpreting the literature that will be subsequently presented.

Operational definitions of mindfulness and applications. *Contemplative Neuroscience* is a broad field of research, referring to the neuroscientific study of contemplative practice (including meditation and prayer) broadly construed [7]. "Meditation" is not a single thing; it is a very broad term that refers to a variety of different practices that may or may not be affiliated with distinct religious or spiritual traditions. Even within the same tradition (e.g., Buddhism), there can be a variety of practices. Mindfulness is generally considered to come from the Buddhist tradition, although there may be some variations in the practice depending on the particular sect of Buddhism (e.g., Theravada vs. Tibetan). This becomes more of an issue when trying to generalize findings across long-term practitioners. There are many inherent problems in operationalizing mindfulness, and these often pertain to the (presumed) mechanism of action of mindfulness. It is beyond the scope of this review to explore this issue in detail; we would direct interested readers to recent work by Van Dam et al. [1].

Mindfulness-based stress reduction (MBSR), first developed by Jon Kabat-Zinn, was the first program designed to systematically bring mindfulness into health care settings. Given the ubiquity of MBSR in healthcare, and the topic of the current chapter, we present Kabat-Zinn's definition of mindfulness – "paying attention in a particular way, on purpose, in the present moment, and non-judgmentally" [8]. In an effort to bring further operational clarity to the term, Bishop and colleagues [9] defined mindfulness as follows: "The first component involves the self-regulation of attention so that it is maintained on immediate experience, thereby allowing for increased recognition of mental events in the present moment. The second component involves adopting a particular orientation toward one's experiences in the present moment, an orientation that is characterized by curiosity, openness, and acceptance" (p. 232). Using these operational definitions, immediately one can see the relevance to individuals with neuropsychological impairments – attention is a highly sensitive (albeit nonspecific) marker of neurological disease and injury, and disordered attention can have downstream effects on other aspects of cognition such as memory encoding and executive functions [10]. Moreover, difficulties in self-regulation are likewise common sequelae of various neurological disorders, including but not limited to acquired brain injuries and neurodevelopmental disorders [11, 12]. Problems in self-regulation can, in turn, be related to difficulties in self-awareness – either hyperawareness of deficits or anosognosia [13]. Finally, emotional symptoms can occur in neurological illness and injury, either as a specific neurologic symptom (e.g., pseudobulbar affect) or in response to the illness/injury itself [14].

In principle, then, mindfulness holds promise to address many of the common symptoms faced by persons with various neurological disorders. There are a variety of MBIs currently in existence, but the most well-known, frequently used, and well-researched include MBSR [8], mindfulness-based cognitive therapy (MBCT) [15], and dialectical behavior therapy (DBT) [16]. Each of these interventions typically involve some active training in mindfulness meditation, using practices such as body scanning, mindfulness of breathing (sitting meditation), and gentle hatha yoga. These practices complement the cultivation of "attitudes of mindfulness", such as non-judging, patience, acceptance, and letting go. Other interventions, such as Acceptance and Commitment Therapy (ACT) [17], may focus more on strategies to support reappraisal or attitudinal shifts, without necessarily asking individuals to engage in active mindfulness practices. MBIs have many potential benefits in the clinical domain; they are often disseminated in time-limited groups, after which individuals can engage in self-led practice. This makes treatment delivery both time and cost-effective. In addition, while MBIs can lead to both physical and emotional symptom

reduction, the focus on cultivating acceptance is highly relevant to persons with neurological illness and injury, persons who may never experience a complete recovery.

MBIs are complex, multi-faceted interventions, and one might wonder what the active ingredients are that lead to therapeutic effects. For example, are observed changes due to the attention training component in sitting meditation, or possibly due to the training in reappraisal of experience through the attitudes of mindfulness? So-called "dismantling studies" [18] could be applied to ascertain what those active ingredients are, and whether they preferentially affect certain symptoms (e.g., [19]). While these are valid questions, one could argue that the holistic, multi-faceted nature of MBIs is actually one of their greatest strengths. While other treatments for neurocognitive and neurobehavioral symptoms already exist (e.g., Attention Process Training, Cognitive Behavior Therapy), MBIs are distinctive in their potential to treat multiple symptoms simultaneously, with a promise to provide a more efficient and holistic treatment approach. This seems pragmatic, given that no two people with the same neurological diagnosis have the same profile of impairments. A further potential benefit of MBIs pertains to *transfer of training*, a perennial problem that has plagued the field cognitive training interventions (e.g., [20]). That is, do interventions done in the clinic or on a computer meaningfully transfer to patients' everyday activities? The whole intent of mindfulness training is that, with continued practice, one cultivates a mindful way of being that inherently translates to all aspects of daily life. This comes through continued and repeated practice of the techniques, as well as explicit instruction in "mindfulness of daily activities".

At this juncture it is important to clarify that "cognitive training" and "cognitive rehabilitation" are sometimes used interchangeably in the research and clinical literature, when they are in fact distinct entities. For the purposes of this chapter, cognitive training pertains to any kind of "drill and practice" activity that is supposed to directly affect a certain cognitive process and then generalize to real-world behavior (although the evidence for this transfer of training remains an issue of debate). Cognitive training is often targeted toward healthy populations (e.g., older adults), and is used in clinical populations as well. By contrast, cognitive rehabilitation is targeted toward persons with clinical impairments, and can involve cognitive training as well as compensatory strategy training and mood and psychosocial enhancement. Outcomes are more tied to an individual's life goals as opposed to improving cognitive performance per se [21]. As a holistic form of clinical intervention, MBIs likely fit better within the framework of cognitive rehabilitation, although as the clinical research reviewed in this chapter will indicate, often researchers will only focus on specific aspects of the treatment.

Mechanisms of action and measurement of outcomes. Over the last two decades, there has been a remarkable proliferation of studies on mindfulness, which have primarily focused on examining group differences between those who do and do not practice mindfulness (i.e., experts vs. controls), or those who do or do not receive it as a clinical intervention. In their meta-analysis of psychological effects of meditation, Sedlmeier, and colleagues [22] note that a majority of prior studies on meditation are largely atheoretical, examining dependent variables without clear hypotheses that come from either the meditative or psychological traditions. Only more recently have researchers begun to systematically investigate the mechanisms of action by which change occurs. For example, is being mindful a trait or individual difference characteristic that leads to other outcomes [23]? This approach is often seen in the social psychology literature [24]. Other times, mindfulness refers to the cultivation of a certain attitudinal stance toward one's experience that leads to a resolution in symptoms such as those of depression and anxiety. Examples of this are seen in certain applications within clinical psychology, such as ACT [17]. At yet other times still, mindfulness is referred to an active practice or skill that cultivates changes over time in cognitive and emotional functions. This approach is most commonly taken in the literature from cognitive neuroscience.

In practical application, mindfulness likely encompasses all of these mechanisms to some degree, although researchers in specific disciplines may choose to focus on one or another of these specific mechanisms of state, trait, or attitude. Within a neurorehabilitative context, a common distinction in mechanism of action is *restitution* versus *compensation* [25]. Applied to mindfulness, do we expect to see restitution in underlying brain or cognitive function (e.g., enhancement of attention)? This will necessitate the use of objective measures of change, such as cognitive/behavioral or direct neural measures. Conversely, if mindfulness is meant to promote compensation (e.g., remembering to use a memory book), then self-report measures of variables such as self-efficacy, strategy use, or mood may be more effective outcomes. Again, as Sedlmeier et al. [22] noted in their meta-analysis, researchers infrequently apply this level of theory to assessing mechanisms and outcomes of mindfulness. As such, in interpreting the available literature, it is important to consider whether any null findings may be due to a mismatch in mechanism and outcome measure, leading to a subsequent under-estimation of effects [26].

(1) **Theoretical Basis for the Application of Mindfulness – Evidence from Cognitive Neuroscience Studies in Healthy Populations**

Broadly speaking, the mindfulness literature has progressed along two parallel tracks in the last two decades. One track has examined the clinical impact of mindfulness in various psychiatric and medical populations. A second track has sought to understand the brain, behavior, and psychological correlates of mindfulness in healthy samples, both "novice" and "expert" populations. Many of the studies on healthy samples use cognitive neuroscience methods, integrating self-report and behavioral observations with direct measurements of neural function. Novice studies tend to involve people with little to no background in meditation who undergo short-term meditation training, anything from a brief 15-min exposure in the lab to eight weeks of MBSR. (In some studies, the term "novices" is used to refer to persons who are in fact meditation-naïve.) By contrast, expert studies tend to involve practitioners who have been committed to ongoing practice for a longer period time (e.g., at least 3 years), and who often have adopted a wider system of values and beliefs to support the practice (e.g., Zen Buddhism). It is these novice and expert studies in healthy populations that provide a window into the basic mechanisms of the "mindful brain", helping us to understand the boundaries of structural and functional neuroplasticity associated with meditation practice in individuals with intact nervous systems. This information provides a framework within which to understand the potential clinical applications of mindfulness in neurological populations, as well as paradigms to test the mechanisms of action when salutary effects do occur.

Given the exponential increase of research on the impact of mindfulness [1], it would be impossible to report on individual studies and reach meaningful conclusions. Fortunately, recent years have seen the publication of at least three key meta-analyses that focused on behavioral, neural structural, and functional findings, respectively. Meta-analyses allow for a more comprehensive and rigorous analysis of the available evidence than individual studies, and in turn, more robust conclusions.

Behavioral Effects

Sedlmeier and colleagues [22] conducted a comprehensive meta-analysis on the psychological effects of meditation, focused on nonclinical groups of adult meditators where there was a control group or comparison condition. Although they initially identified 595 possible studies, only 163 met inclusion criteria, and came from a combination of journal articles (125), book chapters (28), and unpublished dissertations (10). Studies were either cross-sectional (i.e., comparisons of "expert" meditators with those with no meditation experience), or pre/post-intervention designs.

Types of meditation studies reviewed were either mindfulness or transcendental meditation (TM). Dependent variables included those related to emotion (e.g., anxiety, emotion regulation, coping strategies, relaxation ability), personality traits (e.g., neuroticism, empathy, and mindfulness), as well as cognitive variables such as attention, intelligence, and learning and memory.

At a gross level, examining across all studies, there was a medium effect size (mean $\bar{r} = 0.28$; $d = 0.58$) for the impact of meditation on psychological variables. This seems to be commensurate with a prior meta-analysis of psychological, educational, and behavioral treatments, including psychotherapy, which also yielded medium effect sizes, i.e., $d = 0.50$ [27]. In other words, the impact of meditation on healthy practitioners is comparable to the impact of behavioral treatments and psychotherapy on clinical samples. Meditation was shown to have appreciable effects that went beyond that expected based on mere relaxation, and a smaller yet still significant benefit over active control conditions such as cognitive training, positive thinking, or sports activity. Interestingly, the benefits of meditation were found regardless of whether the study design was randomized or not. There was no effect of age, and only a very small effect of gender (with a greater impact in males vs. females). Prior claims have been made that TM is superior to all other types of meditation (e.g., [28–30]). When examining only journal articles (judged to have the most rigorous review process and therefore most reliable effect size estimates), the difference in the effect size between TM ($\bar{r} = 0.27$) and mindfulness ($\bar{r} = 0.26$) was found to be negligible.

In terms of the impact on specific dependent variables, the largest effects were seen for positive changes in relationships ($\bar{r} = 0.44$), state anxiety ($\bar{r} = 0.37$), negative emotions ($\bar{r} = 0.34$), and trait anxiety ($\bar{r} = 0.32$). Cognitive measures were also affected, but less so than emotional measures. For example, focused and open attention were associated with medium effect sizes (attention: $\bar{r} = 0.28$; mindfulness: $\bar{r} = 0.28$), similar to the average for the overall effects of meditation. The authors drew attention to the fact that effect sizes were smaller for cognitive versus emotional variables; this is counterintuitive, given the focus in both contemplative and psychological theory on regulating attention and its downstream effects on other variables. The authors interpreted these findings to mean that meditation actually impacts cognitive variables by reducing counterproductive emotions and feelings – in other words, emotion is a moderator of the impact of meditation on cognition.

Overall, meditation – including mindfulness – appears to have salutary effects on both emotional and cognitive variables at a level that could be clinically meaningful in patient populations. The degree of benefit is comparable to that seen in other behavioral and psychotherapeutic interventions, and extends beyond that which would be expected for mere relaxation training and other control conditions. Encouraged by these psychological findings, we now turn to studies focused on neural measures, specifically structural and functional imaging findings.

Neural Structural Effects

If meditation has an impact on the self-report of emotions and behavioral functioning, are such changes represented in the brain in terms of structure and/or function? The first study of structural brain changes associated with meditation was published by Lazar et al. [31]. Since that time, while a large number of studies have been conducted examining behavioral and functional findings, fewer studies have sought to understand the neural substrate differences that may be associated with meditation. Moreover, due to a variety of analysis methods and types of meditation, drawing broad conclusions about the impact of meditation remains challenging.

Fox and colleagues [32] conducted a meta-analysis of 21 neuroimaging studies of 300 healthy practitioners, yielding 123 brain morphology differences across these studies. They included only studies where participants actually practiced meditation (as opposed to studies of

"trait mindfulness"). The brains of long-term practitioners could differ from non-meditators due to a variety of factors unrelated to meditation. As such, the authors conducted additional analyses separating out cross-sectional studies with expert practitioners from those short-term training studies with novice practitioners. The novice studies used randomized, experimental designs involving 5–60 h of meditation. If similar structural changes are shown in both types of studies (i.e., cross-sectional vs. pre/post), then one can be more confident that the brain differences seen in long-term meditators are due to the actual effects of meditation. In interpreting the findings, it should be noted that, while the majority of studies (17/21) included practitioners within the Buddhist tradition, their practice was not limited to mindfulness alone.

Using an anatomical likelihood estimation (ALE) meta-analysis to identify brain regions showing consistent heterogeneities in meditation practitioners, the authors found eight brain regions that were found to be consistently altered in meditators, involving both gray and white matter. The studies analyzed included varied neuroimaging techniques, such as volumetry of a region of interest (ROI), fractional anisotropy of white matter tracts, diffusivity, and gyrification. The ROI included areas implicated in meta-awareness (frontopolar cortex/BA10), exteroceptive and interoceptive body awareness (sensory cortices and insula), memory consolidation and reconsolidation (hippocampus), self and emotion regulation (anterior and mid-cingulate; orbitofrontal cortex), and intra- and interhemispheric communication (superior longitudinal fasciculus; corpus callosum). These differences were relatively consistent regardless of whether the participants were novice or expert meditators, although some areas seemed unique to novices alone (e.g., caudate nucleus, thalamic radiation, and corona radiata). There was also a trend toward greater differences in the left (69) versus the right hemisphere (49) ($\chi^2(1) = 3.39$, $p = 0.066$). The omnibus effect size for the impact of meditation was medium ($d = 0.46$, $\bar{r} = 0.19$). Interestingly, of the 16 studies that reported effect sizes for correlations between structural differences and meditation experience, only 6 were statistically significant and only 2 were based on whole-brain analyses as opposed to ROIs (i.e., nonindependent analyses). Likewise, 9 reported correlations between structural findings and behavioral measures (e.g., perceived stress, pain sensitivity) were significant, but again based on ROI analyses. Regarding the quality of available evidence, the authors raised concerns about publication bias (based on a funnel plot of mean effect sizes), suggesting preferential publication of large positive results, and/or non-publication of negative results (i.e., the "file drawer" problem).

In sum, these findings indicate that meditation – including mindfulness – is associated with structural brain changes in key areas of function that can be affected by neurological illness and injury (e.g., meta-awareness, memory, and emotion regulation). Short-term practitioners may be considered a proxy for clinical samples who undergo time-limited training in mindfulness. Given that similar findings were seen in short and long-term practitioners, this is encouraging in terms of potential for neuroplasticity in the injured brain. That said, greater rigor in future research is needed to strengthen the claims that meditation is associated with, and can cause, structural brain changes.

Functional Effects

Fox and colleagues [33] conducted a more recent meta-analysis focusing on the functional neural effects of meditation. While prior reviews had examined methods such as EEG and ERP (e.g., [34]), this review focused solely on functional MRI (fMRI) and positron emission tomography (PET) studies. The key hypothesis of the meta-analysis was to determine whether practices that differ on the psychological level show distinctive patterns of activation at the neural level. The authors used four different categories of meditation that have previously been articulated in the literature, as described in Table 34.1: focused attention, open monitoring, mantra

Table 34.1 Taxonomy of four broad categories of meditation, cutting across contemplative traditions (after Fox et al. [33])

Meditation type[a]	Description	Purported effects
Focused attention	One brings continuous attention to a particular "object" (e.g., the breath, a body part, or an external object)	Over time, one learns how to more efficiently disengage from extraneous thoughts or stimuli (i.e., mind-wandering)
Open monitoring	One brings attention to the present moment and witnesses all mental arisings with an open, impartial, and accepting attitude, neither accepting nor rejecting what arises	Cultivation of present-moment awareness and a non-judgmental attitude to experiences and events, internal and external
Mantra meditation	Also involves focusing on an object (i.e., the mantra) but with additional oro-linguistic demands	The mantra is said to "purify thoughts", presumably leading to similar reductions in mind-wandering as in FA
Loving-kindness/compassion meditation	One purposefully cultivates feelings of empathy, sympathy, altruism, and joy towards others through active contemplation of the happiness, well-being, and/or suffering of others	An increase in prosocial emotions and behaviors toward others

[a]For a more thorough description of the distinction between focused attention and open monitoring, the reader is referred to Lutz et al. [156]

meditation, and loving-kindness/compassion meditation. Although they conducted ancillary analyses on some other types of meditation (e.g., visualization), given the relative paucity of data on these practices, the primary analyses of interest remained with the four types of meditation previously mentioned. Note that this taxonomy of meditation cuts across contemplative traditions and so, once again, the framework is not unique to mindfulness meditation. That said, within MBSR and MBCT, participants are likely to be exposed to three of the four practices within their training (i.e., focused attention, open monitoring, and loving-kindness). As such, only activations associated with these three practices are discussed below.

Seventy-eight fMRI and PET studies were reviewed, incorporating 527 participants. The authors conducted four separate ALE meta-analyses on each of the four practices, based on a total of 31 experiments from 25 different studies. Similar to the structural meta-analysis, studies included both novice and expert meditators, and a majority, but not all, participants came from various Buddhist traditions. A preliminary effect size meta-analysis based on 17/25 studies found medium effect sizes for both activations ($d = 0.59$) and deactivations ($d = -0.74$). Some brain areas were recruited consistently across multiple techniques – including insula, pre/supplementary motor cortices, dorsal anterior cingulate cortex, and frontopolar cortex. However, as the authors hypothesized, there were reliable differences in activation and deactivation that were found in comparing the four categories of practice, differences that are consistent with the purported aims of those practices. These are presented in Table 34.2. For each of the types of meditation, comparing novice and expert meditators yielded nearly identical results, suggesting that functional differences seen in long-term meditators are, in fact, due to the effects of meditation. Similar to their structural meta-analysis, the authors found evidence of significant publication bias in the current meta-analysis (particularly the non-publication of null results), and neuroimaging studies tend to have smaller sample sizes than behavioral studies. This indicates further methodological issues have to be addressed in future research in this area in order to develop more robust empirical inferences.

Table 34.2 Patterns of activation and deactivation based on the three main styles of meditation relevant to mindfulness, as presented in Fox et al. [33]

Meditation type	Activations and purported psychological correlates	Deactivations and purported psychological correlates
Focused attention	Prefrontal cortex = top-down focusing of attention and voluntary regulation of thought and action (i.e., self-regulation)	Ventral posterior cingulate cortex and left inferior parietal lobule = episodic memory and conceptual processing
Open monitoring	Insula = awareness of viscero-somatic body signals; Left inferior frontal gyrus, pre-supplementary motor area, supplementary motor area, and premotor cortex = voluntary control of action; Rostrolateral prefrontal cortex and mid-dorsolateral prefrontal cortex = cognitive control and metacognitive awareness	Right thalamus = decreased sensory gating of information
Loving-kindness/compassion meditation	Right anterior insula/frontal operculum, secondary somatosensory areas extending into the anterior inferior parietal lobule, and activation near the parieto-occipital sulcus = awareness of bodily sensations and feelings	No areas of deactivation observed

Using Cognitive Neuroscience to Generate a Theory of Application in Clinical Populations

Being able to dissociate different practices by their neural effects is instructive in terms of deciding which practices to apply in different clinical populations. For example, attention regulation is a common clinical problem in many neurologic disorders, which suggests that training in focused attention may be useful in this context. Conversely, individuals with certain disorders such as those impacting the right hemisphere, emotion regulation, and empathy might benefit from training in either or both of open monitoring and loving-kindness/compassion meditation.

It is also noteworthy that these latter two practices involved robust activations involved in interoceptive awareness. A sizeable body of literature has documented the association between impairments in interoception and psychopathology; for example, a lack of access to interoceptive signals, as well as difficulty recognizing, discriminating, or labeling interoceptive signals is often associated with various psychological conditions (e.g., [35–37]). Although traditional evidence-based treatments have tended not to emphasize the role of the body, interoceptive exposure is becoming increasingly acknowledged as a transdiagnostic approach to address a variety of problematic symptoms [38]. Given the findings in both the functional and the structural meta-analyses, this suggests that actively working with patients to develop interoceptive awareness is an avenue worth further pursuit, and could improve certain clinical symptoms in persons with neurological disorders.

Figure 34.1 provides a hypothetical model for the application of MBIs to persons with neurological illness and injury, based on information derived from the cognitive neuroscience literature. This model could be used to inform and test specific hypotheses about the mechanisms of impact and outcomes of mindfulness in neurological populations.

