Clinical Handbooks in Neuropsychology

Lisa D. Ravdin · Heather L. Katzen *Editors*

Handbook on the Neuropsychology of Aging and Dementia

Second Edition

Springer

Clinical Handbooks in Neuropsychology

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Handbook on the Neuropsychology of Aging and Dementia

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Preface

We are excited to bring you this revised and expanded version of the *Handbook on the Neuropsychology of Aging and Dementia*, with the addition of 14 new chapters covering a wide range of topics of practical interest to clinical neuropsychologists working with older adults, as well as updated versions of the original chapters. This contribution to the *Clinical Handbook in Neuropsychology* series (Series Editor, William B. Barr) was envisioned as a departure from typical textbooks by focusing on concrete clinical descriptions and detailed instructions regarding how neuropsychologists evaluate various patient conditions. We asked contributing authors to help us create a "How to" book for neuropsychologists, encouraging experts to describe how they handle their topic of interest in their daily work, asking them to provide the reader with valuable tips to help the reader readily digest the skillful essentials of clinical practice that come from experience.

New chapters expand the breath of topics covered and include expert advice on fitness for duty evaluations, family systems and feedback, identifying elder abuse, assessing the inpatient, postoperative cognitive decline, substance use, pain, performance validity testing, management of behavioral symptoms, cognitive training and rehabilitation, epilepsy, primary progressive aphasia, assessment of patients being evaluated for mechanical circulatory support, and a thoughtful contribution on chronic traumatic brain injury. There's a wealth of useful information for those preparing for board certification as well as essential tips that can benefit even the seasoned practitioner. We certainly feel we learned a lot by preparing this work.

The *Handbook on the Neuropsychology of Aging and Dementia, Second edition* is a unique work that provides clinicians with expert guidance and a hands-on approach to neuropsychological practice with older adults. The authors of each chapter are expert practitioners, recognized by their peers as opinion leaders on their chosen chapter topics. The book is divided into three parts: Part I addresses "Neuropsychological Assessment of Older Adults: The Fundamentals," highlighting issues relevant to what to address in the intake interview all the way to insightful guidance on the feedback session. Part II attends to "Neuropsychological Assessment of Older Adults: Special Considerations/Common Issues." In this section, we focused on bringing you expert guidance on common considerations in the aging population, including issues such as postoperative cognitive decline, fitness for duty, and management of behavioral symptoms in dementia. In Part III, "Late Life Cognitive Disorders," experts provide insights on key elements relevant to

evaluating a specific population or disease state. Suggested test batteries as well as a user-friendly compilation of "clinical pearls" at the end of each chapter consist of expert tips and key take-home messages for that topic.

Once again, we found that contributing authors embraced the approach of providing insightful commentary based on clinical experience, and we appreciate the time they committed to the successful completion of this work. We are grateful for the guidance and support provided by our publisher, specifically individuals such as Janice Stern and Christina Tuballes, and special thanks to Katherine Chabalko for stepping in and overseeing this project through to completion. Thank you Bill Barr for the opportunity to contribute this volume to the Handbook series, and thanks to Hannah Deutsch for her assistance with administrative tasks related to the preparation of the final product.

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Part I

Neuropsychological Assessment of Older Adults: The Fundamentals

1 Special Considerations for the Neuropsychological Interview with Older Adults

Stephanie Assuras and Bonnie Levin

The neuropsychological interview presents a unique opportunity to gather essential data that can be used to guide the testing process and assist in formulating a differential diagnosis. A comprehensive interview not only provides important background information that cannot be obtained from psychometric testing, but it also offers an opportunity for the examiner to gather critical behavioral observations that are often witnessed only in a less-structured setting. Although interviews vary in their focus and depth, they provide a framework from which examiners can assess demographic and referral information, data pertaining to presenting complaints and symptom progression, information regarding activities of daily living, pertinent environmental risk factors, and relevant background information regarding past medical, developmental, educational, and psychosocial history. The interview also offers the opportunity to assess the caregiver's perspective of the patient's cognitive status, additional stressors, and available resources that can be used to guide the treatment recommendations. Thus, gathering information from a collateral source should be a key component of the clinical interview when possible.

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Demographic and Referral Information

The first questions posed by the examiner will set the tone for the rest of the interview. Asking a patient to provide demographic information can be a good way to begin establishing rapport. In addition to essential information such as one's name, date of birth, handedness, gender, educational level, and living arrangement, patients should also explain in their own words, whenever possible, who referred them for testing and the reason for the referral. This is really the first opportunity that the examiner will have to assess the level of insight and ability to formulate one's thoughts. Other important questions that should be addressed before testing begins are medication regimen; their primary language and, when applicable, secondary language; and whether the patient requires glasses, hearing assistive devices, and/or ambulatory assistance.

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Physical, Cognitive, and Emotional Complaints

One goal of the interview is to document the specifics of the complaints and the time course of symptoms. There are several different approaches used to evaluate current physical, cognitive, and emotional complaints. These include (1) having the patient or caregiver fill out a structured questionnaire, (2) asking the patient to elaborate on each of his or her concerns as the examiner records the complaints verbatim, or (3) starting the interview using a structured format where the examiner systematically reviews a predetermined list of possible symptoms. The best approach usually involves a combination of these interviewing techniques such as having patients verbally describe their chief concerns and then following up with a more structured series of questions or having the examiner administer a formal questionnaire before testing begins and then reviewing each item with the patient and caregiver during the interview.

Physical Symptoms

The most common noncognitive neurologic complaints reported by older adults are headache, dizziness, numbness/tingling, visual changes, and problems with balance. Generally speaking, physical complaints can be grouped into motor, sensory, and somatic functions. Important areas to address with regard to motor changes include weakness, gait and balance difficulties (such as shuffling and smaller steps), motor slowing, presence of tremor, stiffness, numbness, difficulty pronouncing words clearly, and difficulty with eye movements (e.g., upward gaze). Some motor symptoms such as tremor and motor slowing may be obvious, but others such as weakness or stiffness are more subtle and would be missed unless the patient is directly questioned. It is also important to follow up individual questions with further inquiry. For example, when the patient confirms that he or she has balance difficulties, it is important to ask about a history of falls. Keeping in mind that falls are the most common reason for hospitalization among older adults [1], this line of questioning will not only provide information with regard to a past history of possible traumatic injury or the presence of a movement disorder, but it will also alert the clinician to possible safety concerns.

Sensory complaints are subjective and require that patients be able to express their concerns. Typical sensory complaints and areas to assess for include pain, visual and auditory changes (including illusions and possible hallucinations), appetite change (e.g., increased consumption of sweets), changes in smell and odor detection, dizziness, and heart palpitations. Somatic complaints, which can be difficult to disentangle from sensory symptoms, are frequent and include an array of gastrointestinal problems (bowel and bladder), headaches, arthritic pain, and sleep disturbances. Since somatic complaints have been linked to depression [2], this area should be carefully addressed with older adult patients.

Sleep quality plays an important role in alertness, attention, and overall cognitive functioning and is often a contributing factor to cognitive decline [3]. Given the high prevalence of sleep disorders in this age group, clinicians should be aware of common complaints such as difficulty falling or staying asleep, sleep-disordered breathing, frequent awakening, snoring, awakening to a choking sensation, use of sleep aids, feelings of daytime fatigue and napping, and increased movements in sleep. If a family member reports unusual behaviors during sleep such as dream enactment (shouting out loud, punching a bed partner, or other forms of acting out a dream), they should be noted and explored in greater detail for possible REM sleep behavior disorder, a condition associated with parkinsonism. Questions regarding urinary function are important and should extend beyond asking about frank incontinence to include inquiries regarding urinary urgency and frequency, since these may be early features of normal pressure hydrocephalus (NPH) [4]. Additionally, somatic symptoms related to autonomic function, such as impotence and dizziness or hypotension, may be relevant when a movement disorder such

Table 1.1 Examples of question topics for interviewing older adults

Cognitive symptoms	Physical symptoms	Emotional symptoms
Difficulty remembering conversations	Difficulty pronouncing words clearly	Lack of interest in activities
Unsure of previous day's activities	Visual or auditory changes, including illusions	Reduced initiation
Repeating questions	Difficulty with eye movements (e.g., upward gaze)	Apathy
Forgetting why you walked into a room or what you need at the store	Changes in smell and odor detection	Irritability
Difficulty coming up with the right word or remembering people's names	Gait changes (e.g., shuffling, smaller steps, slowing)	Restlessness
Poor attention/concentration when reading or watching television	Reduced balance, increased falls	Depressed mood
Slower thinking and problem-solving	Urinary changes (frequency, urgency, incontinence)	Hallucinations (describe content, quality, e.g., if they elicit fear)
Difficulty planning and organizing tasks, multitasking	Constipation	Inappropriate behavior (e.g., approaching strangers, making inappropriate comments)
Inability to complete multiple steps	Dizziness/heart palpitations	Increased nervousness or worry
Difficulty performing routine tasks, such as making coffee	Numbness, weakness, or tremor	Fatigue or reduced energy
Trouble with new directions, getting lost in familiar places	Appetite changes, increase or decrease (e.g., increased consumption of sweets) Sleep changes	Past or present suicidal ideation

as multiple system atrophy or other Parkinson's plus disorder is on the list of differentials (see Table 1.1 for examples to guide questioning of various symptoms) [5].

Cognitive Symptoms

The most common cognitive complaint among older adults is memory [6]. It has been estimated that subjective memory complaints are as high as 56% in community-based samples [7]. Typical memory complaints are difficulty recalling names, faces, and appointments, problems recalling numbers such as phone numbers, repeating questions, word-finding difficulties, misplacing personal items, disorientation while traveling, and losing one's train of thought [8].

It is not uncommon for a patient to report memory difficulties when, in fact, the problem actually stems from a different cognitive vulnerability that impacts memory. For example, upon closer questioning, the clinician may find that the problem is actually difficulty finding words or attending to task demands and may signify deficits in aspects of cognition other than memory, language, or attention. Another common cognitive complaint is associated with executive dysfunction [9], the category of skills involved in sustaining attention, goal setting, problem-solving, planning, organization, and decision-making. The executive functions have been shown to be a major determinant of one's ability to perform instrumental activities of daily living such as financial decision-making and medication management, and they also predict onset and progression of instrumental functional decline [10]. Examiners should ask directed questions during the interview that relate to specific executive abilities. Topics from which to draw interview questions are listed in Table 1.1.

