Carol L. Armstrong *Editor*
Lisa Morrow *Associate Editor*

Handbook of Medical Neuropsychology

Applications of Cognitive Neuroscience

Foreword by Muriel Lezak

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Carol L. Armstrong • Lisa Morrow
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Editor
Carol L. Armstrong
Children's Hospital of
Philadelphia
Division of Oncology/
Neuro-Oncology
3535 Market Street
19104 Philadelphia
Pennsylvania
USA
armstrongc@email.chop.edu

Associate Editor
Lisa Morrow
Western Psychiatric Institute
and Clinic
3811 O'Hara Street
15213 Pittsburgh
Pennsylvania
USA
morrowla@upmc.edu

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Carol L. Armstrong

This book is dedicated to my mentors, especially Peter Phillips and the Children's Hospital of Philadelphia neuro-oncologists, Muriel Lezak, David Hackney, Robert Lustig, Omar Hijab, and the cognitive neurologists now and once at the University of Pennsylvania, particularly Mark D'Esposito. It is also dedicated to all of the patients who have shown so bravely how injury affects a person's life.

Lisa Morrow

Having one mentor is a gift, having five is remarkable. Many thanks to my mentors – Francois Boller, Youngjai Kim, Graham Ratcliff, Christopher Ryan, and Steve Slane.

Foreword

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.

Portland, Oregon Muriel D. Lezak

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Preface

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.

Philadelphia, Pennsylvania C.L. Armstrong

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Contributors

Leonard Abbeduto Waisman Center and Department of Educational Psychology, University of Wisconsin, Madison, WI 53705, USA, abbeduto@waisman.wisc.edu

Julie A. Alvarez Department of Psychology, Tulane University, New Orleans, LA 70118, USA, jalvar@tulane.edu

Eric Anson Department of Kinesiology, University of Maryland, College Park, MD 20742-2611, USA, eanson1@umd.edu

Kevin M. Antshel Department of Psychiatry and Behavioral Sciences, State University of New York – Upstate Medical University, Syracuse, NY 13210, USA, antshelk@upstate.edu

Carol L. Armstrong Division of Oncology/Neuro-Oncology, Children's Hospital of Philadelphia, 3535 Market Street, 19104 Philadelphia, Pennsylvania, USA, armstrongc@email.chop.edu

Peter A. Arnett Department of Psychology, The Pennsylvania State University, University Park, PA 16802-3105, USA, paa6@psu.edu

Jasmohan S. Bajaj Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA 23249, USA, jsbajaj@vcu.edu

Fiona H. Barwick Department of Psychology, The Pennsylvania State University, University Park, PA 16802-3105, USA, fhb103@psu.edu

Joseph E. Beeney Department of Psychology, The Pennsylvania State University, University Park, PA 16802-3105, USA, jeb425@psu.edu

Sue R. Beers Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA, beerssr@upmc.edu

Jean B. Belasco Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Pediatrics, School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA, belasco@email.chop.edu

Allison Berman Cognitive Neuroscience and Brain Imaging Laboratory, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA 19107, USA, allison.berman@jefferson.edu

Juliana Sanchez Bloom Department of Psychology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA, bloomj@email.chop.edu

Bailey M. Bonura Department of Psychology, Tufts University, Medford, MA 02155, USA, bailey.bonura@tufts.edu

Jared Conley Case Western Reserve University School of Medicine, Cleveland, OH, USA, jared.conley@gmail.com

Jennifer B. Dave Neuropsychology Postdoctoral Fellow, The Neurological Institute, Columbia University, New York, NY 10032, USA, d2785@columbia.edu

Robert N. Davis Houston Neuropsychology Group, PLLC, Houston, TX, USA, dr.rob.davis@gmail.com

Gayle K. Deutsch Stanford University Medical Center, Stanford, CA 94305, USA, gdeutsch@stanfordmed.org

David M. Frim University of Chicago Medical Center, Psychiatry and Behavioral Neurosciences, Chicago, IL 60637, USA, dfrim@surgery.bsd.uchicago.edu

Suzanne L. Gharib Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA, sleegharib@yahoo.com

Jennifer M. Glass Department of Psychiatry, Institute for Social Research, Addiction Research Center, University of Michigan, Ann Arbor, MI 48106-2700, USA, jglass@umich.edu

Anna C. Graefe Research Service, VA Boston Healthcare System, Boston, MA 02130, USA, anna.graefe@gmail.com

Laura Grande Psychology Service, VA Boston Healthcare System, Boston, MA 02130, USA; Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA, laura.grande@va.gov

Carol M. Greco University of Pittsburgh School of Medicine, Pittsburgh, PA 15232, USA, grecocm@upmc.edu

Michelle M. Greene Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA, michellemgreene@gmail.com

Marc W. Haut Department of Behavioral Medicine and Psychiatry, Neurology, and Radiology, West Virginia University School of Medicine, Morgantown, WV 26506, USA, mhaut@hsc.wvu.edu

Clarissa S. Holmes Department of Psychology, Pediatrics and Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; Department of Psychiatry, Georgetown University, Washington, DC, USA, cholmes@richmond.edu

Ramona O. Hopkins Psychology Department, Neuroscience Center, Brigham Young University, Provo, UT, USA; Pulmonary and Critical Care Division, Department of Medicine, LDS Hospital, Salt Lake City, UT, USA; Pulmonary and Critical Care Division, Department of Medicine, Intermountain Medical Center, Murray, UT, USA, mona_hopkins@byu.edu

Megan M. Hosey Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD, USA, mhoseyl@umbc.edu

John Jeka Department of Kinesiology, Neuroscience & Cognitive Science Program, University of Maryland, College Park, MD 20742-2611, USA, jjeka@umd.edu

Amy H. Kao Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA, ahk7@pitt.edu

Leslie I. Katzel Division of Gerontology, Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA; Geriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA, lkatzel@grecc.umaryland.edu

Kinga Kertesz Center for Neurological Imaging, Brigham and Women's Hospital, Boston, MA 02115, USA, kingulus@gmail.com

Michelle Kramer University of Chicago Medical Center, Psychiatry and Behavioral Neurosciences, Chicago, IL 60637, USA, michellekramer31@comcast.net

Maureen A. Lacy University of Chicago Medical Center, Psychiatry and Behavioral Neurosciences, Chicago, IL 60637, USA, mlacy@yoda.bsd.uchicago.edu

Cynthia Lippincott-Stamos Department of Psychology, Drexel University, Philadelphia, PA 19104, USA, stamosc@email.chop.edu

Kara Lonser Department of Behavioral Medicine and Psychiatry, West Virginia University School of Medicine, Morgantown, WV 26505, USA, klonser@hsc.wvu.edu

Kathryn Maher Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA, katyemaher@gmail.com

Andrea McDuffie Waisman Center, University of Wisconsin, Madison, WI 53705, USA, mcduffie@waisman.wisc.edu

Michael R. Meager University of Chicago Medical Center, Psychiatry and Behavioral Neurosciences, Chicago, IL 60637, USA, meagermr@yahoo.com

John Stirling Meyer United Neurology Headache and Pain Clinic, 2321 Southwest Freeway, Houston, TX 77098, USA, johnsmeyer@jsmeyer.com

Nancy Minniti Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA, nancy.minniti@gmail.com

Maria T. Moran Department of Behavioral Medicine and Psychiatry, West Virginia University School of Medicine, Morgantown, WV 26505, USA, mmoran@hsc.wvu.edu

Kari L. Morgan Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA, kmorgan81@gmail.com

Terri Morris Adjunct Faculty, Department of Clinical Psychology, Widener University, Chester, PA, USA, tmorrisphd@verizon.net

Kevin D. Mullen Division of Gastroenterology, MetroHealth Medical Center, Cleveland, OH 44109, USA; Case Western Reserve University, Cleveland, OH 44109, USA, kdm@po.cwru.edu

Karol Osipowicz Cognitive Neuroscience and Brain Imaging Laboratory, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA 19107, USA, karol.osipowicz@jefferson.edu

Robert H. Paul Department of Psychology, Behavioral Neuroscience, University of Missouri, St. Louis, MO 63121, USA, paulro@umsl.edu

Cecilia Peralta Department of Neurology, Centro Neurológico, Fundacion Alfredo Thomson, Parkinson's Disease and Movement Disorders Clinic, Hospital Cesar Milstein, Buenos Aires, Argentina, ceciliaperalta@yahoo.com.ar

Silja Pirilä Department of Pediatrics, Tampere University Hospital, Tampere, Finland ; Department of Psychology, University of Tampere, Tampere, Finland, silja.pirila@uta.fi

Priscilla Powell Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA, powellpw@vcu.edu

Sarah A. Raskin Department of Psychology and Neuroscience Program, Trinity College, Hartford CT 06106, USA, sarah.raskin@trincoll.edu

Anthony L. Rostain Behavioral Health Center, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; Department of Psychiatry, University of Pennsylvania Health System, Philadelphia, PA 19104, USA, rostain@mail.med.upenn.edu

Troy Russell Center for Neurological Imaging, Brigham and Women's Hospital, Boston, MA 02115, USA, tmrussell145@hotmail.com

Cynthia J. Schmus Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA, schmus@email.chop.edu

Stephen L. Seliger Division of Nephrology, Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA, sseliger@medicine.umaryland.edu

Sabrina E. Smith Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA, smithsa@email.chop.edu

David F. Tate Harvard Medical School, Brigham and Women Hospital, Boston University Medical School, Boston, MA 02115, USA, dtate1@partners.org

Ayanna K. Thomas Department of Psychology, Tufts University, Medford, MA 02155, USA, ayanna.thomas@tufts.edu

Jeanne Townsend Department of Neurosciences, University of California, San Diego, CA, USA, jtownsend@ucsd.edu

Joseph I. Tracy Neuropsychology Division, and Cognitive Neuroscience and Brain Imaging Laboratory, Thomas Jefferson University/Jefferson Medical College, Philadelphia, PA 19107, USA, joseph.i.tracy@jefferson.edu

Alexander I. Tröster Department of Neurology, School of Medicine, University of North Carolina, Chapel Hill, NC 27599-7025, USA, trostera@neurology.unc.edu

Jaap J. van der Meere Department of Developmental and Clinical Neuropsychology, University of Groningen, Groningen, The Netherlands, j.j.van.der.meere@rug.nl

Jennifer J. Vasterling Psychology Service and VA National Center for PTSD, VA Boston Healthcare System, Boston, MA 02130, USA; Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA, jvaster@bu.edu

Shari R. Waldstein Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD, USA; Division of Gerontology and Geriatric Medicine, Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA; Geriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA, waldstei@umbc.edu

Carrington Rice Wendell Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD, USA, carrington.rice.wendell@gmail.com

Marissa Westerfield Department of Neurosciences, University of California, San Diego, CA, USA, mwesterfield@ucsd.edu

Christine E. Whatmough Department of Neurology and Neurosurgery, McGill University, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote-Ste-Catherine Road, Montreal, QC, Canada H3T 1E2, christine.whatmough@mcgill.ca

Steven Paul Woods Department of Psychiatry, San Diego School of Medicine, University of California, San Diego, CA 92103-8231, USA, spwoods@ucsd.edu

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 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

J.I. Tracy (✉)
Neuropsychology Division, and Cognitive Neuroscience and Brain Imaging Laboratory, Thomas Jefferson University/ Jefferson Medical College, Philadelphia, PA 19107, USA
e-mail: joseph.i.tracy@jefferson.edu

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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 co-opting 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, pre-existing 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) hyper-innervation, (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/non-dominant, 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 post-surgery 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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Chapter 2

Traumatic Brain Injury

Terri Morris

Epidemiology

Traumatic brain injury (TBI) is a serious public health problem, often referred to as a silent epidemic due to lack of public awareness [1]. TBI is still the leading cause of mortality and morbidity in the world for individuals under the age of 45 [2]. In the United States alone, based on population data from 1995 to 2001, 1.4 million people sustained TBI in the United States each year, compared to 176,000 new cases of breast cancer, 43,500 new cases of HIV, and 10,400 new cases of multiple sclerosis [3]. Of these brain injuries, 50,000 died, 235,000 were hospitalized, and 1.1 million were treated and released from hospital emergency departments. Though many patients recover from their injuries, each year an estimated 80,000–90,000 Americans sustain a TBI that results in permanent disability [1]. It is estimated that 5.3 million Americans are living with disability resulting from TBI [3]. Mild TBI alone costs the nation $17 billion annually [4].

Leading causes of traumatic brain injury are falls – 28%, motor vehicle accidents – 20%, being struck by or against objects – 19%, and assault – 11% [1]. In the United States, persons in the 15–24 and 64+ age groups are at highest risk, with males at more risk than females at a ratio of approximately 2.8:1.6 [5]. Sports-related TBI is second only to MVA as a leading cause of injury in the 15–24 age group with 300,000 cases annually in the United States [6].

TBI, particularly closed head injury resulting from blast injury, is a significant source of morbidity in military service personnel in the Iraq and Afghanistan wars [7]. Effects of primary, secondary, and tertiary blast injuries have been an active area of investigation [7–9].

Neurologic consequences of TBI are multiple [10]. Any sensory, motor, or autonomic function may be compromised and long-term sequelae such as movement disorders, seizures, headaches, visual defects, and sleep disorders can result. Non-neurological medical consequences can be pulmonary, metabolic, nutritional, or musculoskeletal. Impairments may be temporary or permanent, causing partial or total functional disability [3, 10]. Even injuries that are classified as mild can result in persistent neurobehavioral impairments.

Etiology

Mechanisms of Injury

While TBI often occurs from a direct blow to the head due to an external physical force such as a blunt object, bullet wound, or fall, injury to the brain can result without direct impact to the head [11]. Mechanisms of injury include contusions (bruises) occurring at the site of impact, known as coup lesions, and bruising due to the force of impact causing the brain to strike the opposite side of the skull, known as contrecoup lesions. The second type of injury is diffuse axonal injury (DAI) which results from sudden momentum or movement change, typically from a motor vehicle accident. DAI

T. Morris (✉)
Adjunct Faculty of Neuropsychology, Department of Clinical Psychology, Widener University, Chester, PA, USA
e-mail: tmorrisphd@verizon.net

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occurs from unrestricted movement of the head, with the brain lagging behind the movement of the skull, resulting in shear, tensile, and compressive strains [12]. DAI is thought to underlie all forms of traumatic brain injury, including mild TBI, due to the destruction of neurofilaments and microtubules running the length of the axon, leading to axonal swelling and disconnection [13]. DAI is the principal pathology producing the continuum of brain injury from mild to severe [12].

Primary and Secondary Injuries

Primary injury is the mechanical damage occurring at the moment of impact, and secondary injuries are the non-mechanical aspects that result, including altered cerebral blood flow and metabolism, excitotoxicity, edema (swelling), and inflammatory processes [2]. 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.

Types of Injury

Traumatic brain injuries are classified as penetrating or closed, and the pathophysiological processes differ for each.

Penetrating Head Injury

Penetrating or open head injuries cause fracture or breach of the skull with laceration or destruction of brain tissue, and the mortality rate is much higher for this type of head injury [14]. Trauma to the skull results from low-velocity bullets, puncture, everyday objects that may become embedded or from a tangential injury whereby an object strikes the skull, causing bone fragments to be driven into the brain [15, 16]. 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 [15, 16]. With penetrating injuries, prevention of infection is key since brain abscesses may develop. Secondary injuries from metabolic and physiologic processes such as edema, ischemia, or posttraumatic epilepsy can be as or more damaging than the primary injury [2].

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 [13, 16]. CHI impacts the frontal lobes, particularly the orbital and polar aspects [17, 18]. 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 [19]. 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 [17]. 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 in CHI include development of subdural hematoma, intracerebral bleeding, increased intracranial pressure, hypoxia, obstructive hydrocephalus, and posttraumatic epilepsy [2]. 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 posttraumatic amnesia (PTA), extent of generalized atrophy, and the location, depth, and volume of focal cerebral lesions [20]. The nature and frequency of the cognitive and/or behavioral difficulties are due to concentration of damage in the anterior regions of the brain [20].

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].

Rating Severity of TBI

TBI severity is based on rating the presence or extent of loss of consciousness (LOC) and posttraumatic amnesia (PTA). Both LOC and PTA 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 [21], which rates verbal responses, eye opening behavior, and best motor responses on a 0–15 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 [16]. More current classification systems have acknowledged that loss of consciousness is not necessary for a diagnosis of TBI [3, 22–24].

Posttraumatic Amnesia

The second measure of TBI severity is posttraumatic amnesia (PTA), defined as anterograde memory loss for events occurring immediately following the injury and retrograde loss for events immediately prior to the injury. During this acute phase, learning and memory are significantly disrupted and memory deficits are on a temporal gradient, with older memories being more resistant to disruption. There are different systems for grading PTA; a commonly used system classifies PTA as follows: mild = PTA of less than 1 hour, moderate = PTA of 1–24 hour, and severe = PTA of greater than 24 hour [16]. Other systems [15] have distinguished six categories: very mild = less than 5 min, mild = 5–60 min, moderate = 1–24 hour, severe = 1–7 days, very severe = 1–4 weeks, and extremely severe = greater than 4 weeks. PTA length is generally more accurate than duration of LOC in predicting recovery of function, with longer periods of PTA associated with more severe brain injury and poorer recovery.

Because it is a prognostic indicator, acute care facilities place emphasis on measuring PTA [25]. One of the most widely used brief instruments that can be administered bedside is the Galveston Orientation and Amnesia Test (GOAT) [26] which measures orientation, retrograde, and anterograde memory loss. It is most appropriate for use in a hospital setting since PTA is often acute and time limited. Other similar measures of PTA include the Oxford PTA Scale [27] and the Rivermead PTA Scale [28].

Due to the nature of PTA, relying of brief screening measures alone is problematic and can result in misclassification [28]. One reason is that recovery from PTA 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 [29]. Attention in particular is noted to be a key component in early recovery after TBI [30], and postconfusional state or 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 [16, 29]. PTA does not end when the patient begins to register experience again but only when registration is continuous [15]. 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.

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].

1. *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) [22] or other systems [23] 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, postconcussive syndrome, traumatic head syndrome, traumatic cephalgia, postbrain injury syndrome, and posttraumatic syndrome. 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, or
b. focal neurological deficit which may or may not be transient.

Furthermore, the severity of the injury cannot exceed loss of consciousness of 30 minutes, initial GCS score of 13–15, or PTA greater than 24 hour. 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 [22].

Mild TBI has greater consequences than formerly assumed [31]. 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 these patients return to the hospital clinic weeks or months afterward complaining of symptoms from the original head injury [32]. Standard neuroimaging, including CT, MRI, and EEG, is often normal yet mental status changes can still occur, indicating that functioning has been altered [22, 33] and that DAI is present, which can result in temporary or permanent damage. Symptoms may also persist 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 [22].

2. *Moderate TBI*. Moderate TBI is defined as involving 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 [15]. Confusion may last from days to weeks, and physical, cognitive, and emotional impairments can persist for months or be permanent [3]. 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.

3. *Severe TBI*. Severe injury involves loss of consciousness with a GCS score of 8 or less, and loss of consciousness can last days, weeks, or months. Recent investigations have noted different subgroups within the severe TBI category [3, 34]. These subgroups include coma, vegetative state, persistent vegetative state, minimally conscious state, akinetic mutism, and locked-in syndrome. *Coma* is a state of 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. *Vegetative state* is 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. The *minimally conscious state* is defined as 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 [34]. *Akinetic mutism*, resulting from damage to the dopaminergic pathways, results in minimal body movement, little to no spontaneous speech, infrequent or incomplete ability to follow commands, and 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. In the rare neurological condition *locked-in syndrome*, the person cannot physically move any part of the body except the eyes, and vertical eye movements and eye blinks are used to communicate [3]. Finally, *brain death* can also result from severe injury, and in this condition, the brain shows no sign of functioning.

Neuroimaging and TBI

Structural Imaging

Computed tomography (CT) and standard magnetic resonance imaging (MRI) detect structural changes within the brain including tissue or fluid volume and have been the most available and commonly used neuroimaging procedures for detection of damage from TBI; however, they are less sensitive to the diffuse axonal injuries in mild TBI. As noted by Bigler [35], 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. 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 [35].

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 [35]. 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 [31, 35]. 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 postinjury [31], 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 and are more sensitive in identifying impairment in mild TBI than standard MRI [33, 36]. DT imaging 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 outcome [13]. In some mild TBI patient samples with no macroscopically detectable or obvious lesions, disruptions of the corpus callosum and fornix have been demonstrated [37]. When performed more than 45 days postinjury 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 [35]. 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.

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 an active area of investigation [38]. 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 [38]. MRS is appropriate for evaluating diffuse injury associated with mild TBI and has been found to be more sensitive at detecting metabolic changes that are associated with poor clinical outcomes yet are not observable on CT or MR imaging [39]. MRS has detected widespread metabolic changes following mild TBI in regions that appeared structurally normal on standard MRI at 1 month postinjury. 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 [39]. Cohen et al. [40] were able to document decline of NAA as well as gray matter and white matter atrophy in mild TBI patients, with whole brain NAA concentrations showing a 12%

deficit on the whole 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 Imaging

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. 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 postconcussive somatic and cognitive symptoms [32]. MEG has been informative in preliminary studies, with significant correlations found between regional abnormalities and specific cognitive problems [32]. SPECT and MEG have demonstrated more sensitivity than routine MRI in detecting abnormalities in mild head trauma patients, with MEG showing the greatest sensitivity; however, MEG is not yet widely available and further studies are needed regarding findings in the TBI population. In one moderate TBI patient sample, PET imaging demonstrated abnormal focal uptake extending beyond the abnormal regions documented on CT and MRI [41]. Ruff et al. [42] demonstrated significant correlation between neuropsychological findings and PET in mild TBI patients, with PET documenting metabolic abnormalities that were pronounced in frontal and anterior temporal regions and no differences were noted in those patients with or without loss of consciousness.

Functional MRI (fMRI), which measures regional changes in blood perfusion and blood oxygenation changes, has also demonstrated ability to detect brain abnormalities in mild TBI that are not detectable on standard imaging [43]. Using fMRI, investigators have shown smaller increases in brain activity in mild TBI patients relative to healthy controls on working memory tasks [44] and have demonstrated significant reductions in activation of right prefrontal and medial temporal regions in mild TBI patients relative to healthy controls [45]. In a study of athletes with mild TBI, Chen et al. [46] found that normal controls showed the expected frontal cortical activations during a working memory task, whereas all TBI subjects showed significantly weaker and fewer activations; in several subjects who had multiple concussions, there was a complete lack of task-related activation. 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 [47].

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. 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; therefore, frontal systems are emphasized in this section.

Distinct behavioral and cognitive syndromes correspond to three frontal lobe systems: the dorsolateral, orbitofrontal, and anterior cingulate circuits [17, 48], with the orbitofrontal system being substantially impacted in TBI of all severities. 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 [17, 49–51]. 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 sends projections to the ventral striatum [17]. The two systems overlap in anatomy and behavioral functions [17]. 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 [17, 49].

Socially inappropriate behavior is evident in TBI patients and has been well documented in studies of patients with damage to the orbitofrontal regions [52–54]. One of the more famous patients was Phineas Gage, a supervisor of a railroad construction work crew who in the 1800s 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 [55]. 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.

Changes in emotional reactivity and behavior have been demonstrated in more recent studies of orbitomedial damage as well [56–58]. 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" [57]. Damasio et al. [58] 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. [59] 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 [60] and several investigators have demonstrated the role of medial and orbital frontal regions in aggressive and violent behavior. Grafman et al. [61], in a study of 279 Vietnam veterans, found that head-injured veterans who had focal ventromedial frontal lobe lesions had a significantly higher frequency of aggressive and violent behavior when compared to controls or subjects who had lesions elsewhere in the brain. 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 [62].

The orbitomedial prefrontal circuit is thought to mediate social cognition in general [63–65]. 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 [63, 65, 66]. 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, for example, 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. 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 [66]. 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 [65].

Anterior Cingulate

The "motivation circuit" [67] is the anterior cingulate and includes the forebrain, composed of the anterior cingulum, nucleus accumbens, ventral palladium,

and ventral tegmental area. The anterior cingulate is the neuroanatomical basis of motivated behavior, and apathy is the most distinguishing characteristic of damage [67]. The most severe damage to this circuit, akinetic mutism, results from bilateral lesions of the anterior cingulate, resulting 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, with impaired motivation, marked apathy, poverty of spontaneous speech, and poor response inhibition [17]. A method for evaluating and quantifying apathy or loss of motivation is the Apathy Evaluation Scale (AES) [68] 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 [69].

Neuropsychological Assessment of TBI

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

Attention

Impaired attention is prevalent, if not universal, after TBI at all levels of injury, whether diffuse or focal [70]. Attention underpins all aspects of cognition and even mild impairments can restrict other processes such as learning or problem solving. Common complaints from patients reflecting attention problems include mental slowing, trouble following conversation, losing train of thought, or difficulty attending to several things simultaneously.

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 [71] and the Moss Attention Rating Scale (MARS) [72, 73]. The Cognitive Test for Delirium, which was developed to diagnose delirium on the basis of cognitive functioning, has been noted to have acceptable specificity and sensitivity to delirium in TBI patients in the inpatient setting [71]. The Moss Attention Rating Scale (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 [72].

Post-acute assessment of attention includes measures of auditory and visual attention, and several tests are well standardized and widely used. Attention 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, forward span for digits or visual targets from the Wechsler scales are appropriate [74, 75]. 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 [76], the Stroop test [77], or visual search tasks from the Wechsler scale [74]. Shifting or dividing attention between two or more sources of information is generally assessed by tasks such as the Trailmaking Test Part B [78] or the Paced Auditory Serial Addition Test (PASAT) [79]. Visual attention and processing speed can be measured by timed coding tasks such as those on the Wechsler scales [74] or visual scanning via the Trailmaking Test Part A [78], and working memory can also be evaluated by Wechsler subtests of mental arithmetic, digits backward span, and auditory sequencing [74, 75].

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.

Two systems, the episodic or knowing "what" and the procedural or knowing "how," comprise memory. Episodic memory is a multifactorial process, and all phases, encoding, consolidation, or retrieval, may be affected in TBI. Episodic memory for personal information or facts is most impacted after TBI, in contrast

to procedural memory, which is outside conscious awareness; includes memory for procedures, conditioning, and priming; and is relatively spared [80]. When evaluating memory both associative processes, served by the medial temporal lobes and hippocampal formation, and strategic processes, associated with dorsolateral prefrontal functions, must be assessed [80]. 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 are generally affected, reflected by deficits in immediate recall as well as retention.

The neuropsychological evaluation typically involves assessment of acquisition and consolidation aspects of verbal and visual memory. For auditory memory, verbal learning tasks such as the California Verbal Learning Test-II [81] 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 [82] and the Rey Auditory Verbal Learning Test [83]. Additional measures of immediate and delayed auditory verbal memory include paragraph or story recall, such as in the Wechsler Memory tests [75]. Nonverbal memory is generally assessed by visual recall and reproduction of simple designs, recognition memory for faces, or recall of scenes [75]; complex figural memory is evaluated by reproducing complex figures after copying; and tactile and spatial memory can be evaluated by use of tasks that do not allow visual access, such as the Tactual Performance Test from the Halstead–Reitan battery [78].

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 [84]. This regulatory function includes the ability to initiate behaviors, inhibit competing actions or stimuli, select relevant task goals, plan and organize, solve complex problems, shift problem-solving strategies appropriately when necessary, regulate emotions, monitor and evaluate behavior, and hold information in mind in order to guide cognition and behavior [84]. Though executive functions are a critical determinant in functional outcome after TBI [15, 20, 48] and are among the most disabling aspects of cognitive impairment following TBI [85], 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 undertesting and underdetection of deficits associated with this region, and the nature of the standardized testing environment, which is artificial and 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 use of general-purpose or "fixed" batteries such as the Halstead–Reitan Neuropsychological Battery [78], with the advantage that such batteries provide standardized procedures and allow for comparisons, the disadvantage is that none of the fixed batteries are fully appropriate or complete for any one patient [86], and this results in overtesting or undertesting of specific functions. Evaluation of frontal systems functioning has been particularly problematic, as many tests comprising clinical neuropsychological batteries in current usage lack specificity or sensitivity to the differing frontal circuits and/or unique deficits exhibited by the TBI patient and yet are widely used as tests of executive functions [51, 80]. Examples include the Stroop Color–Word Test [77] and the Trailmaking Tests [78] which are sensitive to general cerebral pathology, but are not specific to frontal system functioning in TBI [80]. Widely used tests, such as the Category Test [78], the matrix reasoning subtest from the Wechsler Intelligence Scale [74], the Wisconsin Card Sorting Test [87], and verbal fluency tasks [88], also have demonstrated sensitivity to diffuse cerebral dysfunction in addition to dorsolateral prefrontal functioning. Functional neuroimaging studies using PET, SPECT, and regional cerebral blood flow have demonstrated sensitivity but lack of

specificity of the Wisconsin Card Sorting Test, with widespread activation noted in frontal and non-frontal brain regions during test administration [89], activation of the left dorsolateral prefrontal cortex [90, 91], or activation of the right anterior prefrontal region [92].

Even more recently developed executive function batteries are comprised of tasks that have been linked primarily to general or dorsolateral prefrontal function (card sorting tests, verbal and design fluency tasks, tower tests, etc.), and not orbitofrontal functioning, such as Delis–Kaplan Executive Function System (D-KEFS) [93]. Another example is the Behavioral Assessment of Dysexecutive Syndrome or BADS [94] which has been noted to have few subtests that are sufficiently powerful enough to encompass all executive functions, such that supplementation with other procedures is recommended [95].

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 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 [20]. Ways to correct this situation have been recommended including use of adjunctive structured interviews, self-report, and informant report instruments [85, 96] or by use of questionnaires regarding behavioral disorders [97]. Examples include instruments such as the Behavioral Rating Inventory of Executive Function (BRIEF) [84] and Frontal Systems Behavior Scale (FrSBe) [96], 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.

In addition, as noted by Goldberg and Bougakov [48] 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 [87], Stroop Color–Word Test [77], Category Test [78], 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. Two tasks noted as actor centered and reviewed by Goldberg and Bougakov [48] are the Cognitive Bias Task (CBT) [98] and the Iowa Gambling Task (IGT) [99]. The CBT requires decision making based on preference rather than stimulus characteristics, i.e., subjects are instructed to look at a target card and two additional stimuli that look either similar to or different from the target and then to select the one of the two stimuli that they "like better." The CBT has demonstrated robust effects in patients with frontal lobe lesions and has demonstrated important hemispheric differences as well as gender differences [48]. The IGT has recently been standardized and validated and has demonstrated sensitivity to ventromedial prefrontal lesions [99]. The IGT requires decision making by use of advantageous and disadvantageous strategies, and failure to choose advantageously results from insensitivity to future consequences, with immediate prospects overriding any future prospects [100]. The IGT 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 shown predictive ability in substance abuse, relapse, and ability to hold gainful employment due to decision-making deficits linked to ventromedial prefrontal cortical dysfunction [101]. 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 who had lesions outside these regions [102]. 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 on tests that are veridical [48].

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. Stuss et al. [64] evaluated patients with focal frontal and non-frontal lesions with 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). Lesions throughout the frontal lobes, with most robust findings in the right frontal lobe, were predictive of deficits in visual perspective taking, and 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 [64]. ToM tasks are not yet in common clinical usage, as validity and reliability studies are still in progress.

3. *The Laboratory Testing Environment*. A 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 that includes planning or decision making is more difficult to fully capture in a controlled environment [63, 84, 103]. In particular, patient errors when performing everyday activities are less likely to be manifested in the laboratory than they are in the natural setting [104]. 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 [104].

The Naturalistic Action Test (NAT) [105] has been 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; 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, omitting 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 [106], and adaptations of the NAT have been useful in differentiating patients with Alzheimer's dementia from normal controls [107]. 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 a unitary construct. Given the diversity of the frontal systems underpinning the executive functions, no one test can be sensitive to all aspects of dysfunction [48, 95, 108].

Subdividing the executive functions to correspond to distinct frontal systems has been recommended [80, 97, 109]. Different systems for this subdivision have been offered, including executive cognitive functions, behavioral self-regulatory functions, activation–regulation functions, and metacognitive processes [80]. 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 [80, 97]. Assessment of executive functioning must therefore include measures of the *cognitive* aspects, generally mediated by the dorsolateral prefrontal circuit, such as planning, organizing, monitoring, working memory, set shifting/set maintenance; the *behavioral self-regulatory/social–emotional* aspects regulated by orbitofrontal circuit and limbic nuclei, such as emotional reactivity, preferences and biases in judgment in problem solving, ability to take another's perspective, personality changes, empathy, and mood changes; and the *activation* aspects, served by the anterior cingulate such as activation and motivation.

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, such as 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 dynamic in terms of being flexible and accommodating to the emergent cognitive and behavioral changes marking the phases of recovery.

In the acute phase of TBI recovery, the focus will be on evaluation of attention, information processing, and memory and may require administration of short tests or repeated interviews. Briefer testing of postconfusional state and posttraumatic amnesia via use of short instruments, behavioral observations, and history, as well as attention to mental status observations from treating health professionals and caregivers over the course of days or weeks, will be necessary. Additional measures to evaluate concomitant delirium and agitation should be employed. 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 "score." This will help with adjusting expectations about the patient's capabilities and insure proper treatment planning. In this phase of recovery, the neuropsychologist must emphasize to those concerned with patient treatment that recovery from the acute confusion, delirium, and/or posttraumatic amnesia can be a slow, nonlinear process.

In the more stable or chronic phase(s) of TBI, after the patient has regained sufficient alertness, attention, and/or motivation, a more thorough evaluation of neurocognitive functioning should be undertaken with a comprehensive battery. Within the context of a comprehensive assessment, there should be detailed and thorough evaluation of functions known to be particularly vulnerable to TBI, i.e., attention, memory, and, most importantly, the executive functions. When evaluating the executive functions multiple procedures will be required, including self-reports, naturalistic observation or tasks measuring everyday action errors, tasks sensitive to dorsolateral and orbitofrontal circuits, and experimental measures. Use of multiple measures that reflect the different frontal circuits will be necessary. Due to the often protracted nature of recovery of TBI, serial evaluations at different points in time will be warranted to coordinate with or help guide rehabilitation efforts.

Summary

Traumatic brain injury is prevalent in the United States and the world, resulting in long-term neurological, cognitive, emotional, and behavioral sequelae and causing long-term disability in a significant number of patients. The economic costs alone are staggering. Mild closed head injury, the most common form of TBI, is prevalent and has greater consequences than previously assumed. Accurate detection of TBI is critical to adequate treatment and recovery.

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), magnetic resonance spectroscopy (MRS), and magnetoencephalography (MEG), holds promise in detection of microscopic abnormalities in mild TBI that have been minimized by more conventional structural imaging. These newer imaging methods are also delineating and correlating separate cognitive functions to distinct neuroanatomical regions, furthering understanding of frontal systems and injuries in TBI.

Executive functions, served by three distinct frontal circuits, are particularly impacted by TBI. Neuropsychological 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 and consisting of subdivisions and employing tests/procedures that measure those functions associated with each subdivision. A combination of assessment procedures, including standardized tests, informant and self-rating inventories, naturalistic observations, and thorough interview of patients and caregivers, is essential to evaluate all aspects of cognitive, behavioral, emotional, and social consequences of TBI. Use of experimental measures is also advised as supplementary to more standardized procedures.

TBI is not an "event" but an ongoing process in any patient, and neuropsychological evaluation(s) must reflect this. The assessment battery in general should be tailored to the stage of recovery of the patient. Assessment must be dynamic in nature to accommodate the evolving nature of TBI, so serial evaluations will be necessary to adjust patient and caregiver expectations and to help plan future treatments.

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Chapter 3

Neuropsychological Problems in Neuro-oncology

Carol L. Armstrong, Cynthia J. Schmus, and Jean B. Belasco

Introduction and History

Neuropsychological studies in the field of oncology are often 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 neurocognitive underpinnings of composite test scores. Other cases present fascinating modular deficits 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 sixteenth and seventeenth 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 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. 3.1, 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

C.L. Armstrong (✉)
Division of Oncology/Neuro-Oncology, Children's Hospital of Philadelphia, 3535 Market Street, 19104 Philadelphia, Pennsylvania, USA
e-mail: armstrongc@email.chop.edu

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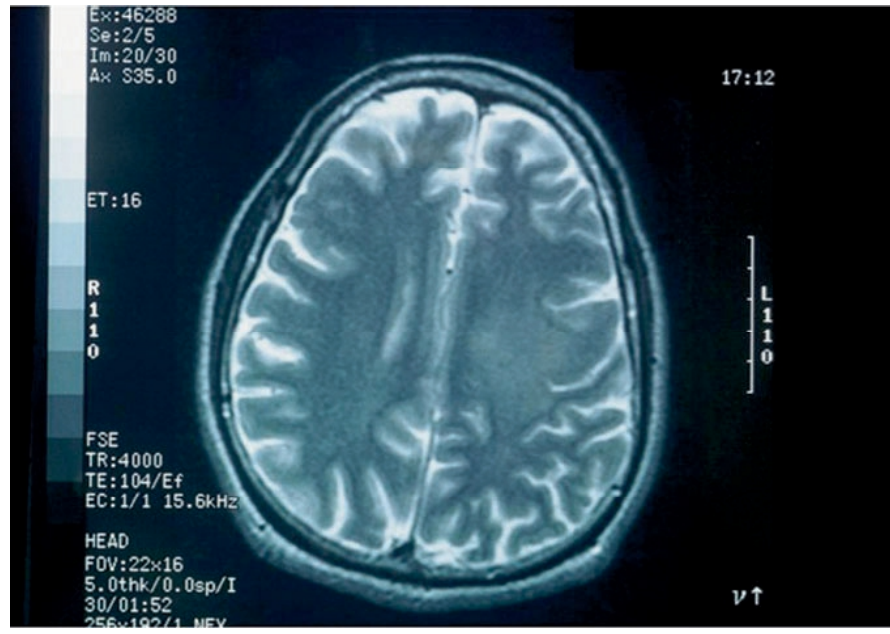

Fig. 3.1 Large, white, cloudy area of left frontoparietal region on T2 weighted MRI, is a presumed low-grade glioma, which cannot be biopsied or resected; before radiation therapy

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 radiation injury to epithelial, glial, and neuronal cells; their effects on brain tissue; and resulting inflammatory processes in the brain.

Incidence 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 (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 5-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 dysregulated 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, and Rb) act to inhibit cell proliferation and growth, so that cells have a normal life span. 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. Inactive 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., neurofibromatosis 1) 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 are the following:

(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 and 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 tumors in adults, but not in children [7, 8].

(c) *Neurofibromatosis*. Neurofibromatosis occurs both as an autosomal dominant trait disorder and as a spontaneous mutation. The higher incident neurofibromatosis 1 (NF1: 1 in every 4,000 births), also called von Recklinghausen neurofibromatosis, 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 8-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 is even higher [23]. Some studies have examined the effects of ionizing radiation treatments encompassing the brain for non-neoplastic 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 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 pre-existing 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: choroid glioma of the third ventricle to 3: astroblastoma
- *Perineurioma*: 0: perineurioma, NOS, and 3: malignant perineurioma
- *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 to 1: hemangiopericytoma and 3: Kaposi and Ewing's 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

[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).

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 to 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. Pre-operative 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 result 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 a 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 4 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 to measure tumor hypoxia, and diffusion tensor imaging and tractography can reveal loss or displacement of white matter fiber tracts caused by tumors (Fig. 3.2).

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

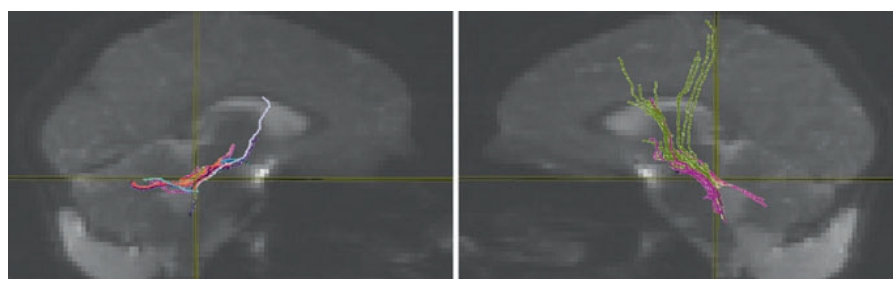

Fig. 3.2 Fiber tracking in a child with a resected cerebellar tumor and history of radiotherapy. Fiber tracks on the left are ipsilateral to tumor and contralateral to tumor on the right (from Timothy Roberts, Ph.D., Children's Hospital of Philadelphia)

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 chemotherapy and radiotherapy. Goldstein and colleagues examined the assumption that verbal fluency impairments would be associated with brain tumors of the left hemisphere more than the right, 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 toward 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. There was a higher proportion of the left hemisphere tumors that were in the temporal lobe (50% versus 25% of tumors in the right hemisphere), and the left hemisphere group reaction times may have been slower because of greater difficulty reconstructing memory. However, there was no effect of laterality of hemisphere on the hit rates (accuracy) of recognition. If the problem in memory had been caused by the higher proportion of temporal tumors, lower hit rates would be expected because reaction 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 many 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 7-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 cancellation 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 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 6-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 are 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 6 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 3 months of recovery [36]. Our longitudinal research at the Department of Neurology, University of Pennsylvania, and Children's Hospital of Philadelphia has shown that cognitive function takes at least 2 years for recovery, based on a continuous slope of improvement over that time period [50]. This was seen in improvement both 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 4–6 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 in the 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 pre-existing 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. 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 10 by Dr. Jeanne Townsend, 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 3 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

[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 4 months, and is followed by dysarthria that improves over time and more subtle present linguistic disorders [79–83].

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. Seizure 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 have 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.

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) is used, and more recently, protons. (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 or proton 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 non-disseminated 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 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 multi-modal (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, 93–95]. 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 1970s and 1980s that reported cases of dementia and mental retardation. Converging results of multi-disciplinary 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, 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 (1,800 cGy) of whole brain radiation in children with brain tumors that often disseminate.

Multiple phases of radiotherapy effects: There are presently three known 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 6 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 1 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 5 years posttreatment [50, 106]. Our laboratory's studies to 8 years posttreatment show that the associative memory impairment is more general than in the early-delayed phase and continues to decline from 5 to 8 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 1 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 1 year of treatment while radiation-related damage to the white matter is more often reported after 1 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 the surrounding brain tissue are seen with positron emission tomography of blood flow and both glucose and amino acid metabolisms (e.g., [117, 118]).

Age 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 a year or two of time in school, or receiving minimal academic exposure, are not uncommon. The decline in IQ postradiotherapy 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 5 or 6 years. Another study found an initial decline at 2 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 6 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 2 years posttreatment, with a plateau by 6 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, raise 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. Recovery of neural function, such as hippocampal plasticity, must also be considered.

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 8 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.

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 cell's 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 occurs in a cascade of events called the cell cycle and this cycle is further divided into phases. The classic anti-tumor 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 non-specific. 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).

Nitrosoureas are groups 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 the 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 (mercaptopurine) 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 microtubulin. 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 (aminoglycosides) weakens the outer cell membrane and interferes 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 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 are the targets of translational neuro-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 is 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 of 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 are 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 antimetabolite 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). Ifosfamide 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 paresthesias 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 also found 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, nitrosoureas, 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].

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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Chapter 4

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 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 4.1).

C. Peralta (✉)
Department of Neurology, Centro Neurológico, Fundacion Alfredo Thomson, Parkinson's Disease and Movement Disorders Clinic, Hospital Cesar Milstein, Buenos Aires, Argentina
e-mail: ceciliaperalta@yahoo.com.ar

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Table 4.1 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	

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 4.2).