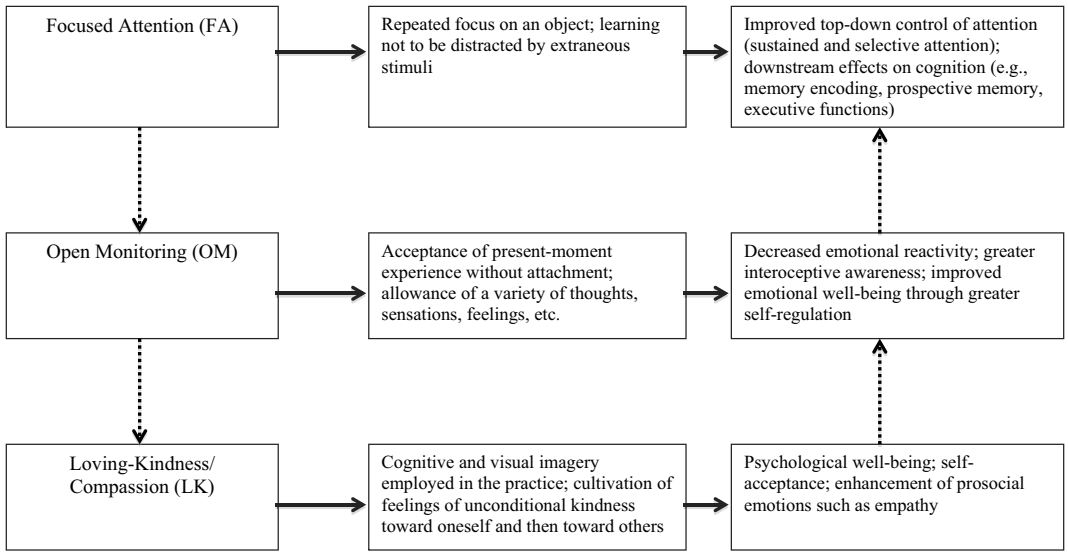

Fig. 34.1 A cognitive neuroscience-informed model of the hypothetical pathways through which mindfulness could impact brain, behavior, and psychological functioning in persons with neurological illness and injury. *Notes*: [1]Although FA and OM are discussed in the literature as separate practices, in certain traditions (e.g., Tibetan Buddhism), FA is a precursor to OM (i.e., *shamatha–vipashyana*) [159]. Novices spend more time training in FA, and with proficiency, develop effortlessly into a state of OM [156]. Depending on the particular practice session, the practitioner may go back and forth between FA and OM in an effort to self-regulate their current mental state. This is consistent with neuropsychological theories of attention [10], whereby sustained attention is a prerequisite to selective and divided attention. [2]Both within MBIs, as well as in many Buddhist traditions, training in FA and/or OM is needed to effectively practice LK, in order to be able to stay with intense present-moment experience including feelings of sadness or grief as well as positive emotions [160]

Considerations in Interpreting the Literature

In sum, a fairly sizeable body of literature has accumulated to document the brain–behavior impact of mindfulness training in healthy individuals. Novice studies, by definition, tend to involve active interventions, so one can more comfortably use the language of neuroplasticity, meaning that structural and functional brain changes are a direct result of the practice. Particularly for those studies that use a randomized controlled trial (RCT) design, one can have a certain degree of confidence that the actual practice of mindfulness resulted in the observed changes in outcome measures. Expert studies tend to be more observational in nature, based on comparisons of long-term meditators with meditation-naïve controls. For those seeking precision in the use of terminology, expert studies do not allow us to conclusively say that meditation has led to neuroplasticity. Rather, we can conclude that individuals who practice mindfulness long-term demonstrate structural and functional brain differences (and differences in self-report and behavior) as compared to controls. The findings from the Fox et al. [32, 33] meta-analyses suggest that these differences are associated with meditation, given that they were similar to those observed in novices.

That said, one cannot rule out the contribution of other factors. For example, individuals following a Buddhist path may follow certain precepts such as refraining from alcohol or eating a vegetarian diet, factors which may positively impact cardiovascular and cerebrovascular function and, in turn, cognitive function [21, 39]. Additionally, such individuals may be part of a community of other practitioners and benefit from regular social support, something that has been shown to enhance psychological well-being [40].

Individuals predisposed to long-term meditation may also possess certain personality traits that support overall health, including brain health, such as increased openness to experience and conscientiousness and decreased neuroticism [41–43]. Being able to disentangle these factors is no easy undertaking, and indicates that group differences may be attributable to factors beyond the practice of mindfulness techniques. The Shamatha Project [44] is an innovative study in this regard, using a prospective, longitudinal design to establish the short and long-term impact of mindfulness in individuals with limited prior exposure to the practice. Van Dam et al. [1] also draw attention to the small sample sizes that tend to be included in neuroimaging studies, and the need for greater replications and larger samples to generate more convincing conclusions.

One final consideration is the apparent divergence between structural, functional, and behavioral findings. Both structural and functional imaging methods indicate that meditation is associated with changes in brain regions associated with various cognitive functions such as attention, self-regulation, interoceptive awareness, and memory. However, self-report and behavioral findings suggest that effects are greater for emotional versus cognitive tasks. How does one interpret this dissociation? One hypothesis pertains to neuroplasticity. That is, our understanding of the timescales of change in brain structure, function, and manifest behavior, and how these interact, remains poorly understood. It may be that neuroimaging methods are more sensitive to detect change in the brain before it becomes manifest in outward behavior [45]. This speaks to the necessity of conducting studies with multiple outcome methods and longer term follow-up, in order to understand the dynamic nature of change over time [46, 47]. Another hypothesis is that it is an artificial distinction to separate "cognition" from "emotion" in terms of the effects of meditation, and in fact, cognition, emotion, and interoception are likely to interact in dynamic and reciprocally influential ways. In a laboratory, one can easily administer "cold cognitive" tasks such as *n*-back working memory tasks or continuous performance tests of attention. However, in the actual practice of mindfulness (and even in everyday life), such distinctions may become less meaningful. For example, in the early stages of the practice, the novice meditator is simply learning the basic technique of orienting one's attention to the present moment over and over again. With greater ease in the technique, it is at this point that individuals may become more aware of how lapses in one's attention associated with self-referential thoughts, as well as feelings, can trigger negative emotional reactions. This is often the time in the practice when non-judgmental awareness is emphasized. Likewise, for the person with neurological injury or illness, cognitive slip-ups and errors – even cold cognitive ones – could be a trigger for emotional reactivity [48]. Future studies could tease these relationships apart by using tests of "cold" versus "hot" cognition [49] and seeing if mindfulness preferentially affects performance on such tests.

(2) Clinical Application of Mindfulness in the Neurorehabilitation Context: A Review of the Available Evidence

The previously reviewed literature suggests that mindfulness may be beneficial in improving different aspects of psychological functioning, such as attention, working memory, emotion regulation, and psychological well-being. Naturally, then, one would ask whether mindfulness could be effective when individuals have frank impairment in these domains. That is, while MBIs have been shown to improve cognitive and emotional functioning in non-neurological populations, is a certain minimal level of cognitive ability a prerequisite to actually engage in the intervention itself? Consider, for example, the fact that while cognitive training has some demonstrated benefit in healthy older adults who are cognitively intact, such training has limited benefit in persons with dementia [21].

Recent data suggest that complementary and alternative medicine (CAM) practices, including meditation, are increasing in popularity as more patients seek a holistic approach to healthcare [50]. For example, an estimated 70% of Canadians regularly use CAM interventions to

improve their quality of life [51]. Despite increased interest on the part of patients, only comparatively recently has mindfulness been systematically evaluated in a neurorehabilitation context. This field is in its infancy relative to the wider body of literature on mindfulness. A review of the evidence to date is provided below. In some areas, enough rigorous studies have accumulated to warrant systematic reviews and meta-analyses; in other cases, individual studies are presented. The literature is organized by diagnosis, respecting how a majority of studies are conducted. Note that it would be impossible to review every neurological diagnosis; rather, this review has focused on some of the more prevalent conditions and those most likely to be seen in the context of neurorehabilitation. In addition, the evidence pertains only to interventions where mindfulness as typically conceived was a central focus (e.g., breathing meditation, body scan, loving-kindness). Ancillary practices that are believed to cultivate a state of mindfulness, such as yoga and Tai Chi, were excluded.

Neurodevelopmental Disorders

Attention deficit hyperactivity disorder (ADHD). ADHD was probably one of the first populations in which MBIs were investigated. ADHD is a neurodevelopmental disorder that begins in childhood and is currently classified using either a primarily inattentive type, primarily hyperactive type, or a combined type [52]. Prevalence estimates of ADHD are 11% for children and 8.7% for adolescents, with 4.4% being affected in adulthood [53]. Persons with ADHD experience core difficulties in the self-regulation of attention and behavior. Given that mindfulness has been presented as a practice of self-regulation [9], there seems to be a compelling rationale for why MBIs might be useful in the management of ADHD.

Cairncross and Miller [54] conducted a recent review and meta-analysis of the literature on MBIs for persons with ADHD. They included books and dissertations as well as peer-reviewed articles, as long as data were available to compute an appropriate effect size. Ten studies, typically using some form of MBSR or MBCT, were included in their final analyses. Overall, the authors found medium effect sizes obtained for each group of inattention (d = –0.66) and hyperactivity/impulsivity (d = –0.53). They also examined rater type (self vs. informant) and age as possible moderators. Rater type did not moderate the impact on inattention (self: d = −0.66; informant: d = −0.98) or on hyperactivity/ impulsivity (self: d = −0.57; informant: d = −0.623). For inattention, a larger effect size was seen for adults (d = −0.91) versus children (d = −0.66), suggesting some moderating effect of age on this symptom cluster. For hyperactivity, both adult (d = −0.68) and child (d = −0.47) effect sizes were in the medium range, but again appearing to show a greater effect in adult samples. With medium to large effect sizes being observed, these findings suggest that MBIs are an effective treatment for both youth and adults with ADHD.

The greater observed effects in adult versus youth samples were noteworthy and could have occurred for a few different reasons. The authors draw attention to the fact that little information was available on the exact nature of the practices taught in the youth versus adult groups. One cannot assume that practices taught to adults are developmentally appropriate for youth, and this may explain some of the greater effects observed in adult samples. Youth-oriented MBIs are currently available, such as *Still Quiet Place* [55], and future studies on ADHD may wish to examine whether programs developmentally tailored to young persons are more effective than those that are not. Another possibility the authors raised was that adults have more insight into their symptoms, as well as more readily accessible environmental supports and modifications to actualize the practices in daily life. Both of these points speak to the issue of age as a dimension of *tailoring* MBIs, something discussed in detail below.

Overall conclusions. The findings from Cairncross and Miller [54] suggest that MBIs are an efficacious treatment for children and adults with ADHD, although some interpretive caveats should be made. In terms of the quality of the

evidence, it is unclear whether the authors separated out self/informant report questionnaire data from objective cognitive/behavioral data, and one wonders whether the effects would differ using data type as a moderator. Moreover, unlike other reviews discussed in this chapter, Cairncross and Miller [54] did not restrict their search to only controlled trials, as is common. Rather, their review included several $n = 1$ case series as well as treatment-as-usual comparisons, which means one must temper the overall conclusions that can be made about the efficacy of MBIs in this population. That said, corrections for possible publication bias and the file drawer problem only resulted in minor reductions in the calculated effect sizes. This indicates that the current findings are probably representative of the overall efficacy of MBIs for persons with ADHD, and suggest that this treatment can be quite effective, perhaps more so in adults versus children.

Neurological Injury and Illness in Adulthood

Traumatic brain injury (TBI). TBI is a common and potentially disabling condition. Prevalence estimates vary substantially depending on injury severity (i.e., concussion is more common than more severe injuries), age group (i.e., youth and older adults most susceptible), and context (e.g., injuries sustained through sports vs. other contexts). The Brain Injury Association of Canada [56], for example, reports that 100,000 Canadians will experience a brain injury each year, with approximately 1.5 million individuals living with a brain injury in Canada. No two brain injuries are alike, even within the same so-called severity category. Likewise, symptom profiles can be highly varied and include (but are not limited to) impairments in attention, memory, executive dysfunction, and regulation of mood and behavior [57].

The field of cognitive rehabilitation writ large primarily arose out of the care of persons with brain injuries [10], and persons with TBI remain among those most likely to be referred for neurorehabilitation. Given that MBIs have been shown to improve functioning in many of the areas affected by TBI, it makes sense to consider whether MBIs would be effective in this population. Interestingly, in contrast to many of the other diagnoses discussed subsequently, at present there appears to be no systematic review on the effect of MBIs conducted for the TBI population. Instead, a narrative review of select studies is provided.

Azulay et al. [58] disseminated a modified form of MBSR tailored to persons with chronic mild TBI/post-concussive syndrome. Twenty-two participants (with equal numbers of men and women) were enrolled over a two-year period into mixed etiology groups; this allowed for a critical mass of persons with mild TBI to accumulate with relevant data to be analyzed. The intervention itself took place over 10 weeks instead of 8, and focused on enhancement of attention skills, and additionally drew attention to participants' internal and external experiences that accompanied greater acceptance and non-judgment of themselves. Outcomes included self-report measures as well as neuropsychological tests of attention and memory.

Following the intervention, the strongest effects were seen for perceived self-efficacy and quality of life, particularly as related to the management of cognitive and emotional symptoms (all moderate effect sizes). Post-concussive symptoms decreased with small effect sizes, more so for cognitive and emotional symptoms versus somatic symptoms. Finally, small effect sizes were seen for tests of attention (Continuous Performance Test of Attention and the Paced Auditory Serial Addition Test). Of the 21 individuals with pre/posttest data, one-third of these ($n = 7$) showed clinically significant change from a lower functioning category (e.g., impaired) to a higher functioning category (e.g., average) on either or both of the attention measures. No statistically significant effect was observed for verbal new learning and memory. This study indicated that persons with chronic symptoms post-mild TBI can experience both cognitive and emotional benefits following a tailored form of MBSR. A major drawback of this study was the

lack of a control group. However, all participants were at least 9 months post-injury and had participated in multiple other forms of rehabilitation, which at least minimizes the possibility that any positive intervention changes could be simply due to spontaneous recovery. Additional details on aspects of how this program was tailored are described in a subsequent section.

Depression is a common problem in persons with TBI, with some estimates of prevalence as high as 61% [59]. Not only does depression influence quality of life and well-being, but it may also have a negative impact on engagement with cognitive and physical rehabilitation and health-related quality of life [60]. Bédard et al. [61] conducted an RCT examining the impact of a 10-week MBCT program targeting depression in persons with TBI. This was based on a previous pilot study that examined the impact of an 8-week program in a similar population, but without a control group [62]. In this multi-site trial, 100 participants were randomized either to a 10-week version of the original program (n = 52), or treatment as usual (n = 48). All participants had Beck Depression Inventory-II (BDI-II) scores of 16 or higher and had completed all "standard treatments" for brain injury; concurrent antidepressant use was not an exclusion criterion. The authors provided details on how the intervention was specifically tailored for persons with TBI, including lengthening the overall course but shortening the duration of individual sessions, shortening the duration of meditation practice to 20−30 min, and using simplified language, repetition, and visual aids. After attrition, 38 participants had complete data for each condition and were included in the final analysis. Compared to pretest, the MBCT group showed a greater reduction in depressive symptoms on the BDI-II (medium effect size); however, no such improvement was seen on either the Patient Health Questionnaire-9 or the Symptom Checklist-90-R. Given that the program was cognitive therapy-based, this might explain the preferential effect on the BDI-II, based on the cognitive model of depression. Reductions in depression were maintained at 3-month follow-up. There was a trend toward enhanced mindfulness on two measures (the Philadelphia Mindfulness Scale and the Toronto Mindfulness Scale) but these did not reach significance, each showing small effect sizes. Overall, this well-designed study showed that tailored MBCT can be effective in reducing post-TBI depression with clinically meaningful effects.

The MBIs most commonly administered in a clinical context are MBSR and MBCT. However, in the neurological realm, an additional protocol that is becoming more commonly used is Goal Management Training (GMT) [63]. GMT was designed to aid individuals dealing with executive dysfunction. It is based on Duncan's theory of "goal neglect", the premise that individuals experience executive dysfunction because they fail to maintain attention to goal-relevant steps and become distracted with irrelevant stimuli [64]. GMT is a manualized treatment divided into different modules to support goal management, the early ones being oriented to the active practice of mindfulness in order to decrease "auto-pilot". GMT is somewhat different from programs such as MBSR and MBCT insofar as the entire program is not aimed at cultivating mindfulness for its own sake, but rather mindfulness is a "means to an end" of reducing goal neglect. We highlight the studies below because they put particular emphasis on the mindfulness training component of GMT, and may speak to the impact of mindfulness on goal management.

Novakovic-Agopian et al. [65] applied a modified form of GMT that highlighted the mindfulness training component as a means to cultivate attention regulation in service of goal management. Participants were 16 patients with chronic (i.e., >6 months) acquired brain injury, the majority of whom (n = 11) had TBI and mild to moderate difficulty on a variety of executive domains believed to impact instrumental activities of daily living. The modified GMT program took place over five weeks, comprised of ten 2-h sessions of group training, 3 individual 1-h sessions, and 20 h of home practice. The first half of the course emphasized "mindfulness-based attention regulation training", and the second half focused on strategies to promote goal management. Participants had access to CDs with

guided practices, and to facilitate transfer to daily life, they were given the phrase, "Stop-Relax-Refocus" as a cue to regulate one's attention back to the task at hand. From the information provided by the authors, it appears that, similar to GMT, mindfulness was used primarily as an attention training technique, without the additional "attitudes" of mindfulness such as acceptance, non-judgment, and loving-kindness, nor did it involve the use of mantras, breathing, or visualization. [8]. A pseudo-random crossover design was employed whereby half of the participants started in the GMT condition and half in an education control group; after 5 weeks, both groups switched conditions. After 5 weeks, the GMT group showed significant improvement in standardized tests of attention and executive function as well as memory domains, as compared to the control group who showed minimal appreciable change. Individual tests showing improvement included working memory, mental flexibility, inhibition, and sustained attention, as well as learning and delayed recall memory. No differences were observed for processing speed. There was also a trend for fewer task failures on the Multiple Errands Test [66] for the GMT group, but the findings could not be statistically confirmed due to small sample size. After the groups crossed over into the alternate condition, at week 10 the group receiving GMT showed very similar improvements as the group originally receiving GMT. In addition, the original GMT group maintained their gains after five weeks of education, with further improvements in attention, executive function, and working memory domains. Participants also self-reported improvements in many aspects of goal setting, maintenance, focus, energy, and anxiety.

A follow-up analysis of the same participants (n = 12) by Chen et al. [67] examined whether such cognitive changes were represented at the neural level, based on fMRI responses to a task requiring top-down attention regulation to goal-relevant information. The authors examined specific regions of interest (ROIs) (i.e., extrastriate cortex and dorsolateral prefrontal cortex). They created difference scores based on activations in these ROIs under different task conditions, with positive scores indicating greater clarity of goal representation or attention to goal-relevant information. Nine of 11 participants with pre/post-GMT data showed positive changes in the extrastriate cortex ROI, as compared to only 1/5 participants with pre/post control data. In the original 5-week period, 3/4 GMT participants showed positive scores, compared with 0/3 in the education group. Six of 7 participants who crossed over from education to GMT showed a positive change in this fMRI index following GMT. The authors interpreted these findings to demonstrate that GMT sharpened participants' goal-directed attention regulation through filtering out of irrelevant stimuli. Examining the dorsolateral prefrontal cortex ROI, the findings were less clear-cut, with some participants showing a positive change (i.e., 5/11 in GMT, 3/5 in education) and the remainder showing a negative change. Follow-up analyses indicated that the participants' baseline state modulated their response to intervention as measured by dorsolateral prefrontal cortex activity, so that lower pre-intervention scores predicted greater changes in a positive direction and higher pre-intervention scores predicted greater changes in a negative direction. These findings were unanticipated by the researchers, and were interpreted to mean that individual factors (e.g., strategy use) should be taken into account when applying treatments in individual patients even within a group format.

In addition to the aforementioned studies, additional work has been done examining the impact of MBIs on mental fatigue, a common symptom of TBI and particularly mild TBI/concussion. The impact of MBIs on mental fatigue in persons with various neurological disorders is discussed later in this review.

Overall conclusions. Although a small number of studies have been reported, and the possibility of publication bias exists, the evidence suggests that MBIs hold promise for managing both moods as well as cognitive function in persons with chronic TBI. At present there is no systematic review of the impact of MBIs in TBI, which may be due in part to the extremely broad

and heterogeneous nature of TBI as a diagnosis. Future work looking at specific subgroups may generate meaningful inferences about the impact of MBIs in persons with TBI. For example, persons with mild TBI/concussion often show symptoms of injury such as sensitivity to light and sound, dizziness, headache, poor memory and concentration, and mental fatigue. Conversely, focusing on specific symptoms (e.g., depression), as in two of the studies here, may be more sensitive to detecting significant effects in persons with mixed severity.

Despite the small number of studies, it is encouraging that TBI is one of the few diagnostic groups reviewed here for which mindfulness was examined as a form of restitution, with cognitive and neural measures applied to directly test those effects. The symptoms of TBI are often unremitting and long lasting, so the possibility of MBIs as a form of rehabilitation in this population is unsurprising and encouraging, given that cognitive rehabilitation was largely borne out of work with persons with TBI [10].

The analyses of the effects of GMT are particularly salient given their controlled design and multi-method approach to assessing cognition and neural function in response to an intervention involving mindfulness. Although the sample sizes were small, the significant findings indicate further work in this domain with larger samples may support the validity of this form of rehabilitation for TBI. However, it should be emphasized that GMT is a multi-component intervention of which mindfulness training is only one part. Without specific dismantling studies on GMT, it is impossible to say to what degree mindfulness contributes to specific treatment effects. According to a recent meta-analysis of GMT by Stamenova and Levine [68], the only study that incorporated a specific enhancement of mindfulness was the study already discussed by in this chapter [65, 67]. That said, given that mindfulness is purportedly a foundational skill within GMT, future studies should make efforts to isolate and evaluate the relative importance of the mindfulness component of this intervention.