Emotional Symptoms

Careful questioning regarding mood and personality change is an important part of the interview. First, depression and anxiety complaints, especially at the subsyndromal level, are common among older adults [11]. A survey published by the Centers for Disease Control and Prevention indicated that 16% of suicide deaths were among those 65 years of age and older, higher than the rate of 11 per 100,000 in the general population [12]. Depression in older adults often goes untreated as the symptoms, which may present as somatic or cognitive complaints (e.g., memory problems, confusion, social withdrawal, loss of appetite, weight loss, and irritability), are not recognized as such. Furthermore, symptoms of depression are often mistaken as signs of dementia (see Chap. 4). It is essential that the interviewer take the time to question an individual about past and present suicidal ideation and attempts to self-harm. Any mention of suicidal thoughts or behavior should be carefully followed up with questions aimed at undercovering the seriousness of intent and the necessity for intervention.

Personality change can be an initial symptom of a degenerative disease. In older adults, behavioral symptoms are the presenting feature in frontotemporal lobar degeneration, behavioral variant, and can be observed in various cortical dementias including Alzheimer's disease, early stages of Parkinson's and Parkinson's plus syndromes such as progressive supranuclear palsy, Wilson's disease, Huntington's disease, and myasthenia gravis [13–17]. Symptoms may include disregard for social norms, inappropriate laughing or crying, apathy, and social withdrawal. Although observed more frequently in younger adults, the effect of autoimmune illnesses such as systemic lupus erythematosus and multiple sclerosis can present with psychiatric symptoms, including psychosis [18, 19]. Furthermore, patients with endocrine and metabolic disorders, such as hypoparathyroidism and hypercortisolism, can present with both cognitive decline and psychosis, as well as personality changes [20]. Finally, a careful intake of mood and personality change is especially important in formulating recommendations, which may include pharmacologic treatment, behavioral intervention, or psychotherapy.

Functional Capacity

An individual's ability to perform basic and complex activities of daily living (ADL) is a measure of one's functional status. This is an especially important area to address in the older adult because impairment in social and/or occupational function is a key component to a diagnosis of dementia. A patient's functional capacity should be comprehensively examined, focusing on basic and instrumental ADLs. Basic ADLs include questions pertaining to independence in bathing, dressing, and feeding, whereas instrumental ADLs involve higher-order abilities such as one's ability to pay bills, shop for food and prepare a meal, manage finances, and manage a medication schedule. In some cases, it is challenging to determine whether an individual who lives in a supportive environment (a spouse pays the bills; the staff in the assisted living facility prepares the meals and makes sure patients take their medication) has experienced a change in these abilities or whether the patient has retained the skill but relies on others as a matter of convenience. In this case, it is important to inquire about specific operational skills such as whether the patient is capable of carrying out emergency procedures if left alone, following a recipe if necessary, balancing a check book to pay bills, using email, etc. (see Table 1.2).

Medical History

Documenting a patient's medical history is necessary in order to formulate a differential diagnosis and to make treatment recommendations. A patient's ability to convey this information can be as informative as the history itself. Commonly reported cardiometabolic risk factors known to impact cognition include hypertension, hypercholesterolemia, type 2 diabetes, and heart

Table 1.2 Assessing functional independence/activities of daily living (ADL)

Basic ADLs
Personal hygiene
Toileting (the ability to use a restroom)
Dressing
Feeding oneself
Instrumental ADLs
Managing finances/paying bills
Looking up phone numbers
Doing housework
Using computer
Shopping
Cooking
Making appointments
Driving/traveling
Medication management

disease and vascular conditions associated with ischemia or kidney disease. Clinicians should address past illnesses, surgeries, injuries, and treatments, including metastatic cancer; cardiovascular diseases (e.g., heart disease, stroke); surgeries, especially those involving general anesthesia; alcohol and substance use; prior head trauma, with particular attention to those involving concussion and/or loss of consciousness; periods of confusion; infectious disease (hepatitis C, HIV); and unusual dietary or sleep patterns. How the patient manages these conditions (e.g., checking blood sugar, compliance with blood pressure medication, dietary practices, exercise regimen, etc.) will provide valuable information with regard to an individual's ability to participate in self-care and manage oneself independently. In addition, specific questions should address patient's medication, prescribed and over-the-counter. Past medication and prior hospitalizations should also be addressed with the patient and/or caregiver. Finally, the patient's family medical history should be carefully assessed in order to understand relevant genetic risk factors. This is likely to become an increasingly important area to address given that family health history reflects inherited genetic susceptibility for a large number of neurologic diseases.

Social History

A comprehensive interview should include a careful assessment of one's past social experiences, educational attainment, and occupation. There are many ways to assess this information, but often it is best to probe beyond a simple question. For example, questions pertaining to level of education should always be followed up with inquiries pertaining to quality of education, past history of learning difficulties, school failure, and other issues relating to academic performance, as well as occupational achievement. This can be a challenging area to assess with older adults because societal mores and educational opportunities were different decades ago. Yet, establishing if the patient has a long-standing and developmental vulnerability in cognitive function is critical to understanding if a current level of impairment represents a decline.

Conclusion

The interview is an essential part of a neuropsychological evaluation for patients of any age, but particularly among older adults, because of the myriad of physical, cognitive, psychological, and social changes associated with the aging process. These normative changes are sometimes further compounded by the onset of a disease process. A carefully conducted interview will play a critical role in establishing a diagnosis and generating treatment recommendations. In addition, it provides an opportunity to observe and document information that cannot be obtained from psychometric testing. The interview also creates a forum for establishing rapport with the patient and allows the clinician to verify important demographic and historical information from a caregiver. Guidelines provided in this chapter aim to help develop an interview designed to provide a level of insight and understanding of a patient's presentation, which cannot be obtained through other means.

Clinical Pearls

- The clinical interview provides the opportunity for insight and understanding of a patient's presentation, which cannot be obtained through other means.
- A patient's ability to convey his/her history during the interview session can be as informative as the history itself. Observations regarding a patient's expressive and receptive language, level of insight, and ability to formulate thoughts are as valuable as the test data and scores.
- Use of a combination of interviewing techniques, such as verbal description of complaints, a structured series of questions, and a formal review of each item with the patient and caregiver, is ideal. Using a questionnaire to gather background information can be useful, but this information should always be reviewed with the patient, and follow-up questions should be asked. Patients typically elaborate and provide much more detailed information when questions are asked verbally.
- Do not rely solely on behavioral observations without further probing. For example, motor symptoms such as tremor or paralysis are visible, but other motor abnormalities such as weakness or stiffness are more subtle and would be missed unless the patient is directly questioned.
- Not all complaints should be taken at face value. It is important to ask the patient to give examples of the type of cognitive problems they are experiencing. While memory complaints are the most common, the deficits may actually be in language (e.g., difficulty finding words) or attention (e.g., attending to task demands).
- Personality changes can be an initial symptom of a degenerative disease. Therefore, careful assessment of emotional and behavioral changes is critical. Since patients frequently lack insight into their own behavior, a collateral source should be consulted.
- It can be challenging to determine whether an individual who lives in a supportive environment has experienced a decline in functional independence. Every interview should inquire about specific functional abilities and give examples of instrumental activities of daily living. Knowledge of safety procedures should also be routinely assessed.

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Consideration of Cognitive Reserve

2

Stephanie Cosentino and Yaakov Stern

Introduction to Cognitive Reserve

The idea of reserve against brain damage stems from the repeated observation that there is not a direct relationship between degree of brain pathology or damage and the clinical manifestation of that damage. For example, Katzman and colleagues described ten cases of cognitively normal elderly women who were discovered to have advanced Alzheimer's disease (AD) pathology in their brains at death [1]. In more recent cohort studies, it has been estimated that approximately 25% of individuals who have postmortem neuropathological evidence of AD are not demented during their lives [2]. This discrepancy raises the question of how brain function and structure become decoupled and whether certain person-specific variables provide reserve against the clinical effects of pathological brain changes. Several theoretical models have been put forth to address this issue.

The cognitive reserve (CR) model suggests that the brain actively attempts to cope with brain damage by using preexisting cognitive processing approaches or by enlisting compensatory approaches [3, 4]. Individuals with high CR would be more successful at coping with the same amount of brain damage than those with low CR. In this scenario, brain function rather than brain size is the relevant variable. This characteristic distinguishes the CR model from the brain reserve model in which reserve derives from brain size or neuronal count [5]. According to the CR model, the same amount of brain damage or pathology will have different effects on different people, even when brain size is held constant.

Epidemiological studies have helped to shape our understanding of the nature of cognitive reserve and the person-specific variables which appear to enhance reserve. Many studies have demonstrated the beneficial effects of education [6], occupation [7], leisure [8, 9], and intellectual ability [10] on dementia incidence. In 1994, Stern and colleagues reported incident dementia data from a follow-up study of 593 community-based, non-demented individuals aged 60 years or older [7]. After 1–4 years of follow-up, 106 became demented with all but 5 meeting research criteria for AD. The risk of dementia was increased in subjects with low education, such that the relative risk (RR) of developing dementia over the follow-up period was 2.2 times higher in individuals with less than 8 years of education as compared to those with more years of education. Similarly, risk of incident dementia was increased in those with low lifetime occupational attainment

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(RR = 2.25) and greatest for subjects with both low education and low lifetime occupational attainment (RR = 2.87).

To the extent that aspects of educational and occupational attainment reflect lifetime exposures that would increase CR, it would be logical to expect that environmental exposures later in life would also be beneficial. In a subsequent study, the same group assessed participation in a variety of leisure activities characterized as intellectual (e.g., reading, playing games, going to classes) or social (e.g., visiting with friends or relatives) in a population sample of non-demented elderly in New York [9]. During follow-up, subjects who engaged in more of these activities had 38% less risk of developing dementia. Interestingly, specific classifications of leisure activity (such as purely intellectual activities) did not provide better prediction than a simple summation of all the considered activities.

A meta-analysis examining cohort studies of the effects of education, occupation, premorbid IQ, and mental activities on dementia risk over approximately 7 years revealed that 25 of 33 datasets demonstrated a significant protective effect of these variables [11]. The summary overall risk of incident dementia for individuals with high levels of the protective variable as compared to low was 0.54, a decreased risk of 46%. There is also evidence for the role of education in age-related cognitive decline, with many studies of normal aging reporting slower cognitive and functional decline in individuals with higher educational attainment [12–19]. These studies suggest that the same factors that delay the onset of dementia also allow individuals to cope more effectively with brain changes encountered in normal aging. The concept of CR provides a ready explanation for the manner in which intellectual functioning, education, and other life experiences may allow individuals to sustain greater burdens of brain pathology or age-related changes before demonstrating cognitive and functional deficits.