Table 4.2 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 4.5
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

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 and/or urinary dysfunction, (2) parkinsonism, and (3) cerebellar dysfunction (see Table 4.3).

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 4.4).

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.

Table 4.3 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

Table 4.4 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

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

Table 4.5 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

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 4.5.

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-dihydroxy-phenylserine (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.

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Part II
Vascular System Disease

Chapter 5

Cardiovascular Disease and Neurocognitive Function

Shari R. Waldstein, Carrington Rice Wendell, Megan M. Hosey, Stephen L. Seliger, and Leslie I. Katzel

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 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?

S.R. Waldstein (✉)
Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD, USA; Division of Gerontology and Geriatric Medicine, Department of Medicine, School of Medicine, University of Maryland, Baltimore, MD, USA; Geriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, MD, USA
e-mail: waldstei@umbc.edu

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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 hypertension) [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 $\geq$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 nondemented, 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 $\leq$1 alcoholic drink per day for women and $\leq$2 for men to reduce the risk of CVD disease and dementia while minimizing adverse affects of alcohol [57].

Reviewed elsewhere [154], 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 [155]). In that regard, U- or J-shaped relations have been noted, with moderate levels of alcohol consumption associated with better cognitive performance [156, 157]. 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 [158, 159]. Moderate alcohol intake in middle age has been associated with better cognitive outcomes in older age [160]. 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 [161]. 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, 161]. 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 [162]. Protective effects of dietary poly- and mono-unsaturated fatty acids have also been noted [163]. Conversely, diets high in saturated fat have been associated with cognitive decline [164]. Dietary intake of omega-3 fatty acids has been associated with greater corticolimbic gray matter volume [165].

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 [166]. 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 [167, 168]. 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 [169]. Further, exercise has demonstrated associations with neuroplasticity in animal models and in humans [167, 168].

Psychosocial Risk

Various psychosocial factors have demonstrated prospective relations to CV risk factor and disease outcomes [170, 171] including stroke [172, 173]. 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 [174].

Relations of depression to diminished cognitive function and dementia are well documented, and these disorders may be linked, in part, via inflammatory mechanisms [175]. 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 [176] and a sample of older adults [177]. 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) [178, 179]. 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 [180]. 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 [181]. Enhanced BP reactivity has also been related to carotid atherosclerosis and its progression and silent cerebrovascular disease [182, 183]. 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 [184]. In addition, older, predominantly normotensive, adults with greater BP variability on ambulatory monitoring had the highest severity ratings of white matter disease [185]. Enhanced BP responses to orthostatic manipulation have been associated with a greater prevalence of silent brain infarction in elderly hypertensives [186]. 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 [183].

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 [187–189]. It has also been noted that stress-induced cortisol elevations are associated with decreased learning and memory performance [190]. Consistent with this pattern of association, high levels of cortisol have been associated with hippocampal damage [191]. 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 [187, 188]. This suggests that detrimental effects of cortisol on the brain may extend to the frontal lobes [188]. McEwen and colleagues [192] 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 [193, 194]. 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 [195]. 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 [196, 197]. 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 [198]. 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 [199], 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) [199]. 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 [199, 200]. The presence of silent brain infarction, mainly in cortical regions, is twice as likely among those with AF as those without [199]. Knecht and colleagues reported lower levels of learning and memory, attention, and executive function in conjunction with increased hippocampal atrophy in AF patients [201].

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 [200]. 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 [202].

Important predictors of subsequent cognitive difficulties include delay in the start of CPR and the need for advanced cardiopulmonary life support [203]. Some recovery of function has been noted in 3 months following cardiac arrest, but pronounced residual deficits typically remain [202]. The cognitive consequences of cardiac arrest have been attributed to diffuse and sudden ischemic–hypoxic injury [202, 204]. 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 [205–207]. 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 [205, 208–211].

Atherosclerosis

Atherosclerosis is a known contributor to the development of VaD because of its involvement in cerebral ischemia and stroke [26, 212]. 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, 212]. 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 [213].

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 [214–216]. Overall, current evidence supports a cross-sectional association between carotid atherosclerosis and cognitive function across at least seven population-based samples [217–224], two CV disease samples [225, 226], and another sample at risk for CV disease [227]. 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 [218, 228]. 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 [229–231], 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 [232]. In contrast, our group noted decline on several memory tests as a function

of greater carotid IMT [233]. Studies have also found evidence for a carotid IMT–cognition relation in AD or stroke patients [234–236], 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 [207, 237]. 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 [238]. 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 [239]. In an examination of participants in the Maine–Syracuse Study [240], 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 [241]. 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 [242], and PWV has been found to correlate inversely with MMSE performance among individuals referred for memory deficit [243], even among those without overt vascular disease [244].

Growing evidence also suggests an association between arterial stiffness and cognitive decline that is independent of BP level. Scuteri and colleagues [245] 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 [246].

Endothelial Dysfunction

Endothelial function represents an important component of vascular health and contributes to the maintenance of vascular homeostasis [247]. 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 [207, 248]. 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 [226] 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 [249, 250], 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

[251], 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 [252]. Despite its recognition as a measure of subclinical CV disease among otherwise healthy individuals [205], 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 [253]. Furthermore, baseline LVH predicted decline in MMSE performance over 5-year follow-up. Using data from the Framingham Offspring Study, Elias and colleagues [252] 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 [205, 254–257]. However, relations of subclinical CV disease to cognition are unlikely to be due solely to these shared risk factors [35, 207]. 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 [226, 239, 242, 251]. It should be noted that subclinical disease states often co-occur and may act additively or synergistically in the prediction of diminished cognitive function [205]. 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 [258], 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 [259]. 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 [258]. Others have similarly found cognitive impairment in pre-surgical coronary patients [260]. 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 [261, 262].

Vingerhoets [258] 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 [263] and white matter lesions on MRI [264].

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 [265]. 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 [266]. 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 [267–270].

Both short- and long-term changes in cognitive function have been observed following CABG surgery. In a seminal, though highly debated [271–276] study, Newman and colleagues [277] 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 [278–280]. These short-term effects may include decrements across a number of domains of cognitive function, including memory, psychomotor speed, executive functions, and visuoconstructional abilities [270]. Memory and concentration complaints are the most frequently self-reported cognitive changes, though these findings are not always corroborated by neuropsychological data [270, 281].

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 [265, 282]. 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 [270, 276, 283–286]. These discrepancies are likely a function of the numerous methodologic differences across studies; Selnes and colleagues [270] 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 [267, 270, 287–289]. 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 [290]. 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 [291]. Risk for atherosclerotic events such as MI, PAD, and stroke clusters among individuals [292–294].

Reviewed by Phillips [295], 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 [296–298]. Results of these studies suggested that patients with PVD displayed mild neuropsychological dysfunction [296, 297] or showed similar cognitive function as patients with carotid disease [298].

Comparing PVD amputees and non-amputees with mild to moderate claudication to healthy control subjects and atherothrombotic stroke patients, Phillips et al. [299] 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, perceptuo-motor 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. [217] 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 [229, 232].

Several direct and indirect mechanisms may link PAD to cognitive difficulties and have been reviewed (see [14, 295]). 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 [300, 301]. In the Rotterdam Study, mean ABIs were significantly lower in patients with white matter lesions on MRI [301].

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 [302]. The prevalence of HF has been increasing and is projected to double within 40 years, despite improvements in CV mortality rates over recent decades [302, 303]. 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 [304].

Diminished cognitive function in HF has been the subject of several recent comprehensive reviews [303, 305–307]. 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 [303]. The pattern of impairment associated with HF appears to be diffuse; affected domains include attention, concentration, memory, language, psychomotor speed, and executive function [307–309]. These decrements in cognitive function are associated with an increased risk of hospital readmission, disability, and mortality among HF patients [306, 310, 311]. There is mixed, and very limited, evidence regarding the cognitive consequences of heart transplantation [308]. Although some studies show postsurgical improvement in cognition [312, 313], others show evidence

to the contrary [314, 315], and numerous methodologic weaknesses preclude strong conclusions [308]. 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 [307]. The primary hypotheses involve multiple cardiogenic emboli and cerebral hypoperfusion associated with insufficient cardiac output [303]. Given that the brain receives a large relative proportion of cardiac output [308], 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 [303, 305, 316]. Furthermore, fatigue, depression, medication side effects, and other neurological complications are prevalent in HF and carry independent neuropsychological implications [308].

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 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. 5.1, 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 [317].

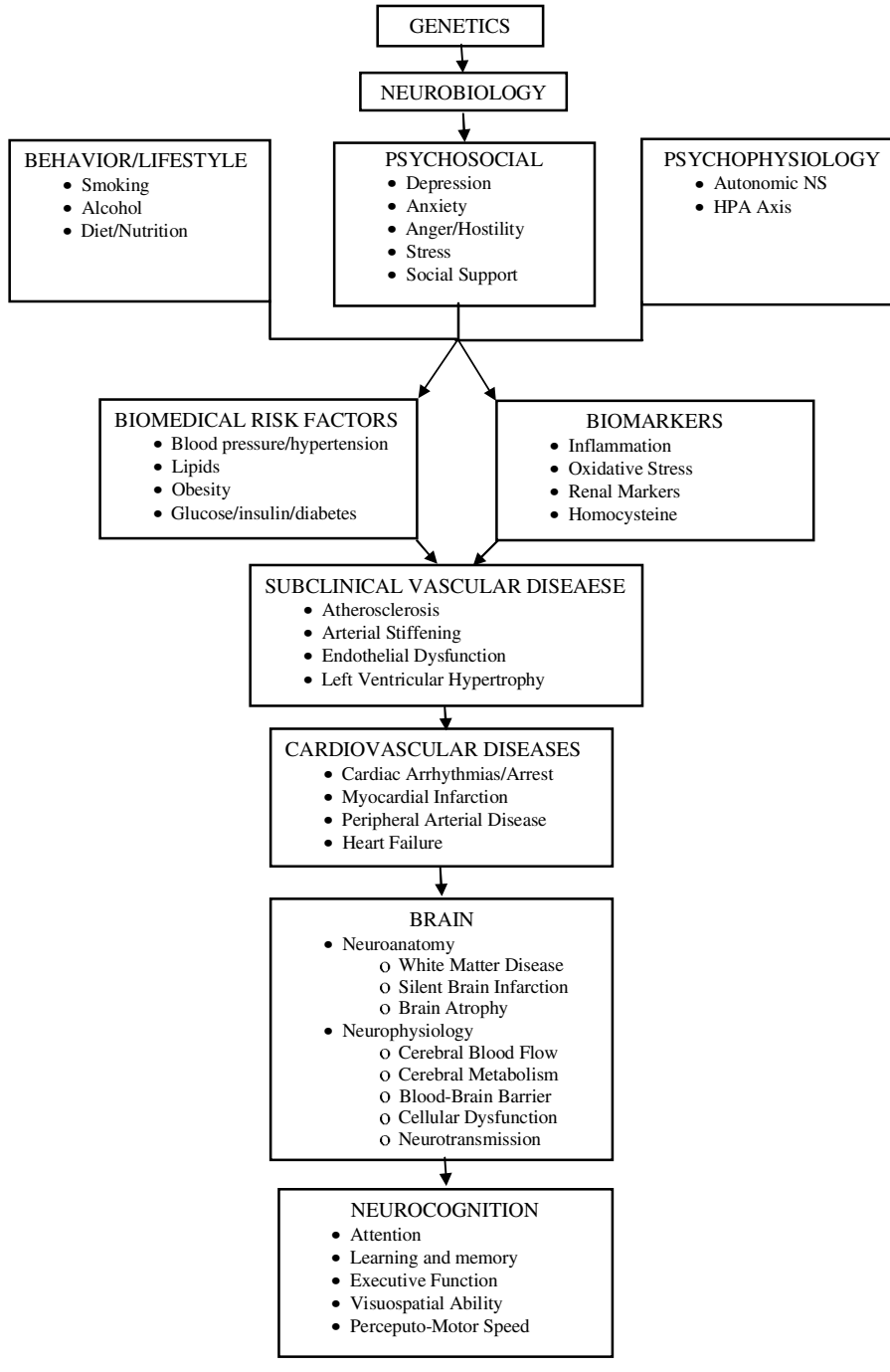

Fig. 5.1 Potential proximal and distal mediators of the relations of CVD risk factors and diseases to neurocognitive function

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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Chapter 6

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 in one small series of children with stroke, 75% had persistent cognitive deficits [3]. Therefore, assessment of neuropsychological function following stroke is an important part of the medical management of these patients.

Medical Information Regarding Cerebrovascular Disorders

The two main categories of cerebrovascular disease are ischemic and hemorrhagic. Ischemic stroke is due to a 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, non-inflammatory vasculopathies, and vasculitis are also associated with stroke [5]. In addition, hematologic abnormalities leading to hypercoagulability may play a 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 post-partum 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

S.E. Smith (✉)
Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
e-mail: smithsa@email.chop.edu

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[4]. Vascular malformations such as aneurysms and arteriovenous malformations (AVMs) are much less common causes of hemorrhagic stroke in adults [9, 10].

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 [11–13]. 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 [14]. Pediatric cerebral venous sinus thrombosis has been associated with dehydration, prothrombotic states, head and neck infection, trauma, surgery, malignancy, and inflammatory conditions [15]. 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 [16]. In contrast, the cause of hemorrhagic stroke in term neonates is often unknown [17].

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 neonatal 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 [18]. 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 [19]. 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 [20]. A type of vascular dementia, subcortical arteriosclerotic encephalopathy (Binswanger's disease), will be covered in greater detail in the chapter on Dementia later 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 [21, 22], see Fig. 6.1. In the acute setting, non-contrast computed tomography (CT) is used to rapidly assess for intracerebral hemorrhage and to rule out non-vascular 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

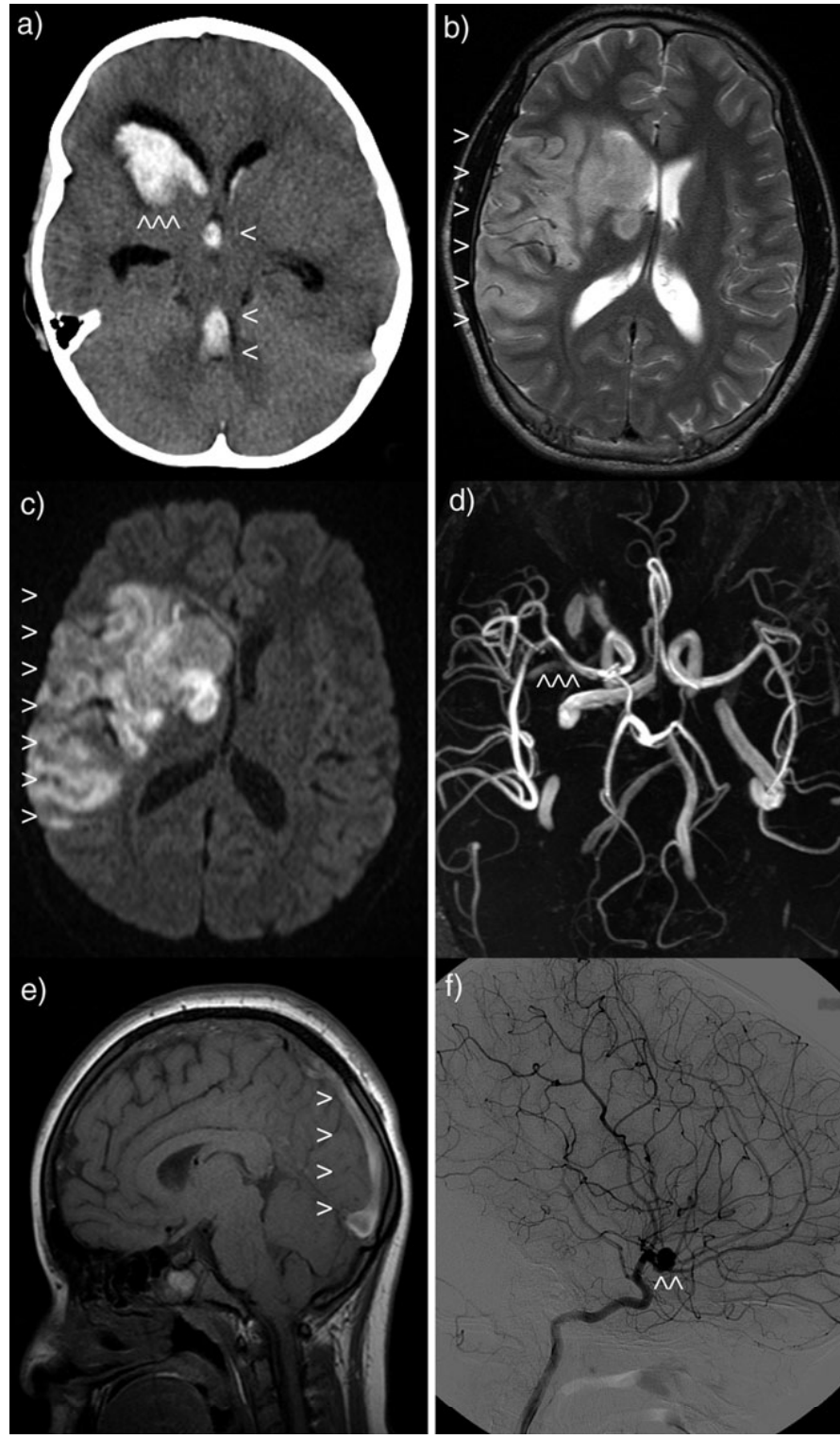

Fig. 6.1 Representative neuroimaging studies from patients with cerebrovascular disease. (**a**) Head CT from patient with acute intracerebral hemorrhage due to cavernous malformation. Blood is indicated by *arrowheads*. (**b**, **c**) Brain MRI from patient with right middle cerebral artery ischemic 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*

hours of stroke onset [23]. 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 with 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 [24].

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 non-invasively 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 non-invasive 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 [25]. 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 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 treatment. Widespread use of this drug is limited by the need to administer it within 4.5 h of stroke symptom onset [26], and as a result fewer than 5% of adults with acute stroke receive this treatment [27]. Other acute stroke treatments include aspirin, intra-arterial administration of tPA [28], mechanical clot disruption, and endovascular removal of thrombus with a clot-retrieval device [29]. Surgical decompression can be beneficial in patients with space-occupying infarction [30]. Ongoing studies are evaluating the role of therapeutic hypothermia in the management of acute stroke [31].

To prevent future strokes, treatment with an antiplatelet or anticoagulant medication is recommended [28], 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 [29]. 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 [32]. Chronic transfusion therapy has been shown to prevent stroke in children with sickle cell anemia [33], and revascularization surgery for moyamoya disease also prevents stroke recurrence [34]. Anticoagulation is the treatment of choice for acute cerebral venous sinus thrombosis in adults and children [28, 32].

Following intracerebral hemorrhage, acute treatment may include surgical evacuation of hemorrhage, placement of a temporary ventriculostomy catheter if obstructive hydrocephalus develops, and intraventricular infusion of thrombolytic medications to augment clearance of blood from the ventricles. Infusion of activated recombinant factor VII (a coagulant) has been shown to decrease the amount of hemorrhage expansion and garnered much recent enthusiasm, but this treatment has not consistently been associated with improved outcome [35]. Certain patient populations may benefit from this treatment, but identification of these groups will require further study. 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 [10, 36]. 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 [37]. 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 [38, 39]). 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 (non-dominant) 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 are more variable in this population [40].

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 not only provide detailed information on the patient's deficits but 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) [41], or the Galveston Orientation and Amnesia Test (GOAT) [42]. 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*) [43] and the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) [44] for adults and the Comprehensive Neuropsychological Screening Instrument for Children (CNSIC) for children aged 6–12 years [45].[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 [45]. 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 (1 year is commonly recommended) may be appropriate.

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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 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 [45, 46].

Intellectual Functioning

Assessment of intellectual functioning following a stroke is important in order to establish a 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 [47], 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 [48] and *Wechsler Adult Intelligence Scale*, Third Edition [49]), 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 [50]. In addition, brain injury in general and stroke in particular often leads to decline in attention [50], working memory, and/or processing speed skills [51], which also may impact performance. For this reason, index, factor, and subtests analyses are 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) [52], Universal Nonverbal Intelligence Test [53] (UNIT), and Comprehensive Test of Nonverbal Intelligence [54] (CTONI)) and for children, adolescents, and adults (e.g., *Test of Nonverbal Intelligence*, Third Edition [55] (TONI-3) and Raven's Progressive Matrices [56]). 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 [57], 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) [58] and the Wechsler Test of Adult Reading (WTAR) [59]. 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 [60].

Language

Aphasia is a common consequence of stroke, particularly left hemisphere stroke, and occurs in approximately one-third of adult stroke patients [8, 61]. 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 [62]. 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 [63]. 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 [63]. Damage to the arcuate fasciculus results in conduction aphasia, which is defined by poor repetition with relatively fluent speech and intact comprehension [63]. 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 [62]. 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 [63] and in Beeson and Rapcsak [62].

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 [8, 64]. 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 [65]. 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 [46]. There are a number of tests that are designed to provide a comprehensive assessment of aphasia, including the Boston Diagnostic Aphasia Examination [66] and the Multilingual Aphasia Examination [67] (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 [46]. Assessment of phonological and rapid naming skills, which are the core cognitive processes underlying reading acquisition [68], 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 post-stroke 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 1 year or more [69]. 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 on 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., [78]). 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 [70]. 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 [51].

Lesions within diencephalic structures have been strongly implicated in anterograde amnesia. Damage to the anterior thalamic nuclei and the mammillary bodies has 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 is 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, and (6) personal–autobiographical memory. Test selection should allow for 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 [71]. 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 [72]. 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 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 [73] or Conners' Kiddie Continuous Performance Test [74]) 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 [49].

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 [75, 76]. In adults neglect is more persistent and severe following right hemisphere injury although it occurs with injury to either hemisphere [77]. 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) [78]. 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 to the environment [79]. 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 [80].

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 [81]. 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 [82]. 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 [83]. 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 [84]. Numerous studies have provided support for this account of neglect using a cuing paradigm [85]. 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 [86]), 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 cancellation tasks in which the patient is provided a page with numerous small targets and is 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 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 [87, 88]. In an ongoing 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 five tasks: line bisection (Fig. 6.2a, b), cancellation (Fig. 6.2c, 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. 6.2e). Line bisection and conjunction search were the most sensitive tasks for the detection of neglect but did not detect neglect in all subjects (Fig. 6.2f) [89]. 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 toward 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 [46]. Aspects of attention and working memory are related to executive functioning, and successful performance of these tasks is often dependent on 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 [51]. 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 [51].

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 [51] for a review of these syndromes in stroke). Deficits in response rapidity are particularly common following stroke [51]. 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 are an excellent predictor of long-term impairment [90]. 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

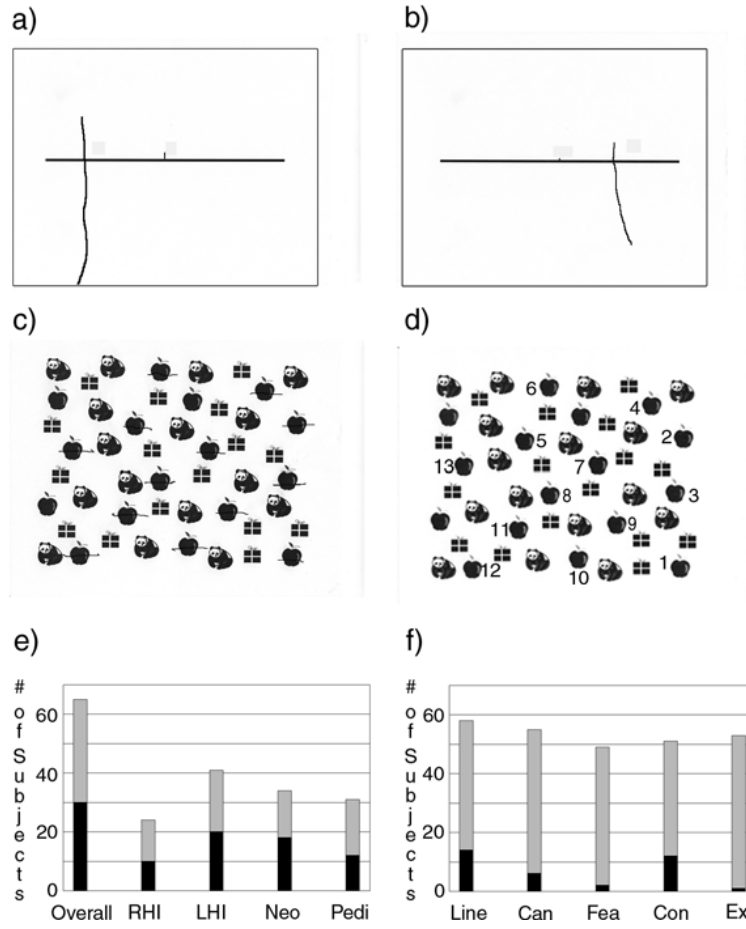

Fig. 6.2 Data from study of visuospatial neglect in children following unilateral neonatal or pediatric arterial ischemic stroke or parenchymal hemorrhage [89]. Presence of neglect was determined by comparison to normal distribution of performance by age-matched controls. (**a**, **b**) Examples of neglect on line bisection task from subject with left hemisphere stroke (**a**) and right hemisphere stroke (**b**). (**c**, **d**) Examples of neglect on cancellation task from subject with right hemisphere stroke. Subject omitted more targets from the left hemifield than the right (**c**) and cancelled left-sided targets significantly later than right-sided targets (**d**). Numbers depict order in which targets were cancelled. (**e**, **f**) Summary of performance of 65 pediatric subjects aged 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 1 month of age (Neo) as compared to later in childhood (Pedi). (**f**) Number of subjects showing neglect on each of five tasks: line bisection (Line), cancellation (Can), featural visual search (Fea), conjunctive visual search (Con), and visual extinction (Ext)

whether and how well they can structure themselves" ([46], p. 611). Behavioral questionnaires completed by family members can be critical in identifying post-stroke behavioral change, such as the Frontal Systems Behavior Scale (FrSBe) [91]. Similarly, the Behavior Rating Inventory of Executive Function (BRIEF), which has parent, teacher, and self-report forms for children and adolescents [92], 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) [93], the Tower

of London [94], and the Wisconsin Card Sorting Test (WCST) [95] 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. Research studies have found that between 34 and 75% of patients with stroke had impairment on higher-order visual tasks [90, 96], 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 occipito-temporal structures (ventral stream), while object location ("where") is mediated by occipito-parietal structures (dorsal stream) [97]. 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 [98].

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 [107]. A similar pattern of performance has also been found in children who experienced perinatal brain injury such as stroke [40].

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 in *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 [99].

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 [100]. Deficits in visuospatial ability can be assessed through line orientation measures (e.g., Judgment of Line Orientation [101]).

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)

[93], 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 [50]. It is important to assess fine motor functioning for use as an indicator of the lateralization of lesions or dysfunction [46], 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 [45, 46]. 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 [102]). While most common following strokes affecting the left parietal lobe, apraxia can occur following damage to extra-parietal 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 [47]. 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 [103]), speed and dexterity via a pegboard test (e.g., Purdue Pegboard Test [104] and Grooved Pegboard Test [105]), 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 are 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 [50]. 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 [45].

Emotional and Behavioral Functioning

Emotional and behavioral changes are common occurrences following stroke [71, 106], with both neurologic and situational factors likely influencing the development of symptoms. In adults, post-stroke depression is common (10–40% of stroke survivors) and is associated with impairments in executive functioning [106], poor affective modulation, and anterior lesion location [107]. Anxiety disorders, and symptoms of post-traumatic stress disorder in particular, are also

common in adults following stroke [107]. Mania, associated with right hemisphere lesions, and psychosis following stroke have been documented but are rare [107]. 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 [71].

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 [108], 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 [108]. 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 [108].

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 depend 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 [109–111]. Furthermore, long-term cognitive outcome is also 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 [112, 113].

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 [114]. According to this review, neuropsychological impairment in sustained attention, apraxia, pathological emotional reactions, and language deficits has 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 has prognostic value for long-term outcome. One study with a large cohort of patients 3 months post-ischemic stroke found that medical and psychiatric comorbidities predicted mortality at 3 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 3 months [115]. Similarly, a second study demonstrated that functional status (such as dependence

for ADLs) 6 months post-stroke predicted long-term survival, with less than half of patients with severe disability surviving 5 years [116].

In children who have survived ischemic stroke, the majority experience persistent neuropsychological deficits, specifically with regard to attention, concentration, and processing speed [111]. In one study of children who have survived hemorrhagic stroke, approximately half of the patients presented with cognitive deficits [117]. Furthermore, the majority of these patients presented with low self-esteem and/or difficulties with mood and behavior [117]. Pediatric stroke survivors are also likely to have academic difficulties and require special education services [111, 118], with one study finding that only 50% of patients were able to return to a regular classroom [119].

The effects of stroke on neuropsychological functioning are, in general, more extensive than the typically expected deficits associated with the specific lesion [50]. 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 [50, 120]. 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 [121]. 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 [122]. 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 [123]. 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 [124, 125]. The literature supporting specific cognitive interventions is described in the review by Cicerone and colleagues [124] and is treated in this volume in Sarah Raskin's chapter, "Current Approaches to Cognitive Rehabilitation." 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 [126]. 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) [124]. 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 [127]. Novel treatments which hold promise for cognitive rehabilitation include transcranial direct current stimulation (tDCS) [128, 129], caloric vestibular stimulation [128], and repetitive transcranial magnetic stimulation (rTMS) [130]. 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.

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Chapter 7

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, 9] and changes in posterior cerebral cortical excitability predisposing to photopsias [10]. 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 [11] 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. 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

J.S. Meyer (✉)
United Neurology Headache and Pain Clinic,
2321 Southwest Freeway, Houston, TX 77098, USA
e-mail: johnsmeyer@jsmeyer.com

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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 "headache-present" 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 [12]. 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. [13] 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 [14–18], among headache sufferers. Test instruments used proved to be highly reproducible [14–16] 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 [15]. 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) [19, 20] and cognitive capacity screening examination (CCSE) [21–23] 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 [20–26]. 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 7.1.

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 migraine headaches had become many times more frequent, exceeding 15 or more headache days each month [7, 8]. Table 7.1 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

Table 7.1 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. [14].

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 7.2). As shown in Table 7.2, 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 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 7.2, there were significant declines in CCSE and MMSE test scores when "headache-present" intervals were compared with "headache-absent" intervals.

Table 7.2 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.
*$p < 0.0001$; **$p < 0.001$.

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.

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Chapter 8

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].

R.O. Hopkins (✉)
Psychology Department, Neuroscience Center, Brigham Young University, Provo, UT, USA; Pulmonary and Critical Care Division, Department of Medicine, LDS Hospital, Salt Lake City, UT, USA; Pulmonary and Critical Care Division, Department of Medicine, Intermountain Medical Center, Murray, UT, USA
e-mail: mona_hopkins@byu.edu

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 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

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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 anoxic-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 $\geq$36 years (odds ratio 2.6; $p = 0.005$) and CO exposure intervals $\geq$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 $\leq$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 [177, 164]. 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.

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Part III
Developmental, Genetic, and Structural Disorders

Chapter 9

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 nonprogressive brain lesions involving motor and postural abnormalities that are noted during early development [1]. Recently, 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].

According to the new definition, 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 eight 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 leukomalacia (PVL), and/or complications of intraventricular haemorrhage: periventricular haemorrhagic 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 27th week of gestation age [8]. In the same study, no relation was found between 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

S. Pirilä (✉)
Department of Pediatrics, Tampere University Hospital, Tampere, Finland; Department of Psychology, University of Tampere, Tampere, Finland
e-mail: silja.pirila@uta.fi

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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 noninvasive 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]. Recently, the predictive power of both instruments was investigated in a prospective 2-year cohort study in premature 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 such as volume measurements [27], diffusion tensor imaging [28], and functional magnetic resonance imaging [29] have become available.

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 or 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 2 or 3 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) [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 2 years and re-assessed at 9 years and 4 months with a mean interval of 6 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 1,000 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 ataxic 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.

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 [36] 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 [37].

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 [12, 13, 38–43]. 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.

Visual-Perceptual Impairments

Reduced nonverbal 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 [44]. They reported among others no significant association between visual-perceptual impairments and reduced nonverbal to verbal intelligence and concluded that nonverbal intelligence subtests assess a complex of cognitive skills that are distinct from visual-perceptual abilities and that the assessment of nonverbal 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 [45]) 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 [46], 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 parieto-occipital periventricular brain lesions [47]. Based on this and other findings, the dorsal stream of the visual system projecting from the primary visual cortex to the parietal lobe [48] is suggested to be compromised in children with CP [49].

Also Posner's orienting task [50] 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 [51, 52]. 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 [53].

Grasping and object manipulation tasks demonstrated that spastic CP is characterized by overall slower movements that consist of more submovements, a stereotypical shoulder–elbow recruitment order [54], more variable hand trajectories [55], increased trunk movement [56], and an anticipatory movement planning deficit [57, 58]. 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 [59]. Mutsaart and colleagues [57, 58] 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.

Attention Dysfunctions

All in all, the outcome of in-depth perceptual-visual motor experiments suggests that CP is not solely a motor execution problem [60] but also attention dysfunctions are part of the problem. Although some studies failed to report an attention deficit in children with CP [61], others reported attention deficits (distractibility) [62, 63]. 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 [64] 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 [65] 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 recently to evaluate the effects of MPH directly in classroom environments [66]. 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 [67]. 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 nonverbal function. Anatomical correlates of the crowding hypothesis are, however, modestly provided by recent fMRI studies in children, adolescents, and young adults with early left periventricular brain lesions [68–71]. 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 which extent it takes place in individual cases [69]. Moreover, the notion of a hemisphere being crowded seems to be an oversimplification of the modular approach of brain functioning [72] and is especially hard to reconcile with modern assumptions of the brain as a flexible arrangement of cortical networks [73, 74]. 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 [68].

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 [75–77]. 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 [78]. Also an inconsistency between literacy skills and intellectual and verbal abilities has been reported in CP [79–83]. 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, 81]. 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 [84]. That the severity of the motor impairment plays a role in expressive and comprehension skills is also demonstrated by Pirila and colleagues [13]. In this study, children with an 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 [85].

Arithmetic Difficulties

Evidence is increasing that arithmetic difficulties are somewhat more prevalent than reading difficulties [32, 86–89]. 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]. As far as our knowledge goes, the Falkman and colleagues study [104] is the only available source suggesting that children with severe speech problems and CP have difficulty solving tasks requiring a ToM. The findings based on six children suggest that these children follow a normal pattern of ToM development but with a severe delay. The small sample size calls for an in-depth study on ToM and CP.

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 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 [82] reported a decrease in IQ points between the ages 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 norm course of cognitive development appears to become visible even in children at about 2 and 4 years of age [78].

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 [78] reported that epilepsy emerged as a significant predictor on several measures of cognitive and language outcomes, 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. Recently, 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 9–10 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. Some of the most common are Vineland Adaptive Behavior Scales (2nd edition) and the Portage method in order to gather information about adaptive and functional behaviours.

Another reason why some children with CP are difficult to test is because they are nonverbal. Although the exact prevalence of communication disorders associated with CP is not known, it has been estimated that approximately 20% of the children with a diagnosis of CP have severe communication impairment and are classified as nonverbal [77, 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 recent study [43] indicated that nonverbal reasoning abilities may go undiagnosed 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 functions independently of motor and communication disabilities would provide invaluable information about the cognitive capacity of the children without possibilities to 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 nontraditional responses [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 assessment 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 waits in-depth research in the field of CP.

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 [114, 115] are, for instance, the Pediatric Evaluation of Disability Inventory (PEDI) [116] and the Gross Motor Function Classification System (GMFCS) [108, 117, 118]. Both measures have sound psychometric properties in most areas and are apt to use in studies exploring the treatment outcome [119].

PEDI is usually given to the primary caregiver who has observed the child across 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, and 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 1–12 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: 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) [118, 120]. 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) [121, 122], 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.

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. Recently, 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 [123]. 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 supra segmental effects on cortical functions [51]. 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 programmes 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 [124, 125].

That onset, duration, and intensity are factors of importance for assessing the efficacy of therapy programmes, is shown in an evidence-based summary of research on the neurodevelopmental treatment (NTD) method [126]. The basic tenets of NDT 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 [127]. So far, no studies were found that reported results of treatment started under 5 months of age and only 4 out of the 21 reported studies initiated treatment under 12 months of age. The longest duration of treatment was 21 months [126]. Some have demonstrated that programmes with a high frequency of NTD treatment resulted in a better outcome [128, 129], while others have shown no differences [130]. The latter study also revealed that intensive therapy seems to be very demanding for children resulting in low compliance. Others reported that intermittent physiotherapy scheduled four times a week for 4 weeks separated by 8 weeks without therapy led to an improvement in motor function [131]. The same extent of improvement was reported when physiotherapy was organized either as intermittent or continuous therapy [132].

Horseback riding therapy and hippotherapy have become popular to complement traditional physical and occupational therapy. The review of Sterba [133] on the efficacy of these therapies provides valuable information: five of six studies showed improved gross motor function. Improvement in these studies and in many studies discussed earlier 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 [77]. They concluded that direct SLT focussing on communication and expressive skills using operant and micro-teaching techniques has been effective for the children who participated. However, for some areas for intervention, no evidence 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.

Earlier reviews on the effects of early intervention concluded that the evidence favouring early intervention was inconclusive [134, 135]. In a recent review [124], the authors came to a more encouraging conclusion: the field has moved a little way forward. Twenty of 34 studies had fair to high internal and external validity. Six of them were able to demonstrate a significant beneficial effect of intervention on motor development. Of the 14 studies with limited methodological quality, half reported a positive effect of intervention. The authors suggested that specific training and developmental programmes in which parents learn to promote infant development might produce a positive effect on motor development. In a salutary review, also Jansen and colleagues [136] advocated that the effects of therapy on both parents and children should be evaluated. Indeed, 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 video-taping, counselling, parent support, and discussion groups, etc. might help caretakers to recognize more precisely their child's strengths and deficits which, as a result, widen their range of opportunities for interaction [75, 103]. This is relevant because parental malfunctioning and stress are associated with the severity of the disorder and additional problems associated with CP [138–140].

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] on literature on parental participation in physiotherapy for children with physical disabilities, it was 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. It, 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 [114, 142].

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 sub types: 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) [143]. 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 [144, 145]. Studies that fulfil basic requirements are encouraging: science is in action.

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Chapter 10

Autism and Asperger's Syndrome: A Cognitive Neuroscience Perspective

Jeanne Townsend and Marissa Westerfield

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.

The symptoms described by Kanner and Asperger remain the core diagnostic symptoms for autism and associated disorders. Autism spectrum disorders (ASDs) as specified in the DSM-IV TR (a text revision of the DSM-IV) include autistic disorder (classic autism), Asperger's disorder, pervasive developmental disorder not otherwise specified, Rett's disorder, and childhood disintegrative disorder [3]. This chapter is limited to discussion of autistic disorder and Asperger's disorder.

J. Townsend (✉)
Department of Neurosciences, University of California, San Diego, CA, USA
e-mail: jtownsend@ucsd.edu

Biological Underpinnings

Neuroanatomic Abnormalities

Studies of neuroanatomic abnormality in autism are generally inconsistent and often controversial. There has been a veritable explosion of the number of MRI anatomic studies in the last decade. The methods are quite variable, samples are usually small, and, with a few exceptions, there is little agreement overall. Some newer smoothing and normalization techniques used to process MRI data require, at the very least, the questionable assumption that ASD brains can be warped accurately to a standard normal template. Some studies make strong claims about small structures (e.g., the amygdala) when their image analysis has "smoothed" across an area that is similar in size to the structure of interest. That is, they very well may have included surrounding tissue in the measurement of the structure of interest.

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 findings include abnormalities in the brain stem, cerebellum, limbic system, and overall brain size.

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Postmortem Studies

Recent reviews of the postmortem literature [4–8] summarize neuropathology in a total of 58 postmortem cases. The most consistent findings are in the cerebellum and brain stem. Autopsy studies have found reduced numbers of Purkinje neurons in the cerebellar vermis and hemispheres [9–14]. Purkinje neuron loss in autism is patchy, and the amount and distribution of loss across the cerebellar hemispheres and vermis differs from individual to individual. Neural ectopias in the inferior cerebellar peduncle and malformation of the inferior olives, a crucial afferent structure of the cerebellum, have also been found [9, 12, 15]. In total, cerebellar anatomic abnormality was present in 21–25 of all 29 (72–86%) cases in which the cerebellum was examined. These findings are from six independent lab groups.

Abnormality in limbic structures (hippocampus, amygdala, subiculum, entorhinal cortex, anterior cingulate gyrus, mammillary body, septum) was present in a majority of autism cases examined [9, 10, 16, 17]. When present, limbic system abnormality involved increased packing density of neurons and reduction in neuron sizes or a reduced number of neurons [18]. In total, cerebellar anatomic abnormality was also present in 9 of 14 (64%) cases in which the limbic system was examined.

Few abnormalities have been reported in cerebral cortex on postmortem exam. Five groups have examined neocortex in 15 cases and found no differences from controls except for 5 cases in which cells in the anterior cingulate were poorly laminated [19]. However, a number of irregularities in cell migration and white matter have been identified including thickened cortices, high neuronal density, neurons in the molecular layer, irregular laminar patterns (poor gray–white matter boundaries), and ectopias [9]. Smaller and less compact minicolumns in frontal and temporal lobes were found in nine autistic subjects [20].

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 [21]. A review of 21 postmortem cases found that compared to a large database of 8,000 control cases, 17 were normal weight, 1 was microcephalic, and 3 were megalencephalic [22]. A more recent review of 55 postmortem autism cases [23] shows highly variable brain weight results. On average, the autism cases were 6% (SD 12%) heavier than age-matched controls (a large averaged database). The brains of young children (ages 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 [24]. This combined with evidence that brain weight may be greater than normal in autistic children and somewhat smaller than normal in adults with autism suggests an ongoing neuropathological process in autism [5].

MRI Studies

The first quantitative MRI studies identified abnormally reduced size of cerebellar hemispheres [25, 26] and sub-regions within the vermis in autistic children and adults [27, 28]. From that time until 2003, 12 additional studies with a total of several hundred subjects from seven independent labs reported significantly reduced size in one or another sub-region of the vermis [29–40] or hemispheres [34] or in overall cerebellar gray matter [41]. In some few cases, cerebellar size reduction was so substantial that it could be detected by visual inspection [42]. Similar hypoplasia in the brain stem has also been reported [35].

While postmortem findings are highly consistent regarding cerebellar and brain stem abnormality, a number of MRI studies have failed to find cerebellar hypoplasia in autistic subjects, e.g., [43–45]. Some have reported larger than normal overall cerebellar volume in autism [46, 47], but these effects are 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). So, power is a huge issue. Most samples are quite 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 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 [48, 46]). It is generally the case that studies finding no difference in cerebellar vermal measures have studied autism samples with normal or above normal verbal IQ.

Reduced parietal volume in adults [49] has been reported. Consistent with parietal volume loss are reports of reduced thickness of the posterior corpus callosum [50–52, 39]. There are reports of abnormal frontal gyrification patterns [53] and sulcal shifting in frontal and temporal cortex [54]. MRI studies have also found the following in autistic patients: reduced amygdala or hippocampal volume [55, 56, 36, 57]; enlarged amygdala or hippocampal volume [58, 59]; and reduced cross-sectional area of the dentate gyrus [60]. Some of the variability in these findings may be age-related with young children showing enlarged limbic regions [59, 47] but adolescents–adults showing no difference [61, 62, 39] or smaller limbic regions [55, 57].