Stroke and Vascular Disease. Lawrence et al. [69] conducted a systematic review of MBIs for persons with transient ischemic attack (TIA) and stroke. The rationale for this review was the documented role of psychosocial factors in cerebrovascular disease, including perceived stress [70], as well as the incidence of anxiety [71] and depression [72] in poststroke recovery. Given MBIs' documented success in ameliorating symptoms of stress, depression, and anxiety, there seemed to be a clear rationale for investigating whether similar effects would be observed specifically within a TIA/stroke population. The result was a systematic review of four studies (3 using MBSR, 1 using MBCT) including 160 participants. The studies comprised one waitlist RCT, one case-control study, and two case series. Participants were younger in most studies than the average age for stroke [73]. In terms of key outcomes, there was mixed evidence of reduced depression (2/2 studies), anxiety (2/3 studies), and fatigue (1/1 studies). One study reported immediate posttest benefits in physical and mental quality of life that were maintained at 3-month follow-up, while mobility and upper extremity function was found to be improved only at the 3-month follow-up. Only one study, one of the case series [74], assessed blood pressure; there was a trend toward reduction in both systolic (i.e., $p = 0.059$) and diastolic (i.e., $p = 0.062$) blood pressure after 8 weeks of mindfulness training. Moreover, analysis of heart-rate variability, a measure of autonomic regulation, indicated improvements in different HRV parameters including standard deviation normal to normal (SDNN, $p = 0.013$), square root of the mean of sum of the square of differences between adjacent NN intervals (RMSSD, $p = 0.021$), and total power ($p = 0.026$).

Despite some promising findings, the quality of evidence reviewed by Lawrence et al. [69] was not strong. One study was rated as being "mid-level" quality according to predetermined criteria, while the other three were rated as poor, due to small sample sizes, attrition rates, failure to use intent-to-treat analyses, and other issues of

generalizability. Moreover, several studies analyzed pre/post data for the intervention and control group separately, rather than conducting analyses such as repeated measures analysis of variance, which raises a concern about error due to multiple comparisons, particularly in small sample sizes. These limitations preclude any strong statements about the efficacy of MBIs for stress management in persons with TIA or stroke.

More recently, Abbott and colleagues [75] conducted a systematic review and meta-analysis of the efficacy of MBIs to reduce depression and physical symptoms in persons with vascular disease, as well as those at high risk for the development of vascular disease (e.g., persons with diabetes and hypertension). They included only RCTs and studies that used some form of MBSR or MBCT, and considered both qualitative and quantitative outcomes. Nine studies (from 8 RCTs), comprising 578 participants, were included in the final analysis. Most trials used the typical 8-week model, with one trial being longer (10 weeks) and one significantly shorter (3 weeks). Despite all being RCTs, most studies were missing vital information required by the Cochrane Risk of Bias tool [76], resulting in questions about selection bias, blinding of assessor ratings, and attrition.

In terms of key findings, a wide variety of outcome variables and associated measures were used across studies, meaning that key findings could often be generalized based on a small (e.g., 3) number of studies. The authors found that, overall, MBSR or MBCT participation resulted in significant but favorable small to moderate effects for psychological outcomes across a range of clinical samples. This included stress (SMD −0.38, 95% CI −0.67 to −0.09, $p = 0.01$) and depression (SMD −0.35, 95% CI −0.53 to −0.16, $p = 0.001$). These effects were even seen in the brief version of the MBSR "MindfulHEART" intervention [77], although when the data were adjusted for baseline values, age, education and comorbidity, observed effects were only significant for those greater than 60 years of age. A moderate effect size was also observed for symptoms of anxiety (SMD −0.50, 95 %CI −0.70 to −0.29, $p = 0.001$). All five studies reporting on quality of life and well-being (e.g., coping) found significant improvements in these areas. In terms of physical outcomes, findings from four studies revealed a significant moderate effect of MBSR for systolic blood pressure (SMD −0.78, 95% CI −1.46 to −0.09, $p = 0.03$) and diastolic blood pressure (SMD −0.67, 95% CI −1.26 to −0.08, $p = 0.03$). However, this finding seems to have been primarily driven by one particular study which, when removed from the analysis, resulted in these effects being rendered nonsignificant. No other effects were found for MBIs on physical outcomes related to disease status or progression.

The Abbott et al. [75] review and meta-analysis supported the application of MBIs to reduce stress and improve psychosocial well-being in persons with or at risk for vascular disease, an important finding given that psychological factors such as depression can confer independent risk for vascular disease and its worsening [78]. However, caveats of the review were the sizeable dropout rate in some studies, as well as potential self-selection bias given that many of the studies used a waitlist control design. More rigorous research is needed to investigate whether MBIs tailored specifically to this population could have any impact on physical disease variables.

Overall conclusions. At present, there is limited evidence available to determine the impact of MBIs in persons with stroke and TIA, although this may be due to a lack of studies rather than a lack of significant effects per se. There was no evidence of harm caused by MBIs in this population, suggesting that more rigorous future studies in this population seem feasible and worthwhile. More compelling findings are available for persons who may be at risk for vascular disease, surely a worthwhile target population for the prevention of future stroke and associated conditions. This is particularly true given not only the rise in cerebrovascular disease, but also the emergence of vascular dementia as the second most commonly diagnosed dementia after Alzheimer's disease [79]. As such, MBIs may be another lifestyle intervention that could decrease vascular disease risk, along with healthy diet and exercise.

Epilepsy. Stress has been established as a major risk factor for triggering seizures in persons with epilepsy [80], and persons with chronic stress appear to experience a higher frequency of seizures [81]. Moreover, chronic stress can lead to anxiety and depression, which can negatively influence quality of life in persons with epilepsy [82, 83]. Given the documented success of MBIs in mental health populations [5], there is a rationale for considering whether similar interventions could be effective in persons with epilepsy.

Wood and colleagues [84] conducted a systematic review of the available evidence in this area. They found three RCTs, two conducted in the US [85, 86] and one in China [87], and consisting of primarily middle-aged female participants. The US studies were based on an MBCT protocol designed specifically for people with epilepsy, delivered via telephone or Internet, employed in a waitlist/crossover design. The Chinese study employed a form of MBSR consisting of four biweekly (as opposed to eight weekly) sessions and was conducted in person, compared against an attention placebo control group. This study reported a statistically significant decrease in seizure frequency following MBSR; seizure frequency did not appear to have been assessed in the other studies. The two US studies found treatment effects of decreased depression, as well as fewer depressive episodes [85] and decreased incidence of major depressive disorder [86]. This is notable, given that MBCT was originally conceived as a treatment to prevent depressive relapse [15]. There was a nonspecific effect of time on depressive scores in the Tang et al. [87] study. However, this same study found a clinically significant reduction in anxiety specific to the MBSR group. Quality of life was also significantly improved in two of the three studies following MBCT or MBSR. Finally, only Tang et al. [87] assessed cognitive functioning, and although significant improvements were found in verbal and nonverbal memory, the authors caution that this could be due to practice effects with such a brief test–retest interval. Despite some promising findings, two of the three studies [85, 86] were at unclear or high risk of bias, which raises concerns about the methodological rigor of the results obtained.

Mindfulness is typically applied in neurological populations to manage symptoms such as those affecting cognition, mood, and well-being. Yuen and Sander [88] provide a neuroanatomical rationale for how meditation might be directly beneficial for seizure frequency in epilepsy, which was observed in the Tang et al. [87] study. The vagus nerve (or 10th cranial nerve) is intimately involved in autonomic, cardiovascular, respiratory, gastrointestinal, immune, and endocrine systems. It plays a major role in reciprocal connections between the heart and the brain, with top-down and bottom-up modulation of parasympathetic nervous system activity [89]. Persons with epilepsy have been shown to have reduced parasympathetic tone, one marker of vagal nerve dysfunction [90]. Since 1997, vagal nerve stimulation (VNS) has been approved by the U.S. Food and Drug Administration for managing treatment-refractory epilepsy, and subsequently for other conditions such as depression. Although poorly understood, VNS is thought to decrease seizure frequency through both the central nervous system and peripheral anti-inflammatory effects [88]. Given that VNS is a costly and invasive procedure, other means to stimulate the vagus nerve could have salutary effects in persons with epilepsy – one such example being meditation. Heart-rate variability (HRV) is one metric of parasympathetic tone [89], and mindfulness has been shown to increase HRV [19, 91]. Thus, vagal nerve functioning may be one neurobiological mechanism through which mindfulness could improve the condition of epilepsy. Future studies may wish to use HRV (along with seizure frequency) as a potential biomarker of the efficacy of MBIs in persons with epilepsy.

Overall conclusions. Clearly the evidence on the use of MBIs for epilepsy is in its infancy, and it is too early to make definitive conclusions. That said, there is a compelling theoretical rationale for its salutary effects not only on secondary symptoms of mood and psychosocial variables but even on seizure frequency itself. Wood and colleagues [84] note that there are

safety considerations in applying meditation in persons with epilepsy, based on case reports suggesting that meditation may increase seizure risk in certain individuals due to neuronal hypersynchrony. This phenomenon remains poorly understood [92], but suggests that caution and close supervision are warranted when providing MBIs to this population.

Neurodegenerative Disease and Dementia

Multiple sclerosis (MS). Simpson and coworkers [93] conducted a recent systematic review of MBIs for persons with MS. MS is a chronic neurodegenerative disease involving nervous system damage that can impact cognitive and physical functioning. Its course is uncertain, and depends on the subtype of MS (i.e., relapsing/remitting, primary or secondary progressive). Mental health problems are frequent comorbidities, with point prevalence estimates of up to 16.5% for anxiety and 46% for depression [94], as well as poor health-related quality of life [95]. Aside from the obvious effects on well-being, mental health difficulties can significantly interfere with treatment adherence and be associated with greater physical symptoms and functional impairment [96]. In their systematic review, Simpson et al. [93] found three studies (n = 183 participants, two RCTs, one controlled trial) that met inclusion criteria, i.e., studies on adults involving some form of MBSR. The majority (80%) of participants were middle-aged and female (mean age = 48.6 years). Most participants (67%) were diagnosed with relapsing/remitting MS as opposed to secondary progressive (26%) or unspecified MS. Interventions lasted between 6 and 8 weeks, one of which had a simple pre/post design whereas the other two studies conducted follow-up at 3 and 6 months, respectively. Attrition rates varied from 5% to 43%, for reasons such as transportation and a lack of interest. In terms of key outcomes, there was evidence of reduced depression (2/2 studies), as well as mixed evidence of improvement in anxiety (1/2 studies), fatigue (2/3 studies), and quality of life (1/2 studies). Overall, there was considerable heterogeneity in the methods, populations, intervention formats and outcome measures. In fact, only 1 of the 3 studies was considered to have high methodological quality.

Overall conclusions. Clearly the research on MS and MBIs is too limited in scope and quality to make meaningful conclusions at the present time, although there are some promising findings in terms of mental health outcomes. Further studies and greater efforts to improve the rigor of work in this area are needed.

Parkinson's disease (PD). PD is a neurodegenerative disease affecting the motor system, causing symptoms such as tremor, gait disturbance, and bradykinesia [97]. The approximate prevalence of PD is about 1-2 per 1000 of the population at any single time point. PD prevalence increases with age and affects 1% of the population over 60 years of age [98], although there is also an early onset form of the disorder [99]. While PD is often thought of in terms of the primary motor symptoms, affected individuals can also suffer from a variety of non-motor symptoms, such as those affecting mood and cognition [100] – symptoms that can reduce quality of life [101].

McLean et al. [102] conducted a systematic review of the effectiveness of controlled trials of MBSR in PD. Only three papers from two studies met inclusion criteria (total n = 66), which was insufficient to conduct a meta-analysis. Mean age of participants ranged from 61.8 to 65.6 years with primarily male participants (51.9% and 58.3%). The first study used self-report and behavioral tasks, and found a significant intervention effect for self-reported mindfulness, self-reported symptoms of depression and self-reported language functioning, as well as fewer emotional and cognitive symptoms associated with PD. These same participants also showed significant improvement on objective tasks of mental flexibility and complex attention. In the second study, participants showed a significant decrease in the Unified Parkinson's Disease Rating Scale motor score, and an

increase in the Five Facet Mindfulness Questionnaire "observe" facet. Structural MRI showed increased gray matter density in the MBSR group compared to controls in the hippocampi bilaterally as well as the right amygdala. A whole-brain analysis showed a large cluster in the right caudate nucleus and a smaller cluster in the left caudate nucleus, with significant clusters in other areas such as the occipital lobe, thalamus, and temporoparietal junction. Aggregating across papers, both studies showed improvement in various aspects of quality of life. One of two studies showed posttreatment improvement in depressive symptoms; the study that examined anxiety found no treatment effect. In terms of study quality, despite the authors specifying the inclusion of only controlled trials, one of the two studies appeared not to have a control group, which raises questions about the true meaning of pre/post-intervention changes. In addition, no data were reported on adverse events or reasons for attrition in either study.

Overall conclusions. Similar to MS, the sheer lack of published studies in this area – and the resultant inability to subject those studies to meta-analysis – preclude any definitive conclusions about the clinical impact of MBIs in persons with PD. It is notable to contrast the dearth of literature on MBIs in PD, as compared with the relatively robust literature on movement-based mindfulness practices for PD such as Tai Chi and Qi-Gong. For example, a very recent systematic review and meta-analysis by Song et al. [103] found small to medium effects on most motor outcomes (e.g., balance, falls) as well as depression and quality of life. Perhaps given that PD is a movement disorder, interventions that specifically incorporate opportunities for mindful movement may be more effective than typical MBIs where most of the practices, outside of mindful yoga, are typically done in a static position. Given that persons with PD are open to CAM practices [104], future research should be encouraged.

Late-life cognitive decline and dementia. With the increasing aging of the global population, it is predicted that there will be a commensurate increase in the rates of individuals who may be at risk for pathological cognitive decline and dementia. As a result, the public is seeking ways to enhance the lifestyle in order to reduce the risk of cognitive decline. Clinicians and researchers are likewise moving to more of a prevention–intervention agenda for age-related cognitive decline [105]. This has recently included interest in the preventative benefits of meditation in healthy older adults (e.g., [106]). However, this literature on healthy individuals will not be reviewed in detail here, as the purpose is to discuss the efficacy and implementation of MBIs in clinical populations.

Subjective cognitive decline (SCD). SCD has relatively recently emerged in the literature as a condition of interest. In brief, SCD is currently conceptualized as a condition characterized by the complaints of decline in cognitive abilities by apparently healthy older adults who achieve scores within the normal range on standardized neuropsychological testing [107]. Many such individuals were been previously considered as "worried well". However, longitudinal studies indicate that as many as 60% of such individuals may go on to develop Alzheimer's disease (AD) [108], suggesting that SCD may be the earliest prodromal stage of dementia for some individuals. Even in persons who do not develop dementia, other etiologies for SCD including mood and medical conditions can also impair quality of life [109]. Given that non-pharmacological interventions for SCD seem to hold promise for enhancing cognition [26], it makes sense to consider whether MBIs could be similarly beneficial.

Lenze and colleagues [110] conducted a feasibility study of MBSR in older adults with worry and co-occurring subjective cognitive dysfunction. The authors were specifically interested in tailoring the intervention for this population, as well as in maintaining adherence to treatment. In this multi-site trial, participants (n = 34) aged 65 years or older received either standardized MBSR or a longer 12-week version that had the same content but more repetition of topics and techniques. Results indicated

reductions in worry severity, increases in mindfulness, and improvements in memory as measured by paragraph learning and recall after a delay, all with a large effect size. Most participants continued to use MBSR techniques for 6 months post-instruction and found them helpful in stressful situations. There was no evidence that the extended 12-week MBSR produced superior cognitive or clinical outcomes, greater satisfaction, or greater continuation of MBSR techniques than 8-week MBSR. It should be noted, however, that there was no control group for this study, precluding assessment of practice effects and/or demand characteristics in the positive changes over time.

Smart and colleagues [48, 111] piloted a trial of MBSR tailored for healthy older adults with and without SCD (n = 36). In an RCT design, this tailored protocol, *Wisdom Mind* [112], was compared with a standardized program of psychoeducation on cognitive aging, shown to be beneficial in healthy older adults. (More details on the *Wisdom Mind* program are presented below.) The hypothesis was that subtle decrements in attention regulation were underlying the complaints of persons with SCD, and that mindfulness could improve attention, as well as lessen emotional reactivity to cognitive failures. In the first set of analyses [111] results indicated that, compared to the control group, persons with SCD who were trained in mindfulness showed an enhancement in the P300 event-related potential (ERP) associated with attention regulation. All participants trained in mindfulness also showed a reduction in intra-individual variability in reaction time, which is a behavioral marker of attention regulation.

In addition to functional measures, a subset of participants underwent structural MRI, using a 1.5 Tesla GE Signa HDxt scanner, within four weeks prior to intervention and within a two-week window following intervention completion. Data were analyzed by two raters not involved in the dissemination of the intervention. Specifically, MRI scans were first examined for data quality, after which image analysis was conducted using the FMRIB Software Library (FSL) version 5.0 (www.fmrib.ox.ac.uk/fsl) using default settings, with two-time-point percentage brain volume change estimated with SIENA [113] within FSL [114]. Following brain extraction, the SIENA analysis removed non-brain tissue and applied a scaling factor to the time points based on relative size of the images. Then, the algorithms projected an estimated percentage change in overall brain matter between the two time points. The SIENA analysis revealed that the mindfulness group showed an increase in percent brain volume following just eight weeks of training. Finally, all participants (regardless of intervention group) showed a decrease in cognitive complaints and an increase in memory self-efficacy following the intervention.

In a follow-up analysis, Smart and Segalowitz [48] directly examined performance monitoring as a mechanism by which mindfulness exerts its salutary effects. Performance monitoring is known to decrease with age, and can increase the potential for cognitive errors. Moreover, it was speculated that persons with SCD are hypervigilant to these cognitive failures and emotionally reactive toward them, as they may be construed as indications of impending cognitive decline. As such, it was hypothesized that mindfulness could help older adults find an optimal level of performance monitoring, but not so much so that it led to increased anxiety. Two different ERPs were used to test this hypothesis – the error-related negativity (ERN), related to awareness of errors, and the Pe, related to emotional responses to errors. The results supported the authors' hypotheses: compared to the control group, all older adults receiving *Wisdom Mind* (both with and without SCD) showed an increase in the ERN, but without a concomitant increase in the Pe. There was a practice effect, as all participants increased accuracy from pre to post-intervention. However, there was a trend (p = 0.057) toward faster responding in the mindfulness training group. Participants in both groups reported a reduction in self-report of anxiety and self-judgment of one's own mental functioning.

The results of these two studies show that while participants self-reported positive

psychological benefits regardless of intervention type, only mindfulness training improved underlying brain and behavioral function. This speaks to the utility of a multi-method approach in assessing the impact of MBIs, which may be important in designing studies, particularly for samples, such as older adults, in whom neuroplasticity may take place on longer timescales [115].

Mild cognitive impairment (MCI). MCI is another condition considered prodromal to dementia, whereby affected individuals experience demonstrable cognitive decline on standardized testing, yet remain relatively functional in activities of daily living with relatively preserved awareness of one's impairments [21]. Larouche and colleagues [116] proposed a theoretical model of why mindfulness might be useful in persons with MCI, proposing that MBIs could directly impact many of the modifiable risk factors for decline from MCI to AD, including stress, depression, and reduction of the metabolic syndrome, inflammation, and biomarkers of the stress response. Interestingly, the authors did not address the possibility that mindfulness could act as a form of cognitive training to maintain current cognitive ability and support cognitive reserve.

Wells et al. [117] designed a proof-of-concept trial to ascertain whether MBSR could reduce hippocampal atrophy and improve default mode network connectivity in persons with MCI. Fourteen individuals with MCI were randomized at a ratio of 2:1 to standard MBSR or treatment-as-usual, undergoing resting state fMRI pre and post-intervention as well as structural MRI. The reason for focusing on these regions of interest was their implication in MCI and AD, as well as the fact that they have been shown to be enhanced in studies of mindfulness. Results indicated that those in the MBSR group had increased functional connectivity between the posterior cingulate cortex, bilateral medial prefrontal cortex and left hippocampus compared to controls. MBSR participants had trends of less bilateral hippocampal volume atrophy than control participants. In a subsequent analysis, Wells et al. [118] examined the impact of this program on self-report and neuropsychological functioning. Qualitative interviews indicated that participants experienced improved mindfulness skills, well-being, interpersonal skills, acceptance/awareness of MCI, decreased stress reactivity, group benefit, and overall course enjoyment. However, the authors failed to detect meaningful changes in cognitive ability favoring the MBSR group. There was a trend for improvement in the Alzheimer's Disease Assessment Scale-Cognitive change score for the MBSR group, but the very small sample size probably meant the analysis was underpowered. There were also nonsignificant trends for improved resilience, perceived stress, quality of life, hope, and optimism favoring the MBSR group.

The results of these studies are encouraging, although the very small sample size means that many of the analyses were likely underpowered, indicating that larger controlled trials are needed to confirm the stability of any observed results. Moreover, the lack of change in cognitive measures may be due to the relatively brief test–retest window, and the fact that longer time-period may be necessary to show the objective cognitive change in older individuals. Longer term follow-up may demonstrate whether the impact of mindfulness on cognition emerges over time with continued practice.

Dementia. Dementia is an exceedingly disabling condition that involves significant impairment in a variety of cognitive abilities, as well as concomitant impairments in activities of daily living. There are many different types of dementias, the most common of which is AD [21]. Given the severity and multi-faceted cognitive impairment in dementia, it remains an open question whether individuals would have the requisite minimum level of cognitive ability needed to fully participate in MBIs and show any benefit.