Neuroimaging studies have also provided evidence in support of cognitive reserve and have contributed to our conceptualization of this phenomenon. Our original functional imaging study found that in patients matched for overall severity of dementia (i.e., clinical expression of disease), the parietotemporal cerebral flow deficit was greater in those with more years of education [20]. This observation was confirmed in a later PET study in which higher education correlated negatively with cerebral metabolism in prefrontal, premotor, and left superior parietal association areas after controlling for clinical dementia severity [21]. Similar observations have been made for occupational attainment [22] and leisure activities [23] and across multiple markers of pathology including white matter abnormalities [24] and amyloid deposition [25]. The negative correlations between the exposures of interest and pathology are consistent with the CR hypothesis' prediction that at any given level of clinical disease severity, those with higher CR should have greater pathology (see Fig. 2.1).

Results and interpretations of these studies have been further supported by prospective projects with subsequent neuropathological analysis. Specifically, education has been found to modify the association between AD pathology and levels of cognitive function. With brain pathology held constant, higher education was associated with better cognitive function [26] and less likelihood of having received a clinical diagnosis of dementia in life [27]. These studies converge nicely with epidemiological evidence that supports that higher levels of education, occupational attainment, and leisure activity reduce dementia incidence and suggest that these variables influence dementia risk by enhancing cognitive reserve.

Theoretical Issues

Despite the wealth of information that has accumulated in support of the concept of cognitive reserve, there are many aspects of this construct that have yet to be fully elaborated. It is important to highlight these issues prior to discussing the various means of characterizing reserve and considering the clinical implications of cognitive reserve. The intent of the current chapter is not to fully explore these theoretical issues but simply to raise the reader's awareness of the unanswered questions surrounding the construct of cognitive reserve.

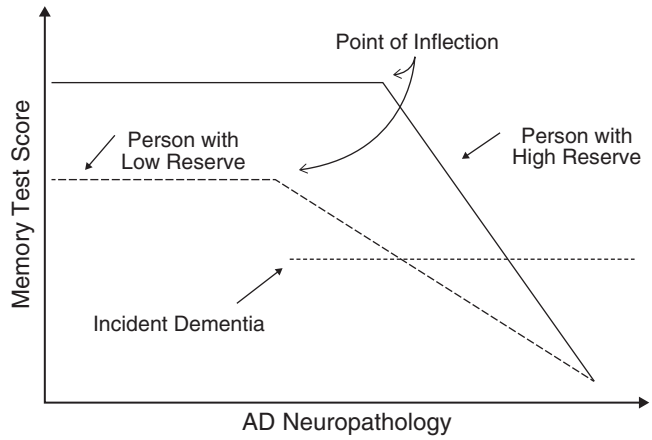

Fig. 2.1 Effect of cognitive reserve on dementia onset and course. Note: Fig. 2.1 illustrates the way in which cognitive reserve may mediate the relationship between AD pathology and its clinical expression. We assume that AD pathology slowly increases over time, and this is graphed on the *x*-axis. The *y*-axis represents cognitive function, in this case memory performance. AD pathology begins to develop many years before the disease is expressed clinically and slowly becomes more severe. At some point, this developing pathology will begin to produce the initial cognitive changes associated with dementia. This is labeled as the point of inflection in the figure. The pathology will subsequently result in symptoms of sufficient severity to allow the clinical diagnosis of AD (indicated by the dotted line labeled Incident Dementia). The cognitive reserve (CR) model predicts that because there are individual differences in reserve capacity, there will be individual differences in the amount of pathology required for the initial expression of clinical symptoms and the subsequent diagnosis of disease. Because people with higher cognitive reserve can tolerate more AD pathology, memory function will begin to be affected later in time, after more pathology has accumulated, pushing back the "point of inflection." Therefore, all other things being equal, dementia should emerge later in people with higher cognitive reserve. This leads to the prediction that the rate of incident dementia should be lower in individuals with higher cognitive reserve. An assumption of this model is that at some point, AD pathology must become too severe to support the processes that mediate either cognitive reserve or memory function. The timing of this final common endpoint will be the same in all patients, regardless of their level of cognitive reserve. It then follows that the time between the point of inflection and this common endpoint will be shorter in patients with higher cognitive reserve. This leads to the prediction that memory decline after the inflection point must be more rapid in patients with higher cognitive reserve. Although this trajectory might appear counterintuitive at first, its theoretical basis is illustrated in this figure, and it has been supported by multiple epidemiological studies

First, the precise manner in which cognitive reserve affords protection from pathology is not understood. As discussed above, we know that across individuals, there is a discrepancy between brain changes or pathology and cognitive change such that in some individuals, cognitive function remains relatively preserved in the face of pathological markers. As such, individuals with high cognitive reserve are not necessarily protected from developing pathology but rather that they are spared the clinical effects of such pathology. Thus, when we refer to the preservation of a cognitive function such as memory in the sections below, we are in fact talking only about memory itself and not the integrity of the brain areas underlying that cognitive function (e.g., hippocampus). Indeed, the concept of cognitive reserve only applies when considering variability in cognitive functioning (i.e., memory) in the face of changes in brain integrity (i.e., hippocampal volume).

This raises one of the puzzling questions surrounding reserve: memory and hippocampal integrity are intimately related, and the mechanisms underlying the decoupling of structure and function are not clear. From a strict point of view, the differences in cognitive processing envisioned by the CR model must also have a physiologic basis, in that the brain must ultimately mediate all cognitive function. The difference is

in terms of the level of analysis. Presumably, the physiologic variability subsumed by cognitive reserve is at the level of variability in synaptic organization or in relative utilization of specific brain regions. Thus, cognitive reserve implies anatomic variability at the level of brain networks, while brain reserve implies differences in the quantity of available neural substrate.

Moreover, it has more recently been recognized that life exposures that are associated with reserve also affect brain structure or brain pathology and not simply cognitive properties. This has been referred to as brain maintenance [28]. Recent studies that support this concept include 1 which found reduced rate of hippocampal atrophy over 3 years in individuals with higher levels of complex mental activity across the life span [29] and another which found microstructural differences in the hippocampus as a function of education [30]. Additionally, the child developmental literature suggests that not only do individuals with higher IQ have larger brain volume [31, 32] but that cognitively stimulating aspects of life experience may also be associated with increased brain volume. It is also now clear that stimulating environments and exercise promote neurogenesis in the dentate gyrus [33, 34]. Both exercise and cognitive stimulation regulate factors that increase neuronal plasticity (such as brain-derived neurotrophic factor) and resistance to cell death. Finally, there is some evidence to suggest that environmental enrichment might act directly to prevent or slow the accumulation of AD pathology [35]. All of these considerations lead to the conclusion that brain maintenance acts to help preserve the brain over time. In this regard we can consider brain reserve the current state of the brain as shaped by brain maintenance.

In sum, there appears to be growing evidence that the experiences that provide cognitive reserve may indeed reflect not only a cognitive advantage but a structural advantage as well. Thus, brain reserve and cognitive reserve concepts are not mutually exclusive, and it is likely that both are involved in providing reserve against brain damage. A complete model of cognitive reserve will have to integrate the complex interactions between genetics, the environmental influences on brain reserve and pathology, and the ability to actively compensate for the effects of pathology.

Setting aside the question of brain integrity, and considering cognitive reserve only, we return to the question of why insult to brain structure does not invariably affect cognition. We have observed that individuals with higher cognitive reserve (defined using a literacy measure) have less rapid memory decline over time than those with lower literacy levels [36]. However, the manner in which this memory advantage is conferred is unknown. It may be that preserved memory reflects preservation of the memory networks per se or use of alternative and supportive skills such as enhanced organizational strategies [37]. Stern and colleagues have described these two potential neural implementations of cognitive reserve as *neural reserve* and *neural compensation* [4, 38, 39]. The idea behind *neural reserve* is that there is natural interindividual variability in the brain networks or cognitive processes that underlie the performance of any task. This variability could be in the form of differing efficiency or capacity of these networks or in greater flexibility in the networks that can be invoked to perform a task. While healthy individuals may invoke these networks when coping with increased task demands, the networks could also help an individual cope with brain pathology. An individual whose networks are more efficient, have greater capacity, or are more flexible might be more capable of coping with the challenges imposed by brain pathology. In contrast, *neural compensation* refers to the process by which individuals suffering from brain pathology use brain structures or networks (and thus cognitive strategies) not normally used by individuals with intact brains in order to compensate for brain damage. The term compensation is reserved for a situation where it can be demonstrated that the more impaired group is using a different network than the unimpaired group.

It is not yet clear whether or when each of these forms of reserve come into play. The answer to this question has several implications, one of which pertains to the applicability of cognitive

reserve under various conditions. Specifically, if the benefits of cognitive reserve are attributable to the flexible application of alternative strategies for completing a task (compensation), specific aspects of brain function may receive less assistance from cognitive reserve than others. It may be that a cognitive skill such as verbal recall can be accomplished in a number of ways that differentially employ serial rehearsal, semantic processing, or working memory. In contrast, there may be fewer cognitive routes to reproduce a complex figure or detect a subtle visual detail amid a complex scene. In this scenario, a compensatory reserve mechanism might be less applicable to spatial skills than to verbal memory. However, it is also possible that critical issue is not task specific but, rather, person specific. That is, based on life experience, one person may have multiple ways of approaching a spatial task but less flexibility for a verbal task, whereas the opposite pattern may exist in another individual. If the crux of cognitive reserve is the ability to apply alternative approaches to accomplish tasks, then the benefit of reserve may be linked directly to the flexibility of the task (and corresponding skill) itself or to a person's premorbid cognitive style.