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) [47] and in children younger than 12 [63]. Cortical volume was enlarged in autism in young (ages 2–3) but not in older children [64, 34]. Increased total brain volume (total gray and white matter only) has been reported in adults with autism [65] as has increased intracranial volume (total gray and white matter and CSF) [66, 67]. Enlarged or normal head circumference has been reported in both children and adults [63, 68, 69], for review, see [6, 23]. However, such findings are not consistent, and decreased gray matter overall has also been reported in children (ages 7–11) [56], as has normal total brain area or volume in ASD adults [55, 41, 70, 71]. For an excellent review of brain size studies, see [72]. 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 section "Postmortem Studies").

Some of the most interesting and promising neuroanatomic findings are those that suggest developmental progression of autism that may guide improved understanding of the origins and potential intervention. The general finding is that of early brain overgrowth followed by slowed or no growth. Consider the following:

- Young children show enlarged limbic regions [59, 47] but adolescents and adults show no difference [61, 62, 39] or smaller limbic regions [55, 57].
- Brain overgrowth in cerebrum (particularly in frontal regions) during the first five post-natal years is followed by abnormally slowed brain growth [29, 64, 34, 73].
- Brain size (indexed by head circumference) is normal or slightly small at birth, undergoes abnormal growth and enlargement during the first 5 years, is stable, and generally found to be normal in adults (for review, see [23]).

Carper and colleagues reported enlarged frontal, parietal, and temporal cortices in young (ages 2–5) but not older children with autism with an association between the size of the posterior cerebellar vermis and abnormal enlargement of frontal lobes [29, 64]. In this study, children with the greatest cerebellar hypoplasia had the greatest overgrowth of frontal cortex. This suggests growth dysregulation in autism in which brain overgrowth (particularly in frontal regions) during the first five post-natal years is followed by abnormally slowed brain growth [29, 64, 34, 73].

White Matter Connectivity

Important for understanding function in autism is that abnormal growth patterns suggest an associated abnormal connectivity during critical periods of development [74–76]. There is some neuroanatomic evidence from white matter studies to support this model. For example, Barnea-Goraly [77] reported reduced fractional anisotropy (FA) in regions adjacent to ventromedial prefrontal cortex, the anterior cingulate, temporal–parietal junctions, superior temporal sulcus, temporal lobes "approaching" the amygdala, occipito-temporal tracts, and in the genu and body of the corpus callosum. The authors suggest that these findings are

consistent with compromised white matter integrity in brain systems associated with social cognition. Lee and colleagues also found evidence on diffusion tensor imaging of white matter abnormality in temporal lobe regions that might be expected to affect language and social communication [78].

Nordahl and colleagues have 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 [7]. Recent work by Lewis and colleagues has 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 [79–81], Lewis and colleagues hypothesized that the early brain overgrowth in autism would result in reduced long-range connectivity [82–84]. 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 [84]. Their results provide theoretical support for a tie between 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 [85]. New studies by Lewis and colleagues have subsequently provided the first direct evidence of structural reduction in long-range connectivity in adults with autism. These studies used DTI with tractography in adults with autism to demonstrate reduced long-range frontal lobe interhemispheric connections via the anterior corpus callosum [86, 87]. The anterior of the callosum is a particular focus of development during the period of maximal brain overgrowth in autism, and so this finding is consistent with the hypothesized impact of the early brain overgrowth on connectivity.

In summary, developmental growth patterns reported from imaging [64, 34] and postmortem studies [21] are consistent with an ongoing pathologic process [5] that involves early overgrowth followed by slowed growth during maturation. These abnormal developmental patterns may result in abnormal white matter connectivity [74–76] and an accelerated loss of brain tissue with aging [5].

EEG Abnormalities and Seizures

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. Epileptiform abnormalities in individuals with ASD are most often multifocal, and there is considerable disagreement in the literature over the distribution of these abnormalities [88–90]. Studies with large sample sizes (more than 100 subjects) have reported epilepsy rates that range from 0 to 39% [89, 91–96]. Fombonne [97] compared data from 11 epidemiological surveys published between 1966 and 2001 that included information about rates of medical conditions associated with autism and found that the rate of epilepsy ranged from 0 to 26%, with 16.8% being the median rate. 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 [98], epilepsy can develop in autism anytime during childhood and adolescence (with some less common instances of onset in adulthood as well). Epilepsy in autism is more common in the severely impaired.

Unsurprisingly, there is a higher incidence of epileptiform EEG activity than of epilepsy itself in autism, although the reported rate of EEG abnormality is even more variable than that of epilepsy. The epilepsy studies cited above show a reported range of 10–60.8% of EEG abnormalities in non-epileptic ASD individuals. A new study by Chez et al. [99] found EEG abnormalities in 60.7% of 889 ASD patients. Samples in these studies could be either biased toward finding epileptiform EEG, as in studies where patients who were suspected of having seizures were more likely to have EEG recordings [100], or biased against finding epileptiform EEG, as in studies where children who had ever had a seizure were excluded [101]. Small [102] found that the observation of abnormal EEG activity in autistic children increased with repeated EEG, and others reported an increased chance of observing abnormal EEG during sleep recordings [103, 95]. For a detailed review of methodological issues, see

Kagan-Kushnir et al. [104]. In any case, there does appear to be a strong relationship between the presence of epileptiform activity in the EEG and epilepsy. Tuchman found that 59% of autistic children with epilepsy had epileptiform EEG abnormalities, while only 8% of those without epilepsy showed epileptiform EEG [95]. Hara [92] followed 130 autistic patients over a 10-year period and showed that EEG abnormalities were observable in 73% of epileptic cases, and all but two of those patients displayed abnormalities before developing seizures. In contrast, EEG abnormalities were observable in only 21% of the non-epileptic cases.

There has been some question about whether epilepsy or epileptiform EEG is associated with regressive autism. Approximately 30% of autistic children undergo a developmental regression by 24 months of age, losing previously acquired language and social skills [105, 95]. Kobayashi [106] reported that epilepsy was twice as prevalent in children that had regressed than in those that had not. Tuchman, however, found no relationship between epilepsy and language regression, although their data did suggest a link between epileptiform EEG activity in non-epileptic children and regression [95]. Using the potentially more sensitive MEG technique, Lewine found EEG abnormalities in the majority, 68%, of autistic children with a history of regression, but this number may be inflated as the authors note that all of the study participants had been referred because of unusual behavioral episodes that might be indicative of a seizure disorder [107]. Other studies have found no evidence for any association between regression and abnormal EEG [101, 99]. One study found that epileptiform EEG could be improved or normalized with antiepileptic medication, but the value of this is unclear as there have been no systematic clinical trials evaluating the effects on development of epilepsy, behavior, or cognition of autistic individuals following such treatments [99].

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 2 years of life and approximately 30% recognize symptoms before their child is 12 months old [108]. Concerns most commonly reported by parents are speech and language delays, abnormal social behavior, problems with attention, and disruption of sleep and eating [109]. In 25–30% of children, ASD manifests as a regression of communication and social skills after 15–24 months of apparently normal development [95, 110, 111]. There is reasonable evidence that ASD can be reliably diagnosed in the second year of life [112, 113] and some possibility that there are much earlier behavioral markers associated with ASD. A large prospective study of high-risk infants with ASD siblings found reliable markers in infants less than 12 months who were later diagnosed with ASD [114]. These behaviors included abnormalities in eye contact, visual attention, 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 2 [115]. A review of findings from studies of infants who are at high risk for ASD because they have a diagnosed sibling has provided some surprising information about early signs and symptoms of autism [116]. Prospective studies of infants who met the diagnosis of ASD by age 3 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 6 months of age, ASD infants showed abnormal motor development and unusual visual interests, but normal 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 [117–119]. The Council on Children with Disabilities has provided a screening tool for identification of children at risk for ASD [120]. 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).

Clinical and Research Criteria

Clinical criteria for the diagnosis of autism are based on the DSM-IV TR and ICD10 specifications [3, 121]. The three diagnostic domains in which symptoms are evaluated are social relationships, language and symbolic capacity, and repetitive behaviors. Criteria for a diagnosis of autism require impaired behavior in each of these domains. While the clinical diagnosis is most commonly based on the DSM criteria and expert judgment, there are a number of assessment instruments used to enhance the specification of clinical features in research and treatment settings. The current gold standard for diagnostic instruments are the Autism Diagnostic Interview, Revised (ADI-R), and the Autism Diagnostic Observation Schedule (ADOS) [122–124]. These instruments score impairment in a number of 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. A number of additional assessments are commonly used to evaluate clinical features of autism. For example, the *Scales of Independent Behavior – Revised (SIB-R)* [125] assess adaptive functioning. The Social Responsiveness Scales (SRS) [126] provide measures of social function and social communication including social awareness, social information processing, 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 [127]. For a brief review of additional assessment and screening instruments, see [128, 129].

Autism is associated with other psychiatric and medical conditions including in a small percentage, fragile X (1%) and tuberous sclerosis (0.4–2.8%) [130]. The diagnosis of other psychiatric conditions in ASD is controversial, but there seems to be an elevated rate of depression and anxiety disorders in Asperger patients while the there is no elevation in the rate of schizophrenia (for a review, see Volkmar et al. [131]).

Increased Prevalence of Autism: It Is Not the Vaccine

Is the prevalence of autism increasing? Considerable media attention has been devoted to a potential increase in the prevalence of autism and 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 [97]. 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 [3] and ICD-10 [121] 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 three times larger – 7.6 per 10,000 [132].

In spite of 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 have been the measles–mumps–rubella (MMR) vaccine and a mercury-based preservative (thimerosal) used in many other childhood vaccines [133–135]. Numerous studies have found no evidence for the association of these vaccines and the increased rate of autism in this country or worldwide (for review, see [136]). 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., [137–139]). There is also no biological evidence to support these allegations (for reviews, see [140, 141]). An unfortunate result of these unsupported speculations can be seen in recent outbreaks of measles in unvaccinated children in Europe, Japan, and the United States [142]. Morton Gernsbacher and her colleagues have provided a thoughtful analysis of some of the reasons for this "disconnection" between scientific evidence and popular perception [143].

Is there a true increase in the prevalence of autism? Probably not. The diagnosis has become increasingly inclusive, and the signs and symptoms are more commonly recognized by parents and physicians. Do autism and related autism spectrum disorders pose an important public health problem? Absolutely. As many as 1 in 150 children have some form of pervasive developmental disorder that affects their ability to learn and to function in a social environment. Early diagnosis and treatment is crucial.

Neurocognitive Mechanisms

Major Cognitive Models

Several major current models attempt to explain neuropsychological function in autism (for reviews, see [144–149]). 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. This model was first tested by Baron-Cohen [150] and has subsequently been tested many times. The results are robust and many (though not all) children with autism consistently show TOM deficits. These deficits are, however, not necessarily specific to autism and are found in other disorders as well [151]. *Executive function deficits* [152, 153] are impairments typically associated with frontal lobe function. These deficits include planning, set shifting, perseveration, working memory, and control of action and inhibition. Children and adults with autism have been shown to be impaired on a variety of executive function tasks [148]. The *Weak Central Coherence* model is based on the bias in autism to process details that result in enhancement of segments of information at the expense of context (reviewed in section "Sensation/Perception"). This model suggests a weakened ability to integrate or bind details into a coherent whole that affects many domains of behavior in autism [154–156].

Although all of the major cognitive models of autism have been associated with underlying neural systems, they are largely descriptive and none explains all of the clinical symptoms. All are important, however, as frameworks within which to advance research and develop treatment interventions. Some newer explanatory models incorporate development and underlying neural mechanisms. Brock has proposed a temporal binding deficit which postulates that many features of autism, such as superiority in processing of detail (local processing) and disadvantage in global processing necessitating integration of information either over space (visuo-spatial perception) or context (integration of words into meaningful sentences), can be explained by a failure of temporal integration, or binding, between cortical areas [157]. A related and promising model of abnormal functional connectivity based on developmental neuroanatomic findings is considered by some to be a logical extension of the "weak central coherence" model [146, 75, 158] and may provide an explanatory base for many of the neuropsychological and social deficits in autism.

Abnormal brain overgrowth in early development (discussed in the previous section) may result in abnormal white matter under- and over-connectivity [74, 75, 84, 76]. Excessive short-distance and reduced long-distance pathways that would result in a failure to integrate processing across brain systems could predict many of the neuropsychological processing abnormalities to be discussed below. There is growing evidence in support of such abnormal functional connectivity in autism. The first of these studies was conducted by Horwitz and colleagues more than two decades ago [159]. This early positron emission tomography (PET) study demonstrated that in subjects 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.

Modern FMRI studies have also begun to provide evidence for reduced long-distance connectivity in autism. Just and colleagues found decreased functional connectivity during a language task among brain region pairs including mid-range (occipito-temporal, occipito-parietal) and long-distance (e.g., occipito-frontal) connections [160]. FMRI studies of working memory, spatial attention, and selective attention suggest dependence upon short-distance local connections (e.g., processing of visual features) rather than integration of attention and verbal networks during these tasks [161–164]. In a study of executive function, Just et al. found reduced synchrony between frontal and parietal regions suggesting a cortical under-connectivity that would result in deficits in neural and cognitive integration [165].

A recent study of resting state EEG in autism also demonstrated patterns that suggest increased short-range and reduced long-range functional connectivity [166]. This study, the first to use reference-independent dense-array EEG coherence to examine functional connectivity in autism, is of particular importance as EEG coherence directly reflects synchrony in oscillations of cortical neural cell assemblies (i.e., a direct functional connection in real time).

The findings suggest weak functional connections between frontal cortex and other cortices which is consistent with longrange *under-connectivity* [160]. Theta band coherence in this study was consistent with short-range *over-connectivity*, (particularly in left hemisphere frontal and temporal cortex) which is also consistent with increased short-range fibers [167] and may reflect a local processing bias in autism [75].

Cognitive 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 problems with orienting have been identified as potential markers in early diagnosis [114–116]. Although individuals with autism have performed in the normal range on standardized tests that measure some static aspects of attention [168, 169], experimental tasks requiring dynamic manipulation of attention have typically found attentional dysfunction manifested in numerous ways, review: [170]. Focused or sustained attention has generally been found to be intact in autism (except that it may be "over-focused"), but more complex attentional operations including orienting or shifting, divided and shared or joint attention have been found to be impaired (for reviews, see [170–172]). 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 [173] 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.

Courchesne and colleagues found that adolescents with autism were slow to shift attention between auditory and visual information [174]. Akshoomoff examined these same attentional skills in children with acquired cerebellar damage and found similar results [175]. 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 2 s to re-orient attention. The involvement of the cerebellum in shifting attention in particular and in cognition in general remains controversial [176–178]. However, a functional imaging study using a task patterned after the Courchesne et al. task reported cerebellar activation associated with non-spatial cross-modal attention shifts [179]. Allen et al. found that distinct regions of the cerebellum were associated with motor response (anterior cerebellum ipsilateral to responding hand) and attention shifts (lateral cerebellar hemispheres) [180]. Slowed manipulation of attentional resources would particularly interfere with dynamic social interactions. Interestingly, a recent study has demonstrated that slowing facial movement and vocalizations significantly improved emotional expression recognition and imitation in autistic children [181]. 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 may be a prerequisite for language acquisition and a skill that is impaired in autism [182–184]. Dawson has demonstrated that children with autism have difficulty orienting to social stimulation and that this deficit is correlated with deficits in shared attention [185].

Spatial attention is particularly affected in autism. Adults and children with autism have been reported to have difficulty disengaging attention from a spatial focus and shifting to a new location [186–188]; slowed shifting of spatial attention [189–191]; difficulty adjusting an attentional lens [192, 193]; and abnormal distributions of visual attention reflecting a narrow "spotlight-like" spatial focus [194]. Recently, Keehn and colleagues [195] utilized the Attention Network Test [196, 197] to investigate the efficiency of alerting, orienting, and executive control networks in children and adolescents with ASD. The authors report that the ASD group evidenced reduced efficiency of the orienting network compared to the TD group.

Landry and Bryson found severe impairment in disengagement of attention from a spatial focus in the majority of children with autism spectrum disorder tested [198]. This study employed a comparison group of children with Down syndrome in whom attentional disengagement was normal. The authors have proposed that such visual attention problems represent a developmental spatial neglect syndrome in autism [199]. Evidence for neuroanatomic abnormalities of parietal cortex in at least a subset of individuals with autism suggests a possible anatomic substrate for spatial neglect [49].

A study that used electrophysiological markers of visual attention distribution illustrates the importance of the underlying anatomic abnormalities to understanding patterns of behavior in autism. A group of adults with autism who had abnormal widening of parietal sulci showed abnormally focused (spotlight) attention, while those with no parietal abnormality showed abnormally broad attentional focus [194]. The group with excessively focused attention showed faster behavioral response and earlier and larger event-related potential (ERP) components associated with visual stimuli at their attended focus. This spotlight attention is consistent with earlier clinical observations of stimulus over-selectivity and over-focused attention [200, 201]. While this sort of spotlight focus may produce superior performance within the attentional spotlight, there is a cost. Gating of surrounding visual information prohibits rapid response to information outside the attentional spotlight. In view of recent models of over- and under-connectivity, this study may provide an example of neural enhancement that results from a local processing bias. These results are also interesting in the context of a recent study that found an association between behavioral measures sensory over-reactivity and over-focused attention in children with autism [172].

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 [202]. 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 (see Fig. 10.1).

Neuroanatomic studies have identified developmental structural abnormalities in both the cerebellum and frontal cortex [24, 29, 33, 73]. An FMRI study of spatial attention in autism has implicated both parietal and cerebellar dysfunction [162]. Haist et al. found abnormal activation in both superior and inferior parietal regions during spatial attention shifts in adults with autism. Reduced activation in dorsolateral prefrontal cortex and the posterior cerebellar vermis in the

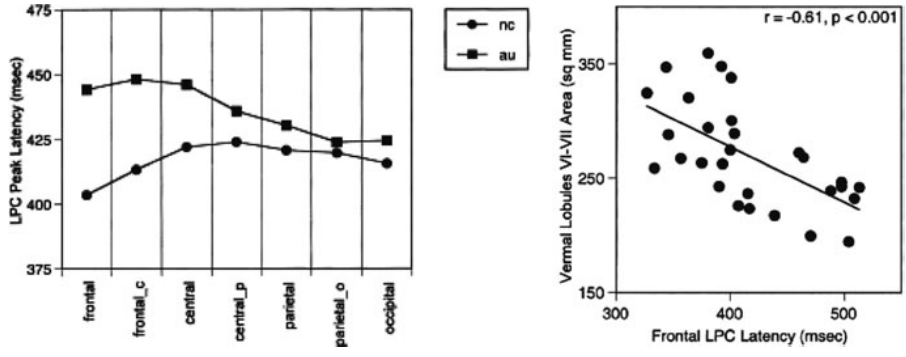

Fig. 10.1 The plot on the left shows the distribution of a late cognitive ERP component that indexes spatial attention orienting. The attention orienting brain response is significantly delayed in ASD subjects over frontal cortex, which is consistent with slowed orienting of visual–spatial attention. The plot on the *right* shows a significant correlation in normal control subjects during the same task for the same frontal attention orienting ERP component as in the plot on the *left*. A greater latency delay over frontal cortex is associated with smaller posterior cerebellar vermal lobules (VI–VII). These data combined with previous data showing similarly disrupted responses in patients with cerebellar lesions and significant correlations in ASD subjects with greater spatial attention orienting delay associated with smaller posterior vermal lobules (VI–VII) [191] suggest disruption in ASD in a fronto-cerebellar network for control of visual–spatial attention. From Fig. 3 (*left*) and Fig. 5 (*right*), Townsend et al. [202]

autism subjects suggested a dysfunctional cerebello-frontal attention system. An FMRI study of visual–spatial processing in autism also found evidence for dysfunction in fronto-parietal networks [203]. 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 reduced long-distance connectivity.

Sensation/Perception

Abnormal responses to sensory stimuli are a commonly reported feature of autism, and as such they form a component of the diagnosis on a number of standardized assessments. For example, the evaluation of sensory responses comprises 3 out of 15 items on the Childhood Autism Rating Scale [127]. Abnormalities in sensory responses are evaluated in some detail by the Diagnostic Interview of Communication and Social Behavior (DISCO) [204, 205] and the Sensory Profile (SP) [206]. 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 [207]. 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 observers documenting greater proportions of sensory-seeking or sensory defensiveness behaviors in autistic individuals than in either normal or other clinical controls [208–211]. 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 do typically developing controls [212, 210]. There is some indication that sensory abnormalities abate with age [208, 213], 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 [210].

Despite the seemingly indisputable association of sensory processing abnormalities with autism, the basic mechanisms underlying these sensory sensitivities are not at all clear. Rogers and Ozonoff [214] 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 the majority of sensory-perception studies have investigated auditory and visual processing (reviewed below), some research on the tactile modality suggests that there are multiple mechanisms to consider regarding somatosensory response in autism. Both O'Riordan et al. [215] and Cascio et al. [216] 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 [217] 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. [218] 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.

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 [219] (see Fig. 10.2).

ASD subjects have demonstrated superior processing of detail on block design sub-tests from the WISC [220]; on detection of embedded figures [221, 222]; on visual search for simple or conjoined features [223–225]; and on reproduction of impossible figures [226, 227]. In processing higher order (or integrated) information, ASD subjects have demonstrated impaired use of context in orientation discrimination [228] and in visual illusion [156] (although note that a subsequent study [229] 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 [230, 215], 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 brain stem by measuring the brain stem auditory-evoked potential (BAEP) [231–237], to examine subcortical sensory gating by measuring pre-pulse inhibition as indexed by the P50 wave [238–240], and to assess processing in auditory cortical areas by measuring early electroencephalographic or magnetoencephalographic potentials [241–243]. Results in each of these areas have been contradictory, with inconsistent findings possibly stemming from differences in the presence of mental retardation in the various autistic samples, differences in study control samples, 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 of 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 [219]. They caution however that the evidence for reduced global processing is less convincing. A review of auditory perceptual studies concluded that the variability in results could be explained by the complexity of the material and the tasks [244]. 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

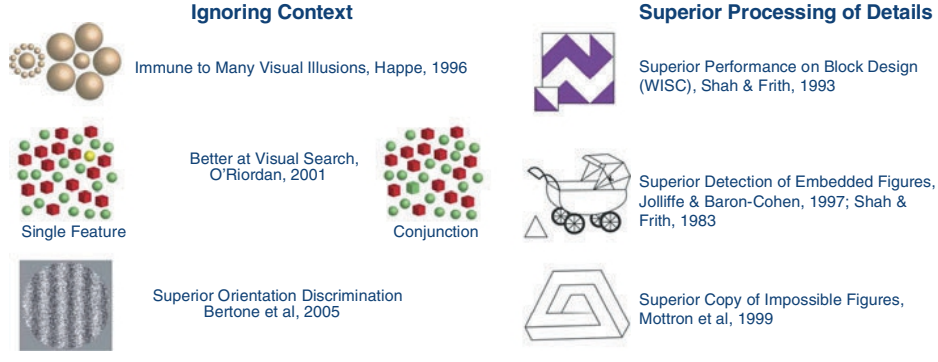

Fig. 10.2 Figures show examples of tasks in which ASD subjects showed superior processing of detail (local processing bias) and superior performance as a result of suppressing or ignoring context. From Fig. 2 of Dakin and Frith [219]

by over-dependence 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 [245, 164]. 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., [146].

Language

Language impairment is a defining feature of autism. Language profiles are considered increasingly relevant for differentiation of sub-phenotypes and understanding the neurobiological bases of this disorder. Lack of delay in language acquisition is the major defining feature that differentiates Asperger's syndrome from autism. The level of language impairment correlates with severity of autistic symptoms, especially when combined with higher level, non-verbal abilities [246, 247]. 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 recent review of language studies in autism [248] 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 pre-school 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 [249].

Several behavioral studies found relatively normal single-word semantic processing in children and adolescents in autism, when stimuli were presented in the visual modality [250–252]. However, higher level semantic processing may not be intact. Behaviorally and with ERPs it has been shown that children with autism have difficulty integrating semantic information, for example, using semantic context in stimulus pairs and sentences [253–258]. In an ERP study, Dunn et al. [253, 254] tested the hypothesis that compared to typically developing peers, language processing in high-functioning verbal children with autism is less influenced by semantic context. They found that 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 [259] have suggested that auditory processing might be a key factor in these deficits. The few studies that have used event-related potentials to examine auditory phoneme discrimination in autism [241, 260, 261] have 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 [262].

An FMRI study done by Just et al. [160] 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 over-reliance on "local," word-level, processing during language comprehension (hyper-activation in Wernicke's area) with diminished semantic and syntactic integration abilities (hypo-activation in Broca's area). Further, this study found decreased functional connectivity among all brain region pairs that yielded significant connectivity measures, including mid-range (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 conclude 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 (see Fig. 10.3) [165].

An earlier positron emission tomography (PET) study on neural organization of language in autism [263] found reversed hemispheric dominance during verbal auditory stimulation; a trend toward reduced activation of auditory cortex during non-verbal acoustic stimulation; and reduced cerebellar activation during non-verbal auditory perception and expressive language. These results are compatible with the downstream effects of cerebellar abnormality on perceptual and language processing in autism and also 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 (for review, see [264–271]).

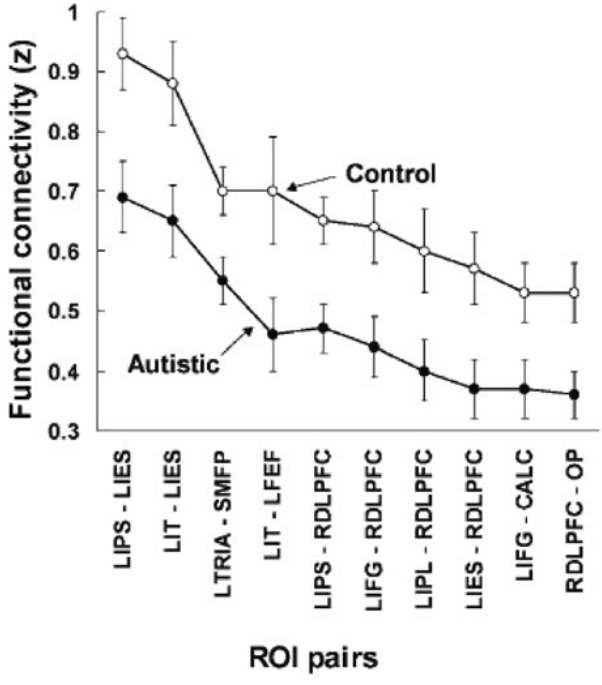

Fig. 10.3 The plot shows similar patterns of functional connectivity from FMRI BOLD activations during sentence comprehension. Mid- and long-range connectivity is reduced in ASD subjects for these regions representing language processing networks. However, the pattern of results suggests quantitative but not qualitative differences. L, left; R, right; CALC, calcarine fissure; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IES, inferior extrastriate; IFG, inferior frontal gyrus; IPL, intraparietal sulcus; IT, inferior temporal; TRIA, triangularis; OP, occipital pole; SMFP, superior medial frontal paracingulate. From Fig. 3 of Just et al. [160]

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 [272, 157, 273]. 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 multi-level integrative mechanisms. These include audiovisual and motor integration at the sensory and phonetic levels of processing during formation of native language-specific phonetic representations [274], since 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 [275]. During language processing, an online integration of semantic word or intuitive representations of meaning must be accomplished [276]. In autism, these many processes might be perturbed by insufficient integration among the neural processors that serve different functions.

Social/Emotional

Social dysfunction in autism is a critical diagnostic feature. Difficulties with social function are among the most troublesome of behavioral symptoms and are

among those problem behaviors most frequently targeted by clinical interventions. The majority of current studies have focused on eye gaze and face processing. 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 (for review, see [277]). 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 [278–280]. However, other studies have found no difference in viewing patterns [281–283]. 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 [284]. 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 [285]. As in previous studies, the autism subjects spent approximately equal time looking at each of the three major facial features (left eye, right eye, and mouth), while control subjects spent significantly more time looking at the two eyes (see Fig. 10.4). 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 [286]. 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 [287].

Additional evidence that abnormal face processing patterns in autism may not reflect gaze avoidance comes from a recent study by Rutherford and Towns [281] 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 [288].

The gaze patterns of people with autism appear to change when dynamic images are used. Klin and colleagues [289, 290] 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.

The other major thrust of social research in autism is functional imaging studies that examine activation in brain systems associated with face processing. In

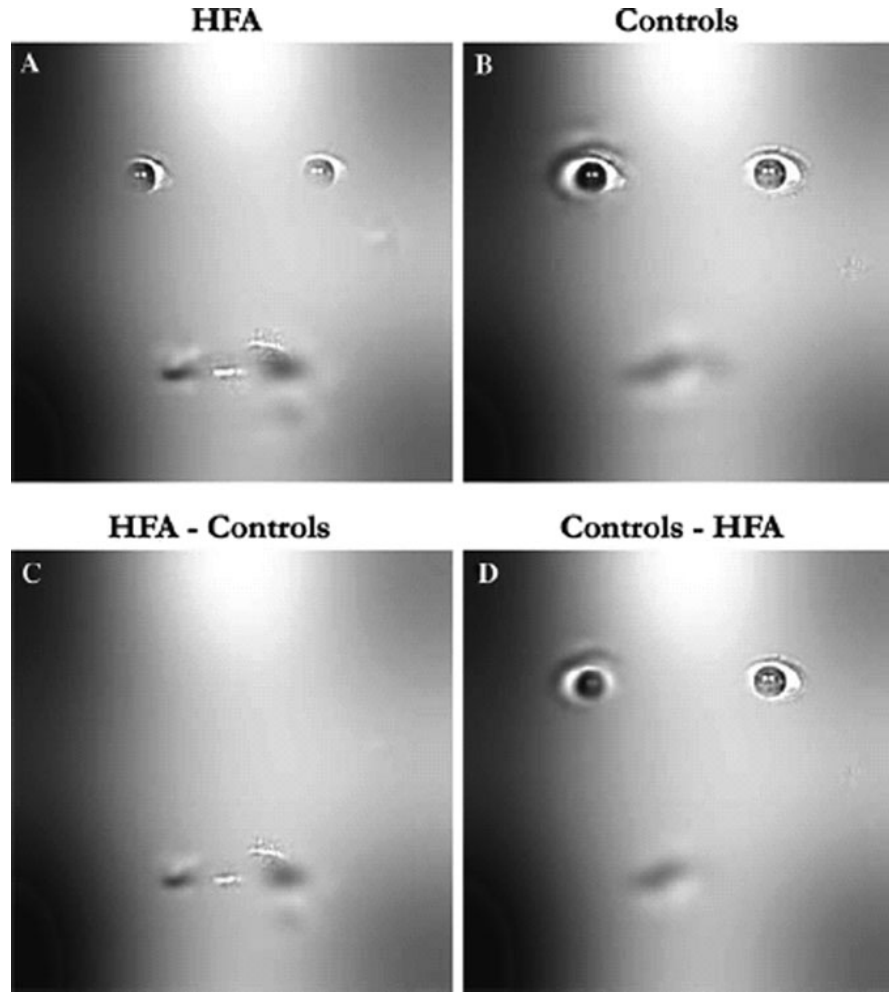

Fig. 10.4 *Top* figures (**a** and **b**) show that high-functioning autistic subjects process each of the major facial features equally, while control subjects spend significantly more time processing the eyes. *Bottom* figures (**c** and **d**) show subtracted images that highlight processing differences between HFA and controls. From Fig. 1 of Spezio et al. [285]

typical function these networks include the fusiform gyrus, the superior temporal sulcus, the amygdala, and prefrontal cortex [291, 287]. 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 [292]. A flood of subsequent FMRI studies reported various abnormalities but particularly reduced activation of the fusiform face area and the amygdala [146, 286, 291, 167, 287]. 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 [278]. 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 [293]. 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 non-vocal sounds, but no preferential activation of this region in the majority of autism subjects [294]. The authors conclude that this may reflect an attentional bias toward non-vocal sounds and that these findings, like those from face processing studies, may

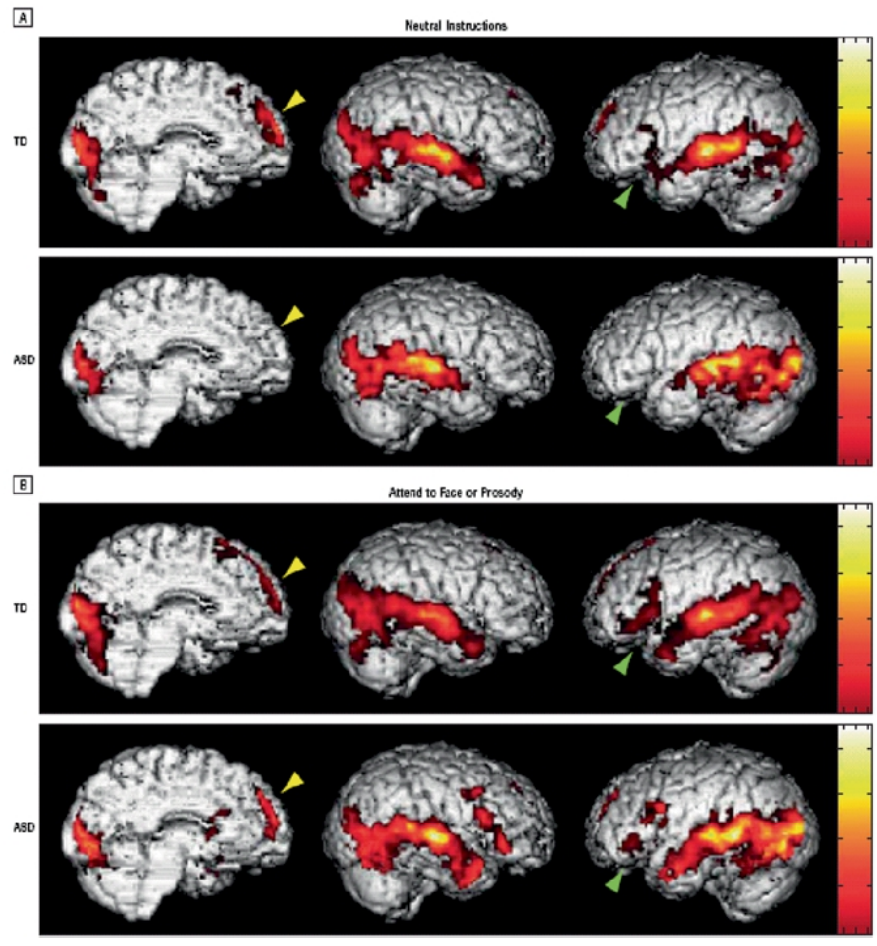

Fig. 10.5 The *top* figure shows lack of frontal activation in ASD during face and prosody processing. *Bottom* figure shows normal frontal activation in ASD during the same task when attention was explicitly directed to the face or voice. *Arrows* in the left column mark medial prefrontal cortex; *arrows* in the right column mark left inferior frontal gyrus. From Fig. 2 of Wang et al. [295]

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 [78], and in reduced functional connectivity among temporal and other cortical and subcortical regions [160, 166].

Interestingly, functional abnormalities observed in both face and voice processing can be normalized by attentional manipulation as can be seen in a recent FMRI study done by Wang and colleagues [295]. In this study, children with autism and typically developing controls viewed cartoon scenarios 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 (see Fig. 10.5). These findings suggest that abnormalities observed in social brain networks may reflect a processing bias that favors non-social 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 recent reviews summarize the most common behavioral and pharmacologic treatments [296–299]. The American Academy of Pediatrics provides comprehensive guidelines for both medical and nonmedical management of children with ASD [119].

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: interventions targeting communication and language development, interventions targeting social competence, and interventions targeting unwanted behaviors [297]. The majority of the treatment methods described below can be effectively applied to targeted behavior in any or all of these categories.

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 [300–302], was the first application of ABA methods for children with ASD. DTT is a rather 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 reinforcement for an appropriate response. The entire "trial" is repeated until the child has mastered the skill.

Other interventions such as pivotal response training (PRT) [303, 304] and incidental teaching [305–307] rely on behavioral techniques and discrete teaching episodes, but attempt to use a more naturalistic approach. In these more naturalistic 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) [308, 309] 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, and 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.

The Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH) [310, 311] 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 in order 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) [312]. This approach emphasizes play and child-centered interactions in the hopes that by fostering positive affect during interactions, the child will learn that communication with others is satisfying and enjoyable. Floortime [313] is a popular offshoot of this technique.

A number of 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 [314]. 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 [315, 316]. 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 [317].

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 [318]. General categories of symptoms and their associated pharmacological interventions are as follows: ADHD-like symptoms such as hyperactivity, inattention, or impulsivity can be treated with psychostimulants, atomoxetine (a selective norepinephrine reuptake inhibitor, SNRI), antidepressants, alpha-2 adrenergic agonists, or Alzheimer's disease therapeutics [319]; aggression, irritability, and self-injurious behaviors can be treated with typical and atypical antipsychotics, antiepileptics, or beta-blockers (see [320, 321]); and stereotypies or repetitive behaviors can be treated with selective serotonin reuptake inhibitors (SSRIs) or clomipramine (for reviews, see [322, 323]).

Summary and Conclusion

Sixty-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 in autism and limited agreement about the nature of cognitive impairments and about which treatments are effective.

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 recent broader diagnostic criteria, the samples drawn for study are extremely heterogeneous. There is as yet no reliable method for creating sub-groups. Of the studies considered here (and many more that we were unable to include) few have sample sizes larger than 15–20 and sample sizes of fewer than 10 are not uncommon. With small heterogeneous samples and widely different methods and tasks, it is no surprise that findings are inconsistent. In spite of this, however, important patterns have begun to emerge.

A few findings have been replicated often enough to be considered robust. Among those are neuroanatomic abnormalities in the cerebellum and brain stem 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 disengagement of visual attention ("sticky" attention) has been replicated in a number of different ways by several independent groups and has reasonable consensus as well. A number of newer studies reviewed above have demonstrated that sometimes simple directions that alter attentional bias can normalize both the 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 (and perhaps excessive short-distance) white matter connectivity that disrupts integrated processing across brain systems. Such under- and over-connectivity could predict many of the neuropsychological and behavioral abnormalities discussed above and explain neural underpinnings of dysfunction in attentional, language, and social brain networks. 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 2 years of age, and so treatment intervention can begin very early when it has the potential to provide maximal amelioration of clinical symptoms.

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Chapter 11

Genetic Syndromes Associated with Intellectual Disabilities

Leonard Abbeduto and Andrea McDuffie

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 and an onset before the age of 18 years [1]. In 1993, the Centers for Disease Control (CDC) estimated that 1.5 million people in the United States had an intellectual disability, a rate of 7.6 per 1,000. More recent research conducted by the CDC based on the ascertainment of school-age children has yielded a prevalence rate of 12 in 1,000 (http://www.cdc.gov/ncbddd/dd/mr3.htm). In the not too distant past, the causes of most cases of intellectual disability were unknown, especially for cases of more mild impairment [2]. Recent advances in genetics, especially molecular genetics, however, have led to the identification of more than 1,000 conditions associated with intellectual disability. Many of these conditions are quite rare, such as 5p- syndrome, or cri-du-chat, which occurs only once per 50,000 births [3]. Nevertheless, genetic abnormalities are thought to account collectively for one-third of all cases of intellectual disability [4]. 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 [3]. 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 syndromes associated with intellectual disability in a single chapter. Moreover, there is little empirically validated information about the typical neuropsychological profile for many syndromes. Consequently, we have focused here on three syndromes: Down syndrome, fragile X syndrome, and Williams syndrome. We have chosen these syndromes because they occur relatively frequently, have been well-studied, and contrast in interesting ways as regards 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 of the phenotype, all of which have relevance to the neuropsychological assessment of affected individuals. In describing these dimensions of the phenotypes, we pay particular 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

L. Abbeduto (✉)
Department of Educational Psychology, Waisman Center, University of Wisconsin, Madison, WI 53705, USA
e-mail: abbeduto@waisman.wisc.edu

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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, Down syndrome (DS) is the leading genetic cause of intellectual disability and has a prevalence rate of 1 in approximately 730 live births [6]. In 1959, Jerome Lejeune found that Down syndrome is caused by an extra whole copy or a segment of chromosome 21 [7], giving rise to the syndrome name of trisomy 21. Chromosome 21 is one of five acrocentric human chromosomes in which the location of the centromere produces chromosome arms of different lengths. Most individuals with DS have a full trisomy, that is, three copies of the 225 genes [8] that are encoded on the long arm (designated q) of chromosome 21. However, 1–2% of affected individuals have a partial trisomy in which only a subset of chromosome 21 genes is triplicated. Understanding the etiology and developmental course of DS presents a formidable challenge to scientists. Unlike fragile X, which involves only one gene, and William syndrome, which involves just a 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 may interact to influence development of the brain and nervous system at different points in time [9, 10].

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 is replicated in virtually every cell of the body [11]. Errors in meiotic cell division leading to DS are overwhelmingly of maternal origin [12] and advanced maternal age is the most important risk factor for DS resulting from nondisjunction [13]. The likelihood of having a child with DS rises from less than 1 in 1,000 at maternal ages under 30 to 1 in 12 by age 40. Sherman et al. suggest that maternal age-related nondisjunction might occur because of the accumulation of toxic environmental effects, degradation of meiotic machinery over time, and/or suboptimal hormonal signaling [14].

An additional 2% of cases of DS are caused when nondisjunction of chromosome 21 takes place during one of the cell divisions immediately following fertilization. In this condition, termed mosaicism, there is a mixture of cells, with 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 [15]. Finally, the remaining 2% of cases are caused by translocation, in which part of chromosome 21 breaks off during cell division and attaches to another chromosome, usually chromosome 14. Although the total number of chromosomes in the cells of an individual with a translocation is 46, extra genetic material is present, resulting in the characteristic features of DS.

As is the case for all genetic syndromes, DS produces both structural and functional abnormalities in multiple organ systems, with a characteristic phenotype emerging across the life span of the affected individual [12]. The phenotype of DS includes cognitive impairment, a characteristic facial appearance, and muscle hypotonia [14]. Other characteristics that are observed with considerable frequency in DS are short stature, congenital heart disease, childhood onset leukemia, gastrointestinal abnormalities, neuropathology leading to dementia, hearing loss, and vision problems. In all, 45 birth defects have been identified as significantly more common in DS relative to the general population, although there is wide individual variability in the number and severity of symptoms displayed in any one individual [16]. Most individuals with DS display IQs between 35 and 70 [17]. The intellectual disability in DS is thought to be associated with specific brain regions and impaired performance on specific cognitive tasks [9, 18].

A critical goal of ongoing DS research is to determine how three copies of all or some of the genes found on chromosome 21 can account for the range of characteristics observed in individuals with DS. That is, which genes on chromosome 21 are relevant to specific features of the DS phenotype and how do we account for individual differences in development? [19] 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, in which only some of the genes on chromosome 21 are triplicated. DNA analyses

of the smallest regions of overlap across individuals with partial trisomies and consideration of genotype–phenotype associations for these individuals initially allowed scientists to identify a relatively small region on the distal end of the long arm of chromosome 21 that was associated with the expression of some of the specific features of DS, including facial dysmorphology and cognitive impairment [20, 21]. This region, which comprises between 5 and 10% of the total length of 21q, is called the Down syndrome critical region (DSCR). The *critical region model* proposes that most of the characteristic features of the DS phenotype are the product of one or a few genes located within this small region [22].

In humans, development cannot be studied at the level necessary to understand the complex processes that are disrupted by trisomy [23]. However, mouse models currently are providing an important tool for scientists as they attempt to isolate specific genes and signaling pathways responsible for the phenotypic characteristics of DS [24]. 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 [25–27]. Trisomic and transgenic mouse models have been developed to investigate the molecular genetics of DS. Trisomic mouse models have the advantage of a behavioral phenotype that corresponds closely to that observed in humans with DS. 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. Transgenic mice, in contrast, overexpress only one or a few candidate genes, allowing a direct genotype–phenotype correlation, although not consideration of interactions between larger groups of genes [27].