Two of the studies conducted in this area have been feasibility studies, ascertaining whether mindfulness training can, in fact, be implemented in persons with dementia and whether any appreciable impact is observed. The first study by Paller et al. [119] sought to establish the

feasibility and impact of MBSR in a group of older adults with presumed AD (n = 9) or MCI (n = 2), as well as their caregivers, presenting to a local dementia clinic. The program was broadly consistent with MBSR, although additional elements were drawn from DBT and ACT, as well as additional tailoring to deal with cognitive impairment, such as repetition and slow pace of instruction. Patients participated together with caregivers in weekly group sessions over the course of eight weeks, with assessment pre and post-intervention. Results indicated that participants endorsed increased quality of life, fewer depressive symptoms, and better subjective sleep quality following the intervention. However, given the lack of a control group, one cannot rule out the possibility of practice effects and/or positive response biases accounting for changes over time.

The second feasibility study was conducted by Churcher Clarke et al. [120], specifically focused on persons with mild to moderate dementia living in care homes. The authors developed a manualized protocol for a 10-session group intervention based on existing MBIs and tailored to older adults with mixed dementia diagnoses, whereby participants were allocated to the intervention plus treatment-as-usual (n = 20) or treatment-as-usual only (n = 11). The main outcome measures pertained to mood, anxiety, quality of life, cognitive function, stress, and mindfulness. Only quality of life was found to significantly increase in the mindfulness group relative to controls. The authors demonstrated the feasibility of the intervention, but called for a larger RCT to further examine the effects. Also, it does not appear that the authors stratified by baseline levels of cognition; given the mixed diagnoses of participants in this study, this could have attenuated significant effects. A one-size-fits-all approach may not be effective depending on the individual cognitive needs of participants, and speaks to the limitations of standardized group protocols in persons with significant, but varied, cognitive impairment. Moreover, if mindfulness is considered a form of "cognitive training", then the lack of significant effects in such a short time-window is perhaps unsurprising, given that the overall literature on cognitive training indicates minimal appreciable benefit in persons already diagnosed with dementia [21].

A recent study has produced some encouraging findings, examining the impact of mindfulness over a 2-year time frame. Quintana-Hernandez and colleagues [121] conducted an RCT with 120 individuals with AD who were medicated with donepezil (Aricept). The study compared mindfulness-based Alzheimer's stimulation (MBAS) to cognitive stimulation, progressive muscle relaxation, and a control condition of donepezil only. Rather than the usual once-weekly format of most MBIs, participants in this study received each intervention condition three times per week over a two-year period. The purpose of the longitudinal design was to determine whether mindfulness would modify the course of cognitive impairment in persons with AD. All participants were co-treated with donepezil and had a Mini-Mental State Exam (MMSE) score of $\geq$18. The main outcome measure was cognition based on the MMSE and the Cambridge Cognition Examination. Results indicated that MBAS plus donepezil was more effective than progressive muscle relaxation plus donepezil or medication alone. The treatment conditions of cognitive stimulation and MBAS were equivalent. MBAS had a large treatment effect size over the two years, compared with a moderate effect size for the relaxation group and a small effect size for the cognitive stimulation group. The large sample size, as well as the longitudinal design and intensive intervention delivery format, may have contributed to the positive findings in this study as compared to the others previously described.

Overall conclusions. With the rapid aging of the global population and greater numbers of individuals at risk for late-life cognitive decline, there is a pressing need to develop interventions that could prevent or delay the rate of cognitive decline. Based on recent reviews of the cognitive/behavioral intervention literature [21], cognitive training seems to be most effective in persons with relatively preserved cognition (i.e.,

healthy older adults with and without SCD), whereas cognitive rehabilitation may be more effective in persons with already manifest cognitive impairment. This suggests that different components of mindfulness may be more or less effective depending on the stage of decline. That is, mindfulness may have greater impact as a form of cognitive training in healthy older adults with and without SCD (i.e., *restitution*), whereas it may be more relevant as a form of *compensation* in persons with more pronounced cognitive impairment. Moreover, tailoring may be necessary to make the program more accessible for persons with significant cognitive impairment [39]. That said, the study by Quintana-Hernandez et al. [121] suggests that even persons with dementia can experience cognitive benefit from mindfulness training under the right conditions. This study was innovative, for two reasons. First, it used a longitudinal design where participants had intensive exposure to all treatments; for persons with severe cognitive impairment, longer time frames may be needed to see positive changes. Second, all participants were taking donepezil; while the impact of dementia medications is hotly debated [39], it may be that medications in concert with cognitive/behavioral interventions provide the greatest impact on cognition. Medications may give individuals enough of a "boost" to be able to fully benefit from non-pharmacological interventions. This is not unlike the case where persons with severe depression often benefit from a combination of medication and psychotherapy more than either treatment in isolation.

Symptoms That Occur Across Diagnoses

Mental fatigue. Mental fatigue can be a highly debilitating symptom of a variety of neurological illnesses and injuries, including but not limited to TBI, stroke, Parkinson's disease, and MS. This form of fatigue is considered to be a specific neurological symptom, and distinct from the normal fatigue that occurs in conjunction with physical exertion or even that associated with nonnervous system diseases such as cancer [122]. Despite the fact that mental fatigue causes high levels of distress [123, 124], it remains poorly understood and there is no single effective treatment available. MBIs have been shown to improve general health and fatigue in persons with non-neurological disorders (e.g., [125, 126]), as well as attention, a common secondary problem associated with mental fatigue [127].

Ulrichsen et al. [122] conducted a recent systematic review meta-analysis to ascertain the effect of MBIs on mental fatigue, building on prior reviews of this topic that did not quantify treatment effects on fatigue specifically (e.g., [128]). They included only controlled trials (randomized or quasi-randomized) of MBIs in persons with neurological disorders or acquired brain injury, where fatigue was either a primary or secondary outcome measure. After an initial search yielded 372 articles, four studies met inclusion criteria, two of which were focused on MS and two containing mixed samples of stroke and TBI (total $n = 257$). All were 8-week programs, three of which were based on MBSR, while the fourth was based on MBCT delivered via Skype-based videoconference. Risk of bias could not be assessed due to the low number of studies. Overall, a significant, small to medium effect size was found ($d = -0.37$) for reductions in mental fatigue. The strongest individual effects were seen in the two studies focused on stroke/TBI, which were medium to large (i.e., −0.59 and −0.78), and had more severely fatigued patients at study entry.

Overall conclusions. Despite a small number of studies, the findings are very promising. Mental fatigue is often treated using pharmacological agents, such as methylphenidate [129], but for those individuals who do not wish to use medications or for whom medications may be contraindicated, MBIs may provide a worthwhile non-pharmacological alternative. While the specific mechanism by which MBIs improve fatigue remains unknown, Ulrichsen et al. [122] draw on prior research to speculate that it may be due to improvements in self-regulation and attentional processes [128, 130]. That is, in

certain neurological conditions, individuals have to exert greater cognitive effort to complete tasks, which can lead to increased mental fatigue. By supporting greater cognitive efficiency and/or attention control, less effort is needed, which in turn lessens fatigue. Moreover, fatigue can be a symptom of depression that can often co-occur in neurological conditions, and it remains unclear to what degree improving depressive symptoms could be another pathway to lessening fatigue.

(3) **Interpretation of the Literature: Critical Methodological Issues and Future Directions for Research**

There is a theoretical rationale for the application of mindfulness in a neurorehabilitation context, and the evidence suggests that mindfulness does, in fact, benefit certain patient populations and certain symptoms experienced by persons with neurological disorders. Nevertheless, in reviewing the current state of the science, it is clear there is a need for more rigorously designed clinical trials to understand the impact of mindfulness as well as its potential mechanisms of action. To that end, there are several methodological issues that warrant further consideration. These issues are explored in detail below; the reader is also referred to Sedlmeier et al. [22] and Van Dam et al. [1] for their in-depth discussion of methodological issues in the meditation literature writ large.

For Whom is Mindfulness an Effective Treatment?

As noted already, the application of MBIs in a neurorehabilitation context is in its relative infancy compared to other clinical populations and also healthy samples. In most cases the relatively few studies available precluded definitive conclusions about the efficacy of mindfulness in specific diagnoses. At present, the most compelling evidence seems to be in support of MBIs for ADHD (both children and adults), persons at risk for vascular disease, older adults with various levels of cognitive impairment, and mental fatigue across diagnoses. TBI is one of the few areas that directly assessed the impact of MBIs on cognition and underlying brain function, with promising results, but with individual studies and small sample sizes contributing data, much more work needs to be done to bolster the observed conclusions. It should be noted that waitlist control groups or treatment-as-usual were the most common comparison conditions. As such, one cannot comment on whether MBIs have comparable efficacy to standard treatments such as CBT. It is imperative that future research use active control groups, including standard empirically supported treatments, to confirm whether MBIs would be a viable alternative in the neurorehabilitation context. Moreover, few studies report on the "dose" of mindfulness obtained within the treatment – that is, how much do participants actually practice the various meditation practices outside of the regular group meetings. There is no clear consensus in the literature as to the ideal dose, particularly given that some studies on healthy populations can show changes in cognitive/behavioral and direct neural measurements after just a few brief training sessions. It remains an open question whether severity of cognitive or emotional symptoms moderates the dose–response relationship in neurological populations, and future studies may wish to gather such data to address this question. More on the dose–response relationship is discussed in the subsequent section on tailoring mindfulness in an $n = 1$ context.

A point that is less frequently discussed but bears mentioning is the potential for mindfulness to increase psychological distress. The National Center for Complementary and Integrative Health states that the greatest risks of harm from complementary treatments such as meditation are "unjustified claims of benefit, possible adverse effects…and the possibility that vulnerable patients with serious diseases may be misled" [131]. While the Buddha conceived of meditation as a means to "alleviate suffering", Davidson and Dahl [132] note that meditation was not designed as a mental health treatment per se but rather to promote human flourishing, well-being, and constructs such as wisdom and insight in

healthy individuals. Some of the reviews spoke directly to safety of MBIs, and the evidence available generally implied that the interventions were well tolerated. However, Van Dam et al. [1] have written in detail about the potential for adverse effects occurring due to mindfulness practice. They caution that rarely do studies seem to explicitly monitor for adverse events, or subsequently report on them, leading to the inaccurate assumption that mindfulness is a universal panacea and benign in its application. In reviewing data from more than 20 published case reports or observational studies, they cite potential meditation-related or "meditation-induced" side effects such as psychosis, mania, depersonalization, anxiety, panic, traumatic memory reexperiencing, and other forms of clinical deterioration. Moreover, as previously mentioned, in persons with already-diagnosed epilepsy or those who are simply predisposed to seizures, meditation practice may be epileptogenic [92]. It is not uncommon for long-term meditation practitioners in spiritual communities to experience what has been referred to as the "dark night of the soul", a temporary increase in negative mood associated with existential despair, questioning, and experiences of "non-self" that arise directly from the practice [133]. However, these reports are based largely on reports of case studies, case series, or observational studies, without a control group. With the support of a mentor or teacher who can provide guidance from the contemplative teachings, individuals can often move through this and experience it as a period of spiritual, mental, and psychological growth. MBIs delivered clinically were expressly designed to be secular and without any spiritual context, which underscores the necessity of persons the ability of persons disseminating MBIs to appropriately support participants who show an increase in psychological distress subsequent to meditation training.

Recommendations for future research. Two issues of concern are raised here: first, clinicians need to be able to recognize the difference between a "dark night" experience and one that indicates a genuine deterioration in psychological functioning. This would imply some working knowledge of the tradition from which the meditation has come (e.g., Buddhism). Second, certain individuals may lack a basic level of psychological stability needed to be able to safely engage in certain meditation practices [134, 135]. For example, in persons with a trauma history, one may need to proceed more slowly in the practice and proceed with greater scaffolding lest they become flooded with experience [37]. Being able to address these issues of concern effectively is more likely if the clinician (or researcher) involved has their own committed mindfulness practice, in order to be able to discern what patients need and when it is safe to proceed. The need for therapist training is discussed again later in this chapter. As Van Dam et al. [1] have suggested, a systematic means of monitoring for adverse events should be part of any clinical trial, and these should be reported in the literature to provide caution to those working with similar populations.

Mindfulness as Restitution or Compensation – or Both?

The three meta-analyses on healthy individuals (i.e., [22, 32, 33]) suggest that the practice of mindfulness can positively impact cognition and neural structure/function. It is surprising, then, how few of the clinical studies mentioned here examined cognition and neural structure/function (e.g., [48, 58, 65, 67, 111, 117]). Most of the studies conducted in the neurorehabilitation context seem to have focused on mental health and well-being, self-report of symptoms, and occasionally disease-specific indicators (e.g., blood pressure).

Given these findings, it could be argued that neurorehabilitation studies have focused more on MBIs as a form of compensation, and less so on their potential for restitution. This lack of focus on cognition seems like a missed opportunity, given the findings in healthy populations. Even if emotional well-being is the main outcome, there could be secondary benefits on cognition, as suggested by the results of Sedlmeier et al.'s [22]

Table 34.3 Framework for connecting mechanism of action to outcome measurement in the evaluation of MBIs for persons with neurological illness or injury

Mechanism of action	Specific example	Outcome measurement
Restitution	Top-down control of attention	• Behavioral tasks (e.g., continuous performance task; go/nogo task) • Neural measures (e.g., P300 ERP, fMRI activations in DLPFC) • Self-report measures (e.g., mindfulness questions related to attention, report of attention failures)
	Memory encoding	• Behavioral tasks (e.g., encoding trials on list learning or story memory) • Neural measures (e.g., fMRI deactivations in ventral posterior cingulate cortex and left inferior parietal lobule) • Self-report measures (e.g., report of everyday memory failures)
	Metacognitive awareness	• Behavioral tasks (e.g., enhanced performance on problem-solving measures) • Neural measures (e.g., fMRI activations in rostrolateral prefrontal cortex and mid-dorsolateral prefrontal cortex)
	Interoceptive awareness	• Behavioral tasks (e.g., heartbeat detection task of interoceptive accuracy) • Neural measures (e.g., fMRI activations in insula and somatosensory processing regions) • Self-report measures (e.g., measures of interoceptive awareness, emotion regulation, mood/affect)
Compensation	Strategy use	• Behavioral measures (e.g., those that benefit from strategy use, such as metacognitive tasks, prospective memory tasks, ecologically valid tasks) • Self-report measures (e.g., perceived self-efficacy)
	Emotional adjustment	• Self-report measures (e.g., mood/affect, well-being, quality of life)

ERP = event-related potential; fMRI = functional magnetic resonance imaging; DLPFC = dorsolateral prefrontal cortex

meta-analysis. These same authors note that, more often than not, mindfulness studies are conducted without due attention to theory derived from either psychology or the contemplative disciplines. Similar issues have been identified in the cognitive training and cognitive rehabilitation literature, where outcome measurement is not always informed by the purported mechanism of action. Being clear about whether mindfulness is restitution, or compensation, or both, is also necessary for selecting the most appropriate measurement of response to intervention [26].

Recommendations for future research. Table 34.3 provides a framework for explicitly connecting mechanism of action to relevant outcome measures of brain, behavior, and self-report of functioning. Using such a framework to design studies will allow for more precision in detecting significant effects, as well as guiding treatment in clinical practice. Where possible, using direct neural measures may show effects sooner than behavioral measures [45]. If researchers and clinicians wish to use neuropsychological tests, several factors must be considered. First, is this a cognitive domain where absolute change is likely to be seen? For example, it may be easier to improve memory encoding as a function of improved attention, but less easy to improve memory consolidation or recall [10]. Rather than simply looking at overall scores, looking at specific trials of a task may be instructive. For example some studies suggest that intra-individual variability in reaction time may be a more sensitive marker of mindfulness than mean reaction time (e.g., [111, 136]).

Second, one must consider the test–retest window (i.e., are any changes simply due to practice effects?). One is advised to derive standard scores for these tests, as is done in clinical practice, and then apply reliable change indices [137] to determine whether that change is clinically meaningful. Finally, a mix of standardized and ecologically valid tasks may increase the likelihood of detecting significant effects. Standardized tasks look at the underlying cognitive

function, while ecologically valid tasks examine performance in a context more similar to everyday function [138]. This will be particularly relevant if the purported mechanism is a compensatory one.

In determining the effects on brain and cognition, researchers should also consider the necessary dose to see effects on cognitive and neural measures [132]. While the meta-analyses on healthy populations [22, 32, 33] indicate significant effects in as little as four weeks, the timescale for plasticity in the injured brain is uncertain. Certainly this is true of older participants, who may require longer training intervals and longer follow-up periods to produce significant effects [115]. Given that MBSR, for example, is a standard 8-week protocol, there seems no reason to reduce this, but rather to use this as a starting point for the time frame of treatment. Very few, if any, studies reported on the frequency or amount of home practice that participants did, which seems another important dosing variable to track. Selecting the appropriate control condition is also a critical issue. Many of the trials reviewed within the systematic reviews used waitlist controls or treatment-as-usual as the comparison condition. A more rigorous test of MBIs would be to use active control groups [1], comparing them to existing treatments or ones where there is some overlap in the mechanism of action. For example, given that a core component of MBIs is attention regulation, it may be worthwhile to conduct studies comparing MBIs to the impact of existing attention training programs (e.g., working memory training), to ascertain which effects are similar and which are unique to MBIs.

Additionally related to cognitive/brain changes, one should consider the course of the patients' underlying diagnosis. For example, for persons with acquired brain injury, the goal may be to show active improvement in certain aspects of cognitive function, after controlling for spontaneous recovery. By contrast, for persons with neurodegenerative conditions, the goal may be less about improving cognitive function and more about maintaining current function or slowing the rate of decline.

Finally, in several of the systematic reviews, it became apparent that mindfulness itself was not actually assessed as an outcome variable. This begs the question, if individuals improved following an intervention, did this occur as a function of increased mindfulness, or due to some other factor entirely? There is no single means by which to assess mindfulness, even as a self-report variable. Several scales exist, such as the Mindful Attention and Awareness Scale (MAAS) [139], the Five Facet Mindfulness Questionnaire (FFMQ) [140], and the Freiburg Mindfulness Inventory (FMI) [141], as well as others. Each scale has its strengths and limitations for use in neurological populations. For one, some scales were designed to tap trait mindfulness (i.e., an individual difference characteristic), so is it reasonable to assume that scores on these measures would change following an intervention? Conversely, some scales are heavily oriented to only the attentional component of mindfulness, and for persons with persistent cognitive symptoms, they may fail to endorse changes on these measures even if they experience benefit following an intervention. There is no ideal mindfulness measure [1, 142]; one future direction could be to develop a mindfulness measure specifically oriented to persons with neurologic disorders.

Ascertaining Change in Persons with Mixed Symptom Profiles

The studies reviewed tended to evaluate the impact of MBIs based on groups of individuals with the same diagnosis. This approach may work better in studies on mental health diagnoses such as a major depressive disorder or generalized anxiety disorder, where one can approximate homogeneity in participant samples (e.g., screening out persons with comorbidities). However, as any clinician knows, no two people with the same neurological diagnosis look exactly the same; not only are they likely to differ in precise cognitive impairments, but they may also differ in their emotional responses to their

diagnosis as well as psychosocial history. From this point of view, trying to detect group-level change could prove challenging and result in a higher risk of Type II error.

Recommendations for future research. Given that many symptoms can occur in a variety of diagnoses (e.g., inattention, emotional lability, and mental fatigue), one alternative could be to take a transdiagnostic approach [143], and stratify participants based on symptom profiles. Toivonen, Zernicke, and Carlson [144], in their review of Internet-based MBIs for persons with physical health conditions, found that the largest effect sizes were observed when treatment targeted condition-specific symptoms (e.g., cancer-related fatigue and IBS symptoms). Ulrichsen et al.'s [122] meta-analysis on MBIs for mental fatigue is one such example of a transdiagnostic approach that seems to be effective. Another example is GMT, which targets executive dysfunction and has a mindfulness component. Preliminary studies suggest that GMT has shown some promise in older adults [145, 146], as well as persons with acquired brain injury [68], and spina bifida [147]. As noted previously, though, ascertaining the unique contribution of mindfulness to this treatment's success remains relatively unexplored. Finally, aside from being tailored to an individual's primary symptoms (see below for more on tailoring), stratification by symptom type may also result in greater sample sizes and, in turn, greater power to detect significant effects.

Efficacy versus Effectiveness

Research on the *efficacy* of a treatment is usually considered the strongest level of evidence, and tends to assume an RCT design using tightly controlled and well-characterized groups. However, as noted, group-level studies based on diagnosis can be problematic for a variety of reasons. Moreover, most of the individual studies and systematic reviews discussed noted the same concern about a lack of sample size. The most commonly used MBIs are delivered in group formats, and it may be very difficult (or take an inordinately long period of time) to accrue a critical mass of patients with the same diagnosis to be able to run a group intervention.

Recommendations for future research. In order to move research in this field forward, efficacy studies need to be complemented with a parallel body of research on *effectiveness*. Clinical trials focused on efficacy naturally prioritize internal validity. In contrast, effectiveness research prioritizes external (or ecological) validity, looking at a more heterogeneous, representative sample of patients in naturalistic settings in order to understand what does and does not work. Van Dam et al. [1] note that only 1% of the clinical intervention studies they reviewed were conducted outside of a research context. Clearly more real-world translation of treatments needs to occur. Both efficacy and effectiveness designs are necessary and complementary forms of evidence [148]. Well-controlled case series may be such an option [149], particularly for clinicians working in settings without research infrastructure, or where there is a low base rate of a certain population. For more information on single-case experimental designs, the reader is referred to the recent SCRIBE guidelines on this topic [150]. The next section of this chapter also provides suggestions as to how group mindfulness protocols may be tailored for individual patients, illustrated with actual clinical examples. Such examples may be instructive should the reader choose to apply mindfulness with individual patients, and conduct their own $n = 1$ case series.