One final question is whether or not deterioration of specific cognitive functions can directly affect cognitive reserve. For example, if cognitive reserve is closely aligned or even overlaps with executive abilities [40], is it the case that cognitive reserve is less able (or unable) to stave off executive deficits as opposed to declines in other domains such as memory or language? That is, is cognitive reserve itself vulnerable to a particular presentation of disease? Or, is cognitive reserve a construct that is "immune" to the regional distribution of pathology, independent of the cognitive abilities that may be affected, functioning universally under a wide variety of lesions? While the answer to this question is not entirely clear, recent studies examining the effects of reserve on information processing efficiency in individuals with multiple sclerosis may shed light on the issue [41–44]. For example, Sumowksi and colleagues showed that the negative effect of brain atrophy on rapid information processing was attenuated in individuals with higher levels of reserve [42], suggesting that reserve confers benefits to cognitive functions whose nature is quite similar to some conceptualizations of reserve. That is, the information processing measure was comprised of the Symbol Digit Modalities Test [45] and the Paced Auditory Serial Addition Test [46], tasks which require mental flexibility and fluidity. Similarly, although speculative, one perspective of cognitive reserve is that it represents the mental flexibility to develop alternative strategies in the face of pathology and to fluidly apply such strategies to the task at hand. The reported benefits of reserve on information processing and efficiency in the above studies are interesting and raise many questions for future work. For the time being, such studies may offer preliminary evidence either that (1) reserve is immune to the distribution of pathology or (2) reserve is fundamentally different than the cognitive skills assessed in these studies.

Estimating Cognitive Reserve

A practical question for the clinician is how to account for cognitive reserve in the diagnostic process. In this section, we review the advantages and disadvantages of several approaches including the following: (1) measurement of individual characteristics (demographic and lifestyle), (2) consideration of cumulative life experiences, (3) estimation of intellectual functioning, (4) implementation of statistical approaches (use of latent or residual variables), and (5) derivation of brain network patterns. Prior to discussing these approaches, it is also important to consider that although epidemiological work has led to the conceptualization of reserve as a reflection of important lifetime experiences, the cognitive advantage which manifests as reserve might also have played an important role early in life to afford individuals the desire and ability to pursue certain life experiences such as graduate school, for example. Thus, the effects of lifetime experiences are not necessarily separate from early life factors. Although certain work has suggested that reserve is a cumulative process built on both

early life and late life experiences [47], the causal pathway of cognitive reserve has not been fully delineated. As the reader considers the clinical implications of cognitive reserve and the various methods for measuring reserve, it is important to be aware of the larger questions surrounding its origins and characteristics.

Individual Characteristics

One of the most commonly used methods of characterizing reserve involves quantifying individual characteristics that have been associated with reduced risk of dementia including education, occupation, intellectual functioning, leisure activity, and social engagement. The advantage of this approach is that these variables are relatively easy to acquire and quantify and, at face value, are generally plausible proxies for reserve. A disadvantage is that these variables may be singular representations of a multidimensional mechanism such that characterization of education in isolation, for example, might account for a relatively small proportion of the variance in overall cognitive reserve. Moreover, these variables are rather agnostic with regard to the source and nature of cognitive reserve and may confound multiple other factors with "true" reserve (e.g., education may impart greater knowledge and access to health care which in turn may promote health-related behaviors and enhance cognitive functioning). As such, use of variables such as those listed above, although convenient, should not be the sole indicators of CR.

Cumulative Life Experiences

A second approach for characterizing cognitive reserve is one in which multiple or cumulative life experiences are synthesized to develop a more comprehensive estimation of an individual's reserve. The purported benefit of this approach is that it synthesizes numerous experiences, all of which have been shown through epidemiological work to confer protection against the development of dementia. The consideration of comprehensive life experiences offers the opportunity to capture a wide array of factors that may uniquely contribute to reserve, if indeed reserve is created through a cumulative process. Valenzuela and Sachdev [48] developed the Lifetime of Experiences Questionnaire (LEQ) as a means of capturing and quantifying various social, academic, occupational, and leisure activities spanning young to late adulthood. The questionnaire showed good reliability and validity and was useful in predicting which individuals would demonstrate cognitive decline over an 18-month period.

While this appears to be a powerful method of capturing a myriad of experiences relevant to the construct of cognitive reserve, there are several issues to consider. It is possible that the summation of experiences within this questionnaire may not be more predictive than any individual variable, and compiling these experiences may even obscure the effect of the most relevant variable. For example, Hall and colleagues found that the effect of education on cognitive decline prior to dementia diagnosis was negligible after accounting for cognitively stimulating leisure activities later in life [49], suggesting one of two possible scenarios raised by the authors. First, it could be that the effects of education were mediated by mental activities late in life or second, that education influenced reserve directly with no additional benefit conferred by later life mental stimulation. Researchers must carefully consider these issues; however, a lifetime approach to characterizing reserve for clinical purposes is certainly useful in that it comprehensively quantifies important experiences that may delay cognitive decline in the face of advancing pathology.

Intellectual Function

A third and very different means of characterizing reserve is the assessment of intellectual functioning, typically via a single-word reading test, such as the Wechsler Test of Adult Reading [50] or the North American Adult Reading Test [51], or a subtest of the Wechsler Adult Intelligence

Scales such as Vocabulary or Information [52]. Word reading measures evaluate an individual's ability to pronounce a series of phonologically regular and irregular words ranging in difficulty and are based on the idea that correct pronunciation of the more difficult items requires previous exposure to such words. Like vocabulary and fund of information, this ability is generally spared early in the course of dementia, reflecting its reliance on long-term, crystallized knowledge versus the more fluid abilities affected early in disease [53–57].

The characterization of IQ is believed to offer a thumbnail sketch of an individual's lifetime intellectual achievement, highly related to, though not necessarily synonymous with, the concept of cognitive reserve. An advantage of using IQ to characterize cognitive reserve is that in contrast to an external exposure variable such as education or occupation, an internal and broadly stable capability such as IQ is presumably more closely associated with the cognitive and neural representation of reserve. Unfortunately, a corresponding disadvantage is that IQ scores do change in the course of disease and therefore can be contaminated by the disease process itself (unlike education or occupation). Moreover, while reading scores are fairly stable in the very early stages of degenerative illnesses, they are certainly not valid estimates of premorbid IQ in a language predominant illness, nor are they valid estimates in nonnative English speakers.

Despite the differences in applying IQ versus an exposure variable such as education, there is statistical evidence that both share common statistical variance that is distinct from cognitive functions more broadly [40]. The presence of both convergent and discriminant validity in this context provides support for both of these variables as independent proxies for reserve, as well as evidence for the construct validity of reserve. This is an important finding because the coherence of cognitive reserve as a construct remains under question, leading several groups to argue that latent variables derived through structural equation modeling may be the most appropriate way to capture the essence of reserve [58, 59]. Although the details of these models are beyond the scope of this chapter, the idea is that through statistical data reduction, we can boil down the overgeneralized concept of reserve into its core elements and identify those variables that are central to its construct versus those that may be extraneous. A necessary drawback, however, is that representation of cognitive reserve through shared variance may not reflect aspects of reserve potentially captured selectively by each unique variable.

Statistical Approaches

A statistical approach to identifying reserve has recently been proposed by Reed and colleagues [60] by decomposing the variance of a specific cognitive skill such as episodic memory. Specifically, the authors partitioned the variance explained by demographic variables (education, sex, and ethnicity), structural brain imaging variables, and a third residual component. By definition, this residual component approximates the concept of cognitive reserve as it represents the unexplained variance in cognitive performance after accounting for brain structure and, in this case, demographics. Interestingly, the authors included education as part of the demographics variable to isolate a component that would be uncontaminated by the indirect effects of education on brain integrity (e.g., access to health care and knowledge of health-promoting behaviors). Results showed that residual scores correlated with another measure of reserve (word reading), modified rates of conversion from mild cognitive impairment to dementia over time, and modified rates of decline in executive function. Finally, baseline brain status had less of an effect on cognitive decline over time in individuals with high residual scores than low residual scores.

In addition to providing an operational measure of reserve that is quantitative, continuous, and specific to the individual, the residual approach to characterizing reserve allows the estimate of cognitive reserve to change over time. This fluid characteristic may or may not be appealing to individual researchers and clinicians,

depending on the particular question or task at hand. The authors also note that a potential problem with this approach is that, depending on the specific brain and cognitive variables used to define reserve, different measures of reserve will be applicable to a person at any given time. Practically speaking, a primary drawback to using residual scores is that it is currently not feasible for the clinician to apply such scores on an individual basis. This may change in the future with greater access to imaging technologies and availability of normative or group data with which to derive an individual's residual score.

Brain Network Patterns

A future goal for representing reserve is through an identifiable brain network or series of networks. Such networks might be derived using functional imaging techniques that capture the neural signature of cognitive reserve. For example, Stern and colleagues examined whether or not a common neural network, whose expression varied as a function of cognitive reserve, could be detected across verbal and spatial delayed match-to-sample tasks [61]. Indeed, in the group of young adults, such a network was identified, and expression of this network was entirely independent of task performance. The invocation of this network on divergent tasks was uniquely related to cognitive reserve, as assessed with a composite of vocabulary and word reading, suggesting that the network may represent a generalized neural instantiation of reserve.

The utility of a brain network for capturing cognitive reserve is multifold. First, to the extent that reserve truly has a neural signature, the identification of a brain network that "behaves" like cognitive reserve (e.g., correlates with traditional reserve variables, persists across divergent task demands, and interacts with task performance in the expected way) would be a more direct way to measure the construct. Second, a brain network would be a nonbiased characterization of reserve that could be used universally in a manner that tests such as vocabulary or single-word reading cannot, due to their influences from culture and language. Third, a brain network is malleable in a way that fixed life experiences are not and thus lends itself to examination in the context of a longitudinal study. For example, interventional studies aimed at increasing reserve could use a brain network to measure reserve both pre- and post-intervention, and unlike cognitive testing, this network would be resistant to practice effects.

Application of Cognitive Reserve in Clinical Practice

While the concept of cognitive reserve is on the one hand intuitive, it is also easily misunderstood and conducive to misapplication in part due to the thorny theoretical and methodological issues discussed above. However, there is nothing magical about the concept of reserve, and most clinicians generally consider the role of reserve in their assessment and case conceptualization (even if not explicitly). In this section, we provide concrete suggestions for the consideration and application of cognitive reserve in clinical practice.

First, when assessing cognition as part of a diagnostic evaluation, it is important to take into account the most appropriate and valid indicator of cognitive reserve for a given patient. In the event that an individual's level of education is not believed to be a good representation of his or her optimal cognitive functioning, assessment of IQ or consideration of occupation may provide a more accurate estimate. Alternatively, in a nonnative English speaker, education may be a better representation than single-word reading to estimate IQ. Although, it should be noted that the availability of tests in other languages is increasing, such as Spanish [62], French [63], Japanese [64], and Swedish [65]. Application of a non-English assessment tool would be appropriate only in circumstances when the remainder of the neuropsychological battery can also be validly administered in the same language, as direct comparisons of IQ and neuropsychological scores would be otherwise impossible.