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 in the human DSCR [22]. 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 cross breeding with Ms1Rhr mice in which the 33 DSCR genes are missing. This manipulation did not eliminate the DS craniofacial phenotype in Ts65Dn/Ms1Rhr offspring. Based on these results, it is now believed that the presence of the genes in the DSCR are neither sufficient nor necessary to generate the characteristic facial appearance of DS [28] 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 non-specific disturbance of gene regulation and expression. This global disruption of gene expression in developmental pathways alters the normal balance of development and determines most of the characteristics of DS [29, 30]. This model is supported by the finding of individual variations in the population of individuals with DS and the observation of characteristics of DS in other syndromes and in the population at large.

Finally, 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 causes a 1.5-fold increase in the expression of gene products, thus leading to the DS phenotype [31, 32]. The secondary effects of a gene dosage imbalance may cause the subsequent over- or underexpression of other genes, and this influence may be highly variable in different cell types, at different developmental stages [33, 34], and across individuals [35]. Recent studies have suggested that only a subset of genes show a significant difference in expression levels between trisomic and disomic individuals and this may provide one source of individual variability in the DS phenotype [34].

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 [36–38]. Auditory short-term memory is typically measured on tasks requiring repetition of digits or nonsense words and can be considered to index phonological memory (i.e., memory for speech sounds). Backward memory for verbal and

visual information is also impaired [39]. 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 (SB-IV) [40], falls behind the ability to analyze and reproduce spatial models, as measured with the Pattern Analysis subtest of the Stanford-Binet [41]. Thus, working memory for both auditory and visual information appears to be selectively impaired in DS.

Another characteristic contributing to 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 [42]. A recent study found that 81% of preschool-aged children with DS had abnormal hearing [43]. Conductive hearing loss in DS may be caused by otitis media – fluid in the middle ear – resulting from dysmorphology affecting the eustacian tube and/or immune deficiencies leading to increased respiratory illnesses [42]. Children with Down syndrome may be especially vulnerable to negative influences on the language learning process resulting from hearing loss [44].

Linguistic Dimensions of the Phenotype

Language may be the domain of development that is most impacted for individuals with DS [41, 45]. In general, language comprehension is less problematic than production, with most children with DS displaying levels of receptive language that are commensurate with their nonverbal cognitive status [46]. By adolescence, syntax comprehension lags behind, and vocabulary comprehension keeps pace with or exceeds, nonverbal mental age [47, 48]. 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, to some extent, on the measures used to assess these domains. When tested with a measure based on frequency of occurrence (such as the PPVT) [49], vocabulary comprehension appears in advance of mental age for adolescents with DS. When tested with a measure based on conceptual difficulty, such as the Vocabulary subtest of the Test for Auditory Comprehension of Language (TACL) [50], vocabulary comprehension is commensurate with nonverbal mental age estimates [51]. As adolescents with DS mature and accumulate additional real-life experiences, they continue to accumulate vocabulary knowledge providing that the underlying concepts are fairly concrete.

In contrast to vocabulary comprehension, syntax comprehension represents a domain of great challenge for individuals with DS. Chapman et al. sought to understand the nature and sources of variation in syntax comprehension [52]. They used hierarchical linear modeling to identify longitudinal predictors of syntax comprehension, across a 6-year period, in 31 participants with DS who were between 5 and 20 years of age at the onset of the study. Syntax comprehension, as measured by the TACL-R [53], was best predicted by three variables measured at the start of the study: auditory verbal short-term memory, visual short-term memory, and chronological age. Age at study start also predicted the change in slope for growth in comprehension. For a child of 7.5 years at study start, the change in comprehension growth rate was positive; for a child of 12.5 years, the slope was shallower, whereas the predicted growth rate actually became 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 different components of a sentence comprehension task requiring participants to act out intended sentence meanings by manipulating objects [54]. The two syntax comprehension subtests of the TACL-3 [55] were also used to provide a more traditional metric of sentence comprehension. The group with DS showed a larger discrepancy (relative to syntax comprehension-matched typically developing participants) between visual cognition and auditory memory (as measured by number recall and nonword repetition), 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 [56].

Abbeduto and colleagues [57] examined associations between syntax comprehension, vocabulary comprehension, and nonverbal MA in 25 adolescents and young adults with DS, matched groupwise for nonverbal MA with 19 adolescents and young adults with fragile X syndrome (FXS), and 24 typically developing 3- to 6-year olds. Participants with DS and FXS were also matched groupwise for IQ and CA. Syntax and vocabulary comprehension were measured using the TACL-R. On average, age-equivalent scores for overall comprehension were found to be significantly lower for participants with DS than for the MA-matched participants with FXS. In addition, participants with DS demonstrated an uneven profile of subtest scores, resulting from a significantly higher score for vocabulary relative to grammatical morphology and syntax comprehension. In comparison, MA-matched FXS and TD groups demonstrated a relatively 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 comprehension.

In the domain of language production, prelinguistic communicative gestures are less likely to be accompanied by vocalizations than in typically developing children [58] and delays are observed in nonverbal requesting behaviors [59]. Nonverbal requesting also is a concurrent correlate of goal-directed problem solving in toddlers with DS, relative to MA-matched typically developing children and CA- and MA-matched children with other developmental delays [60]. 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 [61].

The types of vocalization produced during early development in DS are similar to those of typically developing infants [62], but the transition from babbling to the appearance of first words is substantially delayed, varying from 8 to 45 months [63–66]. On average, both first words and multiword combinations emerge at the same mental ages as reported for typically developing children [66, 67], with early spoken vocabulary displaying a slower than typical rate of development [68].

By adolescence, expressive language in individuals with DS is characterized by deficits in syntax, vocabulary, and speech intelligibility [17]. Chapman et al. examined a variety of measures of language production in 47 children and adolescents with DS, ranging in age from 5 to 20 years [69]. Participants were matched groupwise for nonverbal mental age with 47 typically developing children, 2–6 years of age. Measures of production, including mean length of utterance (MLU), which is a gross measure of syntactic complexity, 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. For both groups, all three measures of language production were higher in narration than in conversation. However, participants with DS had poorer intelligibility in narration, whereas this pattern was not observed for the typically developing group. It is possible that individuals with DS may self-select more familiar words when speaking in a conversational context, whereas the vocabulary used in narration is determined, in large part, by the stimuli used to elicit the narrative sample (e.g., film, book, or pictures).

Chapman et al. examined predictors of language production, using the same participants as Chapman et al. [69, 70]. Measures of production included number of different word roots and MLU in morphemes (both derived from a narrative sample), as well as intelligibility. Hearing status, chronological age, and nonverbal cognition emerged as significant predictors of the number of different words, accounting for 8, 35, and 13% of the variance in narrative production, respectively, for participants with DS. Hearing status, chronological age, and nonverbal cognition were also significant predictors of MLU, accounting for 7, 35, and 24% of the variance, respectively. Finally, hearing status and chronological age accounted for 8 and 24% of the variance in predicting speech intelligibility, with comprehension failing to contribute significant additional variance to the regression model. Although these findings emphasize the importance of language comprehension for the prediction of expressive vocabulary and syntax, they also confirm the contribution

of hearing status to the ability of individuals with DS to produce utterances that are intelligible and syntactically complete.

An important developmental issue is whether language production, and language learning more generally, plateaus at the level of simple syntax for individuals with DS. Chapman and colleagues [52] investigated this issue by conducting 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. Results demonstrated that individuals with DS continued to make progress in expressive language, with average spontaneous 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 [71].

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 typically developing participants [72]. Thus, despite their deficits in expressive syntax, individuals with DS mentioned more of the content of the story depicted in the film than did typically developing children with the same MLU. As expected, MA-matched comparison children produced a greater number of different words in their narratives, 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 report findings similar to those of Boudreau and Chapman [72, 73]. 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 typically developing 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. Narrative assessment is thus a useful complement to standardized language tests and conversational language samples for this population.

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 [74].

Differences in brain function have also been documented in infants with DS [18]. Hill Karrer and colleagues, for example, used event-related potentials to study visual attention in a group of infants with DS [75]. Although there were no behavioral differences in measures of visual fixation and attention, event-related responses to an oddball paradigm (80% familiar, 20% rare) did distinguish the DS group from typical comparison infants in terms of the area of the Nc component as measured at the frontal midline recording site (Fz). The Nc component, a robust characteristic of the infant event-related potential, is a negative deflection occurring at 400–600 ms following stimulus onset. Nc is interpreted as an index of infant cognitive processing and may reflect the updating of a visual memory trace which is expected to decrease in amplitude with repeated exposure to a stimulus. During frequent trials, typical comparison infants demonstrated a rapid decrement in Nc area (i.e., the area measured under the ERP deflection for the Nc component) across early and middle blocks of trials with a plateau from middle to late trials. Infants with DS, in contrast, demonstrated little decrement in Nc area during early and middle trials and had significantly greater Nc area measures across all three blocks of trials. For the rare trials, typical infants demonstrated decreasing amplitude of the Nc component across all blocks of trials, whereas Nc amplitude actually increased from the initial to middle block of the trials for the DS infants and then decreased in amplitude from the middle to final stimulus block. Hill Karrer et al. interpret these findings as indicating that infants with DS may have less efficient memory

processes than typically developing infants, even in the absence of differences that can be detected with traditional behavioral tests of cognitive development.

The neurocognitive effects of DS become more extensive as childhood progresses and are prevalent by early adolescence [18, 41]. Learning impairments in DS are thought to be related to cognitive processes that rely on the hippocampus, prefrontal cortex, and cerebellum [9, 18]. The hippocampus, a large structure that lies between the thalamus and the cortex in the temporal lobe of the brain, is implicated in spatial cognition, flexible learning, and consolidation of long-term explicit (or declarative) memory [76].

It is likely that the hippocampus does not become fully functional until the age of 16–18 months [18]. Uecker et al. report a study in which 10 infants and children with DS, under the age of 30 months and who performed within normal limits on the Bayley Scales of Infant Development (BSID) [77], 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 [78]. Children with DS, who required more trials to learn all three tasks, performed similarly to comparison children in the response and cue tasks but showed severe deficits in the place task, presumed to reflect 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 [9]. Twenty-five adolescents with DS, between 11 and 19 years of age, were compared with typically developing children matched pairwise based on nonverbal mental age, 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). The tests of hippocampally mediated learning included a measure of verbal long-term memory, two tests of visual long-term memory, and a computerized version of the Morris water maze task. The visual long-term memory tasks included a pattern recognition task and a spatial location task requiring participants to remember an association between a pattern and the location in which it appeared. An average z-score across all four tasks was used to create a composite metric of hippocampal function.

Although performances on the prefrontal and hippocampal tasks were intercorrelated, participants with DS performed less well than 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 mental age, after controlling for chronological age. Finally, chronological age and prefrontal task performance, but not hippocampal task performance, accounted for significant variance in predicting syntax development.

Individuals with DS also experience an accelerated aging process; neuropathological changes consistent with Alzheimer's disease (AD) – including senile plaques and neurofibrillary tangles – are observed in virtually all adults with DS by 35–40 years of age [79, 80]. 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 [18, 81, 82].

Age-related atrophy and loss of brain stem cholinergic neurons projecting to the hippocampus is common to both DS and AD [23] and is thought to be related to overexpression of the *APP* gene. In normally functioning brains, neural growth factor (NGF) is produced in the hippocampus and delivered by retrograde axonal transport to the cell bodies of cholinergic neurons in the brain stem. Studies of the brains of Ts65Dn mice (a genetically engineered mouse model containing three copies of about half the genes on human chromosome 21) also have revealed age-related degeneration in cholinergic neurons, and these changes are correlated with impaired performance on tasks of hippocampal function [83]. Ts65Dn mice show increased levels of NGF in the hippocampus, but retrograde transport of this growth factor to brain stem cholinergic neurons is reduced. Cooper and colleagues demonstrated that

direct delivery of NGF to cell bodies in the brain stem restored these cholinergic neurons to their normal number and size [83], suggesting that the presence of an extra copy of the *APP* gene is linked to abnormal retrograde transport of NGF and that this hippocampal deficit may be a potential target for biochemical intervention.

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 impacted for individuals with DS. While 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 facing individuals with DS and may be related to hearing status. Current research is focusing on identifying those genes and gene interactions that affect brain development and organization in Down syndrome, ultimately leading to the emergence of the Down syndrome behavioral phenotype.

Fragile X Syndrome and Related Conditions

Genetics, Prevalence, and Overview

Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability [84]. The syndrome results from a mutation in the *FMR1* gene on the X chromosome [85]. In the healthy allele, there are approximately 55 or fewer repetitions of the CGG sequence of nucleotides comprising the gene [86]. In FXS, there is an expansion to 200 or more repetitions [87]. 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 [88]. 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 [89]. In particular, individuals with the *FMR1 premutation* (i.e., 55–200 CGG repeats) display many of the same behavioral features as do individuals with FXS, albeit typically in a less severe form [90]. Premutation carriers are also at risk for conditions not seen in FXS [89], 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 [91]. Domains that are characterized by especially serious delays or impairments include the ability to process sequential information [92–94], auditory short-term memory [95], and attention, particularly problems in inhibitory control and sustained attention [91, 94, 96–98], Neurocognitive domains that are relatively strong in FXS, although still generally delayed relative to chronological age expectations, include simultaneous processing [99], long-term memory [95], and social cognition – at least as indexed by the ability to distinguish one's own from another's representation of the world [100, 101].

Individuals with FXS also evidence relatively high rates of psychopathology and challenging behaviors [102]. Hyperarousal [103], hyperactivity [97, 99, 104–107], and anxiety, particularly social anxiety [106, 108], are frequent in individuals with FXS. Aggression can also be a problem for those with FXS [3].

There is also a relatively high co-morbidity between FXS and autism [109]. Autistic-like behaviors (e.g., eye gaze aversion, hand-flapping, and other self-stimulating behaviors) are frequent among individuals with FXS [110–113], with some researchers [114]

suggesting that more than 90% of this population displays such behaviors. Moreover, these behaviors are often sufficiently frequent and severe to warrant a co-morbid diagnosis of autism [109]. Although large-scale population-based studies have not been conducted, most reports suggest a rate of autism within FXS near 25–30% [109, 115–120].

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 [121]. The prevalence of affected individuals is 1 in 4,000 males and 1 in 8,000 females [84]. 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 [122]. Nevertheless, males and females with the full mutation of the FMR1 gene appear to display very similar profiles of neurocognitive deficits, psychopathology, and co-morbid conditions [123, 124], 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 rare [121].

There is 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 [85]. 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 [125]. 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 [126]. 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 [112, 127–132]. No doubt other genes are also involved in moderating the effects of the FMR1 mutation [133]; however, little is known about these background gene effects.

Linguistic dimensions of the phenotype. Language problems are common in FXS [134]. Children with FXS make the transition from communicating nonverbally into their first words and language many months later than do their typical peers, and some individuals with FXS never make the transition [135, 136]. Those who do make the transition continue to lag behind their typically developing age peers in all domains of language, although some domains are more problematic than other domains [137].

Vocabulary has been found to be a relative strength for many individuals with FXS. 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) [138], a structured assessment of early social communication development [139]. 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. found that scores on the Word Classes and Relations subtest of the TACL-R [50], a standardized test of spoken language comprehension employing a forced-choice response format, were well below chronological age expectations, but similar to expectations based on nonverbal cognition [57]. Although vocabulary generally is an area of relative strength, children who have autism in addition to FXS are likely to show poorer vocabulary comprehension skills than children with only FXS [140–144]. The extent to which vocabulary development is delayed also varies with gender and age, as well as with task, modality, and contextual factors, such as maternal education [134].

Syntax, or the ability to combine words into phrases and sentences in conventional ways, is an area of relative weakness, although there is variability related to age, autism status, gender, and modality [145]. Receptive syntax, for example, has been found to be below mental age expectations for young boys with FXS [146], but at mental age-consistent levels for older adolescents and young adults with FXS [57, 147, 148]. Syntactic impairments are also greater for individuals with FXS and co-morbid autism than for those with FXS only, even after controlling for differences in cognitive ability [140]. 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 [57]. In contrast to receptive syntax, which appears to catch up to cognitive development by adolescence, expressive syntax is below mental age

expectations for both children and adults with FXS [147]. 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. analyzed the syntactic characteristics of language samples collected in conversational and narrative, or storytelling, contexts from the boys with FXS, with comparisons made to samples produced by typically developing children who were matched to the FXS sample on gross measures of language ability [135]. Boys with FXS were found to be more delayed than the typically developing 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 typically developing children on many other measures; for example, the former made fewer errors in number agreement (e.g., "the boys is"). This variability, 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 [145]. Broad-based measures of adaptive behavior that include an assessment of pragmatic skills (e.g., the Vineland Adaptive Behavior Scales) [149], for example, indicate that scores in the pragmatic domain lag behind scores in other adaptive skill domains [150–152].

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 mental age performance in providing informative descriptions of intended referents in non-face-to-face interactions [153], recognizing and taking steps to correct problems in comprehending other people's messages [154], and producing utterances that are on topic rather than semantically unrelated or tangential [155, 156].

Verbal perseveration (i.e., the excessive repetition of a sound, word, phrase, or topic) is an especially serious problem for individuals with FXS [155, 157, 156]. 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 [121]. Males with FXS produce more perseverative language than do linguistic level-matched typically developing children [135] or developmental level-matched males with autism, DS, or other forms of intellectual disability [156–160], suggesting that it may be syndrome specific, at least for males with FXS [137, 161]. 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.

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, non-specific abnormalities of structure [162]. In fact, individuals with FXS are characterized by an increased volume (relative to typically developing individuals) of many structures, including the fourth and lateral ventricles, hippocampus, caudate nucleus, amygdala, and (at least in females) the thalamus [113]. There is also a relative decrease in the volume of the cerebellar vermis and temporal lobe [162, 163]. 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.

This profile of structural abnormalities in the brain is consistent with what is known about the role of FMRP in the brain. For example, animal studies have shown that the cerebellum and hippocampus are especially high in FMRP expression. More generally, the mGluR5 system is thought to be the source of many features of the FXS phenotype [164].

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 [163].

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 [165]. The volume of the cerebellar vermis has been found to be negatively correlated with severity of autism symptoms, communication problems, and repetitive behavior in affected females such that more severe autism symptoms were associated with a greater decrease in the volume of the cerebellar lobes [166]. 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 [162, 163]. Decreased volume of the temporal lobe and amygdala is thought to contribute to problems in auditory processing and social anxiety, respectively [163]. The amygdala is also involved in the regulation of hypothalamic–pituitary–adrenal (HPA) system, which is known to be dysregulated in FXS [103, 167, 168].

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 typically developing individuals [128, 169]. 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 [170].

In a recent study by Dalton, Holsen, Abbeduto, and Davidson, fMRI was used to gain insight into the association between FXS and autism [171]. The study was based on previous research suggesting that individuals with idiopathic autism have problems in modulating the activity of the amygdala and the neural systems involving it and that this accounts for some of the social–affective features of the autism phenotype, including eye gaze avoidance [172]. In fMRI studies, such problems are manifested as hypoactivation of the fusiform gyrus and hyperactivation of the amygdala during the processing of visual representations of human faces, particularly those clearly depicting emotions such as happiness and fear [173]. Dalton et al. used a task in which the participant had to decide whether photographed faces were depicting emotions or were emotionally neutral, with both eye fixations and brain activation patterns being measured continuously during the task [171]. The participants were adolescents and adults with FXS, autism, or typical development, and most of the participants were reasonably proficient at judging the emotionality of the faces correctly.

Dalton et al. found both commonalities and differences in the profiles of eye gaze and neural activation across the groups. First, like the participants with autism, those with FXS looked less at the eyes in photographed faces than did the typically developing controls. Second, participants with FXS, like those with autism, showed a pattern of hypoactivation in the right fusiform gyrus relative to the typically developing controls. At the same time, however, the participants with FXS showed greater activation than both of the other groups in several other brain regions of interest, including the left hippocampus. Interestingly, the extent of activation in the left hippocampus was positively correlated with the severity of autism symptoms and negatively correlated with IQ for the participants with FXS. This pattern of results suggests that individuals with FXS may have social–affective deficits in common with autism (diminished engagement in mutual gaze) as well as additional deficits that are layered onto those, such as reduced habituation to emotional stimuli (reflected in overactivation in the hippocampus) [171].

Although FXS is a genetic disorder with distinctive brain pathology, it is important to recognize that there are also environmental contributions to the phenotype [174]. 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 [175, 176]. 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 [177–183]. 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 [184]. 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 [174].

Premutation

Less is known about the phenotype of the FMR1 premutation because it was assumed until recently that carriers of the premutation were unaffected; however, this assumption is now known to be false [91]. 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 [185]. In addition, Tassone and colleagues have found levels of FMR1 messenger RNA (mRNA) that are 2–8 times greater than the levels characteristic of individuals with the healthy FMR1 allele [185]. Larger premutations are especially subject to this increase in mRNA levels [186]. Excess mRNA provides a toxic context for neural development, with adverse phenotypic consequences [89], such as the formation of inclusions in astrocytes and neurons [187].

As regards the phenotype, it has become clear from recent studies that the premutation is associated with a distinct behavioral profile. In particular, males with the premutation, on average, have problems (relative to typically developing age-matched peers) in several cognitive domains, including executive function, attention, and long-term memory [90, 188, 189]. They are also at elevated risk for various forms of psychopathology, such as ADHD, anxiety, obsessive-compulsive disorders, and autism [90, 188, 190, 191]. 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 [90].

Females with the premutation, especially those with larger expansions, are at somewhat elevated risk (relative to age-matched typically developing females) for depression, obsessive-compulsive disorder, anxiety, and autism [190–192]. Although several studies have not found support for a cognitive phenotype for premutation females [186, 189, 193], a recent large-scale interview of parents suggests that attention problems and even developmental delays are more common in females with the *FMR1* premutation than for matched comparison children with the healthy *FMR1* alleles [90].

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 FXTAS (fragile X-associated tremor/ataxia syndrome). FXTAS is a neurodegenerative disorder [164]. FXTAS is characterized by intention tremor and ataxia, problems in memory and executive function, and increased anxiety and disinhibition [194, 195]. The condition worsens with age, and many individuals with FXTAS transition into dementia [164]. 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 [196, 197]. The prevalence of the *FMR1* premutation is 1 in 250–300 females and 1 in 700–800 males [84], making it a significant public health concern.

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. The social aspects of language and verbal perseveration are also areas of special challenge. Co-morbid conditions, most notably autism, are common as well. The syndrome is characterized by considerable variation in the phenotype, however, with more severe symptoms in males than females and in those with co-morbid autism. In part, these behavioral variations are relation to variations in the *FMR1*-related protein. Anomalies in brain structure and function are extensive. Alterations in specific biochemical pathways, especially the mGluR5 system, have been documented as well. 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

In the 1970s, Williams syndrome (WS), also called Williams–Beuren syndrome, was advanced 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 [198, 199]. More recent characterizations, however, have revealed strong associations between language and cognition in individuals with WS, in direct opposition to modularity proposals. Although language is a relative strength for individuals with WS, language ability does not exceed nonverbal cognitive levels [200] and pragmatic skills may be significantly impaired [201]. Just as specific associations between cognition and language have been identified for FXS and DS, so too are there associations in WS, although the profile of associations is unique to this syndrome. 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 incidence of 1 in 7,500 live births [202], WS is less common in occurrence than either DS or FXS. WS is caused by the hemizygous deletion of approximately 28 genes located on the long arm of chromosome 7, including the genes coding for elastin *(ELN)* and LIM kinase 1 (*LIMK1*) [202, 203]. More than 98% of individuals with WS have the same deletion break points, referred to as *classic* Williams syndrome [204] and this deletion can be confirmed through the use of fluorescent in situ hybridization (FISH). WS is characterized by 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 [199, 205]. The elastin gene encodes a precursor protein necessary for elastic fiber assembly which peaks during late fetal and perinatal stages of development [206]. Loss of the elastin gene is the single most important contributor to the cardiovascular problems faced by individuals with WS, which include hypertension and a narrowing of blood vessel walls [207].

Behavioral Phenotype

Mean full-scale IQ in individuals with WS averages 58, with ability levels ranging from severe intellectual disability to average intelligence [200, 208–210]. Studies of cognitive ability in individuals with WS typically show a small but significant advantage for verbal relative to performance IQ. For example, Howlin et al. reported mean verbal and performance IQs of 64.6 and 60.8, respectively, for a group of 62 young adults with WS [211]. This relative verbal advantage can be attributed to especially poor performance of individuals with WS on nonverbal subtests measuring visual–spatial construction ability. The assessment of visual–spatial ability typically involves tests of copying (i.e., drawing of a model), construction of a pattern using blocks, or mental rotation. On such tasks, most individuals with WS score at floor levels leading to the characterization of this cognitive profile as being highly specific and nearly universal to WS [210]. Recently, Mervis and colleagues reported scores obtained in response to administration of the second edition of the Differential Abilities Scale (DAS-II) [212] for a sample of fifty-three 4- to 17-year olds with WS; 72% of the sample scored significantly higher on the verbal cluster than the spatial cluster, and 75% scored significantly higher on the Nonverbal Reasoning cluster than the spatial cluster [213].

In contrast to weaknesses in spatial construction, object and face recognition skills as well as the perception of biological motion in individuals with WS are consistent with MA-matched comparison individuals, leading to the proposal that, in terms of brain systems, the dorsal processing stream, rather than the ventral processing stream, is affected [214–216]. Visual–spatial deficits in WS are thought to be due to the absence of the *LIMK1* gene, rather than the absence of the *ELN* gene [217].

Another characteristic of the WS cognitive profile is a hypersociability, with most affected individuals demonstrating overfriendliness and a strong drive for social contact [218]. Early in life, infants and toddlers with WS show a strong preference for social over nonsocial stimuli, demonstrating unusually long and intense looking into the faces of strangers [219]. Intense interest in faces 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 and colleagues examined the emotional responsivity and perspective-taking ability of preschool-aged children with WS by administering an adapted version of the "Yummy-Yucky" task

[220, 221]. In this task, which is administered in the context of a snack, the examiner uses nonverbal affective cues to indicate a strong preference or dislike for a certain food. The child is then provided the opportunity to give one of the foods to the examiner. It was found that children with WS were more likely to mimic and/or intentionally imitate the examiner's facial affect and vocalizations than children in the comparison group [220]. However, this interest in the adult did not improve decision-making performance; children with WS were just as likely to give the experimenter the liked food as the disliked food (39 vs. 36%) and were more likely to attempt to convince the experimenter that the disliked food was likable. In addition, over half the children with WS ate the disliked food and there was not a significant association between mimicry or imitation of the examiner's affect and eating the disliked food.

Despite the traits of friendliness and sociability, individuals with WS are also anxious, distractible, hyperactive, and more likely to experience difficulties with peer relationships than either their chronological- or mental age-matched peers. In fact, Leyfer et al. found that over 80% of children and adolescents with WS, aged 4–16 years, met criterion for at least one DSM-IV diagnosis, the most prevalent diagnoses being ADHD (65%) and specific phobias (54%) [222]. The most common type of phobia was the fear of specific loud sounds and contexts, although the majority of children with hypersensitivity to sound also had other specific phobias. General cognitive ability, as measured by the Differential Abilities Scales, did not distinguish between children with and without either ADHD or phobias (Leyton et al. 2003) [222].

The unusual pattern of social and emotional responsiveness described thus far warrants a diagnosis of autism for many individuals with WS. Klein-Tasman et al. administered the Autism Diagnostic Observation Schedule (ADOS) [223] to 29 preschool-aged children with WS [201]. Approximately half of the participants were classified on the autism spectrum according to the ADOS algorithm. Difficulties in early-emerging prelinguistic gestures used for initiating joint attention (e.g., pointing, giving, and showing) were observed for many participants. In addition, difficulties in response to joint attention and the integration of gaze with gestures were also observed. Interestingly, expressive and receptive language levels did not account for these social communication deficits.

Linguistic Dimensions of the Behavioral Phenotype

For most individuals with WS, language is a domain of relative strength. However, it is rare to find an individual with WS whose language is commensurate with his/her chronological age. Given the contribution of verbal short-term memory to the development of language and the presence of only mild cognitive delays, there is often perception of largely intact expressive language abilities in WS. Nevertheless, weaknesses in language relative to other domains of functioning have been documented, as have unusual profiles of language development.

Administration of the Mullen Scales of Early Learning (MSEL) [224] has confirmed that the WS behavioral phenotype has already emerged in toddlers and preschoolers with WS, with performance weakest in the fine motor domain and considerably stronger for receptive and expressive language [225]. In addition, 2-year olds with WS, although scoring below the 10th percentile in vocabulary acquisition on the Words and Sentences version of the MacArthur Communicative Development Inventory (CDI) [226], have been found to display larger average expressive vocabulary sizes relative to 2-year olds with DS [227]. Mervis and colleagues followed 10 children with WS longitudinally from 3 to 5 years beginning when the children ranged in age from 4 to 26 months [228]. Nine of these 10 children began to produce words several months before they first understood or produced a referential pointing gesture, in contrast to the pattern observed for children with either typical development or DS. This delay in the emergence of referential pointing may be the consequence of a deficit in fine motor skills for toddlers with WS and suggests an atypical pattern in the progression of early language skills for these children.

In general, vocabulary is a relative strength for individuals with WS, although there are areas of weakness within this domain [225]. In a study of vocabulary comprehension, Mervis and colleagues reported that individuals with WS demonstrate higher levels of performance on the Peabody Picture Vocabulary Test (PPVT) [229] than on virtually any other standardized language measure [199]. Of those individuals with WS who were tested, approximately three-quarters scored within the normal range (i.e., above a standard score of 70) and 10% scored above a standard score of

100. In a follow-up study, Mervis and John compared comprehension of concrete vocabulary, as measured by the PPVT [49], with comprehension of abstract relational vocabulary, as measured with the Test of Relational Concepts (TRC) [230], in a group of ninety-two 5- to 8-year olds with WS [231]. Participants with WS were compared to a group of typically developing children [231]. Despite being, on average, 8 months younger than participants with WS, typically developing comparison children achieved mean raw scores and standard scores on both tests of vocabulary that were significantly higher than the participants with WS. Mean PPVT standard scores for the WS participants were over 30 points higher than their mean TRC scores, but group differences in relational vocabulary were observed even after controlling for PPVT standard scores. Mean TRC scores were above the 50th percentile for only 2% of the WS group. Additional analyses, however, suggested that weaknesses in relational vocabulary for the WS group were not restricted to spatial vocabulary items, as might have been expected. The authors suggest that challenges in the processing of spatial, temporal, and quantitative information may underlie both the weaknesses in abstract vocabulary knowledge and the weaknesses in visual–spatial processing that are characteristic of individuals with WS [231].

In contrast to vocabulary comprehension scores as measured by the PPVT, with average standard scores approaching 80, scores on the Expressive Vocabulary Test (EVT) [232] are lower for individuals with WS, with average scores below 65. Mervis and colleagues attribute this discrepancy to the response structure of the EVT. The task of providing a synonym for some of the EVT test items may be more challenging conceptually than simply pointing to a picture in the forced-choice format of the PPVT [199].

As mentioned previously, early claims were made asserting that syntax is intact in WS, thereby providing evidence for a modular organization of the brain in which cognitive skills were affected but language was spared [198, 218, 233–235], In fact, the spontaneous language of individuals with WS is more syntactically complex than that of CA- and IQ-matched individuals with DS [236]. Children with WS are also more proficient at producing tense markings than younger children with specific language impairment who are matched for MLU [237, 238]. However, as Mervis et al. point out, these two comparison groups have deficits in morphosyntax relative to their levels of nonverbal cognition, which leads to an "exaggeration" of the syntactic capabilities of individuals with WS [199].

A different picture emerges if individuals with WS are matched with typically developing children based on chronological age or mental age. Volterra et al. compared the spontaneous expressive language of Italian children with WS to that of younger MA-matched, typically developing children and found that MLU and other measures of syntax were similar for the two groups [239]. In addition, Zukowski found that the ability of older children and adolescents with WS to produce complex sentence constructions (e.g., embedded relative clauses) was similar to that of a typically developing comparison group matched for MA [240]. These 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.

Mervis and colleagues conducted an extensive examination of the associations among MLU, cognitive ability, and grammatical complexity in children with WS [200, 237]. These investigators collected spontaneous 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 (MLUm) and the index of productive syntax (IPSyn) [241] – were lower than scores reported for typically developing children at ages 3–6 years. Thus, rather than being advanced in syntactic development, children with WS were substantially delayed relative to chronological age expectations. Moreover, for children with WS, both MLU and IPSyn scores were commensurate with cognitive ability, but lower than expected based on auditory short-term memory and vocabulary comprehension.

Morris and Mervis compared the morphological abilities of children with WS to a group of younger typically developing 3-year olds matched for MLU in morphemes [204]. Use of noun 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 for the length of their productive utterances. However, the children with WS had larger receptive vocabularies than the MLU-matched, typically developing children, suggesting that utterance length and grammatical complexity are

lower than expected relative to vocabulary size for WS. This discrepancy between vocabulary and morphology was observed despite the fact that English is a relatively uninflected language. Children with WS learning languages that are morphologically more complex than English (e.g., French, Italian, and Hebrew) perform less well than younger, MA-matched, typically developing children [239, 242, 243]. Thus, these studies support the notion 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 an important mechanism for language learning in this population [200]. 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 [244]. Participants with WS were matched to a comparison group of younger typically developing children based on performance on the Test for Reception of Grammar (TROG) [245], a test which examines grammar comprehension. After controlling for chronological age, measures of forward digit span, backward digit span, and nonword repetition showed significant associations with TROG performance 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 performance. Robinson et al. proposed that phonological working memory, represented by nonword repetition performance, and verbal working memory, represented by backward digit span, likely make a strong contribution to the ability of individuals with WS to comprehend and produce vocabulary and grammar [244]. In fact, the group with WS showed a significantly stronger association between backward digit span and TROG performance 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 challenges to language learning that result from relative weaknesses in nonverbal cognitive ability [199].

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 [246]. 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

Evidence is beginning to emerge for the neural underpinnings of the behavioral profile of WS. For example, evidence of atypical processing of faces by individuals with WS is provided by a study using event-related potentials in response to pairs of matched and mismatched faces presented in upright and inverted positions [247]. For upright faces, typical adults showed negative amplitude in the ERP wave form at 320 ms (i.e., N320) following the onset of targets consisting of a mismatched face, and this negativity was localized over the right hemisphere. Adults with WS also showed a larger N320 to mismatched upright faces, but this response tended to be larger over the left hemisphere. For inverted, mismatched faces, adults with WS continued to show a left-lateralized N320 response, albeit attenuated, whereas typical adults did not show such a response. These findings indicate that individuals with WS are using similar neural systems to process inverted and upright facial stimuli, unlike typical adults who do not process inverted faces in the same way that upright faces are processed. In addition, the amplitude of the early N100 component of the ERP wave in response to the target faces for individuals with WS was less than half the amplitude of the corresponding component in the typical adults, whereas the magnitude of the N200 was increased twofold. The authors speculate that the increased N200 amplitude reflects increased attention to faces in individuals with WS [247]. In addition, Mervis and colleagues have identified decreased gray matter and sulcal depth in the area of the inferior parietal cortex and have suggested that such structural abnormalities may provide a roadblock to information traveling along the dorsal processing stream [203, 216]. Such an interruption may help to explain the deficits in spatial processing that define the WS cognitive phenotype.

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. While 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 typically developing 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 Down, fragile X, and Williams syndromes described in the foregoing sections, although based 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 similarly serve to constrain the assessment of 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. 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 considerable attention in any 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 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 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 [248]. Thus, the skillful clinician, who is likely to have but 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 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 is hidden by such a broad 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. Similarly, the relatively strong (at least early in development) visual memory skills of individuals with DS may belie their exceptionally poor auditory memory skills. Moreover, even a conceptually coherent domain, such as syntax, can be comprised of sub-domains that 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 inflectional morphology. In short, gross measures that collapse a wide swath of psychological and behavioral functioning are likely to obscure the profile of relative strengths and weaknesses that distinguishes one syndrome from others.

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. To this end, we have developed a non-face-to-face laboratory-based task to examine the ability of adolescents and young adults with FXS to formulate utterances in which the intended referent would be clear to other people [153]. In this task, the participant was the speaker and a researcher served as listener. The speaker's job was to describe a novel target shape so that the listener could select the corresponding shape from a set of potential referents. There were multiple shapes, and each recurred on multiple trials so as to resemble natural conversation, which entails both introducing new topics and returning to old topics. The speaker and listener were separated by an opaque partition, and thus only the verbal channel of communication could be used to provide information.

Abbeduto et al. found that this task successfully discriminated adolescents and young adults with FXS or DS from younger, typical children matched on nonverbal cognition, as well as the two syndrome groups from each other [153]. In particular, the youth with FXS or DS was less likely than nonverbal mental age-matched (NVMA) typically developing 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 uninformative to the listener. The participants with FXS were also less likely than either the NVMA-matched typically developing 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, they 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. Such inconsistency increased the processing demands on the listener. In contrast, the participants with DS were less likely than those with FXS or the typically developing 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 that are of interest because of their 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.

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 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 vary 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.

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. In a recent study of WS, for example, John, Rowe, and Mervis were interested in the extent to which affected individuals could monitor their comprehension of spoken messages and take appropriate steps to correct any problems identified by asking questions (e.g., "Which one do you mean?") or verbalizing the problem (e.g., "I don't have any like that.") [249]. They found that their young participants with WS signaled noncomprehension in this way in less than half the instances in which it was necessary to so. Moreover, the extent to which they successfully signaled noncomprehension was significantly correlated with their scores on 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 [154]. The implication 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 relationships among the different domains measured by different instruments 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 or storytelling. Narrative tasks, for example, appear to elicit more complex syntactic forms from participants with intellectual disabilities as well as from young typically developing children, whereas conversational contexts tend to elicit more varied vocabulary forms [250, 251]. Even verbal perseveration has been found to vary across these language sampling contexts, such that some types of perseverative language are more common in conversation and other types are more common in narration [252]. 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) [121]. 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 intervention. 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 behavioral phenotypes associated with the genetic syndromes of interest 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, particularly of DS and WS, 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 typically developing 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 [253].

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. demonstrated that, in contrast to young typically developing children who attend to a speaker's direction of gaze as a cue to identifying the referent of a novel word, children with autism assume that the novel word refers to the object that is the child's own focus of attention [254]. We are currently examining the use of a variety of social cues in word learning by children with FXS. 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.

It is important to note two additional limitations of the measures available for assessing the functioning of individuals with the syndromes of interest here and also intellectual disabilities more generally. First, many of the standardized tests available to measure cognition and language offer limited discrimination for individuals functioning in the range of intellectual disabilities. In our own research, for example, tests of receptive language, such as the Test for Auditory Comprehension of Language-3 (TACL-3) [55] or the Test for Reception of Grammar-2 (TROG-2) [255], are normed in such as a way as to ensure that virtually any individual with intellectual disability will receive the lowest standard score possible. This has led us to use the psychometrically less desirable raw scores or age-equivalent, neither of which is satisfactory from the perspective of a clinical assessment of an individual client. Second, there are few tests that are normed in such a way as to be applicable across a wide age range. From a research perspective, this leads us to use different tests of (presumably) the same construct at different points in the life course, with all of the associated interpretive problems. From a clinical perspective, this is especially problematic if interest is in tracking progress during the course of an intervention. These and other limitations of standardized tests for these populations have been eloquently described by Carolyn Mervis (see, e.g., Mervis and Robinson, 2005) [256].

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 [257]. 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. 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 perform poorly on measures of individual emotional well-being and family functioning compared to parents raising a typically developing child [258–260], although some adapt to, and even thrive in the face of, their caregiving responsibilities [261, 262].

At the same time, there are etiology-related differences among parents in terms of their experience of stress and psychological well-being [263–265]. 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" [266–268]. 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 [269–273] and mothers of youth with other disabilities [271, 273–275]. Moreover, mood disorders, especially depression and anxiety, are quite frequent among these mothers [275–278]. 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 full mutation or the permutation) [184]. Etiology-related differences among fathers and siblings have also been documented [257].

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 have argued for a systems approach to assessment [257]. 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.

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Chapter 12

An Introduction to Hydrocephalus: Congenital and Late-Life Onset

Michael R. Meager, Michelle Kramer, David M. Frim, and Maureen A. Lacy

Introduction

This chapter will commence with a basic introduction to the ventricular system and the subsequent development of hydrocephalus. Next, a review of the literature on congenital hydrocephalus will be presented addressing specific cognitive domains. This will be followed by a synopsis of the emotional and adaptive implications of this condition in children.

After summarizing the literature addressing congenital hydrocephalus, the chapter will introduce the most common form of adult-onset hydrocephalus, referred to as idiopathic normal pressure hydrocephalus. A review of the current literature on this condition and the associated treatments will be provided in this section. Finally, the chapter will conclude by summarizing the findings across conditions, along with ideas for future research.

The Ventricular System

Hydrocephalus comes from the Greek words "hydro" meaning water and "cephalus" meaning head and is caused by an abnormal accumulation of cerebral spinal fluid (CSF) in the intracranial ventricles under inappropriate pressure. To comprehend the impact of hydrocephalus, one must have a general understanding of the ventricular system. Cerebral spinal fluid is produced primarily in the choroid plexus that lines the ventricles, with most produced within the lateral ventricles in humans. The choroid plexus acts as a filtering system, only allowing specific substances into the ventricular system. Spinal fluid is produced by modified ependymal cells which line the plexus. These cells are surrounded by capillaries and connective tissue. This epithelial layer acts as a one-way valve, regulating what substances enter or leave the system. In general, spinal fluid is produced as a plasma ultra-filtrate as blood is filtered through these cells.

While the vascular system is vital, the ventricular system may play many important roles in healthy brain functioning. Cerebral spinal fluid can act as a buffer between the brain and the skull. This is especially important in traumatic brain injuries, where acceleration/deceleration results in the brain quickly moving within the skull. Without the CSF, the brain would strike the skull with greater force. Cerebral spinal fluid acts as a protective padding between the brain and the surrounding skull and bony protrusions. Cerebral spinal fluid can also reduce overall pressure on the brain stem. Specifically, buoyancy is created by CSF reducing the effective weight of the brain from about 1,400 to 50 g, allowing it to easily rest on the brainstem. Cerebral spinal fluid also allows waste and neurotransmitters to be filtered out of the system as well as transporting critical agents, such as hormones, to other areas of the central nervous system.

Normally, secretion of CSF occurs at a rate of 0.3–0.4 ml/min, resulting in about 500 ml produced per day. Total replacement of cerebral spinal fluid occurs every 4–6 h or five times/day. Total CSF volume typically ranges from 90 to 150 ml, with higher rates seen in adults. The majority of this CSF is found in

M.A. Lacy (✉)
Psychiatry and Behavioral Neurosciences, University of Chicago Medical Center, Chicago, IL 60637, USA
e-mail: mlacy@yoda.bsd.uchicago.edu

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the subarachnoid and spinal spaces, with only about 30 ml seen within the ventricular system. Within the cavity of the brain, the majority of CSF is found in the two large lateral ventricles, which are lined with CSF-producing choroid plexus. The CSF drains from the two lateral ventricles via the foramen of Monro into the third ventricle. From the third ventricle it drains via the aqueduct of sylvius into the fourth ventricle and then into the subarachnoid spaces via the foramina of Luschka and Magendie. It mostly leaves the subarachnoid space through arachnoid granulations into the venous system. These villi act as a one-way valve system, allowing CSF outside the subarachnoid space, but no blood into the system. 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 state, which aids the CSF passage into the sinus. Normal resting pressure of CSF is between 50 and 200 mm H_2O in an adult human. In an ideal state, secretion equals absorption via these granulations resulting in normal pressure.