(4) **From Bench to Bedside: Practical Clinical Recommendations**

The Need for Tailoring in Delivering Mindfulness Protocols

A majority of published studies (and MBIs themselves) involve group-based protocols that may be administered to persons of a particular diagnosis. However, even patients with the same

diagnosis may differ along a variety of symptom dimensions, as well as moderating factors such as age, cognitive reserve, and psychosocial function. Moreover, clinicians may be working in a setting that does not have access to a critical mass of individuals with the same diagnosis or symptoms needed to run a group. The question arises, then, how might the clinician working with individual patients ascertain whether mindfulness training could be useful, and go about implementing it?

Tailoring [151] refers to the process whereby empirically supported treatments are modified on certain key dimensions (e.g., race/ethnicity, sexual orientation, socioeconomic status) in order to improve the effectiveness of said treatments. Judd [152] has coined the term "neuropsychotherapy" to refer to tailoring psychotherapy specifically for persons with neurological illness and injury. Examples of neuropsychotherapy might include cueing or prompts for persons with memory difficulties, support in scheduling and organizing homework for those with executive dysfunction, and adapting the mode of treatment delivery for persons with language impairment [21]. In this vein, some small trials have already been conducted examining the feasibility of MBIs in persons with aphasia, with promising findings [153, 154].

Managing dose effects is another issue that requires consideration. Although MBIs may be administered to improve someone's cognitive difficulties, it is likewise necessary to consider how said cognitive difficulties may actually be a barrier to the implementation of mindfulness training. We have found across different populations that tailoring to the cognitive needs of the participants can support compliance, thereby increasing the likelihood that they receive a sufficient "dose" of mindfulness training in order to have a significant effect. For example, in our work with individuals with chronic mild traumatic brain injury/post-concussive syndrome [58], we extended the usual MBSR program from 8 weeks to 10 weeks, to ensure adequate pacing and repetition of the material in persons with memory and concentration difficulties. Additionally, often participants forgot to do daily home practice between sessions, due to difficulties with prospective memory. This not only attenuated the dose of mindfulness that some participants were receiving, but also led to many self-defeating thoughts and negative mood states that reinforced the idea that "I am brain-injured and cannot do this". In more recent work with adolescents with fetal alcohol spectrum disorders (FASD), we proactively managed this problem by providing a daily text message and email asking participants, "Did you remember to practice today? There is still time to do your practice". We sent the messages around dinnertime because this was close in proximity to early evening, when the teens would have time to practice without the demands of school. We purposefully did not send the message during school time, as this increased the likelihood that they would have forgotten the cue by the time they actually had free time to practice [155].

Developmental tailoring. In this same study of adolescents with FASD, we used an MBI specifically tailored to a youth population, *Still Quiet Place* [55], to make the program more developmentally relevant. We also turned the treatment manual into a "comic book", complete with color illustrations, to promote interest and engagement in the program and help make abstract concepts more concrete (e.g., the "flashlight of attention" as a way to describe focused attention practice; "training the puppy" as a way to describe loving-kindness practice). As noted above in the review on ADHD [54], developmental tailoring may be an important moderating variable in terms of response to MBIs in different age groups.

In other work, we tailored the standard 8-week MBSR program to healthy older adults with and without SCD. This manualized protocol, entitled *Wisdom Mind* [112], used the same overall format as MBSR but included specific elements that were developmentally relevant to older adults. Some examples were specific to the delivery of the practice, such as spending the first half of the course explicitly training focused attention and the second half on open monitoring [111]. This was done with the understanding that focused attention is a foundational skill (i.e.,

sustained and selective attention) that needs to be cultivated before one can attempt the practice of open monitoring (i.e., more akin to divided attention), consistent with neuropsychological theory of attention [10]. Another practice example involved situating loving-kindness practice in terms of non-judgment and acceptance of cognitive "slips" common to older adulthood [48]. Other aspects of tailoring were contextual, such as discussing cognitive reserve, and how mindfulness could be used to enhance cognitive reserve through curiosity and openness to new activities and experiences.

In providing mindfulness training to one's patients, it is important to consider any and all variables that could influence their uptake of treatment. Aside from cognitive and emotional issues, patients may have practical difficulties in coming to the clinic on a weekly basis, either due to physical disability or socioeconomic limitations. With the increasing interest in telehealth and telerehabilitation [157], there has been an emergence of studies examining the application of mindfulness via Internet-delivery. Toivonen, Zernicke, and Carlson [144] conducted a very recent systematic review of Internet-based MBIs for individuals with physical health conditions. Nineteen published papers involving 16 studies were reviewed, including epilepsy, acquired brain injury, and other miscellaneous health conditions such as cancer and chronic pain. Overall, most studies reported positive effects of Internet-based MBIs compared with treatment as usual on a variety of outcomes including pain acceptance, coping measures, and depressive symptoms. Results were mixed when it came to comparing the effectiveness of these interventions with active control conditions such as cognitive behavioral therapy. As noted above, the largest effect sizes were observed when treatment targeted condition-specific symptoms, which speaks to the utility of tailoring programs to the particular population under study. These findings suggest that Internet-based MBIs may be a viable alternative for individuals who cannot access treatment in person. However, other issues would need to be addressed, such as Internet security and privacy, not providing clinical services outside of one's jurisdiction unless licensed to do so, and ensuring patient/participant access to adequate computing services to access the treatment.

Clinical Examples of *N* = 1 Implementation of Mindfulness Training

To illustrate what mindfulness training might look like tailored to individual patients, actual clinical case formulations are provided.

The case of Brian. Brian is a 32-year-old, right-handed man. He sustained a concussion (mild traumatic brain injury) after his stationary vehicle was struck at high speed approaching an intersection. He experienced a great deal of stress immediately after the accident in having to deal with his insurance company and the insurance company of the other driver, and as a result he was unable to rest and seek relief from his symptoms. Prior to the accident, he had a successful career as an accountant. After a three-week absence from work, he tried to return to usual duties but found that he was unable to function at his usual level. Several months post-injury, he remained unable to return to work due to persistent symptoms of headache, photophobia, and phonophobia, neck pain, mental fatigue, and poor attention/concentration. His partner was very concerned about his emotional state, particularly symptoms of anxiety, depression, and hopelessness, and she urged him to seek psychological treatment.

Brian began treatment at approximately 8 months post-injury. On the first meeting with Brian, two things became immediately apparent: one, his preoccupation with and hypervigilance to somatic symptoms, and two, his catastrophic reactions to those symptoms. As evidence of his catastrophic thinking, he asked in the first session about whether he might be at risk for chronic traumatic encephalopathy based on having suffered a concussion. In conceptualizing Brian's

case, the following case formulation was constructed:

- Providing psychoeducation on symptoms of the post-concussive syndrome will address some misconceptions about physical and cognitive symptoms.
- Using a mindfulness-based cognitive behavior therapy (M-CBT[1]) approach will address other issues:
  - Body-based mindfulness practice will be introduced as a form of gentle interoceptive exposure to deal with overfocusing on physical symptoms.
  - Focused attention (FA) mindfulness will be implemented to improve attention and decrease symptoms of mental fatigue.
  - Training in FA will also increase awareness of negative automatic thoughts about symptoms and recovery (i.e., catastrophic thinking), which can be brought to awareness and actively challenged.
  - Open monitoring (OM) mindfulness will be implemented to promote acceptance and non-judgment of physical and cognitive symptoms, while decreasing emotional reactivity in response to those symptoms.

Brian's treatment began with providing information on his case formulation and soliciting his "buy-in", with the understanding that success would be most likely if he was a willing and active participant. His goals included going back to work, seeing his friends again, and resuming his active lifestyle of hiking, skiing, and mountain biking; his treatment was contextualized within those goals.

Programs such as MBSR typically begin with "body scanning" as the first activity, a practice of 30–40 min in length that involves drawing attention to one's interoceptive experience. Given Brian's anxiety about and preoccupation with his bodily symptoms, it was determined that assigning this activity would be tantamount to flooding, and would likely undermine his self-efficacy and the therapeutic alliance. Instead, he was assigned a practice created by the author, designed to provide a gentler interoceptive exposure and build his confidence in positively relating to his body. This practice, *Finding Safety in the Body*, is a 12-min exercise that focuses first on grounding using the breath in the lower abdomen, followed by a gentle guided instruction to move one's awareness through the body, paying particular attention to parts of the body that feel safe, comfortable, and even pleasurable. When the individual's attention is drawn to symptoms or discomfort, one is cued to gently let go of focusing on symptoms and come back to finding safety and comfort.

This exercise is a gentle form of interoceptive exposure that allows patients to experience the body not only as a source of symptoms, but also as a resource in times of physical or emotional distress. Although guided imagery can be a means of resourcing, finding safety in one's own body in the present moment can be particularly empowering for patients. In addition, the instruction also involves psychoeducation on the benefits of being able to flexibly deploy one's attention to particular aspects of one's present-moment experience. Oftentimes, attending to symptoms is adaptive because it shows us where we need to take action to feel better; however, in the experience of anxiety or medical illness, this attentional deployment can become rigid and inflexible, where the mind is repeatedly drawn to experiences that are not, in fact, inherently threatening. Through this exercise, patients are shown that safety and comfort can actually coexist with physical symptoms. As such, this practice is a precursor to OM practice. This approach is different from distraction, a common CBT exercise used with chronic pain and medical symptoms.

We discussed how Brian would remember to practice each day, and he opted to put a daily calendar reminder on his smartphone. With *Finding Safety*, as with all of the other practices

[1]M-CBT refers to CBT that was flexibly infused with various forms of mindfulness practice. This is distinct from MBCT, which is a standardized, manualized protocol created for depression relapse but also used in other clinical contexts, as discussed elsewhere in this chapter [15].

employed, Brian was provided with guided recordings provided by the author. Based on the author's prior experience, patients (or research participants) typically prefer to hear the voice of the person with whom they are working, rather than another meditation teacher. This speaks to the necessity of the clinician being sufficiently trained in the practices to deliver them effectively to patients. For each practice, Brian was also given a practice log whereby he was asked to track the frequency of his practice, how easy or difficult each practice session was, and his mood before and after the practice. Brian showed excellent compliance with each of the practices provided to him, and the log sheets for each practice became a source of data to track not only compliance but also challenges or breakthroughs associated with the various practices. Brian practiced this exercise for one week, and was able to reliably identify his lower abdomen, as well as his legs and feet, as resources in the body. Once he became comfortable and proficient with this exercise, he then progressed to the regular body scan exercise. Brian reported not enjoying this as much as it was "less relaxing". This provided an opportunity to clarify that while the body scan can be relaxing, the actual purpose of the practice is to enhance interoceptive awareness, and to cultivate an attitude of acceptance toward one's present-moment experience. With this encouragement, he was willing to continue with the practice.

As Brian continued to develop his interoceptive awareness and willingness to be "in his body", this was leveraged into getting him to track his levels of sleep, arousal, fatigue, and mood over the course of daily activities for a week. This tracking showed that Brian's optimal arousal time was mid-morning. Part of his difficulty was trying to push himself at times of the day when his arousal was poor, which would have a subsequent negative effect on his mood. For the following two weeks, Brian was then assigned a 20-min FA practice and told to practice during his peak arousal time. He also continued alternating between *Finding Safety* and the body scan practice, to continue cultivating his interoceptive awareness. Doing this cognitively demanding practice during his peak time was intended to build his cognitive endurance and decrease fatigue. FA also provided access to some of Brian's catastrophic thinking, as well as other cognitive errors. Standard CBT approaches were used, including educating Brian on cognitive distortions and how to reappraise those thoughts into more realistic ones. His cognitive errors were also addressed via the introduction of OM practice. After approximately 3 weeks of FA, Brian was introduced to OM (a 40-min practice). In healthy practitioners, OM often naturally arises out of prolonged FA sessions; as such, the recording provided for the OM practice was a continuation of the original FA recording with which Brian was already familiar. This longer OM session allowed him to engage his attention for longer periods. OM was also intended as another form of interoceptive exposure, as well as a means to let negative thoughts arise and not indulge or pursue them – an alternative to actively reappraising negative thoughts. This seemed to be particularly helpful for Brian, who was prone to worry and using worry as a form of experiential avoidance. The "attitudes of mindfulness" [8] were also employed to support Brian in being able to cultivate acceptance, non-judgment, and loving-kindness toward symptoms that may not remit, and the possibility that some of his symptoms may be long lasting.

After approximately 8 weeks of treatment, Brian experienced a clinically significant reduction in depressive and anxious symptoms, and greater energy. However, he still avoided situations he believed would aggravate his physical symptoms, some of which was based on continued catastrophic thinking. After some discussion of his avoidance behavior, Brian was willing to entertain the possibility that some of what he perceived to be physical symptoms of concussion were actually symptoms of anxiety. A hierarchy of distressing situations was created, and he was more formally introduced to the idea of exposure. The next phase of treatment then focused on slowly and gradually exposing Brian to situations that he was worried would aggravate his symptoms. An exposure protocol was developed whereby he was first instructed to engage in a

brief mindfulness practice (e.g., *Finding Safety in the Body*) for several minutes. Then he was instructed to engage in positive self-talk (e.g., self-statements of loving-kindness and non-judgment) to prepare himself for the exposure and to use during the exposure itself. He would then engage in an exposure to a distressing situation (e.g., driving down a street with potholes) that was time limited so that he would know that it would come to an end at some previously defined time. Following the exposure he would engage in further positive self-talk as well as a personal reward.

After 12 weeks of treatment, Brian was becoming more active in his life; he had taken up a volunteer position in the community and was socializing again with friends. He was more compassionate with himself, while also being more curious about his symptoms and the role that anxiety was playing in perpetuating them. He was tentative, but quietly optimistic about his continued recovery.

The case of Sam. An additional case illustration of tailored mindfulness is provided in detail in Tuokko and Smart [21], where we present the case of Sam, a 66-year-old, right-handed, Italian-Canadian gentleman with Parkinson's disease, social anxiety, slowed processing speed, and executive dysfunction. One of Sam's primary complaints was centered on having difficulty socializing, because it would take him too long to think of what he wanted to say and to organize his thoughts, causing others to disengage from the conversation. Similar to Brian, the application of M-CBT (i.e., standard CBT approaches infused with mindfulness practice) was used to help Sam reach his goal of increased frequency of socialization and decreased social anxiety. In Tuokko and Smart [21] we describe how M-CBT was specifically applied in Sam's case, with a brief overview provided here. It was hypothesized that part of Sam's difficulty was that he was attempting to socialize when he was not at his cognitive best. To test this hypothesis, the first treatment goal was to implement mindfulness practice as a way to build emergent awareness [158] of Sam's current level of arousal, fatigue, and clarity of thinking. Because of his level of cognitive impairment, we began by scaffolding the practice using alarms on his smartphone as a form of "external mindfulness", to support internalization of the practice to overcome prospective memory difficulties.

After a week of collecting data, we were able to discover that Sam's optimal time for arousal and fatigue was mid-morning, after a good breakfast and his first dose of dopaminergic medication. This became our target time for engaging in gentle exposure exercises around social situations, in order for us to set Sam up for success and build his self-efficacy. Sam completed another week of monitoring arousal and fatigue using his smartphone, to verify the results. After this second week, he reported some irritation with the phone reminders, stating that he was beginning to anticipate them ahead of time. We took this as a positive sign that he had begun to internalize the notion of being mindful, and were able to transition into regular mindfulness practice. Session 3 was scheduled at his optimal arousal time (i.e., mid-morning) so that we could engage an *in-vivo* exposure exercise. With Sam, we created a hierarchy of potentially anxiety-provoking social situations, and picked an activity at 4 of 10 (i.e., talking to the barista at the coffee shop). Sam made it through the exposure, but felt somewhat defeated as he had difficulty remembering what to say to the barista because of his anxiety. We used cognitive restructuring on the negative automatic thoughts and underlying beliefs perpetuating his social anxiety. Attitudes of mindfulness were also used as a way to foster non-judgment, loving-kindness, and acceptance toward his cognitive limitations, as well as positive self-talk for being willing to engage in treatment.

Summary and Further Considerations for Implementing Mindfulness Into Clinical Practice

In this chapter, evidence has been presented to demonstrate that mindfulness has significant, positive effects on brain, behavior, and

psychological functioning in healthy individuals. While that same potential is available for persons with neurological illness and injury, the field is clearly in its infancy, but shows promise. Most of the literature focuses on psychological benefits, with less attention having been paid to possible cognitive benefits. Given the potential time and cost-effectiveness of disseminating MBIs, and the public interest in these types of interventions, it is clear that we are approaching a new frontier with the implementation of mindfulness in neurorehabilitation. That said, before enthusiastically rushing ahead to pursue a mindfulness-based research and clinical agenda, some final points are offered for consideration.

To be able to deliver this work effectively, certain skills and training are necessary. Aside from foundational training in clinical neuropsychology and cognitive rehabilitation, the researcher or clinician must also be versed in the practice and theory of mindfulness itself, including participation in formal training to disseminate MBIs such as the MBSR teacher training program available through the University of Massachusetts Medical Center. While one can effectively disseminate many other interventions (e.g., CBT) without ever having participated in them oneself, the same cannot be said about MBIs. Each of the individuals who have created MBIs – such as MBSR, MBCT, and DBT – have all written at length about their own personal journey with mindfulness practice and how this actually informed their creation and application of the various treatment protocols. Likewise, the current author has practiced mindfulness and other forms of Buddhist meditation for 20 years and taught in a variety of contexts for well over 10 years; it was through her own personal experience that she was able to effectively design tailored protocols for persons with neurological diagnoses. The "practice" is not a single thing, but is dynamic and develops over years of experience; this is what distinguishes meditation from mere "cognitive training". Personal experience with the practices is necessary to be able to relate to patients' experiences, as well as helping them navigate through the various challenges along the way, including some of the potential harms and "dark night" experiences previously discussed. A clinician's judicious self-disclosure of practice experiences also reinforces a sense of integrity and encourages patients to continue practicing – "if it's good for my therapist, it must be good for me, too".

References

1. Van Dam NT, van Vugt MK, Vago DR, Schmalzl L, Saron CD, Olendzki A, et al. Mind the Hype: A Critical Evaluation and Prescriptive Agenda for Research on Mindfulness and Meditation. Perspect Psychol Sci. 2008;13:36–61.
2. Goldberg SB, Tucker RP, Greene PA, Simpson TL, Kearney DJ, Davidson RJ. Is mindfulness research methodology improving over time? A systematic review. PLoS One. 2017;12:e0187298.
3. Bohlmeijer E, Prenger R, Taal E, Cuijpers P. The effects of mindfulness based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis. J Psychosom Res. 2010;68:539–44.
4. Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. Psychiatry Res. 2011;187:441–53.
5. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010;78:169–83.
6. Kliem S, Kroger C, Kosfelder J. Dialectical behavior therapy for borderline personality disorder: a meta-analysis using mixed-effects modeling. J Consult Clin Psychol. 2010;78:936–51.
7. Davidson RJ, Lutz A. Buddha's brain: Neuroplasticity and meditation. IEEE Signal Process Mag. 2008;25:174–6.
8. Kabat-Zinn J. Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness. New York NY: Bantam; 2013.
9. Bishop SR, Lau M, Shapiro S, Carlson L, Anderson ND, Carmody J, et al. Mindfulness: A proposed operational definition. Clin Psychol Sci Prac. 2004;11:230–41.
10. Sohlberg MM, Mateer CA. Cognitive Rehabilitation: An Integrative Neuropsychological Approach. New York NY: Guilford; 2001.
11. Heatherton TF, Wagner DD. Cognitive neuroscience of self-regulation failure. Trends Cogn Sci. 2011;15:132–9.
12. Hrabok M, Kerns K. The development of self-regulation: A neuropsychological perspective. In: Sokol B, Mueller U, Carpendale J, Young A, Iarocci G, editors. Self and Social Regulation: Social Interaction and the Development of Social