Integration of the most appropriate and valid measure of cognitive reserve into the diagnostic formulation is critical. Individuals with high

reserve, by definition, will not demonstrate clinical symptoms as early as individuals with low levels of reserve. On the one hand, this issue could partially be a problem with instrumentation, such that (1) more challenging tests with higher ceilings may better detect changes in individuals with very high levels of functioning, (2) tests that are more pathologically specific (e.g., associative learning tasks for the hippocampus) may have greater sensitivity in high reserve individuals, or (3) better normative data may allow for better detection of impairment in individuals with high levels of intellectual functioning. Indeed, quantitative consideration of IQ scores appears to improve the sensitivity of cognitive testing for detecting pathology. Rentz and colleagues [66] found that when memory scores in a group of cognitively "normal" individuals were adjusted based on IQ, the adjusted memory scores correlated with cerebral perfusion in areas vulnerable to the early stages of AD pathology. That is, those with higher IQ (i.e., reserve) had greater pathology despite similar cognitive performance, and these individuals showed greater cognitive decline over the following 3 years than the individuals whose IQ-adjusted memory scores were intact [66].

In theory, there would still be a period of time during which even the most sensitive measures would fail to detect change in those with high reserve given the apparent "lag" between pathological changes and their cognitive sequelae. Therefore, from a clinical standpoint, neuropsychological testing will be less sensitive to the presence of early pathology in those with high reserve *even when we consider current test scores in the context of a person's optimal level of functioning* (e.g., *IQ*, *education*). As such, the only action to be taken by clinicians is to be aware of this conundrum and to appreciate that intact cognition in individuals with high levels of reserve does not preclude the presence of disease.

The standard and generally useful approach taken by neuropsychologists is to formally adjust cognitive scores for education, a procedure which, in theory, allows for the interpretation of current cognitive performance in the context of an individual's expected performance. For example, we know that there are baseline differences in cognitive performance such that in the absence of pathology, a 70-year-old with 8 years of education might recall fewer words over the course of a list learning test than a 70-year-old with 19 years of education. The corollary of this phenomenon is that the patient with 19 years of education would have had to sustain a greater degree of neuropathology to reach a certain score than the individual with 6 years of education, all other things being equal. However, this observation does not, in and of itself, reflect cognitive reserve. Rather, reserve accounts for the ability of the individual with 19 years of education to maintain baseline cognitive functioning for a longer period of time than the individual with 6 years of education in the face of advancing pathology.

Information regarding brain integrity should be integrated with cognitive data for diagnostic purposes, whenever possible. Of course, this process is done regularly in most clinical settings and adds important information and greater clarity to the overall clinical picture. In this context, however, the focus is on the relevance of neuroimaging as a means to understand the influence of cognitive reserve on the clinical presentation. Neuroimaging tools have the potential, particularly in individuals with high reserve who maintain cognitive functioning for an extended period of time, to detect pathological changes when impairment on neuropsychological testing is absent or subtle. For example, at a given level of clinical severity, AD patients with higher education have a more severe pattern of AD-related changes on PET scan than those with lower education [67, 68].

More recently, the sensitivity of a variety of imaging tools for detecting pathological changes prior to cognitive change has been demonstrated on structural MRI [69] and functional MRI (fMRI) [70], as well as through examination of activity level in the default network on resting fMRI [71]. Moving forward, in vivo amyloid imaging, although not currently used in clinical practice, will certainly play an important role in identifying neuropathological changes in asymptomatic individuals as the field moves toward earlier identification of disease. While these various

technologies enable the consideration of cognitive reserve as a factor influencing the clinical presentation and diagnosis of a patient, a current challenge to integrating imaging information is applying results from group studies to individual patients. Ideally, research studies might generate a cutoff value so that performance scores below this cutoff would raise concern for the presence of pathological changes. Such a value would be selected based on its utility in distinguishing between cognitively normal individuals who go on to develop cognitive impairment and other clinical endpoints versus those who remain cognitively healthy. This type of value has been identified for the purposes of distinguishing healthy elders from those diagnosed with AD [72, 73], and future work will aim to make this distinction at earlier time points.

Another recommendation for applying the concept of cognitive reserve to clinical practice is to consider it as a factor that will influence rate of cognitive decline following diagnosis. Although cognitive reserve delays the manifestation of cognitive deficits, symptoms progress fairly rapidly once evident (see Fig. 2.1). In fact, decline is more rapid in individuals with high reserve than those with low reserve, even when accounting for a multitude of other factors that may contribute to the disease course [74–76]. This counterintuitive acceleration in rate of change is believed to reflect the increasingly high pathological burden that the brain can no longer tolerate. Certainly, this has practical implications for the patient, family, and health-care providers. It may also have direct relevance for the effectiveness of treatment.

Cognitive reserve may influence an individual's response to treatment with currently available medications as well as future drug therapies. The treatment of degenerative diseases such as Alzheimer's disease is certain to be most effective when done preventatively, when the burden of pathology in the brain is very low or absent altogether. Thus, in order to develop reasonable expectations about a medication's effectiveness, it will be important to have knowledge of three variables: cognitive performance, cognitive reserve, and pathological burden. As we have reinforced throughout this chapter, it is the combination of these three variables that enables an accurate understanding of disease severity. From a clinical standpoint, treatment in an individual with mildly impaired cognition and high cognitive reserve may be more or less effective depending on the status of the third variable, pathological burden. With little to no evidence of pathology, an individual with these characteristics would be an ideal candidate for therapy. In contrast, in the context of significant pathology, disease-delaying agents may be entirely ineffective, and this possibility should be anticipated by the clinician.

A final insight for clinicians is that while a wide range of evidence exists from epidemiological studies linking certain life experiences and individual characteristics to lower rates of dementia, this evidence is not sufficient to determine definitively whether or not such experiences directly prevent or delay dementia. As mentioned earlier, there may be a separate unidentified variable accounting for the observed relationship between specific experiences (e.g., completing crossword puzzles) and dementia risk. As such, intervention studies are needed to firmly establish causal links between life experiences, individual characteristics, and cognitive reserve, and such studies are underway. Therefore, while recommending that patients engage in certain activities such as mental enrichment and physical fitness is likely not to be harmful and may in fact have numerous positive effects, clinicians should be careful not to present these activities as established treatments or fully proven preventative strategies against dementia.

Clinical Pearls

- When formulating clinical impressions, apply the most appropriate and valid indicator of cognitive reserve for each individual patient. This may be an individual characteristic such as level of education; a representation of cumulative life experiences spanning social, academic, occupational, and leisure activities; or a measure of intellectual functioning. Moving forward, statistically and neuroanatomically

derived measures of cognitive reserve may also become valuable for clinical purposes.
- Integrate neuroimaging tools to complement cognitive data for diagnostic purposes.
- Consider cognitive reserve as a factor that may affect rate of decline. The apparent yet counterintuitive acceleration of decline associated cognitive reserve may reflect a state of increasingly high pathological burden that the brain can no longer tolerate.
- Appreciate that cognitive reserve may be a factor that influences response to treatment.
- Be aware that epidemiological studies linking life experiences to reduced dementia risk are observational, and intervention studies are needed to determine definitively if specific experiences and activities enhance reserve and lower dementia risk.

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3 Neuropsychological Evaluation of Culturally/Linguistically Diverse Older Adults

Monica Rivera Mindt, Alyssa Arentoft, Kelly Coulehan, Angela C. Summers, Kayla Tureson, Maral Aghvinian, and Desiree A. Byrd

The US population is rapidly becoming both older and more culturally diverse [1]. Currently, approximately 47 million people in the USA are older adults (65 years and older), which comprises ~15% of the US population [2]. By 2060, this population is projected to almost double in size to approximately 98 million individuals and will comprise about 25% of the US population [2]. Among older adults, culturally/linguistically diverse populations (particularly Latinx, Asian-American, Native Hawaiian/other Pacific Islander, and multiracial populations) are growing much faster than the non-Hispanic white population [2]. By 2050, ethnic minority individuals will represent approximately 40% of the older adult (65 and older) population in the USA [2]. These changes in the demographic profile of the USA highlight the need for clinical neuropsychologists to be culturally responsive and equipped to competently evaluate the growing population of older adults from culturally/linguistically diverse backgrounds. This chapter offers empirically supported, practical resources specifically targeted toward serving culturally/linguistically diverse underrepresented minority (URM) older adults, with an emphasis on the largest URM populations in the USA (i.e., African American, Latinx, and Asian/Asian-American populations). However, this information may also have implications for considering other racial/ethnic populations, as well as those who represent other important dimensions of diversity (e.g., rural, low SES individuals). For an exceptional overview of neuropsychological assessment and intervention considerations for working with American Indian/Native Alaska populations, please see [3].

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Sociocultural Framework

Working from a biopsychosociocultural theoretical framework [4], the sociocultural level of analysis includes consideration of how social, socioeconomic, institutional, and cultural (i.e., the shared attitudes, values, goals, and practices that characterize a group from one generation to the next) [5] factors modulate an individual's or a group's behaviors. Further, issues of oppression, privilege, discrimination, and historical trauma merit careful consideration for all URM clients [3]. Sociocultural issues are critical for understanding neuropsychological test performance and neurobehavioral functioning [6–11]. In particular, it is important to consider sociocultural issues as they relate to health disparities, cognitive aging, and neurologic disease among culturally/linguistically diverse URM older adults.

Health Disparities

A health disparity refers to a significant discrepancy in the overall disease incidence, prevalence, morbidity, mortality, or survival rates in a specific population as compared to the general population. This is mutable and disproportionately affects vulnerable populations [12, 13]. In the USA, many culturally/linguistically diverse populations are disproportionately impacted by higher rates of poverty and limited access to, or use of, healthcare services, which contribute to greater vulnerability for particular medical disorders and worse disease burden [14–16]. Of particular interest to neuropsychologists, several culturally/linguistically diverse URM groups (particularly African Americans, Latinx, and American Indians/Alaska Natives) are disproportionately affected by medical conditions (e.g., hypertension, HIV/AIDS, hepatitis, diabetes mellitus, etc.) that may increase their need for neuropsychological services compared with the general population [16, 17].