Hydrocephalus occurs when there is some disruption in this pathway. Dandy and colleagues first proposed a dichotomous classification of hydrocephalus [1]. Basically, they punctured the ventricles and injected dye and then performed lumbar CSF taps. If the dye was found in the spinal tap it was termed a communicating form; if not, it was deemed a noncommunicating form. In present clinical practice, communicating hydrocephalus typically refers to hydrocephalus caused by the obstructed flow within the subarachnoid space, deficient reabsorption of CSF in the arachnoid granulations, or less commonly by overproduction of CSF. In contrast, noncommunicating hydrocephalus typically refers to a clear intraventricular obstruction blocking CSF flow [2]. A more etiological description of these states is "obstructive" hydrocephalus versus "absorptive" hydrocephalus [3].

Recently, the communicating versus noncommunicating distinction has been thought to be misleading as all forms of hydrocephalus involve some obstruction. Rekate advocated a return to Ransohoff's et al. 1965 proposition that all hydrocephalic states are due to either intraventricular or extraventricular obstruction [1]. *Intraventricular* hydrocephalus involves obstruction at the aqueduct or foramina of the fourth ventricle. If the etiology of the hydrocephalic state is proposed to be related to scarring of subarachnoid spaces or failure of absorption by the villi it should be referred to as *extraventricular* hydrocephalus [1].

In a recent review, Rekate [1] noted that the definition of hydrocephalus varies across studies and thus proposed a simplified definition: (1) it is an active state (2) with documented ventriculomegaly (enlargement of ventricles) and (3) a mismatch between CSF production and absorption. Using this definition, pseudotumor cerebri (benign elevated intracranial pressure), which involves a failure of CSF absorption without ventriculomegaly, would be excluded, as would individuals with shunt failure who have increased ICP without dilation. Congenital hydrocephalus and normal pressure hydrocephalus are thus considered CSF circulation disorders and will be the focus of this chapter. While hydrocephalus may be caused by secondary conditions such as tumors and brain injuries, this chapter will focus on reviewing only primary hydrocephalus due to congenital conditions or defects in absorption.

Neuropsychological Outcomes in Congenital Hydrocephalus

While there are multiple etiologies, congenital hydrocephalus is often related to per ventricular hemorrhage. In surviving neonates, the prevalence of infantile hydrocephalus is 0.57 per 1,000 [4]. Less common etiologies include meningitis, trauma, Arnold Chiari malformations, tumors, aqueductal stenosis, and Dandy Walker syndrome [3]. Diagnosis is based on imaging and clinical observation such as enlarged head. Prototypically, normal sylvian fissures and sulci are seen in the context of enlargement of the anterior recess of the third ventricle and dilation of the lateral ventricles [5]. The prognosis for children with congenital hydrocephalus has drastically changed since the introduction of extracranial CSF shunting with pressure valves. Prior to the availability of shunting procedures, mortality occurred in about 50% of cases [6].

Shunting addresses the problem of CSF obstruction and overproduction. Standard treatment involves surgical placement of small tubing into the lateral ventricle often via the right frontal or parietal lobe that allows the excess or obstructed spinal fluid to drain outside the cavity of the brain, often into the

peritoneal cavity in the abdomen. Today, shunts have valves that allow for adjustments in pressure as needed (e.g., cutaneous programmable shunts), with shunt-related technical improvements ongoing. Following the development of shunting procedures, the mortality rate of hydrocephalus decreased drastically to around 15%. While requiring constant monitoring of pressure and valve functioning to assess for blockage or infection, at present hydrocephalus is considered a treatable disease. While there is no national registry, NINDS estimates that hydrocephalus affects 1 in 500 births.

Given the rising survival rates, researchers have begun to examine the cognitive and psychiatric status of these children. Studies examining cognitive functioning in individuals with hydrocephalus have consistently reported worse performance in this group compared with normal controls as well as other individuals with other medical conditions across several domains [4, 7]. In the following sections we will present the current literature on the cognitive functioning of children with hydrocephalus across the most investigated cognitive domains. Research addressing the underlying etiology will then be reviewed in the context of the cognitive profile. An important caveat in reading the literature on cognition in hydrocephalus patients is that hydrocephalus, as an entity, can be etiologically multifactorial and associated with a variety of specific underlying diseases. It is difficult to separate the effects of the hydrocephalus, as opposed to the effects of the underlying etiology (i.e., prematurity) in determining the cause of cognitive weakness. For example, this is especially important in such disease entities as myelomeningocele (spina bifida aperta) within which up to 90% of patients will develop hydrocephalus. However, children born with myelomeningocele have an obligate association with a variety of congenital brain malformations, such as Chiari malformation type 2, polymicrogyria, medullary kinking, breaking of the tectum, and enlarged massa intermedia. The presence of such anomalies in a population of hydrocephalus patients must be taken into account when generalizing observations about cognition made in that population.

Intelligence

Prior to the application of shunting to the treatment of 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 [8, 9]. Since the advent of shunting devices, survival, and intellect has greatly improved in this population. In a recent study examining intellect in children shunted within the first year of life, 74% of survivors achieved intelligence scores above 70 [10]. Despite this improvement, the average Full Scale IQ is often documented to be below peers, often one to one and half deviations [10, 11].

While there are consistent findings of a lower than average intellect in children with hydrocephalus [10–12], 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 [12] of a nonverbal learning disability in hydrocephalus [13–15]. The majority of these early studies were limited to children with spina bifida and hydrocephalus. In a recent review of 147 studies examining cognition in hydrocephalus, only 8 excluded patients with myelomeningocele (MMC), traumatic brain injury, or other neurologic conditions [12]. 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 versus PIQ discrepancy has not been documented [10, 12]. Thus, etiology may be relevant to 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 [4]. 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 [10] and intelligence appears to decline with advancing age [12]. This pattern reflects the long-term aversive developmental impact of this condition. Animal experiments indicate that neuronal damage is often progressive in hydrocephalus and not completely reversed by shunting [16]. In terms of the impact of shunt revisions on cognition, studies with lower rates tend not to show a significant impact [10, 12]. 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

0 to 100. Thus the etiology itself may impact the number of revisions [17]. Certain conditions such as MMC may result in a more unstable hydrocephalic state, which may uniquely impact cognition. Improvements in surgical techniques over the last decade, including shunting mechanisms, may also result in less revisions and possibly better overall outcomes.

Attention and Executive Functioning in Children

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 distraction in this population compared to peers. Two studies in particular found that children with spina bifida and hydrocephalus produce more visual distractibility errors [18] and required more time during focused attention tasks with auditory distracters [19]. Problems have also consistently been seen on tasks requiring focus and shifting of attention [20, 21] and less so on sustaining attention tasks [22]. Some have argued that the attentional dysfunction in hydrocephalus is related to right posterior attention system, while others have not found support for this theory [12].

Regardless, of the cause, 31% of children diagnosed with spina bifida and hydrocephalus met criteria for attention deficit hyperactivity disorder; with 23% meeting criteria for inattentive type in a recent study [23]. 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 [24]. Tarazi and colleagues [25] 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, yet continued deficits in inhibition [26]. 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 [27].

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, hypothesized to reflect executive dysfunction [28, 29]. In some studies, children with hydrocephalus have consistently performed below peers on similarities, block design, object assembly, and picture completion subtests [4, 10]. Studies assessing other executive components or skills are lacking at this time.

Memory

Children with congenital hydrocephalus consistently display learning and memory deficits [30]. Results across studies have been mixed over 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 [4, 11, 31, 32]. In contrast, other studies have found no benefit from recognition paradigms suggesting more of an encoding-based deficit, consistent with noted attentional dysregulation [33, 34]. 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 criteria, with scores ranging from 70 [29] to 90 [31], while others do not address intelligence. Studies that use IQ cutoffs are more likely to report a profile of retrieval deficits [4, 29, 31, 32], while those without IQ cutoffs are more likely to report encoding deficits [33–35]. Research has also varied with regard to other exclusion criteria. Some studies exclude individuals with psychiatric histories, despite the high rate of depression and ADHD in this population [23].

Language

A review of the literature describes speech disturbances in children with congenital hydrocephalus as reflecting “a cocktail party syndrome” (CPS) [36, 37], yet this appears primarily in early studies and related to lower ranges of intellectual functioning [7]. More recent research has suggested that most

of these children display intact linguistic skills but experience problems with semantic–pragmatic aspects of language [30]. Linguistic expression is typically fluent and mostly well structured [38]. However, when talking about stories or situations, children with hydrocephalus tend to become verbose, disorganized, and leave out important details [38]. They omit certain grammatical aspects of language [39] and fail to make semantic and structural links between pieces of stories [40]. 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 respond appropriately [41]. When structured productive language tasks are presented, hydrocephalic children in some instances have demonstrated minimal to no verbal fluency deficits [1, 39], while other studies have shown impaired performances compared to normal peers on fluency tasks with constraints [42].

With advancing age, reading comprehension, receptive language skills, written language, and spoken language deficits emerge [35, 43–49]. Children with hydrocephalus have also been shown to manifest difficulties compared to peers on tasks requiring production of antonyms and synonyms for words [48] and on tasks requiring the ability to break down words phonologically at a basic level of language comprehension [42, 44]. In contrast, children with hydrocephalus have been shown to read single words and nonsense words adequately [48].

Visuospatial

As noted previously, early studies suggested that children with hydrocephalus have a nonverbal learning disability based on reports of a verbal IQ versus performance IQ strength. More recent studies, especially examining hydrocephalus without spina bifida, have not found this disparity [4, 10, 12]. In a recent review, Yeates et al. [30] concluded that children with hydrocephalus displayed variability in visual perception skills. They found some abilities, such as facial recognition, maybe stronger than others, 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 subtests, require speeded responses. 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 [49].

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) [50, 51]. In general, children with spina bifida tend to have more motor dysfunction than children with periventricular hemorrhagic (VH)-related hydrocephalus [52]. In cases of hemorrhage and aqueductal stenosis, 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 [53, 54]. For example, cerebellar dysfunction often seen with Chiari malformations can cause ataxia and oculomotor apraxia when associated with cerebellar vermis malformations [55–57]. These deficits can subsequently cause visuomotor impairments [58]. In spina bifida, spinal lesions affect upper and lower limb function [59]. Pyramidal tract deficiencies result from damage to the cerebral cortex [60]. Behaviorally, this is demonstrated as loss of strength and sluggish reaction [60, 61]. Children affected by hydrocephalus, with resultant motor deficits, have been shown to require more practice in learning the skills necessary to function in their environments than normal functioning children [62].

Emotional Functioning

Children with hydrocephalus experience higher rates of depression, anxiety, and attentional difficulties. 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 [63, 64]. 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 [65]. Notably, children with lower intelligence scores were more likely to experience behavior problems. Along with the Conner's, behavioral and emotional adjustment can be assessed using the Behavior Assessment Scales for Children [66], which assesses the presence and severity of a range of behavioral and emotional difficulties.

In 2003, the Hydrocephalus Association began collecting survey data from patients and their caregivers (http://www.hydrocephalusdatabase.org). Gupta et al. [66] reported the results of this 2003–2005 survey, which included 1,459 individuals diagnosed with hydrocephalus. The majority of surveys were completed by parents or grandparents of children. Examining a subset of 718 patients diagnosed 10 years prior to the survey, they found that almost all had placement of a shunt (95%) and had at least one shunt revision (80%), with 32% requiring 10 or more revisions. Rate of revision was reduced in those diagnosed after age 1½ years. The frequency of infection was much lower, ranging from 29 to 5%. Interestingly, 68% of patients with congenital hydrocephalus diagnosed before age 18 months reported being single and having a history of depression, with 45% receiving psychiatric treatment. Over 40% of the younger onset patients reported not being employed at the time of the survey as did a 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.

Overall Profile in Congenital Hydrocephalus

In summary, children born with hydrocephalus tend to display intelligence scores at least one standard deviation below peers. Most recent research does not support a VIQ to PIQ discrepancy, but rather a diffuse impairment and patients display verbal and visual memory difficulties. A review of the current literature suggests either an encoding or retrieval-based problem with a relative consistent finding of intact consolidation. Executive problems primarily characterized by attention, response inhibition, working memory, and planning deficits have been documented in this population. Language impairment tends to be subtle, affecting the semantic and pragmatic aspects of language. Visuospatial deficits have consistently been found, although this may reflect executive difficulties [49]. 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.

Infections, etiology, revisions, type of infection, and age at surgery may all impact cognition [30]. 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) [17], while in newer studies shunt revisions are much less common (<5) [10]. Thus, to say shunt revisions did or did not impact outcome may be a factor of patient selection.

Another major issue emerging from the literature is the lack of a unified testing battery to assess cognition in children. At present, the NIH is funding a study to develop a unified testing battery to assess cognition across the lifespan: http://www.nihtoolbox.org/WebPart%20Pages/Cognition.aspx. The use of a caregiver or parent assessment of adaptive and executive skills is also advocated to assess the functional impact. Several studies have shown that parent rating of functioning and neurocognitive data may not correlate possibly due to the limitation of the testing environment and ecological validity of the tests. The Scales of Independent Behavior-Revised [67] and the Brief Rating Inventory of Executive Functioning [68] are short and elicit a good deal of useful data. Imaging data, such as diffusion tensor imaging or diffusion tensor tractography to track white matter develop would be especially useful in understanding the cognitive profile in childhood hydrocephalus.

A unified battery will certainly improve the generalizability of findings, although different inclusion and exclusion criteria in studies will still hinder interpretation. In terms of time to test in children, Tarazi and colleagues [69] have shown that there appears to be an interaction with skill maturation, in that deficits

emerge with advancing age. This is hypothesized to be the result of initial insult and accumulating injury with disruption during critical growth spurts due to infections and blockages requiring revisions. Thus, given that this disease may impede initial myelination, it may be important to study patients across time. It is also imperative to complete a brief reassessment following infection and revision, as these factors have been shown to impact cognition [17].

Etiology of Profile

The etiology of this cognitive profile is hypothesized to be related to disruption of periventricular white matter tracks due to enlargement of ventricles [70], 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 [3]. In some studies cognitive impairment has correlated with white matter neuropathology [71], but not others [72].

Late-Life Onset: Idiopathic Normal Pressure Hydrocephalus

When adult neurologists and adult neuropsychologists refer to hydrocephalus, they are typically referring to normal pressure hydrocephalus (NPH), the most frequent form of chronic hydrocephalus diagnosed in adults [76]. It is often idiopathic (INPH) but can be secondary to another trauma, such as a head injury or tumor. This section will focus on idiopathic normal pressure hydrocephalus (INPH) as it is often considered a potentially reversible dementia if diagnosed early and accurately.

Normal pressure hydrocephalus is a type of communicating hydrocephalus in which accumulated CSF is not at equilibrium with absorption, so that intracranial pressure (ICP) is slightly elevated and CSF may reach a high normal level. INPH can affect individuals as young as 40, but typically occurs in the sixth to seventh decade. Brean and Eide reported an incidence of 5.5 per 100,000 [77], and Shprecher et al. reported prevalence of 21.9 per 100,000 [78]. Currently it is estimated that there are 40,000–175,000 people in the United States with INPH [79]. Surprisingly, fewer than 2 patients in 100,000 receive proper and prompt treatment [76]. The Hakim series found 5–10% of all cases of dementia may suffer from this disorder [80]. Hejl et al. found that 3% of their 1,000 consecutively presenting dementia cases were eventually diagnosed with hydrocephalus and made up 18% of the 185 reversible cases [81]. These rates may vary primarily due to the difficulties with accurate diagnosis between clinics, researchers, and providers.

Currently INPH is defined as ventriculomegaly out of proportion to cerebral atrophy without documented macroscopic obstruction to the circulation of cerebral spinal fluid [79]. Ventriculomegaly is typically defined as an Evans index of >0.03, which refers to the ratio of the maximal width of the frontal horns to the maximal width of the inner tables of the skull at the same level. While it has a high sensitivity, ventriculomegaly alone is not diagnostic as this is found in other disease processes, such as Alzheimer's and vascular disease. While sensitivity has been estimated as high as 80%, specificity is estimated at 50% [82]. Surprisingly, ventriculomegaly is not consistently predictive of outcome following shunting [83]. Infact, better clinical outcomes have been seen in patients without change in ratios following intervention [84].

Clinical Presentation

Since imaging has a low specificity, clinical presentation is key to diagnostic accuracy. Historically, it has been thought of as a rapidly presenting clinical triad (Hakim triad) of incontinence, gait instability, and mental status changes in the context of enlarged lateral ventricles [78, 85]. More recently, it has been noted that this Hakim 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 (see Relkin et al., for review of clinical features) [79]. Many elderly individuals may experience gait problems, incontinence, and confusion for a variety of other reasons. In 2005, specific criteria for probable and possible NPH were offered by Relkin et al. emphasizing the integration of clinical history, neuroimaging, clinical presentation, and physiological data (i.e., CSF pressure measurement) in achieving accurate and reliable diagnosis.

Cognitive Profile

The prototypical neurocognitive profile often cited is one of prominent executive dysfunction leading to impairment across domains, primarily due to disruption of frontal subcortical white matter tracks and connections [78]. 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 thalamocortical loop, with prominent frontal involvement [86]. As a result of this disruption, patients diagnosed with INPH often present with mental and motor slowing, along with deficits in memory retrieval, concentration, mental flexibility, planning, and problem solving, but rarely frank cortical features such as aphasia [87, 88]. It is often referred to as a fronto-subcortical dementia [88]. While they rarely show signs of major depression, they are often noted to present with apathy, inertia, and slowness [79]. A specific battery has been proposed by Devito and colleagues, which takes approximately 2–3 h to administer, but the results have yet to be utilized in published studies and thus sensitivity and specificity issues are unknown [88]. Surprisingly, the degree of ventriculomegaly does not predict the level of behavioral impairment and reduction of ventricles post-shunting does not accurately predict clinical improvement [89].

In a recent study, neuropsychological impairment correlated with impaired gait, incontinence, and sleep disruption [85]. Furthermore, in this study comparing cognitive performance between healthy controls and NPH patients, the discriminability efficiency of most neurocognitive tests was rather high, almost 90%. There was no association between reported symptom onset and cognitive or clinical symptoms. In addition, patients with vascular comorbidity performed worse on cognitive tests, but were not different in terms of gait, sleep, or incontinence.

In terms of discriminability, INPH patients display greater executive dysfunction and less memory impairment when compared with aqueductal stenosis [90]. AD pathology has been documented in 26–41% of clinically diagnosed hydrocephalus patients and thus should be considered as a diagnostic differential especially when enlarged ventricles due to atrophy (e.g., ex vacuo hydrocephalus), insidious onset, and anomia are noted [91]. Interestingly, Savolainen and colleagues found larger hippocampus volumes in NPH versus AD patients and a trend toward larger volumes in those patients who benefited from surgery [92]. Anomia or reduced naming skills has also been found to be more indicative of Alzheimer's disease and poor shunt response [91]. Beta amyloid (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 NPH patients and in animal 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 [93].

Traditional Treatment: Shunting

As previously noted, despite the high incidence of NPH, fewer than 2 in 100,000 NPH patients receive treatment, primarily thought to be due to limited awareness [76]. Treatment of hydrocephalus begins with the assessment of gait and cognition followed by a lumbar drain trial, which involves CSF drainage via an extended spinal tap. Given that these evaluations are often completed in the hospital, an efficacious battery of tests is recommended, although there is no consensus in the literature. Recently, the Idiopathic Normal Pressure Hydrocephalus Grading Scale (INPHGS) was advocated for assessing shunt responsiveness and may lead to a better understanding of ideal candidates for surgical intervention [94].

Cognitive Impairment

0	Normal
1	Complains of amnesia or inattention but no objective memory or attentional impairment
2	Existence of amnesia or inattention but no disorientation of time and place
3	Existence of disorientation of time and place but conversation is possible
4	Disorientation for the situation or meaningful conversation impossible

This scale rates cognition based on digit span, MMSE, trail-making test, frontal assessment battery, and observations from caregivers and physicians. There are no clear guidelines for ratings, and thus clinician judgment is paramount in making the ratings. At present, there is no unified test battery across studies, although as noted above one has been suggested by Devito and colleagues [88]. Ideally, a battery that allows for multiple assessments and emphases attention, memory, and naming skills (e.g., to discriminate from Alzheimer's disease) is warranted. In our own clinic, given the predominance of inpatient referrals, the following battery has been found to be useful and takes approximately 1 h to administer: Repeatable Battery for the Assessment of Neuropsychological Status sublimated with executive tasks such as the Stroop Color-Word test, the Trail-Making test, and the Lafayette Grooved Pegboard test.

During the shunt trial, reassessment of gait and cognition is typically completed in 3–5 days. If significant changes are noted, placement of a ventriculoperitoneal shunt device is the most common treatment. The success rate in terms of cognitive improvement and duration of status varies greatly across clinics with estimates reported from 26 to 80% [95]. Research has found that prognostic indicators of good outcome are shorter duration of cognitive impairment, gait disturbance as the initial symptom, and more minimal corpus callosum distortion [96, 97]. In a 2007 review [79], the following were listed as prognostic indicators of good outcome: onset less than 2 years prior, 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 mmHg/ml/min during CSF lumbar infusion test. Despite the common findings of prognostic indicators, studies vary significantly in determining candidates [92].

In terms of cognition, in one recent study only 52% displayed significant post-surgical improvement, specifically in verbal memory and motor speed. Patients who displayed significant deficits on the immediate verbal memory task presurgically were fourfold less likely to show improvement with an even worse outcome if this was associated with executive or construction deficits [98]. In comparing patients with INPH to patients with secondary hydrocephalus, preoperative mental status appeared to partially predict outcome. The relative risk of failure was twofold in patients presenting initially with concentration deficits on examination. 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 [99]. In a review of noninvasive biomarkers, including structural imaging, volumetric studies, post-contrast MR imaging, and functional imaging, Tarnaris [100] and colleagues reported promising sensitivity and specificity rates for (1) CSF flow void on MR imaging, (2) SPECT *N*-acetylaspartate/choline ratio, and (3) phase-contrast MR imaging for responsiveness to shunting. Examination of functional MRI revival patterns on cognitive and motor tasks after CSF drainage has yielded positive results for finger tapping yet not cognitive tests [101].

New Treatment Approach: Endoscopic Third Ventriculostomy

Shunt failure rates range from 25% to almost 40% within the first year with a 10% infection rate [102, 103]. Across a lifespan an individual with congenital hydrocephalus is almost certain to have at least one revision [102]. Given the high rate of revision, alternative techniques are being explored for the management of hydrocephalus.

The introduction of ventriculoscopy came in the early 1900s [104, 105]. One of the first surgeons to employ the procedure was Walter E. Dandy, who performed a choroid plexectomy in an individual with communicating hydrocephalus [105]. The first endoscopic third ventriculostomy (ETV) was performed by W.J. Mixter in the 1920s using an ureteroscope [106]. 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 [105]. Despite this finding, the use of this 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 [105].

Endoscopic third ventriculostomy, which avoids the complication of infection or revision is becoming the treatment of choice for hydrocephalus caused by intraventricular obstruction (e.g., noncommunicating hydrocephalus), at the level of the aqueduct of sylvius. In ETV, infection rate is less than 5% of cases [107], but the occurrence of other complications (e.g., hematoma, diabetes, and hygromas) ranges between 6 and 20% [108].

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 [107] 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 ventriculostomy. A case study report [109] 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 [110] 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 [111] described a 20-year-old male who developed a dense amnesia and bulimia post-stereostatic ETV. In our own study [112], 10 patients with aqueductal stenosis assessed on average 2 years following ETV intervention, continued to display memory and executive 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) [113]. 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 [114], 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.

Summary

Regardless of age of onset, hydrocephalus impacts cognitive, emotional, and adaptive functioning. This cognitive profile is characterized by significant attention dysregulation often 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, fluency, and planning. Emotionally, internalizing symptoms are prominent, such as anxiety and depression. Limited longitudinal studies indicate significant aversive impact on adaptive functioning. In children, earlier onset results in worse outcome. The cause of the cognitive dysfunction in children appears to be related to ventricular enlargement and subsequent disruption or poor myleinization along with reduced gray matter volume. There appears to be some progressive decline or lack of maturation across time. In adult cases, chronicity of at least 2 years often results in an irreversible dementia. In adults, the damage is related in part to enlarged ventricles impacting frontal subcortical pathways. Comorbid vascular disease appears to worsen outcome. While there are few longitudinal studies, survey data from childhood and adult-onset patients indicate significant adaptive and functional impairment.

Future research must include longitudinal studies to assess the impact of hydrocephalus on development. Imaging data combined with neurocognitive data will be especially beneficial in improving our understanding of the impact of this condition over time. A standardized unified battery must be identified to allow for comparisons across etiologies. As it is clear that congenital hydrocephalus impedes cognitive development, early remediation studies should be pursued. A review of the child literature revealed few studies of treatments for the executive or memory problems in children. It may be useful to determine if an early intervention proves beneficial in this population.

In adults, studies focused on conclusively identifying candidates for intervention using uniformed batteries, larger sample sizes, imaging, and pathology are warranted. Public awareness is also important as early intervention appears to influence outcome.

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Chapter 13

Learning Disabilities

Gayle K. Deutsch and Robert N. Davis

Learning disability (LD) refers to a condition in which a child fails to develop adequate academic skills, such as reading, writing, or calculation. LDs involve inadequate development of academic skills, rather than representing a loss of previously acquired function, although brain lesions may certainly result in cognitive deficits that affect reading, writing, and calculation (for a review, see Heilman and Valenstein) [1]. Most research on LDs has involved children, who are the focus of this chapter. For a review of LDs in adults, the interested reader is referred to Mapou [2]. In this chapter, we will first present a conceptual overview of LDs and types of LDs. Second, we will offer recommendations on how to effectively triage 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 [3]. 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 mental retardation, 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. 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 an LD if he or she demonstrated reading abilities within the 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 indicative of LD.

Academic achievement deficits that result from primary visual or auditory impairment, mental retardation, or inadequate exposure to quality instruction should not be regarded as LDs; in such instances, academic skill deficits would be expected. Similarly, children with limited exposure to English should not be regarded as having an LD for this reason alone. As reviewed extensively elsewhere [3, 4], we do not view an IQ–achievement disparity as either necessary or 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 [3]. Moreover, the use of cutoff and/or

G.K. Deutsch (✉)
Stanford University Medical Center, Stanford, CA 94305, USA
e-mail: gdeutsch@stanfordmed.org

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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 second part of the term unexpected 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? Some researchers (e.g., Dombrowski and colleagues) [4] have suggested incorporating a combination of national and local norms in making the determination of underachievement. Specifically, these authors argue that LD identification should be based on (1) a standard score of 85 or below on a nationally normed measure of academic achievement and (2) evidence of educational impairment (based on grades, curriculum-based assessment, and teacher reports or ratings). A weakness of this proposed identification method is that the use of a specific cut point (e.g., standard score of 85 or below) is problematic due to measurement error. Nonetheless, the second criterion of Dombrowski et al.'s [4] approach includes consideration of the child's academic performance at a local level. This criterion does not eliminate the measurement error problem associated with measuring academic achievement at a single point in time and with a fixed cut score. However, it does supplement the score with highly relevant data pertaining to the child's academic performance in his or her most immediate environment.

Fletcher and colleagues [3] advocate a hybrid model for identifying LD that combines features of low achievement and response to intervention (RTI) approaches. RTI is not a new concept, but with changes in educational law based on the Individuals with Disabilities Education Act (IDEA 2004), a shift was made to take into consideration the role of instruction and performance over time. This model involves considering a child's response to instruction, serial curriculum-based assessments of the academic domain at issue, and evaluations of instructional quality. A child who demonstrates an inadequate response to instruction would next receive norm-referenced assessments in the achievement domain. A comprehensive evaluation that screens for comorbid conditions and addresses other possible causes of underachievement (e.g., mental retardation, speech/language impairments, and/or behavioral problems) is also conducted. Assessment and consideration of psychosocial variables (e.g., home environment or native language) occurs as well.

We are in general agreement with Fletcher and colleagues [3] regarding the hybrid model, as it clearly addresses many of the flaws inherent in other models. Our primary concern about the model, though, is that not all schools may have the resources and personnel who are able to carry out assessments and interventions of the type proposed. Moreover, change seems to happen slowly in large bureaucracies, and we are aware at present (September 2009) that many schools continue to operate with outdated models, assessment practices, and intervention techniques. This is not to blame the schools, as many of them likely lack the necessary funding and/or staff training to carry out such programs. It simply means that something must be done in the interim or in situations when the hybrid model cannot be applied. We believe that a low-achievement model is reasonable to be used as a conceptualizing framework in instances when RTI cannot be applied. Utilizing an approach such as that outlined above [4] with appropriate consideration given to potential exclusionary factors (but not IQ) appears to be a reasonable and practical way to identify children at risk for LDs.

Prevalence Rates of LD

Estimates of the prevalence of LDs vary according to the criteria by which they are defined. In some studies, LDs are considered as a disorder category and are not fractionated by type. At a very general level, the 2004 National Survey of Children's Health reported an 8% lifetime prevalence of LD among children 3–17 years of age. 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 disability?" Lifetime prevalence rates differed by sex: 9.5% of boys were reported to have an LD compared to 6.3% of girls [5]. 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 sample 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 two-parent stepfamily situation, higher parental aggravation, and not discussing ideas with the child calmly [6].

Another approach is to examine data on children who receive special education services under the Individuals with Disabilities in Education Act (IDEA). The most recent available data (2006–2007 school year) show that 5.4% of children in the United States received services due to an LD [7]. It should be noted that this value (5.4%) represents a point prevalence figure, i.e., the percentage of children identified as having LD and receiving services under IDEA, as contrasted with the lifetime prevalence data reported above in the 2004 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 17.5% [8, 9], and dyslexia affects approximately 80% of children identified as having an LD [10]. 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 [3].

Epidemiological studies suggest that males are 1.5–2 times as likely as females to have dyslexia [11]. Math LDs have been found to be present in approximately 4–6% of children [12]. Although data are limited, the prevalence of written expression LDs has been found to range from 6 to 22% as a function of geographic region, gender, and ethnicity [13].

The Process of Diagnosis

The role of the neuropsychologist is likely to diminish over time as more schools adopt a hybrid low-achievement/RTI model such as that proposed by Fletcher et al. [3]. During this transitional period, clinical neuropsychologists will almost certainly continue to receive referrals that involve questions of LD. One might imagine that a child is in one's office for evaluation, and his or her parents are concerned about their child's academic achievement; what should the practicing neuropsychologist do in cases when RTI or a hybrid model cannot be utilized? In the future, it is hoped that most issues related primarily to academic skill deficits will be easily and comfortably referred to the local school district for identification and intervention. In instances when well-developed RTI programs already exist, then we would advocate referring suspected LD cases to competent school personnel unless there is a reason to suspect that the child would also benefit from a complete neuropsychological evaluation (such as when a child has a primary medical condition affecting cognitive functioning).

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. Even in such cases, though, children would ideally also be directed to an RTI program in a local educational setting for confirmation of the LD. It remains to be determined if interventions designed to improve academic skills among children with LDs differ in effectiveness for children who have LDs in the context of a primary medical disorder.

It has been our experience that the neuropsychological evaluation in conjunction with a hospital-based school reentry program is an important bridge among parents, the child, and school personnel. For example,

the Lucile Packard Children's Hospital at Stanford offers the HEAL program for children with medical conditions who may have problems transitioning back to school. The results of the neuropsychological evaluation are incorporated into a school plan. Personnel from the HEAL program also visit the school to observe the child and to meet with school personnel as needed. It may not be possible for neuropsychologists in private practice to provide this service, but it demonstrates how the neuropsychological evaluation in a medical setting can be helpful in making appropriate recommendations for school-age children.

Evaluating Children at Risk for LD

Having considered when to evaluate children with concerns about their academic skills, 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 [3].

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. The term "at risk for LD" is used since one cannot likely diagnose LD with confidence in the absence of an evaluation of RTI, at least among children [14]. The child's level of intellectual functioning may be considered, although we do not consider an IQ test to comprise an essential component of the test battery unless mental retardation is suspected. In such cases, assessment of the individual's level of adaptive behavior should also be undertaken.

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 – Third Edition (WJ-III)*. Another popular achievement battery is the *Wechsler Individual Achievement Test – Second Edition (WIAT-II)*.

Academic skill	WJ-III	WIAT-II alternate
Oral word reading	Letter–Word Identification	Word Reading
Reading fluency	Reading Fluency	–
Reading comprehension	Passage Comprehension	Reading Comprehension
Calculation	Calculation	Numerical Operations
Spelling	Spelling	Spelling
Phonological decoding of print	Word Attack	Pseudoword Decoding

It is commonly believed that the WIAT-II was co-normed with the Wechsler intelligence tests (e.g., WISC-IV and WAIS-III), but this is not the case. Rather, the test publisher administered the WIAT-II and Wechsler intelligence tests to relatively small samples of examinees in order to determine the correlations between the respective tests [15]. In contrast, the WJ-III was completely co-normed with the *Woodcock–Johnson Tests of Cognitive Abilities*. We prefer the WJ-III to the WIAT-II for several reasons. First, the WJ-III normative sample ($n = 8{,}818$) is nearly twice the size as the WIAT-II normative sample ($n = 4{,}879$). Second, the WJ-III may be used with individuals ranging in age from 2 to 90+ years (vs. 4–85 years for the WIAT-II). Third, the WJ-III has alternate forms (Forms A and B), as well as a third form that recently became available (Form C). Thus, there are three parallel forms that contain the same core subtests, but with distinct items within each test. Fourth, we have found the WJ-III to be faster and easier to administer than is the WIAT-II. Fifth, the two batteries compare favorably in terms of psychometric properties, with any major disparities favoring the WJ-III.

In addition to the tests listed above, we prefer to include Writing Samples, Quantitative Concepts, and Oral Comprehension from the WJ-III when possible. Writing Samples provides a more thorough assessment of handwriting and quality of written expression than Spelling alone offers. Quantitative Concepts can be helpful to assess the child's mastery of math facts that are less dependent on formal calculation procedures. Oral Comprehension is very similar to Passage

Comprehension in its processing demands, but all inputs occur through the auditory (rather than visual) modality.

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) 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.

In some cases, modifications to the test battery will be necessary. The Peabody Individual Achievement Test – Revised (PIAT-R) may be suitable for children with significant motor deficits, as no writing is required on any of the subtests. Children with expressive language difficulties may also be good candidates for the PIAT-R Reading Comprehension subtest, in which the child reads a sentence and then points to one of the four pictures that best describe the sentence. The PIAT-R also arguably comes closer than other achievement batteries to measuring the individual's "pure" academic skills, since none of its subtests are timed.

The extent to which it is necessary to include measures of cognitive functioning other than academic skills depends on the reason for evaluation. When deciding whether or not to include additional measures, the primary criterion should be whether performance on the respective measures might reveal strengths or weaknesses that could be useful for intervention planning. For example, it might be useful to assess an individual's level of receptive word knowledge using the *Peabody Picture Vocabulary Test – Fourth Edition* (PPVT-4). If performance on this measure is markedly above that of oral word reading performance, for example, then such information would point toward a deficit in recognizing printed words, as opposed to a lack of word knowledge per se. Neuropsychologists are advised to be judicious, though, in selecting the additional measures, since there appears to be little empirical support for the notion that addressing strengths and weaknesses in cognitive skills (apart from academic skills per se) relates to intervention outcomes [3]. For example, an intervention attempting to improve a child's naming skills would not necessarily be expected to result in improved word reading. As noted by Fletcher et al. [3], "Gains are specific to what is taught. If interventions do not teach academic content, little transfer occurs" (p. 273).

On the other hand, 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 the side of seizure onset [16].

To summarize, circumstances continue to exist in which clinical neuropsychologists may contribute to the assessment and possible identification of children at risk for LD. Although there is a welcome movement toward using a dynamic RTI approach for identifying LDs, not all individuals presenting for assessments will be enrolled in an educational setting, and not all educational settings will have well-developed RTI programs. Furthermore, some individuals will have medical conditions that affect cognitive functioning, including academic skills. It seems reasonable for clinical neuropsychologists to continue to be involved in LD assessment, provided that they are aware of the limitations that non-RTI approaches possess. Individuals who appear to have deficits in core academic skills that are not clearly attributable to causes such as visual impairment, hearing impairment, or mental retardation may be considered "at risk" for having an LD, which then would ideally be confirmed through an

evaluation of RTI. For opposing viewpoints on this issue, the interested reader is referred to two recent papers [17, 18].

Biological and Neuropsychological Mechanisms

Genetic Influences

Considerable evidence indicates that genetic factors influence the development of LDs. Dyslexia, for example, tends to run in families, and family history is an important risk factor. In children of parents with dyslexia, rates range from 23 to 65% [19]. The prevalence rate of dyslexia among individuals with an affected sibling is approximately 50% [20]. Twin studies consistently reveal higher concordance rates for dyslexia among monozygotic compared to dizygotic twins [21]. Sizeable heritability estimates have also been obtained for reading comprehension [22], and measures related to reading fluency, such as rapid naming [23]. Nine loci where dyslexia genes are encoded have been identified (*DYX1* through *DYX9*). *DYX2* has been the most replicated locus which is located on the "p" arm of chromosome 6 in band "22" (6p22) [10]. Meng et al. [24] recently proposed that *DCDC2* encoded on 6p22 is a candidate gene for reading disabilities. Math disabilities [25] and disorders of written expression also show evidence of heritability [26], but no specific candidate genes have yet been identified.

Brain Mechanisms and Correlates of Dyslexia

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 on lesion studies [27–30], advances in technology have made it possible to investigate brain differences between individuals with and without LD and extend prior research. By far, most of this work has been in the area of developmental dyslexia, but developmental dyscalculia has also been studied. In contrast, there is a notable lack of research examining the neural mechanisms underlying developmental dysgraphia. This section of the chapter will summarize the relevant research regarding the neural bases of developmental dyslexia, dyscalculia, and dysgraphia based on studies with alphabetic languages.

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 developmental dyslexia is a heterogeneous disorder, but there is now a consistent and broad area of research showing that a core deficit in developmental dyslexia is problems with phonological processing. We would like the reader to be aware that there are other theories regarding brain mechanisms contributing to dyslexia, including the magnocellular theory [31, 32], rapid auditory processing theory [33, 34], and the cerebellar theory [35–37]. For a review, see Ramus et al. [38]. There is also research indicating that naming speed plays a role in a child's ability to become a fluent and automatic reader [39, 40]. However, researchers debate whether the naming speed deficit is part of a phonological factor or whether rapid naming is a unique contributor to reading achievement [41, 42]. Lastly, there is a plethora of research identifying specific subtypes of developmental dyslexia, although there is little empirical evidence that subtyping and targeting the deficits delineated by this process leads to improved outcomes. A variety of functional and structural imaging methodologies, including functional magnetic resonance imaging (fMRI), positron emission topography (PET), magnetic source imaging (MSI), voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and related techniques such as event-related potentials (ERP), have shown differences in activation patterns and brain structure comparing dyslexic and typically achieving children and adults in an anterior left frontal region and two posterior left hemispherical regions. More specifically, the left inferior frontal gyrus (IFG; anterior), the left temporal parietal, the left occipital temporal

regions, and 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 (for reviews, see Schlaggar and McCandliss [10] and Shaywitz, Gruen, and Shaywitz [43]).

The left IFG has been associated with articulation and naming [44], the left temporal parietal region with the integration of phonological processing and orthography [45, 46], and the left occipital temporal regions with processing the visual features of letters and words [47, 48]. This area has been termed the visual word form area (VWFA) 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 [48, 49].

Cross-sectional studies comparing children and adults with and without dyslexia using PET and fMRI have indicated hyperactivation in the left frontal gyrus and hypoactivation in the left perisylvian regions and left occipital temporal regions in the participants with dyslexia during reading-related and phonological awareness tasks [50, 51], in both age-matched and reading-matched groups [52, 53]. The latter study by Hoft and colleagues also incorporated voxel-based morphometry (VBM) in order to more closely examine the structural brain differences that may underlie the concomitant functional differences in dyslexia. VBM is a method that makes voxel-by-voxel comparisons in the concentration of gray matter between two groups. They found reduced gray matter volume in the left parietal region that corresponded to areas of reduced activation in participants with dyslexia relative to nondyslexic participants. Atypical gray matter morphology in the left temporal region has also been reported in other studies using VBM [54, 55]. Along these lines, Galaburda's post-mortem microscopic analysis of brains of individuals with dyslexia revealed abnormalities in the form of ectopias, dyslaminations, and scars, which provides evidence for a disruption in gray matter [56, 57].

Brain activation patterns have been studied longitudinally with fMRI in response to reading intervention programs [49, 58]. These studies further confirm the importance of left temporoparietal regions in reading. They also reveal that some children with dyslexia evidence normalization of activity, whereas others have more persistent problems.

Cross-sectional studies of children with dyslexia using MSI, which measures the location and time course of brain's magnetic activity, have shown an absence of a left lateralized response in perisylvian regions when reading words [59]. Children with dyslexia showed greater activation in the right temporoparietal area that the authors interpreted as indicating a compensatory role of the right hemisphere. Similar to the fMRI studies showing normalization of activity after intervention, Simos and colleagues have shown that similar areas previously showing timing differences in children with dyslexia were also normalized [60, 61] after a combination of two interventions. The first intervention targeted phonological and decoding skills (*Phono-Graphix*) [62] and the second intervention assisted with reading fluency (*Read Naturally*) [63]. A weakness of these studies, though, is that they did not employ an objective approach to determining the number and location of magnetic sources (cf. Papanicolaou et al. [64]).

While these functional imaging studies have focused on gray matter, a special type of structural MRI scan, diffusion tensor imaging (DTI), allows measurement of white matter. For a review of white matter pathways in reading, see Ben-Shachar [65]. Although conventional MRI is excellent at discriminating white matter from gray matter, it is poor at discriminating the fine tissue structure within the white matter. DTI provides information about the alignment and integrity of white matter axons in the brain by measuring intracellular and extracellular water diffusion. Fractional anisotropy (FA) can be derived from DTI. FA values are a measure of microstructural features within a voxel and reflect the orientation dependence of diffusion; high FA values within a voxel suggest the presence of highly directional diffusion such as that seen in normal white matter fiber tracts. Studies looking specifically at white matter pathways using DTI have shown that the left temporoparietal region in children [66, 67] and adults [68] yields lower FA values among poor readers. In children, this area has been identified within the superior portion of the corona radiata at the level of the corpus callosum. DTI was also used to study fibers from the temporal lobes to the corpus callosum [69]. White matter diffusion was inversely related to phonological awareness performance in the posterior corpus callosum. The authors hypothesized

that the finding may reflect that better phonological awareness performance is related to fewer but larger axons in this region connecting the right and left temporal lobes. Larger axons allow for faster conduction of signals compared to smaller axons. This result is consistent with the temporal processing theory of dyslexia, which purports that good readers are better at processing rapidly changing visual and auditory information [70, 71].

Brain Mechanisms and Correlates of Dyscalculia

Development of quantitative abilities includes an abstract sense of numbers and quantity, counting, and calculation, and has not been studied as extensively as reading. Unlike reading, which must be learned, humans are believed to be born with an innate sense for number estimation and simple calculations [72, 73]. However, there are also higher level math skills that require explicit teaching.

Dehaene and colleagues [74, 75] 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 horizontal segment of the intraparietal sulcus (HIPS) in both hemispheres, 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 [76, 77], the HIPS regions have been shown to activate alone during number detection and number comparison tasks regardless of the modality [78, 79].