Understanding and Executive Functions. New York NY: Guilford; 2010. pp. 129–54.
13. Bach LJ, David AS. Self-awareness after acquired and traumatic brain injury. Neuropsychol Rehabil. 2006;16:397–414.
14. McGrath JC. Fear, anxiety, and depression. In: Tyerman A, King NS, editors. Psychological Approaches to Rehabilitation After Traumatic Brain Injury. Malden MA: Blackwell; 2008. pp. 260–93.
15. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-Based Cognitive Therapy for Depression. 2nd ed. New York NY: Guilford; 2012.
16. Dimeff LA, Koerner K. Dialectical Behavior Therapy in Clinical Practice: Application Across Disorders and Settings. New York NY: Guilford; 2007.
17. Hayes SC, Strosahl KD, Wilson KG. Acceptance and Commitment Therapy: The Process and Practice of Mindful Change. 2nd ed. New York NY: Guilford; 2011.
18. Papa A, Follette WC. Dismantling studies of psychotherapy. In The Encyclopedia of Clinical Psychology. 2015;1-6.
19. Hunt M, Al-Braiki F., Dailey S, Russell R, Simon K. Mindfulness training, yoga, or both? Dismantling active components of a mindfulness-based stress reduction intervention. Mindfulness. 2017; https://doi.org/10.1007/s12671-017-0793-z.
20. Melby-Lervåg M, Redick TS, Hulme C. Working Memory Training Does Not Improve Performance on Measures of Intelligence or Other Measures of "Far Transfer": Evidence From a Meta-Analytic Review. Perspect Psychol Sci. 2016;11:512–34.
21. Tuokko HA, Smart CM. Neuropsychology of Cognitive Decline: A Developmental Approach to Assessment and Intervention. New York NY: Guilford; 2018.
22. Sedlmeier P, Eberth J, Schwarz M, Zimmermann D, Haarig F, Jaeger S, Kunze S. The psychological effects of meditation: a meta-analysis. Psychol Bull. 2012;138:1139–71.
23. Rau HK, Williams PG. Dispositional mindfulness: A critical review of construct validation research. Pers Individ Dif. 2016;93:32–43.
24. Quaglia JT, Braun SE, Freeman SP, McDaniel MA, Brown KW. Meta-analytic evidence for effects of mindfulness training on dimensions of self-reported dispositional mindfulness. Psychol Assess. 2015;28:803–18.
25. Hart T, Tsaousides T, Zanca JM, Whyte J, Packel A, Ferraro M, et al. Toward a theory-driven classification of rehabilitation treatments. Arch Phys Med Rehabil. 2014;95(S33–44):e32.
26. Smart CM, Karr JE, Areshenkoff CN, Rabin LA, Hudon C, Gates N, et al. Non-Pharmacologic Interventions for Older Adults with Subjective Cognitive Decline: Systematic Review, Meta-Analysis, and Preliminary Recommendations. Neuropsychol Rev. 2017;27:245–57.
27. Lipsey MW, Wilson DB. The efficacy of psychological, educational, and behavioral treatment. Confirmation from meta-analysis. Am Psychol. 1993;48:1181–209.
28. Alexander CN, Rainforth MV, Gelderloos P. Transcendental meditation, self actualization, and psychological health: A conceptual overview and meta-analysis. J Soc Behav Pers. 1991;6:189–247.
29. Alexander CN, Robinson P, Orme-Johnson DW, Schneider RH, Walton KG. The effects of transcendental meditation compared to other methods of relaxation and meditation in reducing risk factors, morbidity, and mortality. Homeostasis. 1994;35:243–64.
30. Eppley KR, Abrams AI, Shear J. Differential effects of relaxation techniques on trait anxiety: A meta-analysis. J Clin Psychol. 1989;45:957–74.
31. Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, et al. Meditation experience is associated with increased cortical thickness. Neuroreport. 2005;16:1893–7.
32. Fox KC, Nijeboer S, Dixon ML, Floman JL, Ellamil M, Rumak SP, et al. Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. Neurosci Biobehav Rev. 2014;43:48–73.
33. Fox KC, Dixon ML, Nijeboer S, Girn M, Floman JL, Lifshitz M, Ellamil M, Sedlmeier P, Christoff K. Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. Neurosci Biobehav Rev. 2016;65:208–28.
34. Cahn BR, Polich J. Meditation states and traits: EEG, ERP, and neuroimaging studies. Psychol Bull. 2006;132:180–211.
35. Dodd DR, Smith AR, Forrest LN, Witte TK, Bodell L, Bartlett M, et al. Interoceptive Deficits, Nonsuicidal Self-Injury, and Suicide Attempts Among Women with Eating Disorders. Suicide Life Threat Behav. 2017;https://doi.org/10.1111/sltb.12383.
36. Paulus MP, Stewart JL. Interoception and drug addiction. Neuropharmacology. 2014;76 Pt B:342-350.
37. Van der Kolk B. The Body Keeps the Score: Brain, Mind, and Body in the Healing of Trauma. New York NY: Penguin; 2014.
38. Boettcher H, Brake CA, Barlow DH. Origins and outlook of interoceptive exposure. J Behav Ther Exp Psychiatry. 2016;53:41–51.
39. National Heart Lung and Blood Institute (n.d.) Coronary Heart Disease Risk Factors; c. 2018 [cited 2018 Feb 28]. Available from: https://www.nhlbi.nih.gov/health-topics/coronary-heart-disease-risk-factors.
40. Bonelli RM, Koenig HG. Mental disorders, religion and spirituality 1990 to 2010: a systematic

evidence-based review. J Relig Health. 2013;52:657–73.
41. Caspi A, Roberts BW, Shiner RL. Personality development: stability and change. Annu Rev Psychol. 2005;56:453–84.
42. Jackson J, Balota DA, Head D. Exploring the relationship between personality and regional brain volume in healthy aging. Neurobiol Aging. 2011;32:2162–71.
43. Low LF, Harrison F, Lackersteen SM. Does personality affect risk for dementia? A systematic review and meta-analysis. Am J Geriatr Psychiatry. 2013;21:713–28.
44. MacLean KA, Ferrer E, Aichele SR, Bridwell DA, Zanesco AP, Jacobs TL, et al. Intensive meditation training improves perceptual discrimination and sustained attention. Psychol Sci. 2010;21:829–39.
45. Campanella S. Why it is time to develop the use of cognitive event related potentials in the treatment of psychiatric diseases. Neuropsychiatr Dis Treat. 2013;9:1835–45.
46. Rast P, Macdonald SW, Hofer SM. Intensive Measurement Designs for Research on Aging. GeroPsych (Bern). 2012;25:45–55.
47. Sliwinski M. Measurement burst designs for social health research. Soc Personal Psychol Compass. 2008;2:245–61.
48. Smart CM, Segalowitz SJ. Respond, don't react: The influence of mindfulness training on performance monitoring in older adults. Cogn Affect Behav Neurosci. 2017;17:1151–63.
49. Simon D, Stenstrom DM, Read SJ. The coherence effect: Blending cold and hot cognitions. J Pers Soc Psychol. 2015;109:369–94.
50. Forfylow AL. Integrating yoga with psychotherapy: A complementary treatment for anxiety and depression. Canadian Journal of Counselling and Psychotherapy. 2011;45:132–50.
51. Public Health Agency of Canada. Complementary and alternative health; c. 2008 [cited 2018 Feb 28]. Available from: http://www.phac-aspc.gc.ca/chn-rcs/cah-acps-eng.php.
52. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5™. 5th ed. Arlington VA: American Psychiatric Publishing, Inc; 2013.
53. National Institutes of Mental Health (2017) Attention-Deficit/Hyperactivity Disorder; c. 2017 [cited 2018 Feb 28]. Available from: https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml.
54. Cairncross M, Miller CJ. The Effectiveness of Mindfulness-Based Therapies for ADHD: A Meta-Analytic Review. J Atten Disord. 2016; E-pub ehead of print.
55. Saltzman A. A Still Quiet Place: A Mindfulness Program for Teaching Children and Adolescents to Ease Stress and Difficult Emotions. Oakland CA: New Harbinger; 2014.
56. Brain Injury Association of Canada. Acquired Brain Injury (ABI) Information; c. 2014 [cited 2018 Feb 28]. Available from: http://braininjurycanada.ca/wp-content/uploads/2007/05/BIAC-Fact-Sheet-2014.pdf.
57. Schoenberg M, Scott JG. The Little Black Book of Neuropsychology: A Syndrome-Based Approach. New York NY: Springer; 2011.
58. Azulay J, Smart CM, Mott T, Cicerone KD. A pilot study examining the effect of mindfulness-based stress reduction on symptoms of chronic mild traumatic brain injury/postconcussive syndrome. J Head Trauma Rehabil. 2013;28:323–31.
59. Rapoport MJ. Depression following traumatic brain injury: epidemiology, risk factors and management. CNS Drugs. 2012;26:111–21.
60. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS. Rates of major depressive disorder and clinical outcomes following traumatic brain injury. JAMA. 2010;303:1938–45.
61. Bedard M, Felteau M, Marshall S, Cullen N, Gibbons C, Dubois S, et al. Mindfulness-based cognitive therapy reduces symptoms of depression in people with a traumatic brain injury: results from a randomized controlled trial. J Head Trauma Rehabil. 2014;29:E13–22.
62. Bedard M, Felteau M, Marshall S, Dubois S, Gibbons C, Klein R, et al. Mindfulness-based cognitive therapy: benefits in reducing depression following a traumatic brain injury. Adv Mind Body Med. 2012;26:14–20.
63. Levine B, Robertson IH, Clare L, Carter G, Hong J, Wilson BA, et al. Rehabilitation of executive functioning: an experimental clinical validation of goal management training. J Int Neuropsychol Soc. 2000;6:299–312.
64. Duncan J, Emslie H, Williams P, Johnson R, Freer C. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cogn Psychol. 1996;30:257–303.
65. Novakovic-Agopian T, Chen AJ, Rome S, Abrams G, Castelli H, Rossi A, et al. Rehabilitation of executive functioning with training in attention regulation applied to individually defined goals: a pilot study bridging theory, assessment, and treatment. J Head Trauma Rehabil. 2011;26:325–38.
66. Burgess PW, Alderman N, Forbes C, Costello A, Coates LM, Dawson DR, et al. The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. J Int Neuropsychol Soc. 2006;12:194–209.
67. Chen AJ, Novakovic-Agopian T, Nycum TJ, Song S, Turner GR, Hills NK, et al. Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury. Brain. 2011;134:1541–54.
68. Stamenova V, Levine B. Effectiveness of goal management training in improving executive

functions: a meta-analysis. Neuropsychol Rehabil. 2018; https://doi.org/10.1080/09602011.2018.1438294.
69. Lawrence M, Booth J, Mercer S, Crawford E. A systematic review of the benefits of mindfulness-based interventions following transient ischemic attack and stroke. Int J Stroke. 2013;8:465–74.
70. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Psychological distress, major depressive disorder, and risk of stroke. Neurology. 2008;70:788–94.
71. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta analysis of observational studies. Int J Stroke. 2013;8:545–59.
72. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry. 2013;202:14–21.
73. Centers for Disease Control. Stroke Facts; c. 2017 [cited 2018 Feb 28]. Available from: https://www.cdc.gov/stroke/facts.htm.
74. Joo HM, Lee SJ, Chung YG, Shin IY. Effects of mindfulness-based stress reduction program on depression, anxiety and stress in patients with aneurysmal subarachnoid haemorrhage. J Korean Neurosurg Soc. 2010;47:345–51.
75. Abbott RA, Whear R, Rodgers LR, Bethel A, Thompson Coon J, Kuyken W, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. J Psychosom Res. 2014;76:341–51.
76. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S. The Cochrane Collaboration, editors. Cochrane Handbook for Systematic Reviews of Interventions; 2008.
77. Nyklicek I, Dijksman SC, Lenders PJ, Fonteijn WA, Koolen JJ. A brief mindfulness based intervention for increase in emotional well-being and quality of life in percutaneous coronary intervention (PCI) patients: the MindfulHeart randomized controlled trial. J Behav Med. 2014;37:135–44.
78. Ayerbe L, Ayis S, Crichton SL, Rudd AG, Wolfe CD. Explanatory factors for the increased mortality of stroke patients with depression. Neurology. 2014;83:2007–12.
79. National Institute on Aging. What is Vascular Dementia?; c. 2017 [cited 2018 Feb 28]. Available from: https://www.nia.nih.gov/health/what-vascular-dementia.
80. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav. 2005;6:85–9.
81. Maguire J, Salpekar JA. Stress, seizures, and hypothalamic-pituitary adrenal axis targets for the treatment of epilepsy. Epilepsy Behav. 2013;26:352–62.
82. Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy Behav. 2005;7:161–71.
83. Kanner AM. Depression and epilepsy: a new perspective on two closely related disorders. Epilepsy Curr. 2006;6:141–6.
84. Wood K, Lawrence M, Jani B, Simpson R, Mercer SW. Mindfulness-based interventions in epilepsy: A systematic review. BMC Neurol. 2017;17:52. https://doi.org/10.1186/s12883-017-0832-3.
85. Thompson NJ, Walker ER, Obolensky N, Winning A, Barmon C, Diiorio C, et al. Distance delivery of mindfulness-based cognitive therapy for depression: project UPLIFT. Epilepsy Behav. 2010;19:247–54.
86. Thompson NJ, Patel AH, Selwa LM, Stoll SC, Begley CE, Johnson EK, et al. Expanding the efficacy of Project UPLIFT: Distance delivery of mindfulness-based depression prevention to people with epilepsy. J Consult Clin Psychol. 2015;83:304–13.
87. Tang V, Poon WS, Kwan P. Mindfulness-based therapy for drug-resistant epilepsy: An assessor-blinded randomized trial. Neurology. 2015;85:1100–7.
88. Yuen AW, Sander JW. Can natural ways to stimulate the vagus nerve improve seizure control? Epilepsy Behav. 2017;67:105–10.
89. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann Behav Med. 2009;37:141–53.
90. Lotufo PA, Valiengo L, Bensenor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia. 2012;53:272–82.
91. Mankus AM, Aldao A, Kerns C, Mayville EW, Mennin DS. Mindfulness and heart rate variability in individuals with high and low generalized anxiety symptoms. Behav Res Ther. 2013;51:386–91.
92. Lustyk MK, Chawla N, Nolan RS, Marlatt GA. Mindfulness meditation research: issues of participant screening, safety procedures, and researcher training. Adv Mind Body Med. 2009;24:20–30.
93. Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis–a systematic review. BMC Neurol. 2014;14:15.
94. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. The burden of mental comorbidity in multiple sclerosis: frequent, underdiagnosed, and undertreated. Mult Scler. 2009;15:385–92.

95. Klevan G, Jacobsen C, Aarseth J, Myhr KM, Nyland H, Glad S, et al. Health related quality of life in patients recently diagnosed with multiple sclerosis. Acta Neurol Scand. 2013;129:21–6.
96. Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. Psychiatr Clin North Am. 2007;30:803–17.
97. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79:368–76.
98. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna). 2017;124:901–5.
99. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol. 2006;5:355–63.
100. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci. 2017;18:435–50.
101. Simpson J, Lekwuwa G, Crawford T. Predictors of quality of life in people with Parkinson's disease: evidence for both domain specific and general relationships. Disabil Rehabil. 2014;36:1964–70.
102. McLean G, Lawrence M, Simpson R, Mercer SW. Mindfulness-based stress reduction in Parkinson's disease: a systematic review. BMC Neurol. 2017;17:92.
103. Song R, Grabowska W, Park M, Osypiuk K, Vergara-Diaz GP, Bonato P, et al. The impact of Tai Chi and Qigong mind-body exercises on motor and non-motor function and quality of life in Parkinson's disease: A systematic review and meta analysis. Parkinsonism Relat Disord. 2017;41:3–13.
104. Wang Y, Xie CL, Wang WW, Lu L, Fu DL, Wang XT, et al. Epidemiology of complementary and alternative medicine use in patients with Parkinson's disease. J Clin Neurosci. 2013;20:1062–7.
105. Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. Biochem Pharmacol. 2014;88:661–70.
106. Gard T, Holzel BK, Lazar SW. The potential effects of meditation on age related cognitive decline: a systematic review. Ann N Y Acad Sci. 2014;1307:89–103.
107. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014;10:844–52.
108. Reisberg B, Prichep L, Mosconi L, John ER, Glodzik-Sobanska L, Boksay I, et al. The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. Alzheimers Dement. 2008;4:S98–108.
109. Rabin LA, Smart CM, Amariglio RE. Subjective Cognitive Decline in Preclinical Alzheimer's Disease. Annu Rev Clin Psychol. 2017;13:369–96.
110. Lenze EJ, Hickman S, Hershey T, Wendleton L, Ly K, Dixon D, et al. Mindfulness-based stress reduction for older adults with worry symptoms and co-occurring cognitive dysfunction. Int J Geriatr Psychiatry. 2014;29:991–1000.
111. Smart CM, Segalowitz SJ, Mulligan BP, Koudys J, Gawryluk JR. Mindfulness Training for Older Adults with Subjective Cognitive Decline: Results from a Pilot Randomized Controlled Trial. J Alzheimers Dis. 2016;52:757–74.
112. Smart CM. Wisdom Mind. Unpublished clinical manual. Victoria BC: University of Victoria; 2012.
113. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage. 2002;17:479–89.
114. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23(Suppl 1):S208–19.
115. Jellinger KA, Attems J. Neuropathological approaches to cerebral aging and neuroplasticity. Dialogues Clin Neurosci. 2013;15:29–43.
116. Larouche E, Hudon C, Goulet S. Potential benefits of mindfulness-based interventions in mild cognitive impairment and Alzheimer's disease: an interdisciplinary perspective. Behav Brain Res. 2015;276:199–212.
117. Wells RE, Yeh GY, Kerr CE, Wolkin J, Davis RB, Tan Y, et al. Meditation's impact on default mode network and hippocampus in mild cognitive impairment: a pilot study. Neurosci Lett. 2013;556:15–9.
118. Wells RE, Kerr CE, Wolkin J, Dossett M, Davis RB, Walsh J, et al. Meditation for adults with mild cognitive impairment: a pilot randomized trial. J Am Geriatr Soc. 2013;61:642–5.
119. Paller KA, Creery JD, Florczak SM, Weintraub S, Mesulam MM, Reber PJ, et al. Benefits of mindfulness training for patients with progressive cognitive decline and their caregivers. Am J Alzheimers Dis Other Demen. 2015;30:257–67.
120. Churcher Clarke A, Chan JMY, Stott J, Royan L, Spector A. An adapted mindfulness intervention for people with dementia in care homes: feasibility pilot study. Int J Geriatr Psychiatry. 2017;32:e123–31.
121. Quintana-Hernandez DJ, Miro-Barrachina MT, Ibanez-Fernandez IJ, Pino AS, Quintana-Montesdeoca MP, Rodriguez-de Vera B, et al. Mindfulness in the Maintenance of Cognitive Capacities in Alzheimer's Disease: A Randomized Clinical Trial. J Alzheimers Dis. 2016;50:217–32.
122. Ulrichsen KM, Kaufmann T, Dorum ES, Kolskar KK, Richard G, Alnaes D, et al. Clinical Utility of Mindfulness Training in the Treatment of Fatigue After Stroke, Traumatic Brain Injury and Multiple Sclerosis: A Systematic Literature Review and Meta-analysis. Front Psychol. 2016;7:912.

123. LaChapelle DL, Finlayson MA. An evaluation of subjective and objective measures of fatigue in patients with brain injury and healthy controls. Brain Inj. 1998;12:649–59.
124. Ingles JL, Eskes GA, Phillips SJ. Fatigue after stroke. Arch Phys Med Rehabil. 1999;80:173–8.
125. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. J Psychosom Res. 2004;57:35–43.
126. Van der Lee ML, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. Psychooncology. 2012;21:264–72.
127. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet. 2004;363:978–88.
128. Immink M. Fatigue in neurological disorders: A review of mindfulness-based interventions. Fatigue: Biomedicine Health Behavior. 2014;2:202-218.
129. Dobryakova E, Genova HM, DeLuca J, Wylie GR. The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. Front Neurol. 2015;6:52.
130. Valentine ER, Sweet PLG. Meditation and attention: A comparison of the effects of concentrative and mindfulness meditation on sustained attention. Ment Health Relig Cult. 1999;2:59–70.
131. Briggs J, Killen J. Perspectives on complementary and alternative medicine research. JAMA. 2010;310:691–2.
132. Davidson RJ, Dahl CJ. Outstanding challenges in scientific research on mindfulness and meditation. Perspect Psychol Sci. 2018;13:62–5.
133. Britton W. The Dark Knight of the Soul; c. 2014 [cited 2018 Feb 28]. Available from: https://www.theatlantic.com/health/archive/2014/06/the-dark-knight-of-the-souls/372766/
134. Preece R. The Psychology of Buddhist Tantra. Boston MA: Snow Lion; 2006.
135. Welwood J. Toward a Psychology of Awakening: Buddhism, Psychotherapy, and the Path of Personal and Spiritual Transformation. Boston MA: Shambhala; 2002.
136. Jensen CG, Vangkilde S, Frokjaer V, Hasselbalch SG. Mindfulness training affects attention – or is it attentional effort? J Exp Psychol Gen. 2012;141:106–23.
137. Duff K. Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. Arch Clin Neuropsychol. 2012;27:248–61.
138. Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychol Rev. 2003;13:181–97.
139. Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol. 2003;84:822–48.
140. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment. 2006;13:27–45.
141. Walach H, Buchheld N, Buttenmüller V, Kleinknecht N, Schmidt S. Measuring mindfulness: The Freiburg Mindfulness Inventory. Pers Individ Dif. 2006;40:1543–55.
142. Bergomi C, Tschacher W, Kupper Z. The assessment of mindfulness with self-report measures: Existing scales and open issues. Mindfulness. 2013;4:191–202.
143. Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalgleish T. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. Clin Psychol Rev. 2015;40:91–110.
144. Toivonen KI, Zernicke K, Carlson LE. Web-Based Mindfulness Interventions for People With Physical Health Conditions: Systematic Review. J Med Internet Res. 2017;19:e303.
145. Levine B, Stuss DT, Winocur G, Binns MA, Fahy L, Mandic M, Bridges K, Robertson IH. Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. J Int Neuropsychol Soc. 2007;13:143–52.
146. van Hooren SA, Valentijn SA, Bosma H, Ponds RW, van Boxtel MP, Levine B, et al. Effect of a structured course involving goal management training in older adults: A randomised controlled trial. Patient Educ Couns. 2007;65:205–13.
147. Stubberud J, Langenbahn D, Levine B, Stanghelle J, Schanke AK. Goal management training of executive functions in patients with spina bifida: a randomized controlled trial. J Int Neuropsychol Soc. 2013;19:672–85.
148. Chambless DL, Hollon SD. Defining empirically supported therapies. J Consult Clin Psychol. 1998;66:7–18.
149. Chambless DL, Baker MJ, Baucom DH, Beutler LE, Calhoun KS, Crits-Christoph P, et al. Update on empirically validated therapies. II. Clin Psychol. 1998;51:3–16.
150. Tate RL, Perdices M, Rosenkoetter U, Shadish W, Vohra S, Barlow DH, et al. The Single-Case Reporting Guideline In BEhavioural Interventions (SCRIBE) 2016 Statement. Phys Ther. 2016;96:e1–10.
151. Kreuter MW, Skinner CS. Tailoring: what's in a name? Health Educ Res. 2000;15:1–4.
152. Judd T. Neuropsychotherapy and Community Integration: Brain Illness, Emotions and Behaviour. New York NY: Kluwer Academic/Plenum Publishers; 1999.
153. Goodrich E, Wahbeh H, Mooney A, Miller M, Oken BS. Teaching mindfulness meditation to adults with severe speech and physical impairments: An exploratory study. Neuropsychol Rehabil. 2015;25:708–32.