Culture and Cognitive Aging

Neurocognitive Disorders

Evidence suggests that rates of diagnosed neurocognitive disorders differ substantially between culturally/linguistically diverse URM and non-Hispanic white older adults, and that the former are diagnosed with major neurocognitive disorder (i.e., formerly referred to as dementia) at much higher rates. Prevalence estimates suggest that African American, Latinx, and Asian-American older adults have higher rates of vascular neurocognitive disorder compared to non-Hispanic white older adults [18, 19], and African American and Latinx older adults have higher rates of Alzheimer's disease (AD) compared to their non-Hispanic white counterparts [20]. Evidence also suggests that Latinx older adults have an earlier onset of AD symptoms compared to their non-Hispanic white counterparts [21]. In contrast, some research has shown that African Americans have lower rates of Parkinson's disease-related neurocognitive disorder [22]. Preliminary research suggests that rates of AD and vascular neurocognitive disorders among Asian-Americans are similar to non-Hispanic whites [28, 29], although this has not been thoroughly investigated, particularly with representative samples of Asian-American subpopulations (e.g., Chinese, Japanese, Vietnamese, Hmong, Korean, Native Hawaiian, South Asian). Overall, the growing body of evidence suggests that African American and Latinx populations are at greater risk for both AD and vascular neurocognitive disorders than non-Hispanic whites and that Asian-Americans are also at greater risk for vascular neurocognitive disorders.

The mechanisms that contribute to the differing rates of dementia among different URM groups remain poorly understood. For instance, some genetic markers have been strongly associated with certain neurologic disorders among non-Hispanic white adults, but not in certain

URM populations (e.g., African American, Latinx). A salient exemplar of this issue can be found in AD. Among non-Hispanic whites, *APOE* ε4 allele appears to be robustly associated with increased risk for AD. However, in African American and Latinx populations, the research is inconsistent. Further, among Latinx populations of both Caribbean and Mexican heritage, the *APOE* ε4 allele is less common, confers less AD risk, and does *not* appear to impact age of AD onset [23, 24]. While methodological limitations (e.g., underrepresentation of URMs in large-scale genetics studies, recruitment bias) may at least in part account for these potential group differences, the lack of understanding of potential sociocultural and environmental mechanisms makes these genetics studies difficult to interpret. Further research in this area is needed.

In addition, URM individuals, particularly individuals of low socioeconomic status (SES), are at greater risk of developing cardiovascular disease [25, 26]. Moreover, URM individuals also have higher rates of hypertension, diabetes mellitus, heart disease [25], cancer, obesity, and HIV/AIDS [17]. Many of these conditions are risk factors for neuropsychological sequelae. For instance, evidence indicates that the presence of vascular risk factors (e.g., diabetes mellitus and hypertension) among persons diagnosed with AD is associated with worse neuropsychological test performance at the time of diagnosis compared to those without such risk factors [27]. However, higher rates of diagnosed neurocognitive disorders among these URM groups may also be significantly affected by the lower diagnostic accuracy of many of the neuropsychological measures utilized to diagnose URM individuals [28, 29].

Risk for Misdiagnosis

A well-established body of research indicates that neuropsychological test performance among neurologically healthy adults across the life span significantly differs between URM and non-Hispanic white adults, even after statistically adjusting for other demographic factors (e.g., age, education, and gender) [30–37]. Further, the poor specificity of many neuropsychological tests often results in misdiagnosis of neurocognitive disorders among African Americans and Latinx populations [31, 38–44]. Although utilizing normative data that correct for race/ethnicity (in addition to age, education, and gender) substantially reduces the risk for misdiagnosis [37], such norms do not address the source of these performance differences.

An increasingly robust body of literature points to the significant impact of numerous sociocultural factors on neuropsychological test performance among URM individuals, including quality of education [45–47], acculturation [30, 48–51], language (including bilingualism) [4, 47, 52, 53], stereotype threat [54, 55], and perceived discrimination. There is also potential test bias due to the lack of support for the cultural equivalence and construct validity of several measures with culturally/linguistically diverse URM populations [10, 56, 57]. Thus, it is important for clinical neuropsychologists to be aware of these research findings to more accurately diagnose and serve URM patients.

Health disparities and their potential to increase risk for neurocognitive disorders as well as misdiagnosis, together with poor construct validity and limited appropriate normative data, set the stage for a unique set of assessment challenges for working with URM older adults. In the following section, these challenges, and suggestions for addressing them, are considered at each point in the evaluation process.

Ethical Issues and Competence

The American Psychological Association's (APA) *Ethical Principles of Psychologists and Code of Conduct* [58] provides some guidance on the ethical standards necessary to conduct a culturally competent neuropsychological evaluation. For example, Ethical Standard 2.01 [59] explains that "cultural expertise or competence at the individual level is essential for the clinician who is working with cross-cultural populations." But how does a clinician actually ascertain

whether or not she/he is competent to evaluate an ethnic minority older adult?

Rivera Mindt et al. [10] proposed a cultural competence in neuropsychology (CCN) model [59–62] that assists neuropsychologists in examining their cultural competence by evaluating their own cultural awareness and knowledge of the culturally/linguistically diverse populations that they would like to serve. If a neuropsychologist determines that she/he does not currently have the requisite competence to evaluate a particular URM patient, she/he may be able to cultivate that competence through the acquisition of specific, culturally appropriate assessment, intervention, and communication skills necessary to work effectively with individuals from specific URM groups [10]. For instance, supplemental training can be acquired through readings, consultation, and continuing education courses or workshops focused on working with culturally/linguistically diverse populations (such as those offered through the Hispanic Neuropsychological Society [HNS], the American Academy of Clinical Neuropsychology [AACN], the Society for Clinical Neuropsychology [SCN; APA Division 40], or the National Academy of Neuropsychology) [10]. In addition, neuropsychologists are also responsible for carefully considering the cultural competence of their psychometrists or graduate students, if used in the assessment process. Some common ethical challenges, particularly related to linguistic competence, are integrated below to highlight considerations for resolution.

Considerations for Neuropsychological Evaluation with Culturally/Linguistically Diverse Older Adults

In terms of day-to-day practice, prior to the evaluation of a culturally/linguistically diverse older patient, some relevant demographic information about the patient should first be collected (i.e., patient's age, years of education, race/ethnicity, birthplace, and language use and history) preliminarily to determine if one is competent to evaluate the older client. The issue of linguistic competence is particularly important for planning the evaluation. Although detailed discussion of linguistic competence is beyond the scope of the current chapter, useful guidance on determining one's own linguistic competence to examine non-English or bilingual patients is available elsewhere [4, 63–65]. To further inform this decision, the neuropsychologist may also consider explicitly asking about a patient's linguistic preference prior to the evaluation, although for bilingual clients – further objective language assessment is indicated (detailed below).

In cases in which a neuropsychologist is unsure of their cultural competence to examine a particular URM patient, consultation with colleagues with expertise in cultural neuropsychology who are competent to work with patients from this cultural/linguistic background is recommended. Extensive resources for such consultation are available elsewhere [10]. If a neuropsychologist determines that they do not have the requisite competence (either due to language or other concerns), it is recommended that the patient be referred to a more appropriate clinician. If such a referral is not feasible due to geographic location or other barriers, then the neuropsychologist should consider how best to evaluate the patient, through use of a well-trained interpreter (which is less than ideal but sometimes necessary), or to work in consultation with a neuropsychologist who does have the necessary cultural competence to ethically provide supervision. More thorough discussion of ethical obligations and competency issues related to neuropsychological evaluation with URM individuals is provided elsewhere, and the interested reader is encouraged to review the available literature [10, 58, 59, 65–67].

The Physical Space

Once the decision has been made to evaluate a URM older patient, neuropsychologists are encouraged to consider each aspect of the evaluation through a "sociocultural lens." For instance, what is the potential impact of a neuropsycholo-

gist's physical space (i.e., the office or hospital environment) on their ethnic minority older patients? Expanding on Rivera Mindt et al.'s [10] original recommendations, neuropsychologists are encouraged to consider the following:

1. *First impressions*. Does your practice (or facility) contain images of diverse people (e.g., age, gender, race/ethnicity) via brochures, websites, or flyers, anti-discrimination statements, diversity intentions, or related services? Is your practice accessible and convenient for patients with physical or transport limitations (i.e., parking and close to public transport)?
2. *Waiting area*. Is your waiting area a welcoming place for ethnic or linguistic minorities (i.e., written signs, symbols, magazines, art, decorations, greetings, staff)?

Clinical Interview and History

The clinical interview and history taking portion of a neuropsychological evaluation are critical for the purposes of establishing rapport, ensuring accurate diagnosis, and developing appropriate follow-up recommendations. However, sociocultural issues can significantly impact this process.

Preinterview

Working from the CCN model, it is recommended that neuropsychologists have some empirically based knowledge of the culture of origin of their older ethnic minority patients prior to beginning the clinical interview, if possible. The literature in multicultural counseling and community psychology may be particularly useful in this regard and may help identify any culturally accepted social norms that may come into play during the interview or latter portions of the evaluation. Although not specific to older adults, the reader is encouraged to review Sue, Gallardo and Neville [68] for case examples of working with culturally/linguistically diverse populations.

Establishing and Maintaining Rapport

Prior to test administration, sufficient time should be dedicated to rapport building. While this is a common practice for all patients, it is particularly true for URMs because health professionals may not be perceived as reliable as they are for majority group members [69]. Furthermore, research indicates that level of formality, authority, eye contact, and personal space can all have an impact on establishing and maintaining rapport among persons of different culturally/linguistically diverse populations [70–72]. These issues, along with cultural attitudes about the age and gender of the neuropsychologist or psychometrist, may be especially salient points for consideration among older URM patients who may be less acculturated to majority culture (i.e., mainstream US culture). For instance, in terms of verbal and nonverbal communication, consider how to initially approach the patient. The communication of respect may be particularly important with older patients. For instance, it may be best to have the patient introduce herself/himself to determine whether or not she/he wishes to be called by their first or last name. Do not assume that the patient is comfortable with the use of their first name unless she/he specifies, as this may be interpreted as disrespectful or overly familiar [70].