Both fMRI studies and lesion studies have shown that areas within the HIPS in both hemispheres are critical for number processing (for a review, see Dehaene [75]). The HIPS is activated when performing mental arithmetic (greater activation for subtraction vs. multiplication) and number comparison (right hemisphere greater than left hemisphere). HIPS 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, but may not be a specific finding as the left AG has connections to the reading and the language system. Dehaene et al. [75] 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 HIPS in that it does not mediate subtraction tasks, number comparisons, or number representations. 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 [80, 81]. Changes in activation patterns of the left AG have also been associated with math complexity [77].

Finally, the PSPL has shown activation during tasks requiring number comparison [79, 82], number estimation [83], subtraction [84], and counting [85]. This area has also been associated with mediation of visuospatial tasks, attention, eye orientation, and spatial working memory [86, 87]. Dehaene et al. acknowledge a degree of caution in interpreting these findings and the need for further research to substantiate their provisional claims about this region.

Early imaging work exploring the neural basis of impaired arithmetic processing was conducted in females with Turner syndrome (TS) and fragile X, populations in which a deficit in arithmetic skills is present. PET [88] and anatomic MR studies in patients with TS [89, 90] showed glucose hypometabolism in bilateral parieto-occipital regions and reduction in brain volume in bilateral parieto-occipital regions. In an fMRI study, girls and young adult females with fragile X showed activation in the left parietal and bilateral frontal regions during tasks of arithmetic calculations involving two and three operands, while control subjects showed bilateral frontal and parietal activation [91]. Further support of these circuits' involvement in arithmetic processing comes from fMRI studies in children with developmental dyscalculia. The first fMRI study in children with developmental dyscalculia ($n = 18$) compared to control children ($n = 20$) found significantly less activation in the left intraparietal sulcus (IPS), the right IFG, and the right middle frontal gyrus (MFG) during a task of approximate calculation and that activation in the left IPS, the left IFG, and the right MFG correlated with behavioral performance [92]. The same researchers, using VBM, found that children with developmental dyscalculia ($n = 12$) compared to control children ($n = 12$) exhibited significantly less gray matter volume in the right IPS, the anterior cingulum, the left IFG, and the bilateral

MFG, as well as significantly decreased white matter volume in the left frontoparietal lobe and the right parahippocampal gyrus [93].

One study used DTI to investigate white matter integrity in children and adolescents with velocardiofacial syndrome [94], a genetic syndrome. Performance on a mental arithmetic task correlated with FA values in white matter tracts in left inferior parietal regions in children and adolescents with velocardiofacial syndrome. This finding was not present among healthy participants. A second study used DTI to investigate the relationship between white matter and math skills in typically developing children [95]. Performance on two written tests requiring mathematical calculations and application of math principles correlated with FA values in two left hemispherical regions, the left superior corona radiata and the left inferior longitudinal fasciculus [95]. More research is needed to clarify the role of white matter in developmental dyscalculia.

Brain Mechanisms and Correlates of Dysgraphia

Spelling, composition, and handwriting are the skills needed for writing development [96]. There is less consensus regarding the identification of disorders of written expression compared to reading and math disorders, and many times writing disorders are included with other learning disabilities. Although developmental dysgraphia is defined as impairment in the ability to write, it includes difficulty in handwriting, spelling, and written expression [3]. Components of writing are related to reading (mapping of phonology to orthography), but writing is not the inverse of reading. Berninger and colleagues [97] 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 is based on the assumption 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 [98]. To date, our understanding of brain regions involved in writing is based on lesion studies in individuals with acquired agraphia. There have been no functional imaging studies in adults with developmental dysgraphia while they are performing spelling or writing tasks. There is one fMRI study with children who are good and poor writers [3].

Neuropsychological studies of focal brain lesions mostly implicate left perisylvian and left superior parietal regions [99]. These studies have demonstrated that lesions to the left AG, the posterior MTG, the inferior temporal gyrus, and the inferior occipitotemporal region may produce lexical agraphia (greater difficulty in spelling irregular words). Damage to the anterior supramarginal gyrus and/or the insula may yield phonological agraphia (greater difficulty in spelling unfamiliar words or nonwords) (for a review, see Henry and colleagues [100] and Roeltgen [101]). As Fletcher et al. [3] report, it is not known whether these same locations are essential for the development of writing, or if they are compromised in individuals with developmental dysgraphia.

In the few fMRI studies that have examined either children or adults performing spelling tasks in English, healthy participants were used [102–104]. Increased activation was exhibited in the left IFG and the left fusiform gyrus in children. When adults were compared to children, greater activation in bilateral AG and bilateral superior SPL areas was demonstrated. Richards et al. [105] attempted to isolate brain regions that mediated writing skills during an fMRI task contrasting finger sequencing and finger tapping in children at the end of fifth grade who had participated in a longitudinal writing study. Both poor and good writers were included in the study. They identified 11 brain regions with an activation pattern that correlated with both handwriting and spelling. They also found a gender difference in the left superior parietal region with boys showing hypoactivation in this area compared to girls. More studies are needed, especially in children and adults who have been diagnosed with developmental dysgraphia.

Treatment

Information regarding specific intervention programs for LDs is outside the scope of the chapter, but we would like the reader to be aware of some background information and resources for additional information.

It is clear that LDs do not resolve without intervention. Most emphasis in this area has focused on treatment for developmental dyslexia. 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. However, common school-based interventions are more likely to stabilize reading rather than remediate it [106]. There are many commercial programs available, some of which are research based. Interventions need to be intense, systematic, explicit, and delivered in small groups [107]. Gains have been maintained for about half of the children for at least 1 year once they have returned to their standard curriculum [106]. Shaywitz [108] 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 [109].

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 [108, 110], 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 [110, 111]. The National Reading Panel [112] reports that effective reading instruction requires the incorporation of phonemic awareness, phonics, fluency, vocabulary, and comprehension.

Interventions for developmental dyscalculia have focused on number sense, math facts, calculations, conceptual knowledge, and procedural knowledge. Unlike developmental dyslexia, in which there is consensus of research over the past 30 years pointing to a core deficit in phonological awareness, there has been no core deficit identified in developmental dyscalculia until recently. Wilson and colleagues [113] have recently postulated that number sense is a core deficit in developmental dyscalculia, which they define as a deficit in both the ability to represent numerical magnitude and the ability to connect quantity and symbolic representations of numbers [113, 114]. They have developed a computerized adaptive intervention program ("The Number Race") that is just beginning to be investigated. 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 [115] 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.

Even less is known about interventions for developmental dysgraphia, with most interventions focusing on spelling and written expression. In a recent review of 19 studies examining both spelling and reading interventions on spelling outcomes, the authors identified five key factors that contributed to improved spelling: 1) instructional delivery (error correction procedures in which the teacher reproduced the student's error prior to presentation of the correct response), 2) limiting the number of words sequentially learned, 3) computer-assisted instruction, 4) multisensory training, and 5) systematic study and practice [116]. Another recent review of handwriting remediation from an occupational therapy perspective compared 11 studies with a variety of treatment approaches, including perceptual–motor, visual–motor, motor control, individualized interventions/exercises, and supplementary handwriting instruction [117]. The authors found that overall interventions were effective mostly with regard to legibility, but not speed.

For more specific information regarding interventions for LDs, see Fletcher et al. [3, 118] and Hale and Fiorello [118]. 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 [2] may be consulted.

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. Such a process is likely (now or in the future) to occur primarily through the child's school. Neuropsychologists may continue to screen for academic skill deficits in children; provided that such deficits are not due to mental retardation, sensory impairment, or inadequate exposure to quality instruction, such children may be identified as being at risk for LD. Neuropsychologists also need to be aware of medical disorders (such as epilepsy) that may result in academic skill deficits and remain the most appropriate professionals to consult regarding a child's cognitive functioning in the context of a known or suspected medical disorder.

Screening for LD should, at a minimum, include measures of word reading, reading fluency, reading comprehension, calculation, and written expression. Approximately 5.4% of children in the United States received special education services due to LD in the most recent year for which data are available. Dyslexia remains the most common LD, followed by dyscalculia and dysgraphia. Family history is a significant risk factor for all LDs, and some candidate genes have recently been identified.

Brain-imaging studies have revealed that the left IFG, the left temporoparietal, and the left occipitotemporal regions tend to be hypoactive in children with dyslexia. Among children with dyscalculia, the horizontal segment of the IPS (bilaterally), the left AG, and the left posterior SPL have been implicated as critical for mathematical operations. The left perisylvian region and the left IFG appear to be important for spelling and writing operations.

Treatment for LDs is necessary, as they do not remit without intervention. Numerous approaches have demonstrated evidence of improvement in the academic skill(s) targeted, with phonological awareness training being a key area for dyslexia interventions. Increasing attention needs to be given to interventions for dyscalculia and dysgraphia.

Our knowledge of LDs has dramatically expanded over the past two decades, particularly with the advent of sophisticated brain-imaging techniques, but there continues to be a lack of evidence-based research identifying effective interventions for individuals with LDs. One reason for this is the heterogeneous nature of LDs and the difficulty in defining and classifying individuals with LDs. Furthermore, many studies have not isolated important demographic variables, intervention delivery methods, and types of intervention. In addition, there is a lack of randomized controlled trials comparing interventions. Nonetheless, the move toward operationalizing LDs as failure to respond to instruction holds promise, as it puts attempts at treatment in the forefront. We look forward to continued research that highlights the importance of interventions that work.

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Chapter 14

Frontal Lobe Disorders in Pediatric Neuropsychology: Attention-Deficit Hyperactivity Disorder and Tourette Disorder

Anthony L. Rostain

Introduction

This chapter will review current understanding of two neurodevelopmental disorders involving dysregulation of 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 along with behavioral disinibition, which are the hallmarks of the disorder and which account for 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 presents 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, 2]. At present, 3–6% of elementary schoolchildren 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.

Definition

The most widely used definition of attention-deficit disorders is provided by the *Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)* of the American Psychiatric Association [3], which outlines two major dimensions for the disorder:

DSM-IV 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

A.L. Rostain (✉)
Behavioral Health Center, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; Department of Psychiatry, University of Pennsylvania Health System, Philadelphia, PA 19104, USA
e-mail: rostain@mail.med.upenn.edu

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degree that is maladaptive and inconsistent with developmental level:

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 (not due to oppositional behavior or failure to understand instructions).
e. Often has difficulty organizing tasks and activities.
f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework).
g. Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools).
h. Is often easily distracted by extraneous stimuli.
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:

Hyperactivity

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.
c. Often runs about or climbs excessively in situations in which it is inappropriate (in 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."
f. Often talks excessively.

Impulsivity

g. Often blurts out answers before questions have been completed.
h. Often has difficulty awaiting turn.
i. Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Some hyperactive–impulsive or inattentive symptoms that caused impairment were present before the age of 7 years.
C. Some impairment from the symptoms is present in two or more settings [e.g., at school (or work) and at home].
D. There must be clear evidence of clinically significant impairment in 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. Types of ADHD

1. Combined – if both criteria A1 and A2 are met for past 6 months
2. Predominantly inattentive type – if only criterion A1 is met for past 6 months
3. Predominantly hyperactive–impulsive type – if only criterion A2 is met for past 6 months

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 [4]. 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 the 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

30 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 [5].

One particular 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 2.5 – 3 times. The presence of both of them along with smoking increases the risk nine fold [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. The motor circuit includes 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 premotor cortex, supplementary motor area, and motor cortex. Neural networks in this pathway are hypothesized to be disrupted in ADHD [7].

In addition to motor circuitry, 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 major subsystems of attention also 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 [8]. Imbalances of these and other pathways have been implicated in ADHD.

Pliszka et al. [9] 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.

Other recent reviews [10–13] implicate three related circuits that may be dysregulated in ADHD. The frontostriatal circuit is associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning. The frontolimbic circuit is associated with symptoms of emotional dyscontrol, motivation deficits, hyperactivity–impulsivity, and proneness to aggression. And the frontocerebellar circuit is associated with motor coordination deficits and problems with the timing and timeliness of behavior.

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 some to redefine ADHD as a developmental disorder of executive functioning (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 the EF are not fully developed at birth and show continuous development into early adulthood. The maturation 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. As Denckla has noted [14], "ADHD is a label for a heterogeneous group of

dysfunctions related to each of several nodes along the attentional/intentional network… from cerebellum up to and including prefrontal cortex… including neural substrates of activation, orientation, motivation and vigilance as these connect with and influence executive function."

Functional neuroimaging findings in ADHD date back to 1990 when Zametkin et al. conducted a PET study of 25 ADHD adults compared with 50 normal controls [15]. The ADHD subjects showed 8.1% decreased cortical activity in areas that were hypothesized to be underfunctioning (i.e., premotor cortex, prefrontal cortex, and basal ganglia). Subsequent structural and functional imaging studies have shown smaller, less active, and less developed brain regions in three areas: (1) *orbital-prefrontal cortex* (primarily right side) (genetics contributes to underdevelopment of this region, whereas acquired ADHD may be related to smaller inferior dorsolateral frontal region); (2) *basal ganglia* (mainly striatum and globus pallidus); and (3) *cerebellum* (primarily central vermis area, mostly right side) [10].

In addition to these areas, the anterior cingulate gyrus has been shown to be underactivated in ADHD patients who are performing an error detection task. The size of this network is correlated with degree of ADHD symptoms, particularly inhibition. Interestingly, there appears to be a 3-year lag in brain development with patients achieving typical brain volumes by age 16. Moreover, these results are not due to taking stimulant medication [16].

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 supersensitivity 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 metabolism, lending strong support to the role of NE and DA 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. Zametkin and Rapoport [17], in an excellent review of the neurobiology of ADHD, conclude: "Given the current interest in frontal lobe function in this disorder and the intricate relationship between cortex and striatum, a comprehensive model of the pathophysiology of this disorder and drug action should postulate the inhibitory influences of frontal cortical activity, predominantly noradrenergic acting on lower (striatal) structures that are driven by both direct dopamine agonists and controlled or modulated by higher inhibitory structures sensitive to adrenergic agonist. Such a model might account for the wide array of agents effective in treating symptoms of ADHD. Different sites of dysfunction in this 'circuit' would account for the array of presenting symptomatology from the pure attentional to the more impulsive" (p. 684).

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 behavior; 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 [1]. In addition, special populations have high rates of ADHD including patients with Tourette Syndrome, obsessive–compulsive disorder, autistic spectrum disorder, 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, and 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 disorders.

Among the impairments caused by ADHD, traffic violations and motor vehicle accidents are of particular concern. Long-term effects in adulthood include reduced educational attainment, lower income, more frequent job changes, unstable interpersonal relationships, and higher rates of arrest and convictions.

Assessment

The diagnostic evaluation of ADHD begins with a careful description of problem behaviors. When interviewing parents, it is important 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. 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.

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. Particular attention should be paid to potential toxic exposures such as lead and carbon monoxide [18, 19]. 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 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 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 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 be noted for signs of affective disturbance (i.e., anxiety, depression, and irritability), autism and other developmental disorders, and general intellectual functioning. Standard grade-level screening tests (e.g., Slosson Oral Reading Test) and perceptual motor tasks (including drawings and the Bender-Gestalt) 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 clinical 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 in order 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. Specific measures of attention and impulsivity are not required, although they may be helpful in assessing the effects of medication.

Treatment: Overview

Multimodal treatment of children with ADHD includes psychoeducational counseling, 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 the family, it is clear that no single treatment approach is sufficient and that in order to be effective, treatment must extend over long periods of time.

Children belong to several social systems including family, school, peer group, and community. Children with ADHD may relate to several additional professional helpers (both within and outside the school) including psychologists, counselors and other mental health and educational specialists. These professionals need to form cooperative relationships with the family, the child, and one another in order to maximize the chances of successful treatment. This requires close communication and occasional meetings to discuss overall treatment goals and plans for achieving these.

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 that the clinician offers the child and the family sufficient time to discuss their concerns and answer their questions. Factual information should be provided in a comprehensible fashion so as to clarify misunderstandings or confusion about the disorder. The clinician should emphasize the child's positive traits and the parents' strengths in order 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.

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, symptom severity, impairment, comorbidity, and parental attitudes. Children under 5 years of age are less likely to respond to medications and are at greater risk of having adverse side effects. School-age 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 may 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 medication is 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.

Psychostimulants

Modern medicinal use of psychostimulants dates back to the nineteenth 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 α-adrenergic and β-adrenergic receptors as well as on dopaminergic receptors via three mechanisms: (1) release of stored catecholamines (dopamine and norepinephrine); (2) direct post-synaptic stimulation; and (3) inhibition of presynaptic reuptake of released catecholamine. (Note: methylphenidate works primarily via mechanism 3, whereas amphetamine works via all three mechanisms.)

It is estimated that over 80% of children 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 [1, 19–21].

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, stomachaches). Irritability, dysphoria, heightened anxiety, lack of spontaneity, and over-sedation 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 actually be demonstrating early signs of a mood disorder rather than ADHD. This should prompt a change in medication and closer monitoring [21, 22].

Extremely serious side effects such as delusions, paranoia, and frank psychosis are rare but can be seen with overdosage and abuse of the medication. Recently, 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 nonresponse 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 problem 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 the clinical and adverse effects on a regular basis. If the child begins losing weight, the dose and schedule should be revised in order 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 the 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 the family to handle, it may be necessary to adjust or switch medications.

Atomoxetine

The first nonstimulant medication to be FDA approved for the treatment of ADHD is atomoxetine, a norepinephrine reuptake inhibitor that has been shown to have a moderately high effect size (0.4–0.6) in several studies involving children, adolescents, and adults with ADHD. The advantage of this medication is that it has milder side effects compared to the stimulants, and it is not a potential drug of abuse. The increase in CNS norepinephrine levels seen with this medication is associated with downstream increases in dopamine levels in the frontal cortex without changes in levels found in the nucleus accumbens or the basal ganglia. 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.

Guanfacine and Clonidine

Guanfacine and clonidine are alpha2-adrenergic agonists that were first introduced as antihypertensive agents. Both medications have subsequently been used as adjunctive treatments for ADHD, particularly in combination with psychostimulants. They modulate the tonic and phasic activity of the locus coeruleus and also have direct effects on neurotransmission in the prefrontal cortex, greatly enhancing the effects of norepinephrine and dopamine [7]. These agents 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. Guanfacine has been shown to improve symptoms of both impulsivity/hyperactivity and inattention and has received FDA approval for the treatment of ADHD.

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.

Behavior 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 reinforcement, rewards, response cost, punishments, contracts, token economies, extinction procedures, environmental manipulation, and stimulus controls, parents and teachers can be taught to exert a positive influence on behavior.

The first step in developing a behavior 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 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 behavior 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 she/he actually 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, managing anger, 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 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 should 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 upset 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 she/he 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 a sufficient number of 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) in order 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 in order to insure that it is helping the child to achieve the desired behavior 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 80% of the time. If she/he 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 at it. 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.

It should always be kept in mind that the purpose of any behavior 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 behavior management program running. Although it takes a great deal of patience, resourcefulness, and perseverance, parents can look forward to modest 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.

Long-Term Outcome

While it was once believed that hyperactive children "outgrew" their condition, evidence is accumulating that ADHD persists into adolescence and adulthood. It appears that over 50% of children with ADHD will continue to exhibit some symptoms of the disorder (e.g., inattention, impulsivity) in later life. Associated difficulties for adolescents include school failure, aggression, antisocial behavior, poor social skills, emotional immaturity, low self-esteem, and interpersonal conflicts. Adults have an increased incidence of anxiety, low self-esteem, personality disorders (especially antisocial personality disorder), alcohol and substance abuse, interpersonal difficulties, and occupational changes. For instance, Kessler et al. [23] found that 4.4% of adults surveyed in the National Comorbidity Survey Replication study (2006) met criteria for ADHD, and a substantial proportion of these individuals also met criteria for other psychiatric disorders. Negative outcomes are associated with factors such as aggression and antisocial behavior, severity of hyperactivity and impulsivity, lower intelligence, lower socioeconomic status, and the presence of additional individual and family psychopathology (e.g., alcohol or substance abuse) [1, 24, 25].

Although follow-up studies raise serious concerns about the long-term outcomes of ADHD children, it should be kept in mind that individual outcomes cannot be predicted from group-derived statistics. Given that ADHD is a heterogeneous condition and that the poorest outcomes are associated with aggression and antisocial behavior rather than with the core symptoms of ADHD, it is best to regard the prognosis as uncertain and mediated by factors other than ADHD. Professionals and parents need to take a "long view" of ADHD as a chronic condition in order to avoid a sense of failure or frustration if the course of treatment is long and arduous.

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, non-rhythmic repetitive movement, gesture, or utterance that typically mimics some fragments of normal behavior.

Simple motor tics are usually fast, darting, and meaningless (e.g., shoulder shrugging, eye blinking, head jerking, face grimacing, and 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, and 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 [26–28].

Simple phonic tics are similarly fast, darting, and meaningless (e.g., coughing, grunting, yelping, humming, sniffing, throat clearing, barking, and 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-IV criteria for Tourette Disorder include the following: [3]

- Multiple motor and one or more phonic tics at the same time
- Multiple tics, usually in bouts, nearly daily or intermittently for more than 1 year – no tic-free period for more than 3 months
- Marked distress or significant impairment in social, occupational, or other important area of functioning
- Onset before 18 years
- Disturbance not due to direct effects of substances (e.g., stimulants) or underlying medical condition

Other DSM-IV clinical syndromes involving tics include transient tic disorder; chronic motor or vocal tic disorder; and tic disorder, not otherwise specified. 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. During 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. Leckman et al. [29] 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 end 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 focal perceptions or sensations that a tic is about to occur. They are usually localized to a specific body part and are seen in about 37% of young children and up to 90% of adults. 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 "unvoluntary" responses to involuntary sensations [28].

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 h 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 [30] which can be distinguished from typical symptoms seen in OCD by their somatosensory, visceral quality. Several studies point to the prominence of a sense of "incompleteness" and of "imperfection" ("just not right") that separates tic-related OCD from non-tic OCD [31, 32]. From the standpoint of intervention, 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 is highly variable due to differences in both epidemiologic study methods and genetic variations across populations. For instance, a study of British schoolchildren 13–14 years of age found 185 cases per 1,000 (1.85%) [33]. A US study of 4,000 schoolchildren found a TD prevalence rate of 1 per 1,000 (0.1%) [34]. This wide variance in prevalence points to the problems of ascertaining TD cases in the general population.

Risk factors for TD include gender (male predominance), perinatal adversity, presence of pervasive developmental disorders, and heredity. 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% [35–37]. 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 [38, 39].

Unfortunately, despite compelling evidence from twin and family genetic studies pointing to the heritability of TD, the set of genes contributing to the expression of the disorder has not yet been identified. This is due to several factors including difficulty in defining the phenotype, a more complicated mode of inheritance that 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 the majority of cases in the population. For example, recent studies have found atypical genes in several TS patients (including chromosomal translocation, point mutation, and missense mutation) at the *SLITRK 1* locus [40, 41]. 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 [42]. It appears that the protein expressed by this gene is associated with projection neurons of corticostriatal–thalamocortical (CSTC) circuits, and that it plays a significant role in the development of these circuits [43]. While it is clear that these mutations at the *SLITRK 1* locus are *not* found in most TS patients [44], this line of research may prove helpful in linking specific genetic mechanisms to neurodevelopmental psychopathology in TD and related disorders of CSTC circuitry.

Another interesting proposed etiology for TD and tic disorders is based on neuroimmunology. In 1998, Swedo and colleagues [45] proposed that a subset of children with tics, TD and/or OCD whose course is marked by sudden onset and rapid exacerbation of symptoms were due to the sequelae of streptococcal infection. This syndrome, referred to as PANDAS (for pediatric autoimmune neuropsychiatric disorders

associated with streptococcal infection), remains controversial. On the one hand, there is evidence showing that first-degree relatives of children with PANDAS have higher rates of tic disorders and OCD than do the general population [46] and that susceptibility for the syndrome is conferred by a trait marker for rheumatic fever: the monoclonal antibody D8/17 [47]. Moreover, additional cohorts of PANDAS patients have been identified, and a double-blind treatment study of plasmapheresis versus intravenous immunoglobulin therapy showed that tics and obsessive–compulsive symptoms were reduced in those patients receiving plasmapheresis [48]. On the other hand, two longitudinal prospective studies failed to find an association between Group A beta-hemolytic strep infection and the onset of neuropsychiatric symptoms [49, 50]. A prospective study of 40 matched pairs of children, one set with PANDAS and the other set with chronic tic disorder and/or OCD, failed to find an association between Group A strep infection and exacerbation of tic or OCD symptoms in the PANDAS group over the 2-year study period [51], leading the authors to question the validity of the diagnosis itself. Another study failed to find any correlation between serial immune markers and clinical exacerbations in patients with diagnosed PANDAS [52]. Thusfar, the evidence for a clear link between streptococcal infections and symptom exacerbation of tics and OCD is contradictory at best, raising the possibility that other neuroimmunologic triggers may be involved in the pathogenesis of TD and related disorders. A great deal more research needs to be carried out to elucidate the precise links between immune response and neuropsychiatric disease, and to distinguish between PANDAS and conditions like Sydenham's chorea (a proven neuroimmunologic disease).

Neurobiology

A growing body of scientific research is converging on the role of corticostriatal–thalamocortical (CSTC) circuits in the pathophysiology of tic disorder, TD, and related conditions. There are several excellent reviews of progress in this area [27, 28, 53, 54] 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, the subthalamic nucleus, the globus pallidus, and the 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. 14.1).

The basal ganglia act to enhance desired behaviors and inhibit unwanted or competing behaviors. 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, in turn, 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 nicely diagrams key features of the pathophysiology of TD as it is currently understood (Fig. 14.2).

A number of 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. Recent PET studies of dopaminergic systems have demonstrated increased dopamine receptor density in the ventral striatum of patients with TD [55] suggesting hyperinnervation in these structures. Other studies have documented high concentrations of dopamine transporters along with increased intrasynaptic dopamine release. Taken together, these findings indicate that TD results, in part, from atypical dopamine functioning in the CTSC. Singer [28] 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

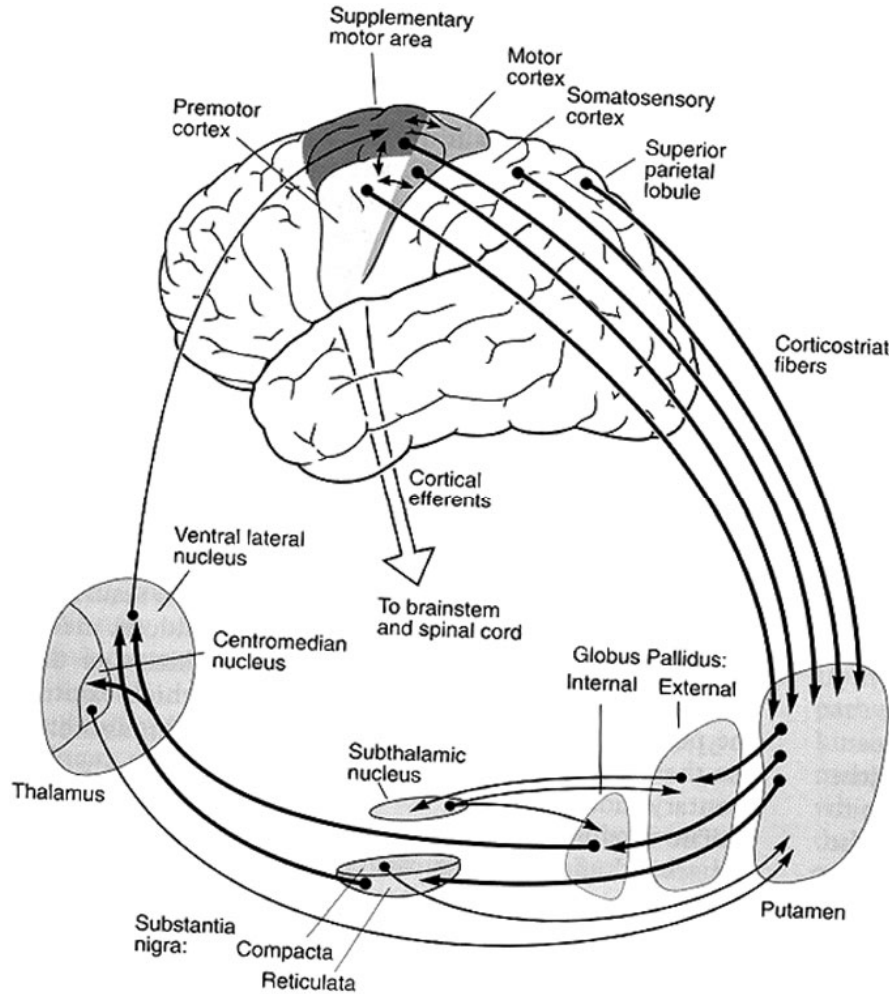

Fig. 14.1 Neuroanatomic connections of the cortico-striato-thalamo-cortical (CSTC)

of dopamine. If TD is associated with excess nigrostriatal dopaminergic activity, either via supersensitive dopamine receptors, dopamine hyperinnervation, or abnormal pre-synaptic terminal function, a substantial hyperkinetic effect is expected... Because dopaminergic fibers arise from the ventral segmental area and form synapses on both pyramidal neurons (stimulate) and interneurons (inhibit) within the prefrontal cortex, we have hypothesized a prefrontal dopaminergic abnormality" (p. 154).

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 results are impairments of CTSC circuits which cause impaired inhibition (tics), decreased restraint or self-control (impulsivity), and impaired executive functioning (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 such as impulsivity, poor attentional control, tics, obsessive–compulsive patterns, and emotional dysregulation emerge. Indeed, recent reports suggest that functional disturbances within these frontostriatal circuits lead to problems with "self-regulatory control" which may form the

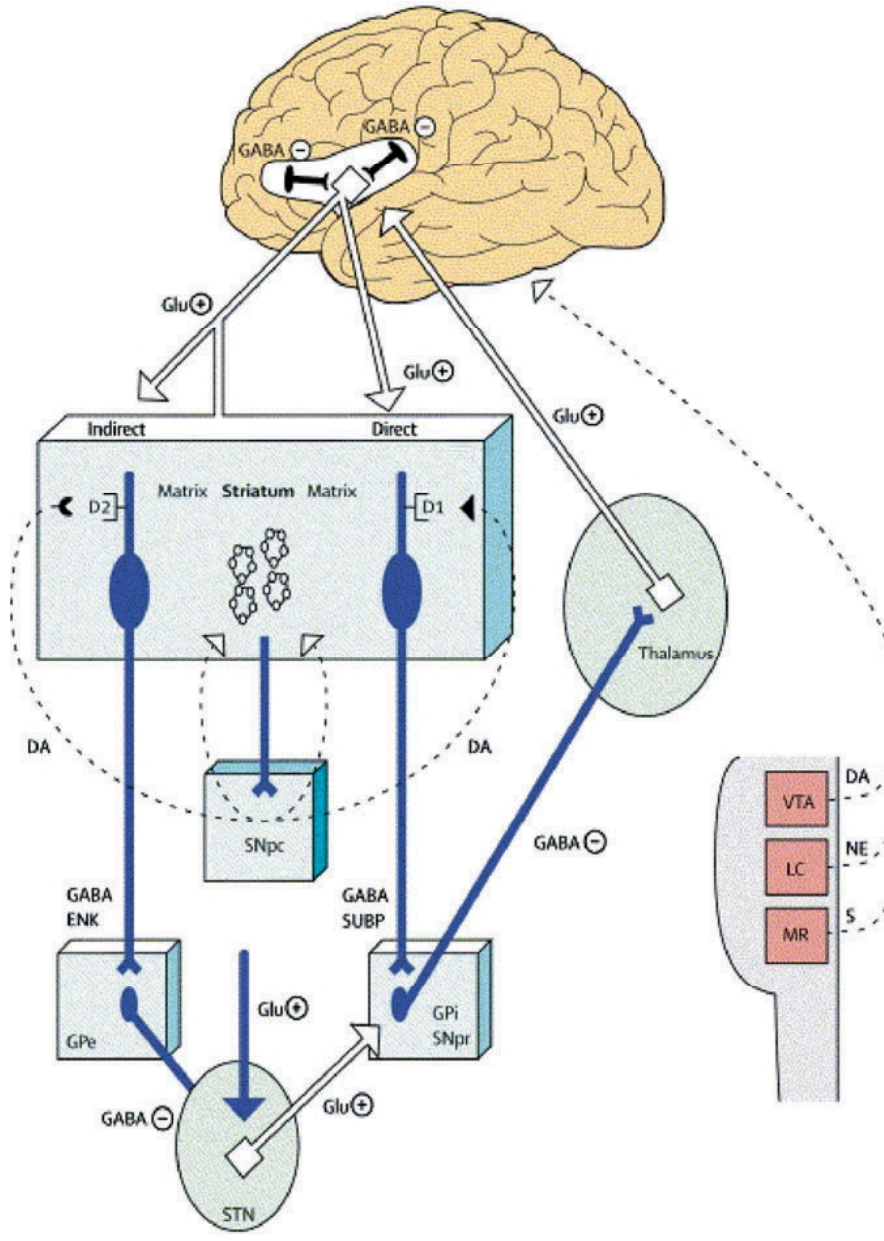

Fig. 14.2 Pathophysiology of TS. This figure shows the corticostriatal–thalamocortical pathway and ascending cortical inputs. Hypothesized abnormalities have included disorders of excess excitation or diminished inhibition; disruptions in frontal cortex, striatum, or striosomes; and abnormalities of various synaptic neurotransmitters. DA, dopamine; ENK, enkephalins; Glu, glutamate; GPe, globus pallidus externa; GPi, globus pallidus interna; LC, locus coeruleus; MR, median raphe; NE, norepinephrine; S, serotonin; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; SUBP, substance P; STN, subthalamic nucleus; VTA, ventral tegmental area (from Singer [28])

underpinnings of several childhood psychopathologies including Tourette disorder, obsessive–compulsive disorder, trichotillomania, bulimia nervosa, and anorexia nervosa [56].

Associated Conditions/Comorbidity

As mentioned above, tic disorders and TD are often accompanied by other psychiatric conditions, most notably ADHD, OCD, other 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 [57, 58]. The community prevalence rate of ADHD is roughly 5%, so the 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 of the aggression and delinquency seen in the TD population (i.e., TD-only patients show the same rates of these problems as control populations). 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 do the control population. 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 patients. In sum, 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.

Obsessive–compulsive disorder is also highly prevalent among patients with TD and carries with it significant risk. Epidemiologic evidence over the past 20 years indicates that whereas the population prevalence of OCD in children and adolescents is between 1 and 3%, the rate in patients with TD is much higher. Ranges of 20–60% have been reported for OC behaviors, and 11–40% for OC disorder [26, 28]. More precise figures are difficult to obtain because of wide variations in methodology.

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 clinical as opposed to community samples. The epidemiology of these conditions in nonclinical 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 [59].

Aggressive symptoms in TD have also been reported in both community surveys and clinical 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 [60]. 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 "RAGE" or "recurrent anger-generated episodes" [61].

Neuropsychological Functions

Learning, memory, and executive functioning disorders have been widely investigated in children with tic disorders and TD. There is still no clear consensus as to whether neuropsychological deficits are a characteristic of the disorder or are better viewed as a comorbid feature [62]. There is general consensus that overall intellectual ability is in the normal range, and evidence suggests that there are lower performance IQ scores in this population. Controversy remains regarding the nature of the discrepancies seen between verbal and nonverbal abilities. 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. [63] 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. A subsequent study by the same group found no deficits in social cognition in TD subjects. The important point to keep in mind is that each child with tic disorder or TD needs to be evaluated individually for the presence of learning, memory, and executive functioning difficulties, and the presence of ADHD symptoms may be a harbinger of other neuropsychological problems.

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 in executive functioning.

Motor and phonic tics should be delineated and quantified as precisely as possible. The best instrument available is the Yale Global Tic Severity Scale (YGTSS) [64], 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 to 25) can be obtained, as can the total tic score (0–50). Scores of >20 are considered to be 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) [65] is a clinician-administered structured interview that identifies the patient's obsessions and compulsions, and 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 (MASC) and the State-Trait Anxiety Inventory for Children (STAIC), as well as the Children's Depression Inventory (CDI) and the Children's Depression Rating Scale – Revised (CDRS-R). Particular attention should be paid to the presence of mood swings and profound irritability which might indicate 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-IV (ADHD RS-IV), the Conner Parent and Teacher Rating Scales (CPRS, CTRS), and the Barkley Symptom Checklist. Other problems such as oppositional defiant behavior, serious rule breaking, temper tantrums, and aggressive acts toward property and people warrant careful review and evaluation. Severe tics coupled with anxiety and moodiness can result in hostile and aggressive acts, 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 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 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 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).

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 TD, helping them to learn about it (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, and classmates) about the facts regarding TD so as to minimize 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 the 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 ultimate 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 best to focus on the most severe, prominent, and impairing symptoms first. For example, if impulsivity and hyperactivity are more disruptive than 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 the 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 untreated. 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 new 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) [66, 67]. The basic components of HRT are awareness training and response practice. 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") so as 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. Relaxation training and contingency management have *not* been proven to be effective in reducing tics.

Other psychosocial interventions that have been shown to be helpful in managing ADHD, OCD, and aggressive behaviors utilize cognitive behavioral therapy strategies. For instance, behavior 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, and 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. 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 for help 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 the collaborative problem-solving model [68] 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. 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.

Medications

Tics should be treated medically only if they are causing functional impairment, interference with social relationships, or physical discomfort and bodily harm. In the USA, the medications most commonly used for tics are alpha2-adrenergic agonists (clonidine and guanfacine) and dopamine-blocking agents (i.e., neuroleptics). While the precise mechanisms of action of these agents are beyond the scope of this chapter, it is important to note that the differences in these two classes of medications permit them to be used together.

The alpha2-adrenergic agonists have been shown to be effective for close to 30 years and also have the benefit of reducing the symptoms of ADHD. They can also be combined with stimulant medications in comorbid TD and ADHD without exacerbating tics. Some papers report lower effectiveness of the adrenergic agonists in controlling tics as compared to neuroleptics, but other studies show comparable tic control. 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.

Dopamine-blocking antipsychotic medications were first shown to be effective in the treatment of tics in the mid-1960s when haloperidol was reported to be successful in a number of case studies. Subsequent controlled clinical trials demonstrated the efficacy of haloperidol, pimozide, and fluphenazine in reducing the severity, intensity, and frequency of tics. In Europe, tiapride is the preferred dopamine-blocking medication because it does not interfere with cognitive functioning. Growing concern about the side effects of 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. Over the past decade, the introduction of second-generation or "atypical" neuroleptics (e.g., risperidone) has led to a shift in the use of these agents because of a more favorable side effect profile. While these newer medications may have fewer side effects, the evidence for their efficacy is not as well established leading some practitioners to prefer the typical antipsychotics [27, 28, 69, 70].

Additional medications that have proven helpful in the treatment of tics include benzodiazepines (e.g. clonazepam), baclofen, tetrabenazine, pergolide, and donepezil. More recently, botulinum toxin injections, topiramate, gabapentin, levetiracetam, nicotine, and delta-9-tetrahydrocannabinol have also shown promise as anti-tic medications, although their use remains investigational.

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, stomachache, 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 seen in patients with tic disorder or TD can be treated with stimulants, alpha2-adrenergic agents or atomoxetine. Earlier caution about worsening of tics from stimulant medications has been challenged by recent studies. The Tourette Syndrome Study Group 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 [71]. 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 section "Attention-Deficit Hyperactivity Disorder", can improve attention and impulsivity as well as tics. Finally, atomoxetine, also discussed before, has recently been shown to be effective in reducing tics in children with comorbid ADHD [72].

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 [61]. 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.

Somatic Treatments

Experimental somatic treatments for intractable TD include deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT) [73]. DBS, a reversible neurosurgical procedure, has been 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 [74]. An RCT of this placement of DBS electrodes also yielded positive results [75]. However, as yet there have been no carefully controlled randomized studies to determine the optimal placement of electrodes nor to evaluate whether the risks (infection, stroke, neurological sequelae, and blurred vision) are worth the benefits of treatment. It is important to exhaust all other pharmacologic options before proceeding with this procedure. Case studies and small case series have reported positive results from rTMS and ECT for severe TD, but it is important to note that these were unblinded and uncontrolled experiments [69, 73]. 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 for adults with severe and intractable TD.

Prognosis/Long-Term Outcomes

In general, the prognosis for TD is very good [76–79]. Most children will outgrow their symptoms by the end of adolescence, with little or no long-term consequences. 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 Association of America can also play a vital role in helping patients and families feel connected to a larger community of support.

Table 14.1 Medications for tics. Adapted from Singer [28] and Srour, Lesperance, Richer, Chouinard [70]

Alpha2 adrenergic agonists	Dopamine antagonists
Clonidine	Haloperidol
Guanfacine	Pimozide
Benzodiazepines	Fluphenazine
e.g., Clonazepam	Sulpiride
	Tiapride
Baclofen	Aripiprazole
Tetrabenazine	Risperidone
Pergolide	Olanzapine
Donepezil	Ziprasidone
	Quetiapine

Table 14.2 Medications for TS + OCD. Adapted from Singer [28] and Srour, Lesperance, Richer, Chouinard [70]

Selective serotonin reuptake inhibitors	
Fluoxetine	Sertraline
Fluvoxamine	Citalopram
Paroxetine	Escitalopram
Serotonin–norepinephrine reuptake inhibitors	
Clomipramine	
Venlafaxine	

Note: High doses of SSRIs and SNRIs may actually worsen tics and OCD symptoms.

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Part IV
Aging

Chapter 15

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) co-occur so that there is a fair percentage of patients who have mixed dementias. This is illustrated in Fig. 15.1 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 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,

C.E. Whatmough (✉)
Department of Neurology and Neurosurgery, McGill University, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote-Ste-Catherine Road, Montreal, QC, Canada H3T 1E2
e-mail: christine.whatmough@mcgill.ca

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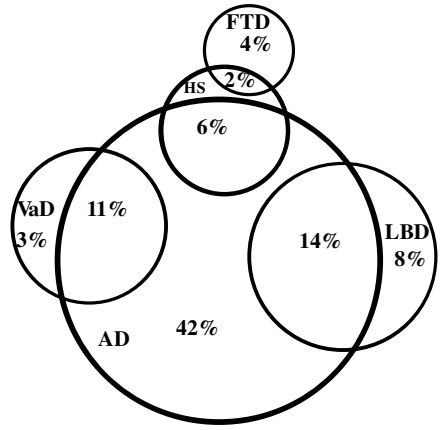

Fig. 15.1 The relative prevalence of dementia diagnosis postmortem from the State of Florida Brain Bank. All had been diagnosed with dementia antemortem. AD, Alzheimer's disease; FTD, frontotemporal dementia; HS, hippocampal sclerosis; LBD, Lewy body dementia; VaD, vascular dementia. Percentages and overlaps of ≤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

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 subtests 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 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 15.1, 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

Table 15.1 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.

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 15.1, 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 15.1) 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. 15.1), 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.

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 15.2, 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. 15.1). 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.

Table 15.2 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.

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 15.1) 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 15.1, 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.

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Chapter 16

Theoretical Perspectives on Cognitive Aging

Ayanna K. Thomas, Jennifer B. Dave, and Bailey M. Bonura

Aging is a broad concept that includes physical changes in our bodies, psychological changes in our minds and mental capacities, social psychological changes in what we think and believe, and social changes in how we are viewed and what is expected of us. We write this chapter to examine the changes in our mental capacity, or cognitive changes, associated with aging. Cognitive psychologists, neuropsychologists, and clinical geropsychologists each bring unique perspectives to our understanding of cognitive aging. The primary function of this chapter is to examine cognitive aging through the varied perspectives offered by cognitive psychologists (i.e., the first author) and clinical geropsychologists (i.e., the second author). We (the authors) attempt to blend our unique perspectives in order to engage in a comprehensive discussion of cognitive aging.