154. Marshall RS, Laures-Gore J, Love K. Brief mindfulness meditation group training in aphasia: exploring attention, language and psychophysiological outcomes. Int J Lang Commun Disord. 2018;53:40–54.
155. Blommaert K, Smart CM, Mulligan BP, Prechotko C. Respond, don't react: The influence of mindfulness on risk-taking behavior in adolescents diagnosed with fetal alcohol spectrum disorder. J Int Neuropsychol Soc. 2014;20(Suppl. 1):84.
156. Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoring in meditation. Trends Cogn Sci. 2008;12:163–9.
157. Peretti A, Amenta F, Tayebati SK, Nittari G, Mahdi S. Telerehabilitation: Review of the state-of-the-art and areas of application. JMIR Rehabil Assist Technol. 2017;4:e7. https://doi.org/10.2196/rehab.7511.
158. Crosson C, Barco PP, Velozo C, Bolesta MM, Cooper PV, Werts D, Brobeck TC. Awareness and compensation in postacute head injury rehabilitation. J Head Trauma Rehabil. 1989;4:46–54.
159. Trungpa C. The myth of freedom and the way of meditation. Boston MA: Shambhala; 1976
160. Ray RA. Indestructible truth: the living spirituality of Tibetan Buddhism. Boston MA, Shambhala; 2002

Chapter 35

Sensory Reweighting: A Rehabilitative Mechanism?

Eric Anson and John Jeka

History and Background

Falls in the elderly are dangerous, debilitating, and costly. Of the population over 65 years of age, one-third to one-half experiences falls annually; of these, half do so repeatedly. Falls are the leading cause of injury in older adults and the primary cause of accidental death in those over age 85. Five percent of falls lead to a fracture, with hip fractures being the most common (greater than 200,000 annually). One in 10 of these individuals will die of complications, and 25% of survivors will never regain their previous mobility. An additional 10% of all older adults who fall will sustain other serious injuries requiring medical care. The cost of direct care for hip fracture patients alone is now estimated to be in excess of 10 billion dollars a year.

Imbalance is a major cause of falls. Further, imbalance in older adults is strongly associated with functional decline and frailty. Certain activities of daily living can no longer be performed or are avoided due to a fear of falling. Unstable elderly persons become increasingly sedentary, homebound, and isolated. Fall-prone elderly persons may display greater than typical reduction in strength and power needed during corrective movements, to recover from perturbations or tripping, compared to healthy elderly and are at increased risk of falling (for review, see [1]). Falls and instability contribute to 40% of nursing home admissions.

While mild declines in balance are associated with advancing age, falls are not a normal part of aging. Prior research has led to the understanding that elderly fallers are different than their healthy, age-matched counterparts. According to geriatrician Mary Tinetti falls "should be treated as an entity in their own right" [2]. The issue of just *how* older adults who fall should be treated is currently of great interest to clinicians and researchers alike. Because the mechanisms of postural control and their decline in older adults who fall are not fully understood, the design of therapeutic interventions is severely hampered.

Presently, there exists a large gap between research into postural control mechanisms and interventions for preventing falls in the elderly. This may be partially due to the multi-faceted nature of postural control. Earlier in the century posture research focused primarily on defining the parallel and hierarchical reflexive pathways that were thought to control upright stance (e.g., [3, 4]). This reflexive perspective has been supplanted in the last 20 years with the view that posture is a complex interaction among multiple neural subsystems which support sensory orientation [5], multi-joint coordination [6], task constraints [7], and cognitive inputs such as attention (e.g., [8]). Because the mechanisms of postural control and their decline in older adults who fall are not fully understood, it remains a challenge to translate this modern view into effective rehabilitative programs for those

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with balance problems. A review of balance training studies [9] points out that ". . .there have been few attempts to improve balance in older adults with theory-based intervention strategies" (p. 355).

Here we focus on one of the major underlying mechanisms of postural control, namely sensory integration, but within an intervention context to foster a better theoretical understanding of how one critical component of such a multifaceted program – sensory integration – may improve balance control. Sensory training may add to our theoretical understanding of postural control and its relationship to sensory information as well as inform the design of clinical interventions.

Sensory Reweighting in Older Adults

Control of human upright stance requires sensory input from multiple sources to detect center of gravity excursions and to generate appropriate muscle responses for upright stance control. Without appropriate knowledge of self-orientation, equilibrium control is severely compromised [10]. Patients or elderly individuals with sensory deficits who perceive their stability limits incorrectly may show inappropriate postural responses or strategies to maintain equilibrium. For example, some individuals may not take a step necessary to recover equilibrium when their center of mass is displaced outside their limits of stability because they misperceive their stability boundaries. In contrast, others may make exaggerated compensatory responses to very small perturbations because they misperceive themselves to be at their limits of stability and therefore at risk for a fall.

Successful responses to balance loss are first predicated on the ability to detect one's own body position and sense instability and second the ability to generate the appropriate corrective response. Estimation of body position is heavily dependent upon the integration of information from multiple sensory systems including visual, vestibular (inner ear), and somatosensory (touch, pressure). The ability to select and reweight alternative orientation references adaptively is considered one of the most critical factors for postural control in the elderly [11]. Elderly individuals who are unable to quickly select the appropriate sensory cue may be prone to balance loss whenever the sensory environment changes. These individuals may also be less able to use alternative combinations of sensory information to compensate for sensory losses or impairments. The reweighting of sensory information may determine whether an older adult can compensate for mild sensory degradation and retain good postural control despite advanced age.

Multisensory reweighting (MSR) is generally held to be impaired in older adults and more so in the fall-prone versus healthy elderly. Teasdale et al. [12] screened both young and (presumably healthy) older subjects to insure intact peripheral somatosensation, then measured their postural sway during the sudden withdrawal and re-insertion [addition] of visual information. As expected, both age groups had increased postural sway with the sudden removal of visual information. For young subjects, postural sway decreased when vision was suddenly added after a period with eyes closed. However, for older subjects sudden addition of visual information led to increased postural sway. Considering that peripheral somatosensation was intact in both groups, these results may point to deficient central MSR mechanisms in the older group. According to Teasdale et al. [12], compared to younger adults, older adults have "poorer central integrative mechanisms responsible for reconfiguring the postural set" (p. 695).

Healthy older adults are as stable as healthy young adults in conditions where only a single sense is altered, but are less stable in conditions where two senses are manipulated simultaneously [13–16]. Although even healthy older adults may lose their balance when first exposed to conditions where both visual and somatosensory inputs are altered, they show improved stability on repeated trials of the same conditions [7, 17, 18]. These findings indicate that healthy older adults can, with little practice, rapidly adapt to changing environments.

Compared to healthy older adults, fall-prone older adults demonstrate instability in conditions where only one sensory input is changing [8, 19, 20]. Fall-prone older adults do not show rapid adaptation to changes in the environment, continuing to lose their balance despite repeated exposure [11, 21]. Fall-prone elders are hypothesized to be more visually

dependent, failing to use reliable somatosensory cues in environments where visual inputs are unstable [22, 23]. Thus, there may be age-related decline in MSR abilities, with further MSR deficits reported in fall-prone older adults. This implies that impaired MSR is associated with increased fall risk.

Sensory deficits associated with aging and poor balance control have two potential sources: (1) loss or degradation of one or more peripheral sensory systems; and (2) degradation of central nervous system processing which integrates information from peripheral sensory systems. Age-related changes in peripheral functioning may adversely affect balance control, particularly with vision, but the healthy central nervous system may also adapt to such changes, especially if these declines are gradual. Moreover, there is no direct evidence that age-related reduction in somatosensory and vestibular sensitivity is related to the balance changes in the elderly [24]. Central processing deficits may be the more likely candidate for age-related balance decrement. Studies show that elderly persons are at a disadvantage when required to control upright stance with the slower, higher level sensory integrative mechanisms [25] .

Balance Training

A number of controlled studies have been undertaken to investigate various intervention strategies to reduce the number and risk of falls (for a review, see [9, 26]). Several of these studies have demonstrated that activity-based interventions can significantly improve balance and reduce the risk for falls in older adults. But most of these intervention approaches lack a theoretical framework, and as yet there is no clearly superior, standardized approach to exercise interventions for fall-risk reduction in the elderly. Moreover, the mechanisms by which activities such as exercise affect postural control processes are not well understood. Until a better understanding of postural control processes and their decline in older adults who fall is achieved, a scientific foundation for activity-based interventions will remain elusive. Likewise, knowledge of the mechanisms through which interventions effect postural control processes is needed before optimal intervention strategies can be developed.

Experimental studies have suggested that poor sensory integration in older adults is a potential source of falls (for review, see [11]). Many older adults may fall not because they are too weak or stiff to respond, but because they do not correctly perceive their spatial position, or changes in their spatial position, preceding a fall. This inaccurate perception may result in inappropriate compensatory responses to correct for loss of stability. Based upon such findings, enhancement of multisensory interactions has been suggested as a potentially fruitful area for new interventions [9]. However, to date, we know of only one study that focused specifically on sensory input manipulation as an intervention approach (i.e., [27]). Despite the positive effect on balance from sensory training in this study, little has been done to expand the multisensory training approach.

The neurophysiological mechanism through which sensory training may effect the postural control system is unknown, but a likely candidate is neuroplasticity. Recent studies indicate that in response to practice or training, the brain reorganizes far more quickly [28] and at a much later age than previously thought possible [29]. Studies with primates indicate that repetitive, goal-directed activity leads to changes in cortical sensory mapping, which in turn affects motor responses [30]. Preliminary work with individuals who have developed hand dystonia related to manual overuse, and in individuals post-stroke, indicates that interventions geared toward sensory re-organization result in improved motor capabilities [31]. Neuroplastic change may be one mechanism by which sensory training improves balance. It is possible that interventions geared toward improving the use of sensory inputs for perception of position in and movement through space may result in improved balance and reduced risk of falls in the elderly.

Current views of postural control recognize the critical role of multisensory integration for accurate perception of body orientation and subsequently appropriate motor behavior. Clinical practice has begun to reflect this view by expanding balance evaluation methods to include tests of peripheral sensory reception and central sensory organization and by developing multi-dimensional intervention programs that include manipulation of environmental constraints to challenge sensory integration processes [32–34]; (for review, see [1]). These comprehensive

interventions are more successful at reducing the risk of falls in the unstable elderly than previous uni-dimensional approaches [9]. However, studies using multidimensional interventions and global balance measures do not permit investigation of the specific mechanisms that may change due to intervention. Until a greater understanding of these particular processes is gained, the individual components of a comprehensive program cannot be optimally developed and maximal benefit from such programs will not be achieved. Below we summarize studies which explore perceptual postural control mechanisms in elderly individuals with and without a history or high risk of falls and the changes – if any – in balance control that may result specifically from interventions designed to promote central sensory integration processes in unstable older adults. With this information, improved intervention approaches may be designed and the risk of falls subsequently reduced.

Multisensory Integration: The Light-Touch/Vision Paradigm

One of the primary methods to investigate "sensorimotor integration" in postural control is motivated from linear systems analysis. Subjects are typically "driven" by an oscillating pattern of sensory information. The resulting postural or orientation responses of the body are measured to determine "system" control properties. For example, the sinusoidal vertical axis rotation (SVAR) technique rotates seated subjects at a range of frequencies to measure the gain and phase of eye movements in the dark, as an assessment of vestibular function [35, 36]. Likewise, an oscillating visual "moving room" has been used to demonstrate the coupling of visual information with whole-body posture [37–43]. These techniques have determined that rate information is derived from sensory stimuli, that is, the vestibular system provides information about angular acceleration of the head and linear acceleration of the body [44], while the visual system is sensitive to the velocity of a stimulus [39, 45].

We have developed similar techniques to study the properties of somatosensory coupling to posture. A series of studies have demonstrated that somatosensory cues derived from light-touch fingertip contact to a stationary surface provide orientation information for improved control of upright stance [46–49]. Subjects stand in a tandem stance while maintaining fingertip contact with a stationary plate that measures the applied forces. Ultrasound receivers or infrared cameras measure head and approximate center of mass movement. An auditory alarm sounds if above threshold fingertip forces are applied, signaling the subject to reduce applied force without losing contact with the plate. This level of fingertip force is not mechanically supportive, but provides sensory information that the nervous system can use to correct deviations of the body from an upright posture. In general, the task is easy for healthy young subjects. After one practice trial, subjects rarely set off the alarm. The results have consistently shown that light-touch contact (<1 Newton (N)) with the fingertip to a rigid surface attenuates postural sway just as well as mechanical contact of 10–20 N. Furthermore, the influence of fingertip contact with a moving surface on whole-body posture is as dramatic as with full-field visual displays [50, 51]. When the contact surface moves sinusoidally, postural sway adopts the frequency of contact surface motion. Predictions of a second order model support the hypothesis that body sway is coupled to the contact surface through the velocity of the somatosensory stimulus at the fingertip. Other studies have replicated and extended these light-touch findings to other task situations [52–55].

We have developed a multisensory experimental paradigm using light-touch contact in combination with vision as sources of sensory information for postural control [56]. Figure 35.1 shows the experimental setup. An advantage of using light-touch contact as a sensory source is that, like vision, it is easily manipulated (i.e., it is easy to add, remove, or vary its movement frequency and amplitude), making it possible to precisely vary vision and touch relative to one another and to investigate multisensory integration with regard to postural control.

Subjects stood within the visual cave with light contact of a small force plate with the right index fingertip. The visual scene and the touch plate moved simultaneously at 0.2 and 0.28 Hz, respectively, in five conditions that manipulated the relative amplitudes of visual and touch motion. Touch and vision

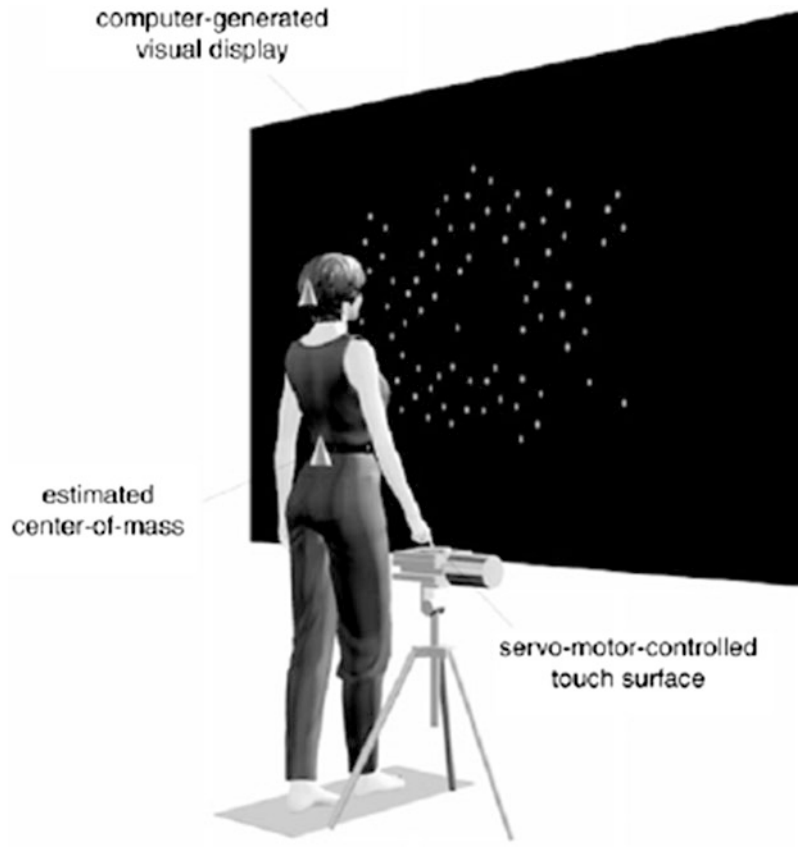

Fig. 35.1 Two-frequency vision and touch experimental paradigm

were presented at different frequencies so that the body's response to each could be measured separately. We then calculated "gain" to each sensory input. Gain is calculated as the ratio of the center of mass amplitude over the sensory stimulus amplitude at the frequency of the stimulus. If the gain to vision is one, this means that the body's response is the same amplitude as the visual stimulus. In other words, the center of mass of the body is moving side-to-side at the same amplitude as the visual stimulus. If the gain is less than one, then the body's response is smaller than the sensory stimulus amplitude. Gain is interpreted as a measure of the coupling or "weighting" of the sensory stimulus. Higher (lower) gain is interpreted as higher (lower) weighting, reflecting how much the nervous system is using the information from that particular input in estimating the position and velocity of the body.

Figure 35.2 plots center of mass (COM) gain in two subjects, who showed both an intra- and inter-modality dependence on vision and touch amplitude. The *x*-axis denotes the relative amplitude of the two stimuli (vision:touch in mm) in each condition. Comparing, for example, condition 2:8–2:4, note how decreasing the amplitude of touch stimulus motion increased the gain to touch (an intra-modality dependence), while at the same time, gain to vision decreased (an inter-modality dependence), even though visual amplitude was held constant at 2 mm across conditions. We refer to this effect as inverse gain reweighting, meaning, that as stimulus amplitude goes up, the response to that stimulus goes down. This reflects that as a sensory stimulus increases in amplitude, the nervous system must decrease (downweight) its influence to remain upright. Without downweighting, a stimulus of increasing amplitude would

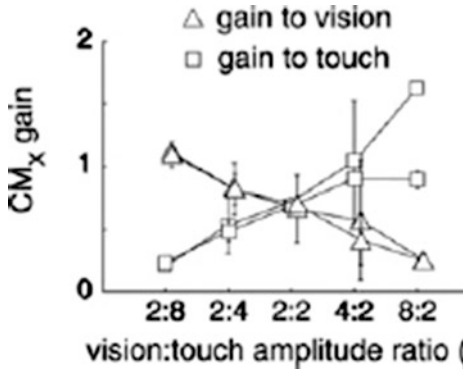

Fig. 35.2 Center of mass gain to vision and light touch showing both intra-modality and intermodality reweighting

eventually lead to loss of equilibrium. At the same time, the nervous system increases (upweights) the influence of a stimulus that decreases in amplitude because more sensory information enhances its accuracy of self-motion estimation and a smaller stimulus does not threaten equilibrium.

The techniques summarized above have allowed intermodality reweighting to be identified rigorously. A crucial aspect of the design was to present stimuli from different modalities at different frequencies so that the response to each stimulus could be quantified separately, thus revealing their inherent interdependence. As we illustrate below, these same techniques can now be applied to populations which have been hypothesized previously to have deficits in sensory reweighting, namely the unstable elderly.

Sensory Reweighting in the Fall-Prone Elderly Population

Are central sensory reweighting deficits responsible at least in part for the postural control problems seen in healthy and fall-prone older adults? Conclusions from previous research seem to indicate so. Earlier studies, however, have typically used postural sway measures such as mean sway amplitude that may not be as discerning for the processes underlying sensory reweighting (e.g., [7, 19, 57]; see [58]). Using the two-frequency light-touch/vision paradigm described above, we investigated sensory reweighting deficits in fall-prone older adults [59]. Elderly subjects were excluded from the study if they had any medical diagnoses known to produce sensory deficits (diabetes, macular degeneration, vestibulopathy, etc.) or if they are found to have sensory loss on a clinical neurologic screening. Subjects performed both the Sensory Organization Test (SOT) and the two-frequency light-touch/vision tests. The SOT uses a hydraulically controlled support platform and visual surround which may be servo-linked to body sway. Measurement of changes in ankle angle that typically accompany forward and backward movements of the body can be attenuated by rotating the support surface around the axis of the ankle. Similarly, the visual surround can also move forward and backward with anterior– posterior body sway, negating any visual flow that typically accompanies such body movements. This is referred to as "sway-referencing" to the movements of the body.

The SOT consists of a series of six different conditions that allow postural performance to be compared under various combinations of visual, vestibular, and somatosensory information. For example, when the support surface is sway-referenced and the eyes are closed (SOT condition #5) or both the support surface and the visual surround are sway-referenced (SOT condition #6), one is left with primarily vestibular information to maintain upright stance. Many patient populations and elderly individuals with balance problems fall immediately in SOT condition #5 and #6, while young healthy individuals are able to maintain upright stance [60], albeit with significantly greater postural sway. Results indicated that our subjects' performance on the SOT is consistent with prior research, that is, they had great difficulty remaining stable under conditions where vision and somatosensory inputs are altered simultaneously (SOT conditions #5 and #6). Because subjects with vestibular deficits were excluded from the study, poor performance on SOT conditions 5 and 6 implied that they have difficulty with sensory reweighting.

In contrast to the SOT results, the same group of subjects displayed clear evidence of multisensory reweighting on the two-frequency light-touch/vision experiment. Vision and touch gains for the fall-prone older adults versus a group of healthy young adults are shown in Fig. 35.3. For the fall-prone older adults,

intra-modality reweighting is apparent for both modalities. Note the sharp decline in vision gain as the visual stimulus amplitude increases from 2:2 to 8:2 and the rise in touch gain as the touch stimulus amplitude decreases from 2:8 to 2:2. Inter-modality reweighting is evident for vision, as there is a significant decrease in the vision gain when the vision stimulus amplitude is constant while the touch stimulus amplitude is decreasing. Mean touch gains also rise, in conditions when constant touch stimulus amplitudes are paired with increasing vision stimulus amplitudes. Thus, fall-prone elderly subjects show a very similar pattern of gain change across conditions when compared to healthy young adults. These data do not support the assumption that multisensory reweighting is deficient in fall-prone older adults.