It is also important to be aware of and sensitive to specific cultural or religious guidelines that may affect the interaction with a particular older URM patient. For example, it may be inappropriate for some women to attend their appointment without a male family member being present. Additionally, women of particular cultural backgrounds may not feel comfortable being evaluated by someone of another gender. Similarly, some Orthodox Jewish individuals do not shake hands with members of the opposite sex [73]. Some individuals from American Indian, Alaska Native, or Asian/Asian-American backgrounds, particularly older individuals, may view direct eye contact as a sign of disrespect [74]. Neuropsychologists should be aware of sociocultural norms that may pertain to their

patient in order to interact appropriately and ensure that the patient is comfortable with the testing process. However, they should also appreciate the heterogeneity in cultural norms, individual attitudes and beliefs, and intersecting diversities across all individuals, and not necessarily assume what is applicable to the patient. In addition to one's training in cultural competence, the neuropsychologist should seek clarification from or follow the patient's lead, when appropriate. If a cultural accommodation requires any deviation from standardized testing procedure, it should be noted in the report.

Interviewing Considerations

In terms of the "nuts and bolts" of interview and history taking, neuropsychologists are encouraged to consider whether the content of their interview is culturally appropriate for the various culturally/linguistically diverse patients they serve [74, 75]. During the interview, information is typically gathered that relates to the referral question, current symptoms and complaints, and the patient's developmental, medical, psychiatric, psychosocial, and sociocultural history. In collecting this information, neuropsychologists are again encouraged to approach this task through a "sociocultural lens" and explicitly consider how sociocultural issues might impact an individual at each level of analysis.

In terms of current symptoms and complaints, knowledge of culturally based idioms of distress is particularly important as symptom reporting can vary greatly across individuals of different ethnic backgrounds and acculturation levels. For example, some literature suggests that Asian and Latinx individuals are more likely to report somatic rather than depressive symptoms [76, 77]. From a development perspective, assess whether the person grew up with stable housing and adequate nutrition. From a medical perspective, consider comorbid medical conditions that disproportionately impact a certain URM population. In terms of past psychiatric history, it may be useful to know about the different base rates of psychiatric disorders, as well as disparities in access and utilization of psychological and psychiatric services, across different URM populations. These issues could significantly inform both current diagnosis and follow-up treatment recommendations.

With regard to psychosocial history, issues related to quality of education (QoE) are particularly important with URM older adults. Caution should be exercised with older patients educated in other countries (particularly non-Western or less-industrialized countries, as this may affect familiarity with Western construct-laden measures), as well as disadvantaged areas in the USA. Moreover, gathering information regarding SES is important considering that there is some evidence indicating SES affects neuropsychological performance, although this has not been thoroughly investigated [8, 11]. For further explanation, see below for QoE discussion.

Finally, it is strongly recommended that information related to sociocultural history is collected when working with culturally/linguistically diverse older adults. While the following is not an exhaustive list, below are some suggestions to consider when taking the sociocultural history. For an exceptional review of sociocultural considerations for working with Latinx patients, see Llorente [66].

1. *Race and ethnicity*. It is essential to ask patients to self-identify their races and ethnicities. It is inappropriate to rely solely on physical appearance. Sometimes, these questions may be challenging for patients. Listing out racial/ethnic categories provided through the US Census can serve as a useful starting point. Further explanation of these categories may be needed, but at least this provides a common nomenclature.
2. *Country of origin and region*. Western or non-Western? Was the region rural, urban, or suburban? Safety and access to resources in the community? Issues related to acculturation are also important and discussed later in this chapter.
3. *Current US region of origin/neighborhood*. Rural, urban, or suburban? Safety and access to resources in the community?

4. *Immigration history (if applicable)*. This would include years in the USA and years educated in the USA, as well as any relevant sociopolitical issues related to immigration.
5. *Linguistic background*. For linguistic minorities, questions about language of origin, how often a patient uses English versus the language of origin (and in which contexts), their ease with the respective languages, and preference for testing are all potentially useful areas of inquiry. Comprehensive discussion about this issue is beyond the scope of this chapter. For more information, readers are referred elsewhere [4, 63, 66, 78].
6. *Quality of education*. Tests of reading level (such as WTAR and WRAT-4) are helpful to disentangle quality of education issues. Further, questions regarding patient's type of school and classroom experience, as well as geographic region, are helpful in this regard.
7. *Social support*. This may include questions about both biological and non-biological family, church-related and spiritual resources, and other potential, nontraditional resources (e.g., community organizations).
8. *Current and childhood SES and nutrition*. This may include questions about having enough to eat and financial resources at present and during childhood.
9. *Access and utilization of health and mental health services*. Beyond health insurance, this may include questions about healthcare access and perceived quality, attitudes about traditional and nontraditional health and mental health services and providers, and health literacy.

Informants

When obtaining collateral information on older patients, it is important to gather reports from a reliable source (e.g., a cognitively intact caregiver, child, or spouse), as older adults may not be reliable historians if they are experiencing cognitive difficulties, particularly memory or executive dysfunction. Among patients with mild cognitive impairment (MCI), some research shows that African American informants may be more likely to underreport the patient's symptoms or functioning, while non-Hispanic white informants may be more likely to overreport [79]. However, anecdotally, one investigator reported that in his clinical experience with Mexican-American patients with dementia, many of his patients' children were hesitant to report their parent's cognitive or functional decline, despite having observed such declines [80]. He noted that the children were only willing to report these observations after lengthy interviews when rapport had been well established, and many apologized to their parent prior to reporting their observations. This example demonstrates the potentially powerful impact of culture on the interview process, and clinicians should consider that reporting deficits may be uncomfortable or culturally inappropriate for many informants and patients [81]. Therefore, rapport building and culturally sensitive but thorough interviewing is imperative.

Testing Considerations

Depending on sociocultural background, URM older adults may be less familiar with assessment procedures than older adults from majority culture [82, 83]. Furthermore, URMs often experience higher levels of mistrust for the healthcare system than their non-Hispanic white counterparts due to higher rates of negative healthcare experiences, social disadvantage, and poorer access to care [84]. They may also have misperceptions about or be wary of the assessment process, so it is important that the neuropsychologist clarify the purpose of the evaluation and make sure that instructions are understood. For example, it may be useful to explain test format or when speeded performance is being assessed, as these constructs may be unfamiliar or carry different valence to culturally/linguistically diverse older patients. Thus, it is critical to clearly explain the purpose of the neuropsychological evaluation to the individual – making sure to avoid using jargon – and to explain aspects of the testing that may be unfamiliar or are particularly important

for the patient to understand. In addition, as noted earlier, if there is any deviation from standardized testing procedure, it should be noted in the report and considered in the final interpretation of the data.

Neuropsychological Test and Normative Data Selection

According to APA Ethical Standard 9.02b [58], "psychologists use assessment instruments whose validity and reliability have been established for use with members of the population tested." Therefore, neuropsychologists have an ethical responsibility to use appropriate and non-biased assessment instruments whenever they are available. However, relatively few neuropsychological tests have been specifically standardized and validated for use with culturally/linguistically diverse older adults. As such, it is often unclear how performance on any given measure may vary with cultural background and whether or not the intended construct is being appropriately assessed [56]. This psychometric uncertainty extends to newer, computerized assessment platforms, which, given their relative novelty, have even less empirical literature supporting their psychometric utility in URM older adults. As such, it is imperative that neuropsychologists take the extra step of researching the measures that they plan to use for empirical evidence of psychometric soundness [85]. Whenever possible, neuropsychologists should use tests that have been normed and validated with individuals from the same cultural/linguistic background as the patient being evaluated. When this is not possible, the clinician should explicitly note such limitations in the report and discuss how this influences the interpretation of data [86].

Screening Instruments

Screening instruments, often the sole measure of cognitive status in resource limited settings, are particularly vulnerable to the influence of the effects of demographic, non-disease-related factors, such as cultural background and education levels [87]. There are some cross-cultural assessments for neurocognitive disorders available. For instance, the Montreal Cognitive Assessment in Spanish (MoCA-S) has also been adopted from the MoCA as a valid screening tool for the identification of mild cognitive impairment and mild neurocognitive disorder in older adults in Colombia [88]. An additional screening instrument includes the Rowland Universal Dementia Assessment Scale (RUDAS) [89]. Moreover, in screening general cognitive abilities, Wolfe [90] suggested that the cognitive abilities screening instrument (CASI) [91] be used in place of the Mini-Mental Status Exam (MMSE), since it has been culturally validated in Japan, China, and the USA, or the Cross-Cultural Cognitive Examination (CCCE) [92], which was developed in Guam and may be particularly useful for individuals with low literacy. Additional brief screening instruments, which have been used for detecting possible dementia among ethnically diverse older adults, include both a measure for patients (i.e., the Taussig Cross-Cultural Memory Test) [93] and informants (i.e., the Informant Questionnaire on Cognitive Decline in the Elderly, also known as IQCODE) [94, 95]. The use of traditional screening instruments in URM older adults may require attention to whether or not the established scoring threshold is appropriate for the specific cultural/linguistic groups served in a given setting [87].

English Language Tests and Normative Data

A key aspect of determining which neuropsychological tests to administer often lies in the availability and appropriateness of the relevant normative data. Demographically corrected normative data that can be used with English-speaking URM older adults are available for some neuropsychological batteries and tests. Heaton et al. [96] provide excellent normative data (corrected for age, education, gender, and race/ethnicity) on the expanded Halstead-Reitan battery for non-Hispanic white and African American adults up to

age 85. The WAIS-IV and WMS-IV provide normative data (corrected for age, education, gender, and race/ethnicity) for non-Hispanic white, African American, and Latinx adults up to age 90 [97]. A particular weakness in the literature is the paucity of normative data available for English-speaking Asian-American/Pacific Islander and Latinx older adults. One notable exception is Kempler et al.'s [98] normative data (corrected for age, education, and race/ethnicity) for verbal fluency measures, which provide norms for non-Hispanic white, African American, Latinx, and Asian-American adults up to age 99.

Table 3.1 provides a list of normative data resources for a subset of URM populations (i.e., African American (AA), Asian/Asian-American (Asian), and Latinx) that include norms for older adults. Of note, this is clearly not a comprehensive list, and only a subset of normative data for the largest URM populations in the USA has been included. It is also important to highlight that there is a particular dearth of norms for certain URM populations (e.g., American Indian/Alaska Native, Middle Eastern) and subpopulations within larger heterogeneous populations (e.g., subpopulations of African/Black, Asian [including South Asian], and Latinx heritage). For more comprehensive resources of normative data, which include normative data that may be useful for culturally diverse older adults, please see Mitrushina et al. [99] and Strauss, Sherman, and Spreen [100].