Historical Perspective

For centuries, transformations in the aging body have been documented and studied, yet the aging brain and higher cognitive functions have been virtually ignored. However within the past four decades, there has been more attention directed toward the aging brain. Through the efforts of neuroscientists, neuropsychologists, gerontologists, and cognitive psychologists, we now have a better understanding of changes in cognitive function that result from normal aging. Present-day neuroscientists and neuropsychologists that examine cognitive aging operate under the paradigm of cortical localization and cerebral dominance. The tradition of cortical localization research dates back to the sixteenth century and Emanuel Swendenborg, who reasoned that cortical localization could be used to explain cognitive changes resulting from brain injury. By using functional localization techniques, Swendenborg identified distinct brain areas responsible for movement [1].

Like Swendenborg, Franz Joseph Gall recognized the importance of functional localization and reasoned that the frontal portion of the brain was particularly important for cognitive function. Gall theorized that the brain consisted of many specialized organs, and that these were reflected in the pattern of bumps on the skull, developing the tradition of phrenology [2]. Although much of Gall's reasoning was flawed, his and Swendenborg's basic premise about cortical localization was correct; different cortical areas give rise to different cognitive behaviors.

Scientists such as Jean-Baptiste Bouillaud, Paul Broca, and Carl Wernicke examined how damage to specific areas of the brain resulted in deficits in cognitive performance. For example, Bouillaud was one of the first researchers to publish cases of patients losing their ability to effectively speak after head trauma. His research and observations led him to propose that the brain houses two types of speech areas, the primary being located in the anterior portion of the cortex [3]. Broca shared many of the same ideas about cortical localization as Bouillaud and further advanced the acceptance of cortical localization into the mainstream of scientific thought. Broca's most famous patient, Leborgne, demonstrated complete loss of speech

A.K. Thomas (✉)
Department of Psychology, Tufts University, Medford, MA 02155, USA
e-mail: ayanna.thomas@tufts.edu

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production, though he was able to comprehend language. After he died, his autopsy demonstrated a large "softening" of the tissue of the third convolution of the left hemisphere's frontal lobe [4]. In addition, due to Leborgne's other deficits in "intellect" as his lesion spread throughout the anterior portion of his brain, Broca reasoned that the frontal lobes must also be crucial for other executive functions besides speech.

The research and observations of these early neuropsychologists serve as the foundation for modern cognitive neuropsychology and cognitive neuroscience. Cognitive neuroscientists have applied the principles of functional localization to the study of cognitive aging, with the understanding that the aging brain, like the aging body, undergoes overwhelming transformations. These transformations are intimately linked to changes in cognitive behavior. In this chapter we will examine the relationship between changes in the brain as a function of normal aging. We will discuss the relationship between these changes and cognitive behavior through the lens of three important theoretical perspectives regarding cognitive aging (processing speed, inhibitory deficit hypothesis, and self-initiated processing deficit). We will examine different techniques used to identify cognitive decline as a function of both normal and pathological aging. Finally, we will discuss clinical approaches employed in dealing with normal changes in cognition as a function of age.

Neurological Changes Associated with Cognitive Aging

Most researchers agree that cognitive change is a nearly inevitable part of advancing age (e.g., [5]). Although a few individuals age "optimally," avoiding cognitive decline with age [6], the majority experience declines after an initial peak in one's mid-twenties. After this peak, there is a gradual loss of cognitive efficiency until one's fifties, at which time the decline may become more rapid. Normal aging results in changes in the brain such as decreased frontal and, to a lesser extent, hippocampal and temporal volume [7]. Age-related changes in the brain are associated with cognitive decline, such as control and maintenance of attention [8], maintenance and manipulation of information in working memory [9, 10], and deficits in encoding and retrieval of information from long-term memory [11–14].

The cognitive changes that accompany advancing age result from several neurophysiological changes. Research in this area suggests that normal aging accompanies neuronal shrinkage [15, 16]. However, more recent research suggests that cognitive impairment in old age may be related to a breakdown in myelin integrity [17]. In support of this hypothesis, Peters and Sethares [18] demonstrated that age-related alteration in myelin results from the accumulation of dense material in splits of some of the myelin sheaths. Myelin alterations correlate significantly with cognitive impairment, and impairment occurs because the conduction velocity along affected nerve fibers is reduced. This neurophysiological change may have its greatest impact in the prefrontal cortex, where speed of processing may be most critical. The relationship between myelin alteration and the prefrontal cortex (PFC) is significant because, as we will demonstrate, the PFC is instrumental in many cognitive tasks that require executive control, and these are the tasks that demonstrate age effects as measured through neuropsychological tests.

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 [19]. More recently, Raz and colleagues [7] found that the PFC exhibited greater sensitivity to aging than the rest of the cerebral cortex. Additionally, using volumetric measures to estimate the volume of specific brain regions, researchers have found little age-related differences in the limbic regions, specifically, the hippocampal formation and the anterior cingulate gyrus [20]. However, significant volumetric changes were found in a cross-sectional comparison of younger and older adults. This research suggests that cognitive changes related to the frontal lobes and specifically the PFC could be more pronounced than those associated with other brain regions.

In the next section, we will relate neurological changes as a function of aging to changes in cognitive processes. Cognitive processes will be examined using three dominant theories of cognitive aging. Experimental and neuropsychological evidence will be provided to support each of these theories. However, as will be demonstrated, none of these theories account for the complex pattern of behavior demonstrated

in cognitive performance as a function of normal aging. Neuropsychological data suggest that as we age, deficits in performance are seen in tasks associated with frontal, medial temporal, and subcortical regions. Yet, the prevalent theories of cognitive aging primarily focus on deficits in executive processing, associated with frontal functioning. Further, the present theories of cognitive aging fail to account for the increase in variability demonstrated in cognitive performance in both experimental paradigms and neuropsychological testing. The authors use their combined expertise to demonstrate the weakness in the present understanding of cognitive aging. We propose an interdisciplinary approach to the study of cognitive aging to ameliorate the present insufficiency in understanding.

Theories of Cognitive Aging

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 [21].

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 become 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 with which many cognitive operations can be executed is hypothesized to be a major contributor to the adult age differences in many measures of cognition [22–28].

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 [29]. 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.

The processing speed theory is persuasive and appealing because it is parsimonious and accounts for many of the cognitive changes associated with normal aging. However, more recent findings examining cognitive control in older adults have demonstrated enhanced speed of processing effects when older adults were compared to younger in the AX-CPT paradigm [30]. In this paradigm, the object of the task is to make a target response to an "X" (the probe), but only when it follows an "A" (the cue). The correct response to "X" thus depends on representation of "A" in memory.

On trials where participants were presented with "A" as the cue and "Y" as the probe, older adults were significantly faster than younger adults at responding on these trials, suggesting that processing speed may not be the only explanation for age-related deficits in cognitive performance. This finding and other research suggest that speed of processing is not the only contributing factor to higher level cognition [31]. While the speed of processing theory may not account for all observed behavioral patterns of cognitive aging, it is consistent with the neurological changes described in the previous section. That is, myelin alterations that occur in normal aging are likely to affect conduction velocity, leading to limited time and simultaneity processing issues described by the speed of processing theory. However, the picture is not complete.

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 [32–35]. Examples of some of the tests are the controlled oral word association test (COWAT) [36], and the digit symbol substitution test from the Wechsler Adult Intelligence Scale-Revised [37–39]. The COWAT involves orally producing as many words as possible that begin with a certain letter in 1 min. Important abilities measured by this test include initiating mental searches, maintaining these searches, and inhibiting irrelevant responses [40]. 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 [41]. 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 [42] reported a mean decrease of four to five words per decade after the age of 59 years for individuals with normal cognition.

Digit symbol substitution 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.

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. While this theoretical perspective is parsimonious and successfully accounts for cognitive changes resulting from normal aging, especially those tied to executive processes and PFC, more recent research suggests that the speed of processing framework may be insufficient.

Inhibitory Deficit Hypothesis

In addition to processing speed, research suggests that older adults may manifest inhibitory deficits in working memory. Hasher and Zacks [9] 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 [43, 44], text processing [45], and speech production [46]. Further, evidence from experimental tasks demonstrates that the PFC is particularly important for efficient inhibitory processes in working memory [47–49].

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 [50]. 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 [51]. 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., [52, 53]).

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 in that area. 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 (as when automatic), age deficits should also be minimal [54]. However, age deficits should increase as the cognitive demands of the task increase [9].

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 is cluttered by irrelevant thoughts and mental processes in older adults.

Hasher and Zacks [9] present compelling evidence demonstrating that older adults were more likely to maintain disconfirmed antecedent information that they previously heard than were younger adults, and that this irrelevant information affects subsequent cognitive performance. Inefficient inhibition enables the initial entrance into working memory of information that is off the goal path. Inhibitory deficits 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, personalistic memories or concerns, and goal-irrelevant interpretations.

Experimentally, researchers have demonstrated that older adults have difficulties in 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., [55]), 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 [56–58]). According to Lustig, Hasher, and Zacks [59], 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 age differences in *processing resources* (see also [60–62]).

Diagnostic tests: Inhibitory deficits have been tied to changes in the PFC and have also been shown in people with frontal lesions on tasks that require inhibition, such as the COWAT, the Stroop test, and digit span [63]. 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 are also demonstrated when individuals provide words beginning with a letter different from the target letter they were given.

The Stroop test has three parts: word reading, color naming, and color–word interference. The important aspect of the test is the length of time it takes to complete each section and the number of items completed in a certain time limit. The typical finding is that people 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 [40, 64–66]. In patient samples, poor performance on the Stroop test has been correlated with damage to the frontal lobes. Studies of lesion patients have implicated different areas of frontal damage, including medial and posterior areas [67, 68]. In normal cognitive aging, older adults exhibit more interference as compared to younger adults [69]. On the Victoria Stroop test, a shortened version of the original, age effects on accuracy were present, even after controlling for baseline cognitive slowing [70].

Digit span from the Wechsler Adult Intelligence Scale (WAIS, multiple versions [63]) is composed of two sections: digits forward and backward. Digits

forward requires the participant to remember and reproduce in order the digits read aloud by the examiner. Digits backward requires the participant to produce the digits in reverse order. Both tasks measure general attention and short-term memory. However, digits backward also measures mental tracking abilities. As it relates to goal relevance in inhibition, digit span backwards has some overlap with another test of complex mental tracking, letter–number sequencing from both the Wechsler Memory Scale – Third Edition (WMS-III [63]) and the WAIS-III. For this task, individuals hear a set of letters and numbers and must rearrange the set so that numbers and letters are grouped and in ascending order. 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 WMS-III and WAIS-III norms). Although these differences might seem inconsequential because of the relatively restricted range of scores, they demonstrate the decline of functions measured by the letter–number sequencing test across the life span. Finally, inhibitory deficits may play a role in age-related impairment on the WCST [40, 71]. This 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. In addition, the rule changes after 10 correct responses. Participants may then have to inhibit the previous rule as it becomes no longer relevant to the present goal. Perseveration performance and categories achieved are two indicators of executive function. Categories achieved are counted when one correctly places 10 cards in the correct pile. The range of possible scores is 0, when no category is completed, to 6, when the test is discontinued. Perseverative errors are calculated by counting the number of cards that are continually placed in an incorrect pile (e.g., matching cards based on the "number" principle after the examiner has repeatedly indicated that principle is incorrect). This sub-score is thought to represent "forming concepts, profiting from correction, and conceptual flexibility" [40] (p. 587).

Self-Initiated Processing Deficits

So far the discussed neuropsychological measures and theories of cognitive aging suggest that deficits in the frontal lobes, and specifically the prefrontal cortex, result in executive dysfunction. Clearly, the PFC is integral for working memory tasks that require conflict resolution and goal maintenance. The theories of cognitive aging have been developed primarily to account for these age-related changes. However, nondemented older adults demonstrate deficits in a variety of other cognitive tasks not directly related to executive function.

Tests of episodic memory, associated with the hippocampus and medial temporal lobes, have been shown to decline as a function of normal aging [72]. Neuropsychological batteries associated with episodic memory also show age-related declines [73]. The deficit seen in tests of episodic memory and neuropsychological tests that are associated with temporal lobe and hippocampal functioning might better be understood within the framework of "self-initiated processing." Craik and Byrd [74] suggested that older adults were deficient in the ability to engage in what they called "self-initiated processing." According to this view, these deficits reduce the kinds of self-initiated activities that are required for efficient task completion at both encoding and retrieval. Thus, older adults may have more difficulty in generating elaborate and distinctive memory traces (encoding resource deficit).

Deficits in self-initiated processes adequately account for numerous age-related cognitive changes seen in experimental paradigms. For example, research has found that older adults have poorer memory for frequency of occurrence as compared to younger adults [75]. However, when given contextual support at retrieval [76], those differences disappear. Thomas and Bulevich [77] found that older adults were more susceptible to distortions in memory unless directed at retrieval as to what cues might be beneficial in differentiating actual experience from imagined experience. Even the reported age deficit in memory for particular items found in tasks such as keeping track of the elements in a series [78], free recall, and list learning (see [79]) can be eliminated when testing provides substantial contextual support for retrieval [80].

For instance, older adults are more likely to correctly assess the veracity of retrieved memories if they are required to make more fine-grained recognition decisions [81]. Specifically, at the time of retrieval, older adults were asked to classify items as falling into one of three categories: items that were old and identical, new but related, and new and unrelated. By using this classification, older adults were less likely to indicate that related lures were old and identical [81]. These findings suggest that when older adults are required to more stringently evaluate their memory decisions at retrieval, they can improve their memory performance.

Older adults can also improve their performance on recognition tests of memory when asked very specific details about the item in question. For example, when older adults are asked to evaluate recognition test items more closely, whether they may try to determine a given item possesses any specific perceptual features that they had also noticed during the study phase and that would serve to vouch for its status as an old and identical item. These possibilities are similar to those proposed by Johnson and colleagues [82–85], which suggested that, compared to simple yes–no recognition, source monitoring tests may require participants to use different criteria – perhaps stricter, but also possibly qualitatively different – in providing their judgments. Thus, forcing participants to make source judgments will lead to improved memory performance, because those source judgments provide the environmental support required to supplement the depleted processing resources.

It is important to note that the task performance benefits most from contextual and environmental support are those that are associated with episodic memory. Research suggests that episodic memory is supported by the medial temporal lobes [86–88]. The MTL, and specifically the hippocampus, demonstrate changes as a function of age [7]; 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 [89]. It has been suggested that the MTL operates by forming associations between sensory, cognitive, emotional, and other content that characterize episodic memories [90, 91]. Thus, the MTL might serve to develop numerous associations that can be influential at retrieval. Without these associations, older adults may have less 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 processing resource 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 may be reduced by providing external support.

Diagnostic tests of Episodic Deficits: Certain neuropsychological tests rely on the ability to effectively encode and later retrieve information from long-term episodic memory. For example, the Logical Memory subtest from the WMS-III assesses ability to recall structured material (i.e., stories) immediately and after a 30-min delay. Scores are based on the total number of story elements recalled and range from 0 to 75 for immediate recall and from 0 to 50 for delayed recall. Neuropsychological evidence from lobectomy and traumatic brain injury patients implicates the left temporal lobe's role in successful logical memory performance [40].

The California Verbal Learning Test is another test used to assess age-related episodic memory changes (CVLT [92, 93]). List of words from four semantic categories are read by the examiner. Participants are then administered free recall and cued recall (cued by semantic category) tests. Recall tests are given after specific intervals, with the last two assessments given after a 20-min delay. A recognition test follows the last cued recall test assessed (only in the CVLT-II). There are a number of possible scores of interest on the CVLTs (e.g., short and long delay free recall, cued recall, recognition hits and false positives, recognition discriminability, intrusions). Each score measures different cognitive abilities, with the basic memory measures consisting of short and long delay recalls.

Recognition of faces from the WMS-III [63] is another proxy for episodic memory changes. Individuals view 24 pictures of faces presented for 2 s each. They are then administered an old/new recognition test. After a 30-min delay, this process is repeated. Scores for both immediate and delayed recall range from 0 to 48. For cognitively normal older adults, there is a progressive decline in scores. For example, the immediate recognition raw score reaching the 50th

percentile for 35- to 44-year-olds is 37–38, whereas for 85- to 89-year-olds, 31 correct responses equate to the same percentile (see WMS-III manual) [63]. Similar declines are evident in delayed recall scores.

What Do We Know So Far?

We know that cognitive aging is associated with changes in the PFC and MTL. We know that several dominant cognitive aging theories can be used to account for the observed behavior found on neuropsychological tests used to assess cognitive function in older adults. However, it is clear from the review to this point that no one theory has yet to adequately explain the complex pattern of cognitive change in non-demented older adults. We suggest that cognitive aging may be better understood if theoretical models account for the increasing variability in cognitive performance found as a function of normal aging. The next section of this chapter will describe several important factors that may influence the increasing variability often found in the cognitive performance of older adults.

Neuropsychological and Neurocognitive Variability in the Older Adult Population

Performance differences on neuropsychological tests have been discussed within the context of three important theories of cognitive aging: processing speed deficit, inhibitory deficit hypothesis, and self-initiated processing deficit. Each of these theories can be viewed within the context of changes in the PFC and MTL, and each is supported by observed performance on specific neuropsychological tests. However, none of these theories adequately accounts for the complex pattern of age-related deficits seen in cognitive performance. Further, theories of cognitive aging often neglect to account for the increased variability in cognitive performance demonstrated by the non-demented older adult population [94]. For example, Morse [95] reported greater diversity in older participants on measures of reaction time, memory, and fluid intelligence. The next section of this chapter will describe several important factors that may influence the increasing variability often found in the cognitive performance of older adults.

Gender

Several studies reveal positive effects of estrogen use on tests of verbal memory, suggesting differences between men and women in some cognitive domains [96–101]. Researchers suggest that the effects of estrogen on cognition might be tied to the PFC [102]. Further PFC might be differentially affected in men versus women. Neuropsychological measures associated with the PFC have confirmed the benefit of estrogen, with estrogen use being related to improved performance on the WCST [103]. Research has also demonstrated differential age-related brain changes in males as compared to females [104]. As one example, Cowell and colleagues [96] found greater age-related reductions in brain volume in men as compared to women. 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., [58, 105–108]). Interestingly, similar results have been found in two studies of spatial memory in rhesus monkeys [109].

Frontal Functioning

While the theories of cognitive aging have not yet adequately accounted for the increased variability in cognitive performance, the variability in the older adult population does allow researchers to compare higher functioning older adults to lower functioning, but still cognitively normal, older adults. This comparison should lead to refinement of theoretical models of cognitive aging. One avenue where such comparisons are made is frontal functioning. That is, when given neuropsychological tests associated with the frontal lobes, some older adults perform close to the level of younger adults. Those older adults can be categorized as high frontal functioning, and an examination of these individuals should lead to a better understanding of brain and behavioral compensation.

On the basis of Glisky and colleagues' factor-analytic work with neuropsychological tests, Thomas and McDaniel [109] assessed frontal function with five tests that have been individually related to frontal lobe function [110]. In this study, older adults were categorized as high or low frontal lobe functioning (FLF) to determine whether FLF may contribute to age differences in encoding processes related to working memory. The four measures used to calculate the composite FLF scores were the number of categories achieved on the modified WCST [111]; the total number of words generated for the letters F, A, and S on the COWAT [112]; the arithmetic score from the Wechsler Adult Intelligence Scale-Revised (WAIS–R [113]); and the Mental Control and Backward Digit Span scores from the Wechsler Memory Scale–III [63]. For each participant, a composite measure of FLF was calculated as the average of age-adjusted z scores on each of the frontal measures. The FLF scores were calculated using an equation that was derived in the same way as has been reported previously [110, 114, 115]. The equation that used was based on a new normative sample tested in Glisky's lab (personal communication, October, 2001).

Thomas and McDaniel [109] hypothesized that frontal functioning would mediate the attention required to maintain and manipulate newly acquired information. Impairment of maintenance and inappropriate manipulation would negatively impact later retrieval of information from long-term memory. They specifically examined how directing attention to specifying item information should improve retrieval accuracy. Retrieval accuracy was measured not only through accurate free recall of previously presented stimuli but also through a reduction in false recall. Specifically, when presented with semantically-related lists (e.g., bed, rest, awake) people often falsely remember "sleep" as having been presented. However, when directed to encode specific item information (environmental support) younger adults reduce these erroneous recollections.

A number of studies have introduced manipulations to enhance the encoding of item-specific information for the target words so as to reduce false recognition (and recall) in older adults. For example, one experiment [116] presented the list items in the context of sentences to promote more individual item elaboration. The assumption was that encoding item-specific features of target words should improve source discrimination between targets and critical lures (which would not enjoy rich item-specific encoding) on recognition testing and thereby significantly reduce false recognition. The consistent finding was that younger adults less often endorsed critical lures in the conditions that fostered item-specific processing as compared to older adults. These patterns have been interpreted as establishing that older adults are less likely to encode or retrieve item-specific information that can be used to effectively monitor the source of activated information, thereby distinguishing presented targets from non-presented lures [116].

The ongoing work by Thomas and McDaniel suggests that theories of cognitive aging needs to be modified to account for individual differences, and specifically frontal functioning. In several experiments, Thomas and McDaniel [109] have demonstrated that the effective use of item-specific information at encoding is associated with frontal lobe functioning. Low-FLF older adults were unable to use item-specific information to aid retrieval when less effortful processes were accessible. The question raised by this ongoing research is why do low-FLF older adults demonstrate an inability to rely on specifying item information? Consider the possibility that low-FLF older adults may be less likely to encode and/or bind specific item information to the target as compared to high-FLF older adults (cf. [117]). Several studies suggest that older adults may demonstrate encoding deficits for perceptual and contextual information ([110, 118, 119]; but see [120]). Older adults are also less likely to integrate unique aspects of the encoding context with the target item as compared to younger adults, resulting in less robust encoding specificity effects [121]. In the case of the results found by Thomas and McDaniel [109], low FLF older adults might persist with relatively high false recognition because they do not encode or bind the discriminating item information to the target. Correct recognition rates also support this hypothesis.

Interestingly, Thomas and McDaniel were able to reverse this pattern of results in another experiment. In this experiment, participants were encouraged to encode item-specific information on an item-by-item basis. Under these conditions, all groups produce similar hit rates, suggesting that the encoding deficit that may impact low-FLF older adults' ability to use item-specific information may be ameliorated by

item-by-item explicit orienting questions or environmental support.

The findings from this set of experiments suggest that low-FLF older adults encode specifying information, but have difficulty in efficiently using this information because of an over-reliance on automatic relational associations. Consistent with this view, Thomas and Bulevich [77] demonstrated that it was more difficult for older adults to use contextual detail extracted from distinctive processing as compared to younger adults. Context memory has been shown to be more sensitive to effects of aging as compared to content memory (for review see [122]). Research examining representational distinctiveness suggests that as people age, declining dopaminergic modulation reduces cortical neuron responsivity and increases neural noise. Consequently, the efficiency of distributed coding of contextual information, which may be acquired through item-specific processing, is reduced [123]. The potential effects of changes in dopaminergic modulation have been tested in a series of simulations that have targeted aging effects on learning rates, interference susceptibility, and working memory. Li and colleagues [123], in a recent simulation, demonstrated that declines in dopaminergic neuromodulation also decreased distinctiveness of internal representations. Low-representational distinctiveness means that the activation profiles formed across the network's hidden units for different stimuli are less readily differentiable from each other. Interestingly, while simulating aging-related deficiency in dopaminergic modulation gave rise to less distinctive representations of studied items, external contextual cues improved the memory performance. This pattern is consistent with the ongoing work of Thomas and McDaniel. That is, when given external support, low-FLF older adults were more likely to encode and/or effectively use distinctive information, even for lists that engendered relational processing.

Mild Cognitive Impairment

The increasing variability in cognitive function and brain changes as a function of age has led to controversy as to the range of normal cognitive decline. At the center of this controversy is mild cognitive impairment (MCI), which has been referred to as a transition stage between normal cognitive aging and more serious pathologies such as Alzheimer's disease. Some researchers believe that it is an early form of Alzheimer's disease, whereas others believe that patients with MCI do not always convert to AD, and thus consider MCI its own, separate diagnosis [124–126]. Regardless of what final stage MCI takes, it is generally agreed that MCI is cognitive loss in excess of expected normal aging.

The clinical criteria for the diagnosis of MCI [126] are (1) presence of memory complaint, (2) objective memory impairment compared to age-based norms, (3) other cognitive domains are generally intact, (4) activities of daily living are intact, and (5) there is no diagnosis of dementia. The "objective memory impairment" criterion has not been specifically defined, but generally ranges from 1 to 2 standard deviations below the mean for age-based peers on standard neuropsychological memory tests [126]. On tests of other domains, performance is usually not significantly (i.e., 1–2 standard deviations) below the mean. Therefore, individuals with MCI often appear to be cognitively normal except for some degree of significant memory impairment.

Although these criteria exist, there is still some uncertainty with regard to what distinguishes MCI from normal aging. Each clinic or practitioner might set the objective memory impairment criteria at a different level. As such, a diagnosis could have different meanings for different clinicians. In addition, random poor performance on one memory task in a battery of tests could result in a false-positive MCI diagnosis. In fact, it can be difficult to differentiate a true case of MCI from normal aging.

Treatment in Light of Cognitive Interactions

Before concluding, we would like to address certain factors outside the direct scope of cognitive aging that may, nonetheless, have peripheral influence on cognitive performance. Specifically, changes in sensory function and mood states may impact cognitive performance and, thus, should be acknowledged. To better understand the possible consequences of sensory changes on cognitive performance, we capitalize on

the Contextual Adult Life Span Theory for Adapting Psychotherapy (CALTAP) model [127]. A few relevant elements of the model include maturational changes and cohort factors. Maturational changes include the brain changes already mentioned and also sensory changes. Specifically, sensory changes could affect assessment if the older adult cannot see or hear the stimuli. In addition, cohort factors may reveal themselves as different levels of education, the quality of education, and types of skills emphasized in school. For example, later-born cohorts with greater exposure to computers may have an advantage over individuals unfamiliar with newer technology.

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 [128]). 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 [129, 130]. Even if there is an apparent resolution of a depressive episode and subsequent return to premorbid cognition levels, these individuals are still at an increased risk for dementia after a 2- to 4-year follow-up [128]. 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 vascular changes in the brain. Vascular depression (sometimes called "subcortical ischemic depression") is a condition in which cerebrovascular lesions or other vascular risk factors (such as diabetes, hypertension) can "predispose, precipitate, or perpetuate" depressive symptoms [131]. 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 problems, in which there is functional impairment (IADLs) and psychomotor retardation or lassitude (i.e., slowness or difficulty initiating activities) [132].

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. [133] found that, compared to age-matched controls, nondemented depressed older adults had worse cognitive performance in the domains of information processing speed, memory, visuo-spatial 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 [87, 134]. 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 what is typical in younger adults [135]. In addition, symptoms may differ. The elderly might not endorse sadness, but instead experience greater amounts of fatigue and loss of interest [136]. Practitioners should also know the base rates of depression in the elderly: currently, 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%. 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.

With that said, there are a number of treatments for cognitive change in cognitively normal older adults. These treatments focus on keeping the brain and/or the body active in the hopes of warding off either normal cognitive decline or dementia. Prevention techniques include cognitive and social engagement, physical exercise, and improvements in diet. 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.

Cognitive engagement and stimulation as prevention or treatment of cognitive changes stems from the disuse view of cognitive aging [137], sometimes also referred to "use it or lose it" (e.g., [138]). This perspective holds that cognitive abilities atrophy as a result of a decrease in cognitive activities. Thus, to counteract this decline, older individuals should engage in various activities that increase mental effort and stimulation. Cross-sectional studies examining this hypothesis indicate that individuals who participate in mental (as well as physical and social) activities have better cognitive performance on various cognitive tasks [139, 140]. However, it is unclear whether these activities cause improvements in cognition or whether individuals who are more cognitively intact tend to remain active and engaged [138]. Longitudinal studies have also been unable to completely disentangle these competing hypotheses, but do continue to indicate that participation in various activities (e.g., cognitive, social, leisure, physical) can lead to better cognitive outcomes [138, 141–144].

Intervention studies have generally found improvements in cognition, most often in the specific cognitive domain tested [145]. For example, in one large-scale study, individuals from three cognitive training groups (memory, reasoning, processing speed) improved compared to a no-contact control group [146]. These enhancements were seen immediately and again at 2-year follow-up. However, the treatment effects did not generalize to cognitive domains other than the one trained. Other studies have reported that cognitive training did indeed enhance performance in other cognitive domains [147, 148].

A comprehensive "healthy longevity lifestyle" program piloted on a small sample examined diet changes, relaxation, cardiovascular exercises, and mental exercises to the treatment group [149]. This group had better word fluency and altered PET activity compared to the control group. Other studies have shown that aerobic exercise can enhance cognitive flexibility [150] or decrease risk for dementia [151]. In addition to specific training programs, older adults can engage in cognitive compensatory strategies to aid in encoding. One technique commonly used is the method of loci, in which an individual first remembers the spatial representation of objects in a familiar place (e.g., a room in one's home). Then the information an individual needs to remember is associated with the different objects. For example, if a person wanted to remember a shopping list, starting with a bag of flour, he could imagine himself walking through the front door to his house, where he sees an antique dining table covered in flour. These associations are meant to enhance encoding and provide additional triggers for memorizing lists or objects. Other cognitive techniques are described elsewhere in consumer-friendly books [152, 153].

Conclusions and New Directions

This chapter reviews the nature of demonstrated deficits in performance on various neuropsychological assessments as a function of normal aging. From a neuropsychological assessment standpoint, older adults demonstrate deficits in performance in assessments ranging from perceptual speed tasks (i.e., digit symbol substitution) to episodic memory tasks (i.e., verbal paired associates). 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 to compensate for the inevitable decline in cognitive functioning.

We present well-supported theories of cognitive aging to account for the changes discussed. The processing speed theory states that all cognitive changes can be accounted for by changes in the speed with which many processing operations can be executed. That reduced speed of processing leads to impairments in cognitive functioning because of what are termed the limited time mechanism and the simultaneity mechanism.

Salthouse (1996) showed a moderate relationship between speed and various measures of cognitive function that are associated with both the prefrontal cortex and the medial temporal lobes. However, the processing speed theory fails to account for faster performance of older adults in certain conditions (i.e., [30, 154]). In addition, while the processing speed theory posits a working memory component in the form of the simultaneity mechanism, research by Craik and colleagues suggests that environmental support may ameliorate problems in working memory. Further, recent research suggests that working memory capacity deficits in older adults previously demonstrated by span tasks can also be ameliorated by reducing interference from previous trials [56]. These data suggest that the processing

speed theory may need to incorporate a mechanism that allows for the involvement of contextual support that mediates often-found age-related decrements in many neuropsychological tests.

Theories of working memory have also been proposed to account for the various changes in cognitive performance as a function of age. Researchers have proposed that older adults exhibit inhibitory deficits. Those deficits limit the capacity of working memory which, in turn, affects cognitive performance. In fact, problems with inhibition manifest on neuropsychological tests such as the Stroop test and the WCST. However, inhibitory deficits as a function of age are sometimes not found. Specifically, in location-based negative-priming studies, older adults demonstrate a similar pattern of negative priming as compared to younger adults [155, 156]. That is, both older and younger adults show an increase in response time when a distracting stimulus becomes a target in a subsequent trial. This increased response time is thought to result from inhibitory processes acting upon the distracting stimulus during the prime trial, to prevent further processing. Older adults show a similar increase in processing time as compared to younger adults. Thus, we can infer that inhibitory deficits are not always present in the older adult population.

As with the processing speed account, the inhibitory deficit hypothesis may not describe all of the cognitive changes that accompany aging because it does not posit an environmental support mechanism. This mechanism, proposed by Craik and Byrd [74], suggests that older adult performance can improve if support and encoding and/or retrieval are instantiated. That improvement suggests an interaction between working memory and episodic long-term memory. That interaction, along with the changes in other cognitive domains and increases in cognitive variability suggest that theories of cognitive aging need to more broadly focus on the interaction between changes in the prefrontal cortex (associated with working memory and executive function) and changes in the hippocampus (associated with episodic memory).

Research over the last 30 years has painted a rather complex picture of cognitive aging. We gerontologists now are beginning to understand the important relationship between changes in the brain associated with normal aging and the resulting behavioral manifestations. However, we have reached the end of this road. The time of independent research programs in aging has come to an end. We must consider an interdisciplinary approach in order to further our understanding of normal cognitive aging. Interdisciplinary research is scientifically necessary to the understanding of the complexity of the global phenomenon of cognitive aging. Thus, it is necessary to put, for example, biomedical researchers and social researchers in dialogue. This emerging knowledge can elucidate the global picture of the complexity of aging. This chapter attempts an interdisciplinary look at cognitive aging through the shared lens of clinical and cognitive psychologists. Through that lens we better understand the weaknesses and holes in our present conceptualization of cognitive aging. Through that lens we can also now begin to develop a perhaps more useful meta-theory to facilitate bridge-building between diverse theories produced in the scientific space of cognitive aging.

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Chapter 17

Neuropsychology of Movement Disorders and Motor Neuron Disease

Alexander I. Tröster 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; in 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. Upper motor neuron disease is characterized by signs such as weakness, increased muscle tone, and hyperreflexia, 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 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.

A.I. Tröster (✉)
Department of Neurology, School of Medicine, University of North Carolina, Chapel Hill, NC 27599-7025, USA
e-mail: trostera@neurology.unc.edu

Parkinson's Disease

Biological Underpinnings and Diagnosis

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 0–29 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-tetrahydropyridine (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), PARK 3, PARK 4 (alpha-synuclein), PARK 5 (*UCHL1*), and PARK 8 (*LRRK2*). Two loci are associated with parkinsonism possibly inherited in an autosomal dominant manner (PARK 10, PARK 11). Four loci have been

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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, lateonset PD.

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 brain stem. 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].

Neuropsychological Mechanisms

Attention and Executive Functions

Whereas patients with early PD perform normally on span tasks [16, 17], they do poorly on tasks demanding of efficient manipulation of information within working memory (e.g., Digit Ordering) [18]. Impairments are also observable on many tasks (e.g., Stroop task, visual search, Trailmaking) requiring divided or selective attention, and both limited attentional resources and attentional set shifting may underlie poor performance [19, 20]. Patients typically show impairments on visual search and cancellation tasks. Working memory deficits in PD have been attributed to reduced capacity of the system [18], difficulty manipulating information within working memory [21], and difficulty inhibiting responses [22, 23]. 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 [24], while some demonstrate also impaired planning accuracy [25, 26]. Studies using card sorting tests typically report that patients with PD have difficulty with one or more of set formation, set maintenance, and set shifting, often early in PD [27, 28]. Set loss, as opposed to a shifting deficit, is more likely to be observed later in PD [29, 30]. Set-shifting ability, in particular, appears to be a critical determinant of whether patients demonstrate difficulty on various executive function tasks [31], 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 [32]. Findings of studies using gambling tasks to evaluate decision making, judgment, and impulsivity yield are somewhat inconsistent. Czernecki and colleagues [33] 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 [34]. The neural basis of executive deficits is being elucidated with functional neuroimaging. Positron emission tomography (PET) has revealed reduced blood flow in the globus [35], the caudate, and the dorsolateral frontal cortex of PD patients compared to controls in response to activation with the Tower of London task [36], which is improved by levodopa [37]. 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 [38]. Executive deficits have also been linked to cholinergic deficits observed on functional neuroimaging [39].

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 [40], and bradyphrenia is particularly evident in demented patients with PD. Early in

the disease, processing speed may be ameliorated by dopaminomimetic medications [41]. 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 [42, 43].

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 [44, 45], but rare studies report subtle naming impairments [46, 47] and naming becomes more compromised in patients with obvious cognitive impairment [48]. Lexical and semantic verbal fluency is often intact in patients without dementia [45]. Two verbal fluency tasks especially sensitive to PD are alternating word fluency (requiring retrieval of consecutive words from alternate semantic or letter categories) [49] and verb fluency tasks requiring naming of actions [50]. Phonemic and semantic verbal fluency impairments, when observed, may be related to general retrieval deficits [51] or to a deficit in an underlying process such as switching but not semantic clustering (i.e., 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, respectively) [52, 53]. Subtle impairments may also be observed in syntactic comprehension and production [54], and underlying mechanisms include grammatical processing deficits [55, 56], slowed information processing [57], and diminished attention [58, 59].

Learning and Memory

Impairments in episodic memory may be evident in the earliest stages of the disease and at diagnosis [60, 61]. Learning of new information is slowed in PD [62]. Free recall is impaired, but recognition is relatively preserved [63], but not necessarily intact [64]. As cognitive impairment progresses in PD, both recall and recognition are compromised [65]. 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 [66, 67], and the rate with which a semantic encoding strategy evolves across word list learning trials is slow [66, 68]. In contrast to semantic encoding, serial encoding appears to be preserved [66, 68], as are serial position effect [69]. 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 [70]. Retention of word lists over time is usually normal [71], 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 [71, 72].

Recollection of information from the past (remote memory) is typically preserved [73, 74] and only rarely are subtle abnormalities revealed [75, 76]. Patients with PD also demonstrate deficits on numerous experimental memory tasks putatively sensitive to frontal dysfunction such as conditional associative learning [77], source memory [78], metamemory [79], recency discrimination [80], temporal ordering [81], subject-ordered pointing [82], and aspects of prospective memory, that is, for intended future actions [83]. Findings with respect to non-declarative memory in PD are inconsistent. The most recent studies provide evidence of abnormal semantic priming [84] and the possibility that these abnormalities may be related to information processing speed, slowed lexical access, and dopaminergic abnormalities [85, 86].

Visuoperception

Visuospatial deficits are quite common in PD and occur independent of motor deficits [87, 88]. Similarly, although impaired saccadic eye movements may contribute to visuoperceptual impairments, they cannot fully account for them [89]. Facial matching tasks reveal impairments in PD [44] and the facial recognition impairment in PD is related to configural, but not componential visuoperceptual processing difficulties [90]. 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.

Neuropsychiatric Factors

Depression is common in PD, occurring in about half of all patients – a recent meta-analysis reported a prevalence rate of 42% in studies using Diagnostic and Statistical Manual criteria [91]. Yet, anxiety and depression are often unrecognized by clinicians treating PD [92], 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 [93]. Despite the considerable prevalence of depression in PD, suicide is uncommon and perhaps rarer in PD than among elderly in general [94]. The most frequently used antidepressants in PD are the selective serotonin reuptake inhibitors (SSRIs) [95]. Dopamine agonists such as pramipexole [96], the tricyclic nortriptyline [97, 98], and cognitive behavioral therapy [99] 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 [100]. The prevalence of anxiety disorders (vs. symptoms) in PD ranges from 5 to 40% [101], though one recent study reported current and lifetime prevalence rates above 40% [102]. One study found that almost 20% of PD patients had generalized anxiety, 20% had a social phobia, and 20% experienced social anxiety [103]. Most patients might have anxiety disorders that do not clearly fit DSM criteria for a specified anxiety disorder [102]. Recurrent panic attacks may occur in up to 24% of patients treated with levodopa [104] and a considerable number of patients have symptoms of OCD [105].

Progressive Supranuclear Palsy

Biological Underpinnings and Diagnosis

Formerly known as Steele–Richardson–Olszewski syndrome [106, 107], progressive supranuclear palsy (PSP) is a neurodegenerative Parkinson-plus disease 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 [108]. 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 [109]. 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 [110]. At the present time there are no effective pharmacological or neurosurgical treatments available for patients with PSP and survival rates range from approximately 5–10 years after diagnosis [111].

As noted above, 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 [112]. These histopathological features are most commonly in subcortical regions, such 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 [113].

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 [108]. An early onset of cognitive deficits may be a harbinger of more rapid disease

progression and mortality [114]. The prevalence of dementia in PSP is estimated to range between 50 and 80% [115], but may be less prevalent in a subset of patients with more traditional parkinsonian features (NB: this clinical phenotype by some is referred by to as "PSP-parkinsonism"), such as levodopa responsive tremor and asymmetric onset of motor symptoms [116]. The neuropsychological profile associated with PSP is commensurate with its frontostriatal neuropathogenesis and is typically marked by prominent executive dysfunction and bradyphrenia [117].

Attention and Executive Functions

Although basic verbal attentional skills are generally within normal limits, deficits in visual attention are common in PSP [118]. Executive dysfunction is also a prominent feature of PSP and is hypothesized to arise from a deafferentiation of the basal ganglia and prefrontal cortex [117], although both frontal and subcortical regions are likely implicated. A broad range of dysexecutive signs may be present, including deficits in planning, problem solving [119], and cognitive flexibility [120]. Deficits in problem solving and cognitive flexibility may be more vulnerable to decline in PSP as compared to PD and MSA [121]. 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 [114] and reliably differentiates PSP from PD and FTD [122].

Motor Skills and Information Processing Speed

Bradykinesia and bradyphrenia are among the most prevalent and severe neurocognitive deficits associated with PSP [123] 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 [119]. Patients with PSP may also display ideomotor apraxia, although to a lesser extent than that which is present in patients with cortical basal ganglionic degeneration [124].

Language

Speech abnormalities such as dysarthria and hypophonia occur earlier [125] and are more common in PSP as compared to other movement disorders [126]. Impairment in verbal fluency follows the classic "subcortical" pattern of letter fluency being more affected than category fluency [127], although the effects of PSP on action (verb) fluency [50] will be important to determine since PSP is associated with greater deficits in naming verbs versus noun [128]. When present, deficits in confrontation naming of nouns may be attributable to visual misperceptions, rather than semantic memory deficits per se [129].

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 [130]. 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 [28], 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 [131]. Non-declarative learning and memory deficits are observed for measures of procedural learning [123] but not on tasks of perceptual priming [123].

Visuoperception

Oculomotor deficits are a hallmark of PSP, with impairment in voluntary vertical eye movements considered a primary diagnostic feature. Other neuro-opthalmological 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 [121], orienting [118], tracking, and attention, which may be associated with greater severity of oculomotor deficits [132].

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 [133]). With some prevalence estimates near 90% [134], apathy is far more common and severe in PSP as compared to PD, which is more likely to present with depression, hallucinations, and delusions [135]. Although apathy is sometimes misdiagnosed as depression, the latter does not present as a prominent neuropsychiatric feature of PSP [134]. Paralleling the above-described deficits in inhibitory cognitive processes, individuals with PSP also exhibit elevated behavioral signs of disinhibition [135]. As many as three-quarters of patients with PSP may evidence changes in "personality" [114], which can include increased irritability [135]. When combined with patients' limited insight regarding their cognitive and behavioral deficits [136], 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 [137]. 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 [138]. 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 cerebello-thalamo-cortical 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) [139]. 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 [139]. Patients with ET also demonstrate lower *N*-acetylaspartate (NAA, a marker of neuronal injury) [140] and higher regional blood flow bilaterally in the cerebellum [141]. Whether these alterations translate into neurodegenerative changes that are viewable with structural imaging techniques remains uncertain [142].

Despite its long-held classification as a "benign" movement disorder, it has become increasingly clear that ET is often accompanied by a variety of nonmotor complications that are consistent with the disorder's cerebello-thalamo-cortical substrates. Individuals with ET report significant declines in the independent performance of both physical (e.g., self-care) and instrumental (e.g., communication) activities of daily living [143]. In fact, as many as 75–95% of ET experience at least one significant disability related to their ET symptoms [144]. Moreover, ET is associated with reduced general health status [145], as well as lower physical and mental health-related quality of life [146]. Functional disability, poorer health status, and lower health-related quality of life are associated with more severe motor symptoms [147], older age [146], affective distress [144], and cognitive impairment [148].