Dynamics of Sensory Reweighting. One explanation for the discrepancy in these results is that prior

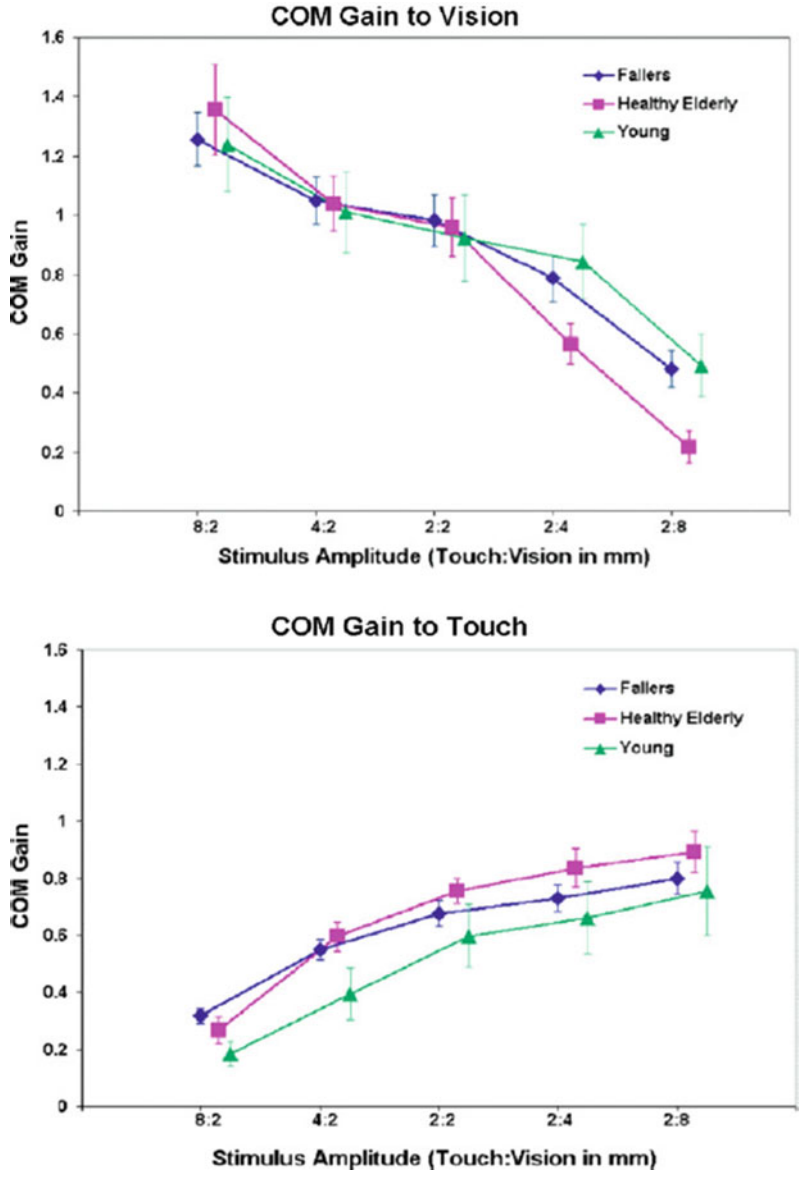

Fig. 35.3 Center of mass gain to vision and light touch in young, healthy older, and fall-prone older adults

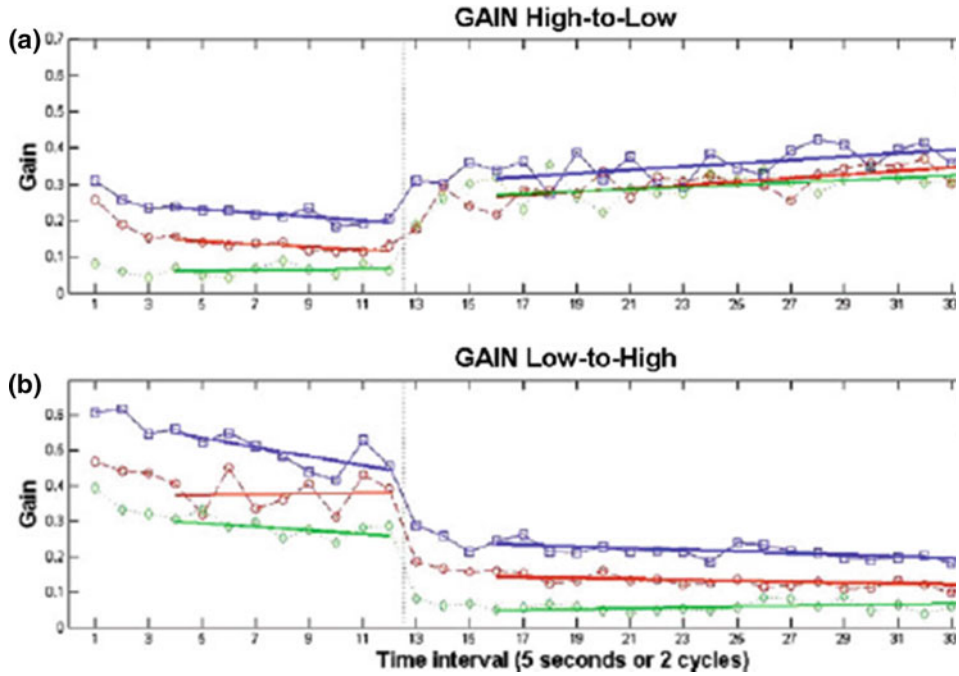

Fig. 35.4 Long-term changes in center of mass gain in young, healthy older, and fall-prone adults after a change in the visual amplitude from (**a**) high-to-low and (**b**) low-to-high

studies used relatively short trials (typically 10–30 s) while Allison et al. [59] employed longer trials (2 min). Healthy and fall-prone older adults may be able to reweight visual and somatosensory information, but perhaps not as quickly as young adults. Support for this view comes from a subsequent study which investigated the "dynamics of reweighting" in older adults. In this study, we measured how quickly older adults responded to a change in a visual stimulus [61].

Subjects stood in front of a visual screen in a standardized foot position and were instructed to stand as steadily as possible without stiffening. The subjects began each trial by looking straight ahead at the blank area on the front wall. The visual scene oscillated sinusoidally in the anterior–posterior direction at a constant frequency of 0.4 Hz. The initial amplitude was either 3 or 12 mm. After 60 s the oscillation amplitude switched from 3 to 12 mm or vice versa and remained at this amplitude for 120 s.

Figure 35.4 shows the results. All groups showed an initial rapid change in gain that reflected reweighting of vision. When the visual stimulus changed from low-to-high, all subjects showed decreased gain, indicating a reduced coupling to vision when the visual amplitude was large. When the stimulus changed from high-to-low, all subjects showed increased gain, indicating an increased coupling to vision when the visual amplitude was small. No differences were observed between groups, suggesting that the initial rapid reweighting process is not dependent on age or fall-prone status.

However group differences were observed for long-term changes in gain. For young adults and healthy older adults, few changes were observed after the initial change in gain implying that the MSR process was completed relatively quickly in young subjects. For fall-prone adults, gains continued to change over the duration of all time segments, demonstrating relatively slow adaptation and implying that the reweighting process in fall-prone adults is not fully achieved during the rapid change in gain. These results may have functional implications for fall risk. Deviations from upright vertical were small and clearly did not approach stability limits. However, fall-prone older adults displayed a prolonged reweighting process that is clearly different than

young and healthy older adults, which may contribute to less stable postural control while navigating through the environment.

A Multisensory Intervention

A subsequent study investigated whether an intervention could change how older adults respond to multisensory information. Participants attended two, 45-min exercise sessions each week for 8 weeks. Prior studies incorporating sensory-challenge exercises and using a similar schedule have demonstrated significant improvements in balance performance [62, 63]. Exercise sessions were "one-on-one" with one of the three "trainers" (two licensed physical therapists and one physical therapist assistant) had been trained in the research exercise protocol. The exercise program was designed to facilitate MSR processes. The purposes of the balance exercise program were to improve (1) estimation of body position and motion in space and (2) adaptation to changing sensory environments.

All exercises were performed on a SMART Balance Master®, a computerized balance testing and training device that permits operator controlled surface and/or visual environment motion and, if desired, provides visual feedback about center of gravity position and motion. Participants were asked to stand as steadily as they could without stiffening. No dynamic balance training (volitional weight shifting) or functional balance activities (transfers, gait training, etc.) were practiced; no strengthening or stretching exercises were given. Hence, this was not a multi-dimensional exercise program designed to maximally reduce fall risk, but a uni-dimensional, impairment-oriented exercise program designed to enhance MSR.

All subjects followed the same standardized exercise progression; however, the initial difficulty level of the exercises was adjusted for each subject based on their balance abilities. Exercises were made progressively more difficult over the 16 sessions by decreasing standing surface and/or visual environment motion, making it harder to detect surface or visual motion. Visual center of gravity feedback was initially provided, then progressively delayed and withdrawn over the first eight training sessions. Advancement of conditions/tasks and/or reduction of feedback occurred as soon as the participant was successful at that exercise four of five tries or better.

The effect of the sensory-challenge balance exercise program is seen in Fig. 35.5a, b which shows that both vision and touch gain values decreased post-training. This post-training reduction in gain values reflects less coupling to the sensory stimulus. The reduced gain values may indicate a change in the ability to discriminate and dissociate self- versus environmental motion, suggesting that sensory estimation processes can be accessed and trained. The fall-prone elderly have been shown to be overly reliant upon visual information. Training to reduce this reliance has potential beneficial effects for balance control.

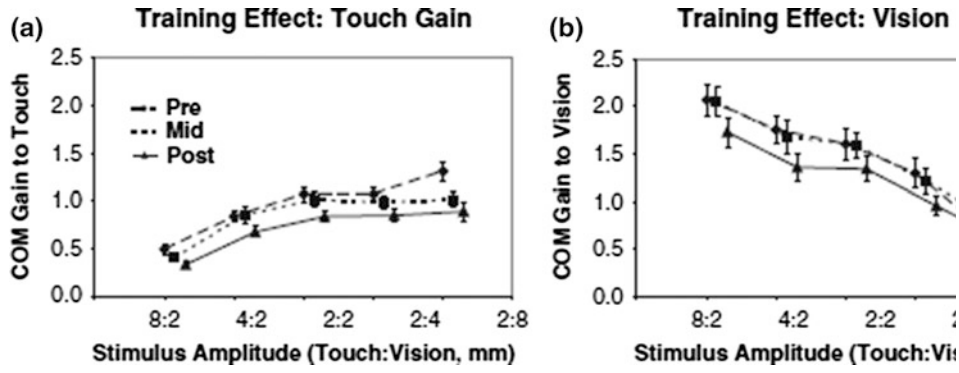

Fig. 35.5 Effect of training on center of mass gain to (**a**) touch and (**b**) vision

Conclusions

Current views of postural control recognize the critical role of multisensory integration for accurate perception of body orientation and subsequently appropriate motor behavior. Clinical practice has begun to reflect this view by expanding balance evaluation methods to include tests of peripheral sensory reception and central sensory organization and by developing multi-dimensional intervention programs that include manipulation of environmental constraints to challenge sensory integration processes [26, 32, 33]. These comprehensive interventions are more successful at reducing the risk of falls in the unstable elderly than previous uni-dimensional approaches [9]. However, studies using multidimensional interventions and global balance measures do not permit investigation of the specific mechanisms that may change due to intervention. Until a greater understanding of these particular processes is gained, the individual components of a comprehensive program cannot be optimally developed and maximal benefit from such programs will not be achieved.

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References

1. Sturnieks L, St George R, Lord R. Balance disorders in the elderly. Neurophysiologie Clinique/Clinical Neurophysiology. 2008;38:467–78.
2. Tinetti M, Speechley M. Prevention of falls among the elderly. N Engl J Med. 1989;320:1055–9.
3. Magnus R. Croonian lecture. Animal posture. Proc R Soc Biol. 1925;98:339–53.
4. Roberts TDM. Neurophysiology of postural mechanisms. London: Butterworth & Co., Ltd; 1978.
5. Nashner LM. Analysis of stance posture in humans. In: Towe A, Luschei E editors. Handbook of behavioral neurobiology, vol 5. Motor coordination. New York, NY: Plenum Press; 1981. pp. 527–65.
6. Kuo AD, Zajac FE. Human standing posture: multi-joint movement strategies based on biomechanical constraints. Prog Brain Res. 1993;97:349–58.
7. Horak FB, Diener HC, Nashner LM. Influence of central set on human postural responses. J Neurophysiol. 1989;62:841–53.
8. Shumway-Cook A, Woollacott M. Attentional demands and postural control: the effect of sensory context. J Gerontol A Biol Sci Med Sci. 2000;55:M10–6.
9. Whipple R. Improving balance in older adults: identifying the significant training stimuli. In: Masdeu JC, Sudarsky L, Wolfson L, editors. Gait disorders of aging: falls and therapeutic strategies. Philadelphia, PA: Lippincoott-Raven; 1997. pp. 355–80.
10. Horak FB, Macpherson JM. Postural orientation and equilibrium. In: Shepard J, Rowell L, editors. Handbook of physiology. New York, NY: Oxford University Press; 1996. pp. 255–92.
11. Horak FB, Shupert CL, Mirka A. Components of postural dyscontrol in the elderly: a review. Neurobiol Aging. 1989b;10:727–38.
12. Teasdale N, Stelmach GE, Breunig A. Postural sway characteristics of the elderly under normal and altered visual and support surface conditions. J Gerontol. 1991;46:B238–44.
13. Baloh RW, Corona S, Jacobson KM, Enrietto JA, Bell T. A prospective study of posturography in normal older people. J Am Geriatr Soc. 1998;46:438–43.
14. Baloh RW, Fife TD, Zwerling L, Socotch T, Jacobson K, Bell T, Beykirch K. Comparison of static and dynamic posturography in young and older normal people. J Am Geriatr Soc. 1994;42:405–12.
15. Shepard NT, Schultz A, Alexander NB, Gu MJ, Boismier T. Postural control in young and elderly adults when stance is challenged: clinical versus laboratory measurements. Ann Otol Rhinol Laryngol. 1993;102:508–17.
16. Whipple R, Wolfson L, Derby C, Singh D, Tobin J. Altered sensory function and balance in older persons. J Gerontol. 1993;48(Spec No):71–6.
17. Woollacott MH, Shumway-Cook A, Nashner LM. Aging and posture control: changes in sensory organization and muscular coordination. Int J Aging Hum Dev. 1986;23:97–114.
18. Wolfson L, Whipple R, Derby CA, Amerman P, Murphy T, Tobin JN, Nashner L. A dynamic posturography study of balance in healthy elderly. Neurology. 1992;42:2069–75.
19. Anacker SL, Di Fabio RP. Influence of sensory inputs on standing balance in community-dwelling elders with a recent history of falling. Phys Ther. 1992;72:575–81.
20. Baloh RW, Spain S, Socotch TM, Jacobson KM, Bell T. Posturography and balance problems in older people. J Am Geriatr Soc. 1995;43:638–44.
21. Masdeu JC, Wolfson L, Lantos G, Tobin JN, Grober E, Whipple R, Amerman P. Brain white-matter changes in the elderly prone to falling. Arch Neurol. 1989;46:1292–6.
22. Simoneau M, Teasdale N, Bourdin C, Bard C, Fleury M, Nougier V. Aging and postural control: postural perturbations caused by changing the visual anchor. J Am Geriatr Soc. 1999;47:235–40.
23. Sundermier L, Woollacott MH, Jensen JL, Moore S. Postural sensitivity to visual flow in aging adults with and without balance problems. J Gerontol A Biol Sci Med Sci. 1996;51:M45–52.

24. Wolfson L (1997) Balance decrements in older persons: effects of age and disease. In: Masdeu J, et al., editors. Gait disorders of aging. Philadelphia: Lippincott-Raven; 1997. pp. 79–91.
25. Stelmach GE, Teasdale N, DiFabio RP, Phillips J. Age related decline in postural control mechanisms. Int J Aging Hum Dev. 1989;29(3):205–23.
26. Lord S, Sherrington C, Menz H, Close J. Falls in older people. New York, NY: Cambridge University Press; 2007.
27. Hu MH, Woollacott MH. Multisensory training of standing balance in older adults: II. Kinematic and electromyographic postural responses. J Gerontol Med Sci. 1994;49:M62–3.
28. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci. 1996;16:785–807.
29. Gould E, Reeves A, Graziano MS, Gross. CG. Neurogenesis in the neocortex of adult primates. Science. 1999;286:548–52.
30. Byl NN, Merzenich MM, Jenkins WM. A primate genesis model of focal dystonia and repetitive strain injury: I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. Neurology. 1996a;47 (2):508–20.
31. Byl NN, Wilson F, Merzenich MM, Melnick M, Scott P, Oakes A, McKenzie A. Sensory dysfunction associated with repetitive strain injuries of tendinitis and focal hand dystonia: a comparative study. J Orthop Sports Phys Ther. 1996b;23(4):234–44.
32. Allison L. Balance disorders. In: Umphred D, editor. Neurological rehabilitation. 3rd ed. St Loius, MO: Mosby; 1995. pp. 802–37.
33. Shumway-Cook A, Woollacott M. Motor control: theory and clinical applications. Baltimore, MD: Williams and Wilkins; 1995.
34. Badke M, Shea T, Miedaner J, Grove C. Outcomes after rehabilitation for adults with balance dysfunction. Archives of Physical Medicine and Rehabilitation. 2004;85:227–33.
35. Howard IP. Human visual orientation. New York, NY: Wiley; 1982.
36. Krebs DE, Gill-Body KM, Riley PO, Parker SW. Double-blind, placebo-controlled trial of rehabilitation for bilateral vestibular hypofunction: preliminary report. Otalaryngol Head Neck Surg. 1993;109:735–41.
37. Berthoz A, Lacour M, Soechting JF, Vidal PP. The role of vision in the control of posture during linear motion. Prog Brain Res. 1979;50:197–209.
38. Dijkstra TMH, Schöner G, Gielen CCAM. Temporal stability of the action perception cycle for postural control in a moving visual environment. Exp Brain Res. 1994a;97:477–86.
39. Dijkstra TMH, Schöner G, Giese MA, Gielen CCAM. Frequency dependence of the action-perception cycle for postural control in a moving visual environment: relative phase dynamics. Biol Cybern. 1994b;71:489–501.
40. Lee DN, Lishman JR. Visual proprioceptive control of stance. J Hum Mov Studies. 1975;1:87–95.
41. Peterka RJ, Benolken MS. Role of somatosensory and vestibular cues in attenuating visually induced human postural sway. Exp Brain Res. 1995;105:101–10.
42. Soechting J, Berthoz A. Dynamic role of vision in the control of posture in man. Exp Brain Res. 1979;36:551–61.
43. Talbott RE, Brookhart JM. A predictive model study of the visual contribution to canine postural control. Am J Physiol. 1980;239:R80–92.
44. Benson AJ. The vestibular sensory system. In: The senses.Barlow HB, Mollon JD, editors. New York, NY: CambridgeUniversity Press; 1982. pp. 333–68.
45. Schöner G. Dynamic theory of action-perception patterns: the “moving room” paradigm. Biol Cybern. 1991;64:455–62.
46. Holden M, Ventura J, Lackner JR. Stabilization of posture by precision contact of the index finger. J Vestibular Res. 1994;4:285–301.
47. Jeka JJ, Lackner JR. Fingertip contact influences human postural control. Exp Brain Res. 1994;100:495–502.
48. Jeka JJ, Lackner JR. The role of haptic cues from rough and slippery surfaces in human postural control. Exp Brain Res. 1995;103:267–76.
49. Jeka JJ, Easton RD, Bentzen BL, Lackner JR. Haptic cues for orientation and postural control in sighted and blind individuals. Percept Psychophys. 1996;58 (3):409–23.
50. Jeka JJ, Schöner G, Dijkstra TMH, Ribeiro P, Lackner JR. Coupling of fingertip somatosensory information to head and body sway. Exp Brain Res. 1997;113:475–83.
51. Jeka JJ, Oie KS, Schöner GS, Dijkstra TMH, Henson EM. Position and velocity coupling of postural sway to somatosensory drive. J Neurophysiol. 1998;79:1661–74.
52. Clapp S, Wing AM. Light touch contribution to balance in normal bipedalstance. Exp Brain Res. 1999;125(4):521–4.
53. Dickstein R, Shupert CL, Horak FB. Fingertip touch improves stability in patients with peripheral neuropathy. Gait Posture. 2001;14(3):238–47.
54. Reginella RL, Redfern MS, Furman JM. Postural sway with earth-fixed and body referenced finger contact in young and older adults. J Vestibular Res. 1999;9(2):103–9.
55. Riley MA, Wong S, Mitra S, Turvey MT. Common effects of touch and vision on postural parameters. Exp Brain Res. 1997;117(1):165–70.
56. Oie KS, Kiemel T, Jeka J. Multisensory fusion: simultaneous reweighting of vision and touch for the control of human posture. Cogn Brain Res. 2002;14:164–76.

57. Whipple R, Wolfson LI. Abnormalities of balance, gait and sensorimotor function in the elderly population. In: Duncan P, editor. Balance: proceedings of the APTA forum. Alexandria, VA: APTA; 1989. pp. 61–8.
58. College NR, Cantley P, Peaston I, Brash H, Lewis S, Wilson JA. Ageing and balance: the measurement of spontaneous sway by posturography. Gerontology. 1994;40:273–8.
59. Allison L, Kiemel T, Jeka JJ. Multisensory reweighting is intact in healthy and fall-prone older adults. Exp Brain Res. 2006;175(2):342–52.
60. Woollacott M, Shumway-Cook A, Nashner L. Aging and postural control: changes in sensory organization and muscular coordination. International Journal of Aging and Human Development. 1986;23:97–114.
61. Allison L, Kiemel T, Jeka JJ (2005) The dynamics of multisensory reweighting in healthy and fall-prone older adults. 35th annual meeting of the Society for Neuroscience, Washington, DC.
62. Cumming RG. Intervention strategies and risk-factor modification for falls prevention. A review of recent intervention studies. Clin Geriatr Med. 2002;18(2): 175–89.
63. Gardner MM, Robertson MC, Campbell AJ. Exercise in preventing falls and fall related injuries in older people: a review of randomized controlled trials. Br J Sports Med. 2000;34(1):7.

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Note: The letters 'f' and 't' following the locators refer to figures and tables respectively.

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