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 twofold risk of incident dementia [149], 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 [150], MMSE scores below commonly used dementia cutpoints 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 [151] and selective attention [152]. Deficits in sustained visual attention are also evident, including on measures of letter cancellation [153] and continuous performance tasks [153]. Speeded measures of divided attention (e.g., Trailmaking Test, Part B), prepotent response inhibition (e.g., Stroop Color–Word Test), and cognitive flexibility (e.g., design fluency) are also sensitive to ET [154]. 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 [153], whereas others do not [155]. When present, deficits in attention and executive functions may be predictive of problems in day-to-day life; for example, Woods et al. [148] 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 [156], including fine-motor speed and coordination [152]. 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 Trailmaking Test, Part A [150], as well as more complex measures like Symbol Search [151]. Deficits are also apparent on nonmotor measures of information processing, including the Color trial of the Stroop Test [152, 155].

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 [157]. Mixed findings exist regarding whether ET is associated with impairment in confrontation naming [150, 158]. Formal neuropsychological evaluation will commonly reveal impairment in verbal fluency, including both letter [154] and semantic trials [152]. Qualitative analysis may show an increased rate of perseverative responses on letter fluency [155], 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 [159], as well as on recognition [152, 155]. 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 [150–152]. In contrast, deficits in visual memory are less [152, 153].

Visuoperception

Deficits in facial recognition [159] and judgment of line orientation [155] may be evident. On the other hand, few patients with ET are impaired in the Visual Organization Test [155, 159]. While deficits in spatial cognition are not commonly associated with cerebellar dysfunction, there is more recent evidence to that effect [160, 161] and they are documented in other movement disorders, such as HD [162].

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 [159] and anxiety in ET, including social phobia [163]. 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 [164]. Nevertheless, depression is a unique predictor of lower psychosocial health status in ET, even after considering the effects of ET disease severity [148]. Studies regarding the prevalence, predictors, and consequences of psychiatric comorbidity in ET are clearly indicated.

Huntington's Disease

Biological Underpinnings and Diagnosis

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 [165]. 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 [166]. HD is transmitted in an autosomal dominant fashion, meaning that offspring of a parent with HD have 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 [167]. Diagnosis is typically made in mid-life (late thirties and early forties), but persons with a greater number of CAG repeats are at risk of earlier onset [168]. 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 15–20 years [169].

The neuropathology of HD primarily involves the loss of medium spiny neurons in the caudate [170], but multiple aspects of the basal ganglia and frontostriatal loops are affected, including the putamen, substantia nigra, and globus pallidus [133]. 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 [171]. Functional neuroimaging data show that the prefrontal cortex is hypometabolic at rest in HD [172], 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 [173].

Neuropsychological Mechanisms

Given the relatively selective involvement of the basal ganglia, HD has long been considered a prototype of the "subcortical" dementias [174], with prominent cognitive deficits in the areas of executive functions, speeded information processing, episodic memory retrieval, and procedural learning. 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) [162], which tend to intensify as the diagnosis nears [175]. Cognitive deficits continue to advance in prevalence and magnitude in the early stages of HD [176] 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 [177]. 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 [178]. Executive dysfunction also runs the gamut of ability areas, such as cognitive flexibility [179], planning [180], problem solving, and abstraction [181], which are associated with both striatal and cortical abnormalities [182]. 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 [183].

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 [177]. Increased variability in the timing of motor functions, but not necessarily accuracy, may emerge prior to diagnosis [184]. 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 [185].

Language

Motor speech abnormalities, most notably dysarthria, are frequently observed even in the early stages of HD [186]. Although less prominent than in AD, HD is associated with deficits in confrontation naming, which are largely driven by visuoperceptual errors [187] and may progress with advancing disease [177]. 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 [188], 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 [189].

Learning and Memory

Episodic memory functions are among the earliest and most severely affected cognitive abilities in HD [181]. 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 [71]. 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 [190], whereas patients with more advanced disease demonstrate broader learning and memory impairment. Relative to AD, patients with HD demonstrate superior novel recognition discrimination [191], generate significantly fewer cued-recall intrusions [192], and do not show a strong temporal gradient on tests of retrograde amnesia [193]. HD is also associated with impairments on measures of implicit memory, including perceptual, motor, and cognitive skill learning, which are typically unaffected in AD [194].

Visuoperception

Abnormal neuro-ophthalmological signs, including increased errors and latencies on anti-saccadic movements, may be an early biomarker of HD [195]. Several aspects of spatial cognition are also affected in HD. For example, Bylsma and colleagues [196] 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 [197]. Impairment may also be seen on measures of spatial orienting [198], as well as on tests of space and object perception [177].

Neuropsychiatric Features

Neuropsychiatric symptoms are salient in HD and are an important predictor of functional status [199]. Depression is perhaps the most prevalent psychiatric comorbidity and is present in approximately 40–50% of patients [200]. Individuals in the early stages of

the disease appear to be at particular risk of depression [201]. Suicidal ideation (9–23%) [201], attempts, and completions (5–10%) [202] are unusually high in HD as compared to other neurological disorders [201]. Risk of suicidality may be greater in individuals with histories of psychiatric disorders and those without significant psychosocial responsibilities [203]. Anxiety and apathy [204], as well as "personality changes," such as increased aggression [200] and irritability [204] are also prevalent in HD, whereas symptoms of obsessive–compulsive disorder, delusions, and hallucinations are less frequently observed [204].

Amytrophic Lateral Sclerosis (Lou Gehrig's Disease)

History and Diagnosis

Charcot in the nineteenth century described the syndromic features of amyotrophic lateral sclerosis (ALS), a progressive, fatal, neurodegenerative disease affecting upper and lower motor neurons. 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 (probably 5%) develop features of a frontotemporal dementia (and the observation that a significant number of patients with frontotemporal dementia develop motor neuron disease 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 [205] and most often involve executive dysfunction (poor planning, abstraction, and word search) [206]. Compromises in visuospatial, language, and memory functions are more inconsistently observed. Also noted are affective and personality changes (e.g., obsessiveness, irritability, pathological laughing, or crying). 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 [207].

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 [208]. 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 [209].

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 [210]. Impairment in selective attention is also demonstrable in ALS [211], but performance on complex tasks such as the Stroop task and Paced Auditory Serial Addition Test (PASAT) may [212] or may not be identified [213–216]. Tasks considered to tap a variety of executive functions are those most consistently demonstrating impairments in ALS, although there is some inconsistency with

regard 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 [212, 217–220], but a few studies have failed to reveal such impairments [214, 215, 221]. Patients with cognitive impairments tend to have greater frontotemporal white matter changes than ALS patients without cognitive impairment [221], and patients with dementia have greater frontal [222] and temporal lobe volume reductions than patients without dementia [223]. Similarly, cognitively compromised patients with ALS have greater frontal lobe pathology than cognitively intact patients [224]. 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 [225] and perform better on neuropsychological tests than do patient with sporadic ALS or other forms of familial ALS [226]. Some patients with ALS and dementia may have mutations in the progranulin gene, also implicated in some forms of frontotemporal dementia [227]. Location of the onset of disease may also partly explain variability in cognitive dysfunction [228]. For example, patients with pseudobulbar symptoms may also have impairments in planning as revealed by the Tower of Hanoi [229]. Deficits in non-verbal (figural) fluency have also been reported in one study [220].

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 [212]. Others have found psychomotor speed to be relatively preserved [230]. Reaction time is reduced in some patients [220].

Language

As noted earlier, deficits in verbal fluency are those cognitive deficits observed with greatest consistency in ALS. Although both letter and semantic fluency can be affected by ALS, some have argued that letter fluency is more consistently impaired [213]. This is consistent with the presumed frontal dysfunction hypothesis of verbal fluency based on functional neuroimaging findings [231], 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 [232, 233], and action naming more than object naming [234], are also consistent with frontal dysfunction. Visual confrontation naming, in contrast to verbal fluency, has been only inconsistently reported to be impacted by ALS [210, 218].

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 [206]. Deficits have been observed in prose [216], verbal paired associate learning [219], and picture recall [214], as well as recall of word lists [218]. 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 [235]. 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 [236], 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 [219], Facial Recognition [216], Judgment of Line Orientation [218], and Position Discrimination [213].

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 [237]. In addition, many patients have reactive depression symptoms after diagnosis. Frontal syndromes consistent with frontotemporal dementia occur in about 5% of persons with ALS [205]. Apathy appears especially common, while disinhibition is rarer. Sixty-three percent of patients may exhibit apathy, irritability, inflexibility, restlessness, and disinhibition [206, 234], and apathy and disturbances of conduct may be more common among patients with bulbar onset ALS [234]. 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. In 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 therapy. Such cognitive and behavioral interventions will be critical to develop and evaluate in movement and motor neuron disorders so as to enhance patient's quality of life.

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Part V
Immune-Mediated Disease

Chapter 18

Cognitive and Affective Neuroscience Theories of Cognition and Depression in Multiple Sclerosis and Guillain–Barré Syndrome

Peter A. Arnett, Fiona H. Barwick, and Joseph E. Beeney

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.

P.A. Arnett (✉)
Department of Psychology, The Pennsylvania State University, University Park, PA 16802-3105, USA
e-mail: paa6@psu.edu

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 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.

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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 neurocircuitry 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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Chapter 19

Neurocognitive Function in Systemic Autoimmune and Rheumatic Diseases

Amy H. Kao, Carol M. Greco, Suzanne L. Gharib, and Sue R. Beers

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.

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.

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 19.1 [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

A.H. Kao (✉)
Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA
e-mail: ahk7@pitt.edu

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Table 19.1 Neuropsychiatric syndromes of systemic lupus erythematosus [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

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 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 19.2 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 19.3. 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

Table 19.2 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
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

Table 19.2 (continued)

Authors	Subjects	Design/assessments	NP domains	Outcomes
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
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

Table 19.2 (continued)

Authors	Subjects	Design/assessments	NP domains	Outcomes
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
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 19.3 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

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 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}H-MRS), 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 WISC-R 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.

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Chapter 20

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 (~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 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

D.F. Tate (✉)
Harvard Medical School, Brigham and Women Hospital, Boston University Medical School, Boston, MA 02115, USA
e-mail: dtate1@partners.org

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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. 20.1. 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,

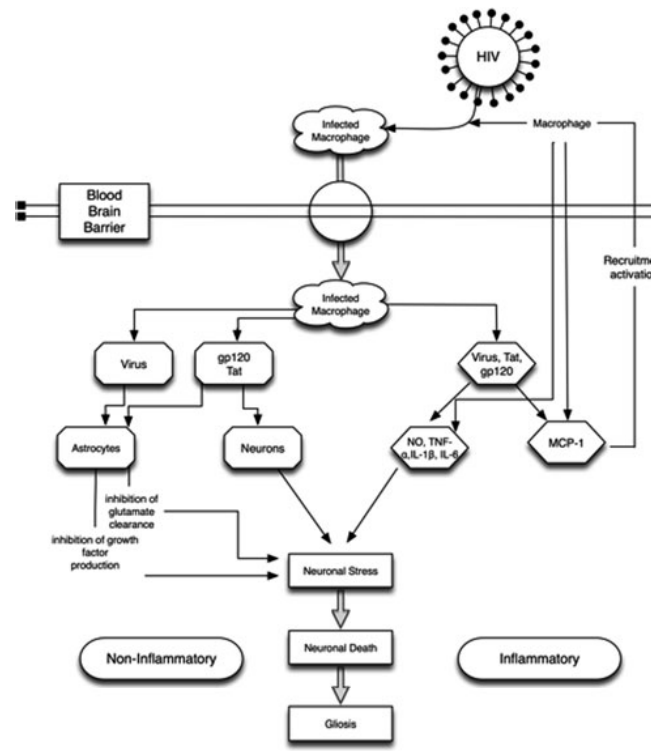

Fig. 20.1 This illustration depicts two common pathways of pathological injury. Adapted from Avison, Nath, and Berger [2]

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 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, antiretroviral 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 subcortical 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 criterion, the World Health Organization (WHO) classification system, and the AIDS Dementia Complex staging. These staging systems are summarized in Tables 20.1, 20.2, 20.3, and 20.4 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 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

Table 20.1 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 20.2 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

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.

Table 20.3 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 20.4 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 for neuropsychiatric or psychosocial function (motivation, emotional control, social behavior)	Acquired abnormality of motor function	Impaired ability to maintain employment Impaired basic and complex activities of daily living (medication adherence, bill paying, cooking, cleaning, driving, etc.)

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

Table 20.5 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 No employment dysfunction	Not the result of delirium Cognitive change not result of another preexisting or comorbid condition
Minor neurocognitive disorder (MND)	Same as ANI	Mild or equivocal impairment of ADLs Mild or equivocal employment dysfunction	Same as ANI
HIV-associated dementia (HAD)	Same as ANI	Marked impairment of ADLs Marked employment dysfunction	Same as ANI

patients [15] due to the evolution of cognitive changes in the era of HAART. This new system is briefly summarized in Table 20.5. 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 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 20.6 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 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

Table 20.6 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 Brief visuospatial memory test – revised	Hopkins verbal learning 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

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 20.6 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].

Cognitive Sequelae

Cognitive 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 20.7).

Table 20.7 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 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 20.6 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 understanding 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 co-infection 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 co-infected 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.

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Chapter 21

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 21.1). 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, non-restorative 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.

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

J.M. Glass (✉)
Department of Psychiatry, Institute for Social Research, Addiction Research Center, University of Michigan, Ann Arbor, MI 48106-2700, USA
e-mail: jglass@umich.edu

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Table 21.1 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
			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

Table 21.1 (continued)

Authors	Date	Title	Measures	Results
Dick et al. [18]	2002	Attentional Fxn in FM, RA, and musculoskeletal pain	Test of everyday attention Selective attention Sustained attention Attention switching Working memory	FM < HC FM = HC FM = HC FM < HC
Grisart et al. [76]	2002	Controlled processes and automaticity in memory fxn in FM: emotional distress and hypervigilance	Process dissociation procedure Controlled processes Automatic processes	FM < HC FM = HC
Zachrisson et al. [7]	2002	A rating scale for fibromyalgia and cfs (FibroFatigue scale)	FibroFatigue scale (uses items from CPRS) Concentration difficulties Failing memory	95% incidence 93% incidence
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) IQ (Block design and information) Wisconsin Card Sorting TestStroop interference Auditory Verb Learning Test Effort testing with AVLT Complex figure test delayed recall Digit span Letter–number sequencing PASAT Digit symbol Symbol search Controlled oral word assoc. test Trail Making Tests A and B	FM > HC FM = HC FM = HC FM = HC 5 FM pts excluded, 0HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC
Sephton et al. [78]	2003	Biological and psychological factors associated with memory function in fibromyalgia syndrome	Wechsler memory scale Visual reproduction, imm Visual reproduction, delayed Logical memory, imm Logical memory, delayed	Lower salivary cortisol levels correlated with visual memory Depression was negatively correlated with logical memory
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 Mental confusion	FM > nonFM FM > nonFM

Table 21.1 (continued)

Authors	Date	Title	Measures	Results
Bennett et al. [10]	2007	An Internet survey of 2,596 people with FM	Forgetfulness Concentration	5.9 (fifth highest sx) 5.9 (fifth highest sx)
Glass et al. [11]	2005	Memory beliefs and function in FM	Metamemory in adulthood quest Strategy Knowledge Capacity Stability Anxiety Achievement Self-efficacy	FM > HC FM = HC FM < HC FM < HC FM > HC FM > HC FM < HC
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 WMS paired associates IQ (vocabulary) Digit span Paced auditory serial add. task Letter–number sequencing Auditory consonant trigram	–0.77 sd of norm –0.37 sd of norm +0.07 sd of norm –1.6 sd of norm –0.93 sd of norm –2.5 sd of norm
Walitt et al. [80]	2007	Automated neuropsychiatric measurements of information processing in fibromyalgia	ANAM Visual short-term memory Visual scanning and learning Spatial processing Short-term memory Arithmetic processing Sustained attention Simple RT Trail Making Tests A and B Stroop word and color Stroop color–word	FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM = HC FM > HC
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 Consonant trigrams held in STM for variable duration (0–6 s)	FM < HC recall 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 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 3's (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 21.2 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

Table 21.2 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

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].

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 co-twin 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 21.2).

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.

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Part VI
Endocrine Disease

Chapter 22

Neuropsychological Sequelae of Type 1 and Type 2 Diabetes

Clarissa S. Holmes, Kari L. Morgan, and Priscilla Powell

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 (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

C.S. Holmes (✉)
Department of Psychology, Pediatrics and Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; Department of Psychiatry, Georgetown University, Washington, DC, USA
e-mail: cholmes@richmond.edu

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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 hypersecretion 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 noninsulin-dependent 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 $\epsilon 4$ 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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Chapter 23

Neuropsychological Functioning of Endocrinology Disorders: Gonadotropic Hormones and Corticosteroids

Michelle M. Greene, Kathryn Maher, and Clarissa S. Holmes

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 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].

C.S. Holmes (✉)
Department of Psychology, Pediatrics and Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; Department of Psychiatry, Georgetown University, Washington, DC, USA
e-mail: cholmes@richmond.edu

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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 postmenopausal 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 testosterone-buffering 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 incorrect-response 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 co-occurring 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 postsurgically [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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Chapter 24

Neuropsychological Assessment of Posttraumatic Stress Disorder (PTSD)

Jennifer J. Vasterling, Laura Grande, Anna C. Graefe, and Julie A. Alvarez

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.

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 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].

J.J. Vasterling (✉)
Psychology Service and VA National Center for PTSD, VA Boston Healthcare System, Boston, MA 02130, USA;
Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA
e-mail: jvaster@bu.edu

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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 "overgeneral" 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 [115, 96, 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, 115, 116, 96, 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), antipsychotic 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.

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Part VII
Metabolic Disease

Chapter 25

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].

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].

J.S. Bajaj (✉)
Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA 23249, USA
e-mail: jsbajaj@vcu.edu

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 25.1). 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.

Table 25.1 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

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].

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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 25.2), we now have a unifying hypothesis of HE which includes particular roles for cytokines and products of oxidative stress (Table 25.2). 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].

Table 25.2 Causes of astrocyte swelling

– Ammonia entry → Glutamine accumulation
– Benzodiazepines (active on peripheral-type binding site)
– Hyponatremia
– Cytokines
– Glutamate

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 25.3). 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 been studied, all of which are based on detecting attention deficits and processing speed [27].

Table 25.3 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

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 25.3). 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.

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Chapter 26

Toxic Disorders and Encephalopathy

Marc W. Haut, Maria T. Moran, and Kara Lonser

The purpose of this chapter is to selectively review the literature on the neuroanatomical, neuropsychological, and emotional/behavioral effects of exposure to three different substances: organic solvents, lead, and carbon monoxide. 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. For each substance, we will review the particulars of exposure and symptom expression, the neurobehavioral symptoms, the neuroimaging changes, and the relationship between 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 finish up by addressing 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.

M.W. Haut (✉)
Departments of Behavioral Medicine and Psychiatry, Neurology, and Radiology, West Virginia University School of Medicine, Morgantown, WV 26506, USA
e-mail: mhaut@hsc.wvu.edu

Organic Solvents

Organic solvents are used in a variety of industries, both in the manufacturing process and in the cleanup operations. In addition, solvents can be a substance of abuse, 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. Thus, 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. We note that there is a classification of exposure-related symptoms that has been proposed [1]. Type 1 is mild, brief intoxication that is reversible. Type 2A focuses on emotional changes, while type 2B is related to intellectual changes. A type 2 classification is of moderate severity, but permanence has not

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been established. 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.

There are a number of very thorough reviews of a wide range of studies examining the neurobehavioral effects of exposure to solvents (e.g., [2–5], Morrow et al., 2001a, [6]). 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 have been observed following exposure to organic solvents. The reader is referred to prior reviews for more in-depth coverage of individual studies (e.g., [4], Morrow et al., 2001). A recent meta-analysis [7] of cognitive deficits in 53 occupational solvent-exposed groups from studies comparing performance to non-exposed 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, Trailmaking test, and Digit Symbol have been widely used in studies of solvent exposure. Other researchers have also found utility in the use of visual perceptual and constructional measures (see Morrow et al., 2001) using a variety of measures 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.

We did want to comment specifically on one particular study [8]. This is a twin cohort study that examined 21 monozygotic twins discordant for solvent exposure. Twin studies are always particularly potent for demonstrating deficits, as the use of discordant twins controls for more of the variance than the typical use of healthy control subjects. 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 [6]. Indeed, a few studies have found specific deficits in complex attention and working memory [9–11]. 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. [12] 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 (e.g., [13]). In addition, it appears that the deficits are reversible in some individuals (e.g., [13]), 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 increase the likelihood of developing permanent deficits (e.g., [14]). 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 [15, 16].

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 [17–20]. These psychiatric symptoms do not appear to be responsible for or to account for the cognitive deficits that patients also experience (e.g., Morrow et al., 2001).

Neuroimaging

There have been few well-designed studies that have utilized neuroimaging following exposure to organic solvents. Early studies were mainly case reports of voluntary solvent exposure/inhalant abuse, such as "huffing" gasoline. These cases focused on changes in the white matter of the brain [21–23]. 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 [24]. They 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 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 [18]. We used magnetic resonance imaging (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 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 will 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, Haut et al.'s [18] study suggests that the frontal lobe functions are affected by the difference in the white matter of the genu, but 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 one small pilot functional imaging study that demonstrated differences in frontal lobe activation during working memory [25]. 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. [18] who demonstrated a relationship between differences in the genu of the corpus callosum and frontal lobe functions. 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 generalized.

This is highlighted by a recent study that used a combination of imaging modalities to examine the effects of solvent exposure [26]. 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 exposed subjects and $N = 11$ for normal controls) differences in dopamine binding using SPECT as well as frontal gray matter changes using MRS were observed. Correlations with cognitive performance were present. White matter differences were not found, but there were methodological differences compared to previous studies. This points to the need for more study on the neuroanatomical substrates of solvent-related cognitive 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 is terminated. However, some individuals will experience permanent deficits, which may be exacerbated by age. 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 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 [27]. For earlier reviews, the reader is referred to [28–30]. We should also note that most of the data on the effects of lead exposure come from chronic, long-term exposure.

Cognitive Function

Only recently have the long-term cognitive effects of past lead exposure been recognized in adults [31]. Shih and colleagues [27] conducted a systematic search of studies published between 1996 and 2006 that examined the relationship between biological markers of recent (i.e., blood lead) and cumulative (i.e., bone lead) 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 [27].

The cumulative effect of lead on cognitive function has been longitudinally studied in three independent groups of individuals: former US 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 [31]. For the former US 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 2-year time period, suggesting that changes in brain function due to prior lead exposure appear to progress and do not merely persist. 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 are 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; [32]). 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 in 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.

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 [27]). Lindgren et al. [33] examined the relationship between current and former lead-smelter workers and mood disturbance. 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 [34]. 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 [27], psychiatric symptoms following modest exposure levels have also been reported (e.g., [34]).

Neuroimaging

There is growing evidence to support the notion that adult exposure to lead has a persistent effect on brain structure, as measured by magnetic resonance imaging (MRI; [35]) and MRS [36, 37]. In addition, these structural changes have been associated with cognitive function [38, 39].

Differences in brain structure were correlated with past organic lead exposure in a large cohort ($n = 532$) of occupationally exposed individuals [35]. 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 [39]. 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 [38].

The cumulative effects of lead exposure have also been associated with differences in brain metabolite ratios using MRS [36, 37]. 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 [37]. 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. [36] 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.

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.

Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless, tasteless gas produced by incomplete combustion of carbon-based fuels [40]. CO is the most common cause of morbidity and mortality by poisoning in the USA. Unintentional exposure accounts for approximately 15,000 emergency room visits and 500 deaths each year [41]. The mechanism of poisoning is frequently accidental, via faulty heating systems. There thus is an upsurge in cases in the fall and winter months [40, 41]. Intentional poisoning from suicide attempt, often via exposure to automobile exhaust, is also common. Diagnosis may be complicated or initially delayed by the non-specific and flu-like nature of the symptoms of CO exposure, including headache, nausea, irritability, confusion, dizziness, and visual disturbances [42]. 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 [43]. In addition, there may be complicating factors of substance intoxication with both accidental exposure and suicide attempts.

CO has a high affinity for hemoglobin, greater than that of oxygen [44], and combines with hemoglobin to form carboxyhemoglobin (COHb). This decreases the oxygen content of blood, resulting in tissue hypoxia [42]. Because of its high oxygen utilization, the central nervous system is highly susceptible to the effects of CO [42]. Toxic effects of CO appear to be related to both tissue hypoxia and CO-related cellular damage [45]. Measurement of carboxyhemoglobin (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 [46, 42, 47, 48, 44]. Treatment involves administration of oxygen, often hyperbaric oxygen therapy, to increase the rate of elimination of CO from the body [44]. It is unclear whether hyperbaric treatment decreases the incidence of sequelae, as the literature is conflicting [49]. When

not fatal, which is often the case, CO poisoning leads to a host of cognitive, behavioral, and neurologic symptoms (see [45] for a comprehensive review). The large 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 [45]. 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 to 93% of patients with moderate to severe poisoning [42, 50]. The cognitive symptoms that have been observed following CO poisoning vary widely and range in severity (see [45]). Most often, CO poisoning is associated with impairment in memory, as well as attention, processing speed, visual–spatial skills, executive functions, and intellect [42, 45, 47, 50, 51]. 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 [43, 52]. In some cases of acute exposure, a pure amnesic syndrome has been reported (e.g., [53, 50]). One series of 21 patients 1 year after CO poisoning described that 76% of their sample had impaired memory, 75% had executive dysfunction, 57% had slowed mental processing, and 45% had impaired attention [42]. 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 [46, 54]. It would appear that the persistence of deficits varies as well, as some individuals experience improvement of cognitive symptoms over time, while others experience continued cognitive impairment [55, 47, 48, 49], Weaver et al., 2004.

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 [46, 52], although there have been rare case reports of OCD and Kluver–Bucy syndrome symptoms (see [45] for a review). Of 21 patients examined 1 year after acute CO exposure [42], 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 [56]. Some emotional symptoms are premorbid, e.g., depression in individuals who are exposed to CO from suicide attempt. Jasper et al. [56] 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. [56], 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., [47, 48]).

Neurological Changes

Neurologically, movement disorders or parkinsonian syndromes have been reported acutely following CO exposure (see [45] for a more thorough review). 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 0.06–40% of CO-exposed individuals [45], but the structural neuroimaging findings and clinical symptoms may resolve [57, 58, 54]. There is some indication of increased risk of the delayed syndrome with increasing age, longer duration of coma, and prolonged anoxia [58].

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 [59]. 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 [50], Prockop et al., 2005.

Atrophy has been described affecting whole brain, fornix, hippocampus, and corpus callosum [42, 46, 47]. Using quantitative MRI, Porter et al. [47] 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. In addition, differences in the volume of the fornix have been reported after CO exposure and these correlate with memory dysfunction [46]. Cortically, there appears to be a predilection for the temporal lobe, although this is relatively uncommon [60]. Bilateral hippocampal infarcts, associated with amnestic syndromes, have also been described [53, 61].

Basal ganglia lesions, particularly affecting the globus pallidus, have long been widely identified using MRI [59, 60, 54] and MRS (Prockop et al., 2005). However, these lesions are not universally found, even in the presence of parkinsonian symptoms (Prockop et al., 2005, [54]). Interestingly, pallidal lesions were present in an individual without concomitant parkinsonian symptoms and absent in an individual with such symptoms, following the same exposure [54]. 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. [62] 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 [49], 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 re-imaged 6 months later.

White matter demyelination may be responsible for the delayed neurological syndrome; delayed cytotoxic edema is hypothesized [63, 55, 59]. 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 [63]. MRI 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 [64]. Interestingly, FA improved in patients from pre- to post-treatment.

In summary, CO exposure often leads to changes in cognitive and emotional functioning. A wide variety of cognitive deficits have 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, and 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 not only having a focused battery based upon the literature, but to also 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 numbers 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 (motor, cortical sensory, visual–spatial and construction, 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 are 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 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., [65]). 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.

Finally, many cases of toxic exposure also involve civil litigation, a worker's 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 [66, 67] and care should be taken to consider performance effort when assessing the effects of exposure on cognition and emotion.

In conclusion, cognitive and emotional changes following exposure to organic solvents, lead, 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. 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.

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Chapter 27

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 (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

K.M. Antshel (✉)
Department of Psychiatry and Behavioral Sciences, State University of New York – Upstate Medical University, Syracuse, NY 13210, USA
e-mail: antshelk@upstate.edu

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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 27.1, 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 27.1 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 27.2, 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 27.2 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.

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Part VIII
Rehabilitation

Chapter 28

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 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, memory, language, and executive functions; and some recent technical additions to rehabilitation efforts.

Rehabilitation is generally thought of as consisting one of the 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 compensation 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 and 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 effected arm to attempt to re-establish pathways affected by the injury.

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.

S.A. Raskin (✉)
Department of Psychology and Neuroscience Program, Trinity College, Hartford CT 06106, USA
e-mail: sarah.raskin@trincoll.edu

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Perhaps one of the most important factors to any rehabilitation approach is the need for generalization [6]. One of the first authors to specify an approach to generalization was Gordon [7]. 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 [8] suggested a set of generalization principles or strategies that could be broadly adapted in both research and clinical practice. These principles, drawn primarily from the applied behavioral literature [9] and from the cognitive psychology literature on transfer of training [10], are to (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 [11]. 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 [12] 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 that 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 [13]. 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 [12, 14].

Another new approach to motor deficits is locomotor training (LT) [15]. 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 [16].

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 [17], mild cognitive impairment [18], and reading disabilities [19]. For cognitive deficits, treatment seems most effective when a combination of compensatory and restorative approaches is 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.

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 ischemic lesions was reported to be alleviated through the presentation of simple auditory alerts [20]. The theoretical basis was data suggesting that the non-spatial 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 [21].

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 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 [22] and the literature on the rehabilitation of attention is now substantial [23].

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 [24] and Attention Process Training II [25] 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 version for children has also been developed (Pay Attention!) and used successfully with children with attention deficits [26].

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.

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 [27]. Improvements have been shown not only on attentional abilities but in demonstrable functional improvements [28].

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 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 [29] 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 [30] and to reduce stress related to careers [31].

Compensatory approaches have focused primarily on the use of datebooks or notebooks [32]. There are many studies that document the efficacy of using external aids for the management of memory disorders [33]. 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 [34, 35]. 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. [36] 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 [37], 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 [38, 39]. 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 subjects were 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. 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 [40]. 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 (identifying 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 3 months follow-up on the assessment of personal problem-solving skills.

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 that occur over a longer period of time, for example, 1 h every day for a week rather than 7 h in 1 day. This schedule seems to allow time for memory consolidation [41, 42]. There is some evidence to suggest that distributed practice has a greater effect on the cortical network that supports retrieval [43].

Prospective Memory Training

One particularly encouraging approach to direct retraining has been prospective memory training [44]. In a study by Raskin and Sohlberg [45], 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. [46] to treat attention and prospective memory impairments in individuals with schizophrenia and by Kinsella et al. [47] in individuals with Alzheimer's disease.

Other 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 [48]. In general, treatments are aimed at problems with encoding, such as elaboration [49] or visual imagery [50]. But there is some evidence that these strategies may actually reduce the cognitive resources available to the individual [51].

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

[52] 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) [53].

TEACH-M is an instructional package designed by Ehlhardt et al. [54]. The acronym stands for *t*ask analysis, *e*rrorless learning, *a*ssessment, *c*umulative review, *h*igh rates of correct practice, and *m*etacognitive 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 e-mail 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 cueing, 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 [55]. In semantic cueing treatment, the clinician might provide antonyms, synonyms, categories, or pictures to help guide the person toward 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 [56].

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) [57]. 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 [58] 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 [59] 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 [60]. Constraint-induced language therapy (CILT) is designed to eliminate the potential learned non-use of individuals (the theory that if individuals start to use compensations, to avoid language, the non-use of language becomes learned) with aphasia [61, 62]. 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 [63]. The therapy is hierarchically organized so that at first only a single word is required and then full sentences, etc. Results suggested improvements generalized to

daily life. In one study, CILT was demonstrated to be superior to PACE [51].

Dyslexia and Developmental Reading Disorders

There has been 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 [64] 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/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 pre-treatment, 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 [65] provided children with dyslexia with a 3-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 activation.

A commercial product, Fast ForWord, which uses acoustically modified speech 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 [66]. In one study [67], 20 children were given this behavioral training in auditory processing and oral language training. These children showed improved reading performance and fMRI demonstrated increases in temporo-parietal cortex and left inferior frontal gyrus. However, other studies have failed to find a specific effect of Fast For Word compared to other behavioral interventions [68].

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. [69] 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 are 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. [70], 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 from a baseline period, during which no cues were given, to the following treatment phase, during which 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 [71] 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 [72].

Training that targets working memory has shown efficacy in children with attention-deficit hyperactivity disorder [73] 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 [74].

Approaches focused on multi-tasking, which is related to divided and alternating attention, also have shown some promise. Stablum et al. [75] demonstrated improvements in dual-task performance with practice over 5 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 ones own behavior through self-talk. Stuss et al. [76] 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 [77] reported successful treatment with such a procedure of a patient who exhibited planning ability and poor self-control 4 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 [78], which demonstrated that verbal mediation strategies can lead to improved performance in daily life. As noted by Onsworth et al. [79], 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. [80] 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 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. [81] 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.

A similar series of studies aimed at metacognitive skills fall under the approach of goal management training (GMT) [82]. 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. [63] demonstrated the superiority of GMT to motor skills training when comparing two groups of individuals with brain injury. This has also been applied to naturalistic tasks such as meal preparation.

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. [83] 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. [84]). One example of this is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) therapies [85]. 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 [86].

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 are 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 [87]. These include spatial inattention, attention-deficit hyperactivity disorder, post-traumatic 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 [88].

A review of virtual reality use in the rehabilitation of people with brain injury [89] 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 [90].

Another area of increased interest is the use of virtual reality for children with ADHD [91]. 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 [92].

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 [93], 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, non-invasive 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 [94]. Similarly, studies in humans using single motor or parietal neuron spike patterns were not applicable to activites of daily living [95].

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 [96]. 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 works in the field of rehabilitation are based on models of cortical plasticity. Robertson and Murr [97] 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 re-establish 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 [98] 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, while only individuals with better vigilance levels showed improvement on the 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.

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 [99].

As the field of cognitive neuroscience provides more evidence for the specific kinds of practice and experience-dependant learning that lead to most effective cortical plasticity, it should also be possible to target rehabilitation efforts to maximize these potential changes.

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Chapter 29

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.

J. Jeka (✉)
Department of Kinesiology, Neuroscience & Cognitive Science Program, University of Maryland, College Park, MD 20742-2611, USA
e-mail: jjeka@umd.edu

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 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

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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 [17, 7, 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 [19, 20, 8]. 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 [26, 9]). 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, 33, 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 29.1 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

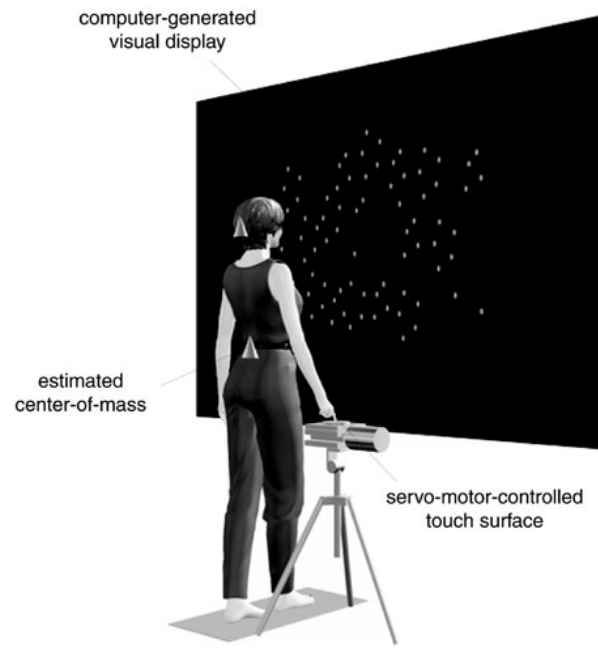

Fig. 29.1 Two-frequency vision and touch experimental paradigm

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 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 29.2 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.

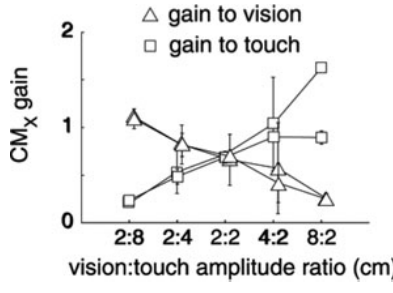

Fig. 29.2 Center of mass gain to vision and light touch showing both intra-modality and intermodality reweighting

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 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. 29.3. 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 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 29.4 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,

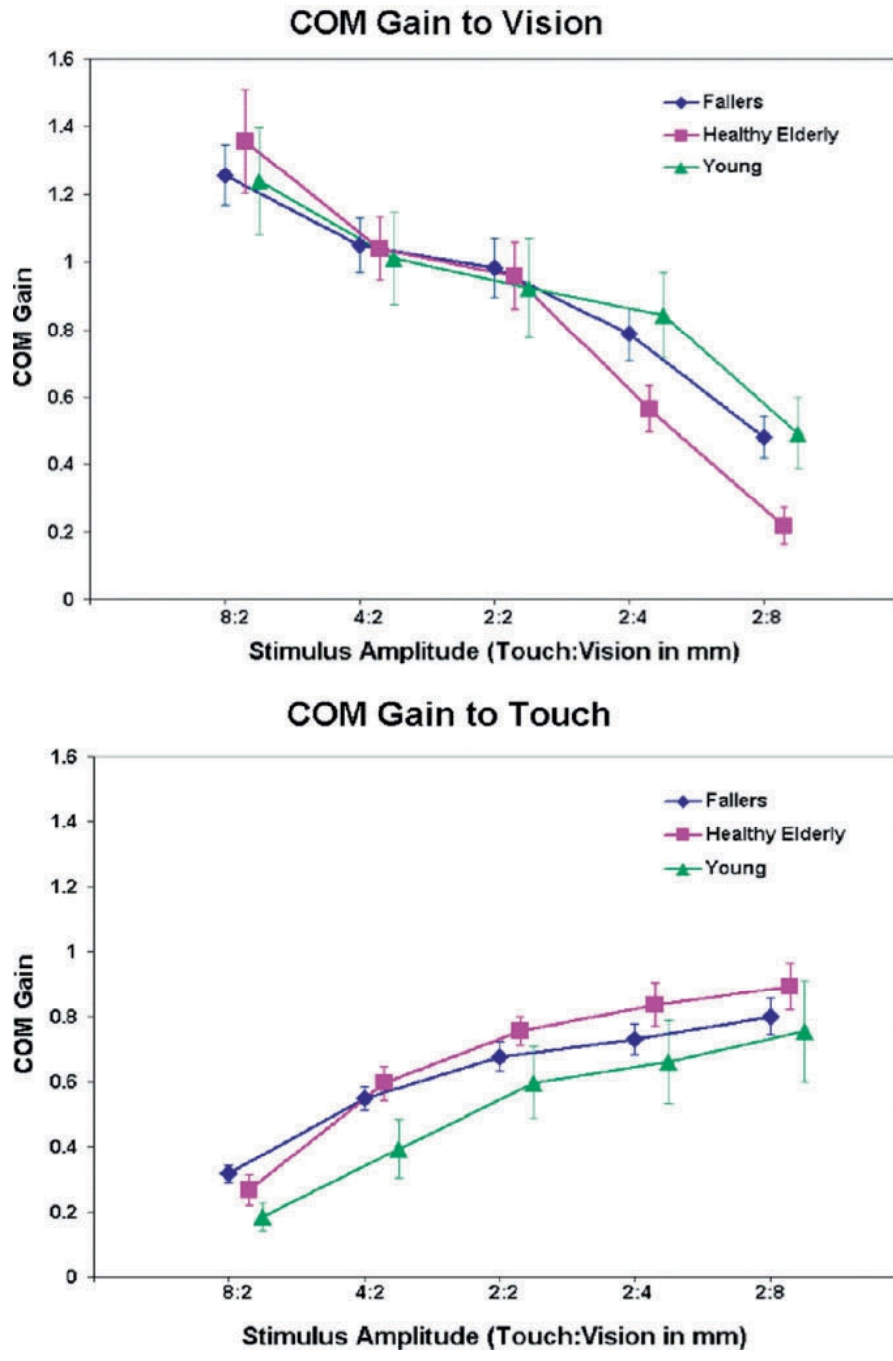

Fig. 29.3 Center of mass gain to vision and light touch in young, healthy older, and fall-prone older adults

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

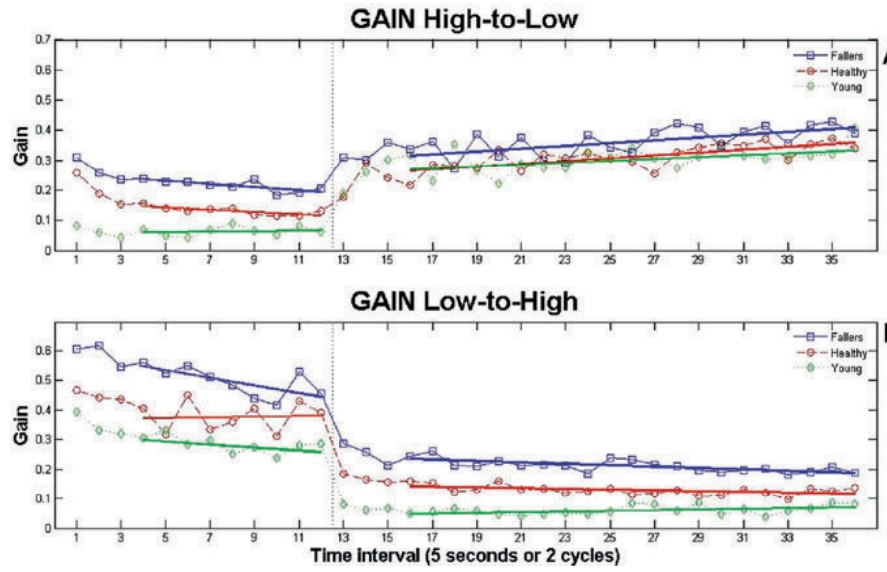

Fig. 29.4 Long-term changes in center of mass gain in young, healthy older, and fall-prone adults after a change in the visual amplitude from (**a**) high-to-low and (**b**) low-to-high

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. 29.5a, 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

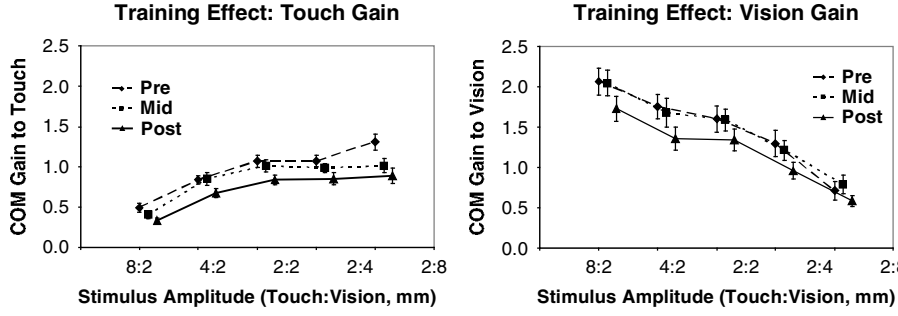

Fig. 29.5 Effect of training on center of mass gain to (**a**) touch and (**b**) vision

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.

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 [32, 26, 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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