Table 3.1 Overview of normative data for African American (AA), Asian/Asian-American (Asian), and Latinx populations

Normative data sources	AA	Asian	Latinx
Acevedo et al. (2000). Category fluency test: normative data for English- and Spanish-speaking elderly [101]			X
Artiola i Fortuny et al. (1999). Manual de normas y procedimientos para la bateria neuropsicologica en Espanol [102]			X
Casaletto et al. (2016). Demographically corrected normative standards for the Spanish language version of the NIH Toolbox Cognition Battery. [103]			X
Arango-Lasprilla, JC (Ed.). Commonly used Neuropsychological Tests for Spanish Speakers: Normative Data from Latin America [Special issue]. [104]			X
Heaton et al. (2004). Revised comprehensive norms for an expanded Halstead-Reitan battery: Demographically adjusted neuropsychological norms for African Americans and Caucasian adults [96]	X		
Hsieh & Tori (2007). Normative data on cross-cultural neuropsychological tests obtained from Mandarin-speaking adults across the life span [105]		X	
Kempler et al. (1998). The effects of age, education, and ethnicity on verbal fluency [98]	X	X	X
Lucas et al. (2005). Mayo's Older African Americans Normative Studies: Normative data for commonly used clinical neuropsychological measures [106]	X		
Moering et al. (2004). Normative data for elderly African Americans for the Stroop color and word test [107]	X		
Sánchez-Benavides et al. (2016). One-Year Reference Norms of Cognitive Change in Spanish Old Adults: Data from the NEURONORMA Sample[108]			X
Schneider et al. (2015). Normative data for eight neuropsychological tests in older blacks and whites from the atherosclerosis risk in communities (ARIC) study [109]	X		

Non-English Language Tests and Normative Data

For linguistic minorities, it is important to note that use of nonverbal measures does not mitigate the impact of linguistic and cultural differences on neuropsychological measures. These tests contain verbal instructions and may still involve verbally mediated approaches. Even when this is not the case, nonverbal measures are still culturally laden, and interpretation may be limited if they have not been validated with culturally diverse samples. For example, research has shown that healthy Spanish-speaking older adults performed significantly worse on several visuospatial and visuoconstructional tasks compared to their non-Hispanic white peers [32]. Therefore, the use of well-validated, empirically supported, and linguistically appropriate neuropsychological tests or batteries for linguistic minority individuals is essential.

Although this overview is certainly not exhaustive, herein we provide resources that we believe would be useful for those working with culturally/linguistically diverse older adults. In the case of Spanish-speaking older adults, there are a number of available batteries that may be appropriate for this population that are intended for use with monolingual Spanish-speaking adults [110], including La Batería Neuropsicológica en Español [63], the NEUROPSI [111], the Batería-III Woodcock-Muñoz [112], Woodcock-Muñoz Language Survey-Revised [113], the Neuropsychological Screening Battery for Latinos (NeSBHIS) [114], the Spanish and English Neuropsychological Assessment Scales (SENAS) [115], and the Spanish NIH Toolbox Cognition Battery (NIHTB-CB) [103].

In addition, the Canadian Study of Health and Aging (CSHA) neuropsychological test battery provides English and French versions of their tests, along with normative data [116]. What is notable about both the SENAS and the CSHA batteries is that they utilized statistical modeling methods to test the cultural equivalence (i.e., invariant structures) of their respective batteries in their dual respective languages. Both Mungas et al. [115] and Tuokko et al. [116] provide empirical support for the crosslinguistic construct validity of their respective neuropsychological batteries utilizing state-of-the-art statistical modeling (e.g., item response theory [IRT] techniques to reduce test bias and covariance structure analysis [117] in the case of the SENAS battery and a relatively straightforward multigroup confirmatory factor analysis [CFA] framework in the case of the CSHA battery). These approaches represent promising methodologies for examining the construct validity (via measurement invariance) of other neuropsychological instruments across a variety of ethnic and linguistic groups [57, 115, 116, 118].

For Mandarin-speaking older adults, Hsieh and Tori [105] provide normative data on cross-cultural neuropsychological tests across the life span (up to age 81). For Korean-speaking older adults, there is a Korean version of the California Verbal Learning Test (K-CVLT) [119] available, which provides norms correcting for ages 20–79. A Korean version of the Boston Naming Test (K-BNT) has also collected normative data, resulting in four age groups (15–44, 45–54, 55–74, and 75+ years) and five education levels (0, 1–6, 7–9, 10–12, 13+ years) [120]. Additionally, a Korean version of the CERAD battery (CERAD-K) was developed as a standardized measure for establishing a diagnosis of AD, with equal reliability and validity to the English version [121]. Age, education, and gender showed significant effects on the performance of various tests in the CERAD-K battery, resulting in four overlapping age groups (60–74, 65–79, 70–84, 75–90 years) with three education levels (0–3, 4–6, 7+ years) [122].

While the resources available for examining culturally/linguistically diverse older adults have significantly improved over the course of the past 20 years, several important limitations merit discussion. First, only two neuropsychological batteries (of which we are aware) provide rigorous empirical support for their cultural equivalence and construct validity (the SENAS and the CHSA). Providing such support is important not only in the case of tests or batteries utilized in different languages but also for tests and batteries utilized across different

cultural/linguistic groups [56]. The absence of this research remains a significant weakness in the literature. Second, no comprehensive batteries or norms exist for adequately characterized English-speaking Latinx adults, Spanish-speakers who are *not* from Spain and Mexico or of Mexican-American origin, Asian-Americans (including Native Hawaiians, Pacific Islanders, and South Asians), American Indians or Alaska Natives, individuals from Middle Eastern backgrounds, and bilinguals. For a more comprehensive discussion of these issues, see Rivera Mindt et al. [10]. Third and perhaps most importantly, use of race–/ethnicity-based norms does not explain performance differences between groups and may inadvertently leave unexplained racial/ethnic differences in neuropsychological test performance open to harmful misinterpretation [10, 123, 124].

Table 3.2 provides a list of neuropsychological instruments that have been designed for or adapted for use in languages other than English. Such instruments may be appropriate for bilingual or monolingual, non-English-speaking adults and include norms for older adults. Of note, this is not a comprehensive list, and only a subset of instruments for non-English speakers for the largest linguistic minority populations in the USA has been included.

Sociocultural Testing Issues

Culture and Acculturation

As noted above, neuropsychologists should inquire about patient-specific cultural background (e.g., does the patient identify as Dominican, Puerto Rican, Cuban, etc.). They should also ascertain the individual's degree of acculturation to majority US culture. For instance, when assessing a Latinx patient, one should determine their birthplace and the birthplace of the parents. This may help guide the selection of appropriate tests, norms, and interpreters (if needed). For example, in the case of Spanish language tests, the neuropsychologist should consider the country where the test was developed, particularly in regard to language and dialect – a test developed in Puerto Rico may contain colloquialisms unfamiliar to a patient from Mexico [129]. Further discussion of the issue can be found elsewhere [10, 66, 114, 130].

For Latinx patients, formal assessments of level of acculturation are available and should be completed. As described in a recent position paper from the National Academy of Neuropsychology [65], the following measures can be used to assess acculturation: Acculturation

Table 3.2 Overview of non-English neuropsychological instruments for Asian/Asian-American (Asian) and Latinx populations

Neuropsychological instruments	Asian	Latinx
Bateria III Woodcock-Muñoz [112]		X
Batería Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales (BANFE) [125]		X
Bateria Neuropsicologica en Español [102]		X
Cognitive Abilities Screening Instrument (CASI) [91]	X	
Consortium to Establish a Registry for Alzheimer's Disease-Korean version (CERAD-K) [121, 122]	X	
Korean Boston Naming Test (K-BNT) [120]	X	
Korean California Verbal Learning Test (K-CVLT) [119]	X	
NEUROPSI [127] & NEUROPSI: Attention and memory [111]		X
Neuropsychological Screening Battery for Latinos (NeSBHIS; Pontón, M. et al., 1996) [114]		X
Repeatable Battery for the Assessment of Neuropsychological Status Update-Spanish (RBANS Update) [128]		X
Spanish and English Neuropsychological Assessment Scales (SENAS) [115, 117]		X

Rating Scale for Mexican Americans-II [131], the Bidimensional Acculturation Scale for Hispanics [132], and Short Acculturation Scale for Hispanics [133]. The Abbreviated Multidimensional Acculturation Scale (AMAS) is also a well-validated tool, which assesses both Latinx and US American identity and acculturation [134]. Unlike other acculturation instruments, which largely used Mexican-American or Puerto Rican standardization samples, the AMAS utilized a heterogeneous Latinx sample that included individuals of Central and South American, Caribbean, and Mexican origins. For other culturally/linguistically diverse groups, where standardized measures of acculturation are not available, degree of English vs. non-English language use and years in the USA have been shown to serve as proxies of acculturation [49, 135, 136].

Cultural influences, such as beliefs about aging, should also be taken into consideration when examining older adults from URM backgrounds. For example, research found that a group of older Korean Americans with less US acculturation held stronger stigmatized beliefs about AD and were more likely to normalize memory loss as a part of the aging process than as a medical condition [137, 138]. Additionally, the impact of culture with regard to caregivers should be considered in assessments and intervention of older URM populations. Culturally tailored intervention strategies for older adults from URM populations (e.g., Latinx) whose care may be largely reliant upon family members [139]. The demands of caregiving can also negatively impact caregivers' health, and family members may be hesitant to report caregiver burden out of respect for the older family member during an evaluation interview. Future studies should consider examination of culturally tailored interventions for URM caregivers.

The practical application of acculturation information to the interpretation of neuropsychological test data is limited by the lack of formalized algorithms or normative data that incorporate acculturation level. However, research overall indicates that lower levels of acculturation to majority culture are associated with worse neuropsychological test performance, particularly in the areas of abstraction/executive functioning, attention, working memory, language, visuoconstruction, learning, and memory [30, 48–50, 80, 140–142]. Therefore, neuropsychologists should consider the *potential* contribution of acculturation level when impaired scores are present in these areas among URM older patients with low acculturation to the dominant culture.

It is also important to note that acculturation is a multidimensional construct with both linguistic and nonlinguistic cultural factors, which may independently contribute to neuropsychological performance. However, few studies to date have examined the impact of acculturation in both dominant and non-dominant cultures on neuropsychological performance among Latinx individuals. In one study, US acculturation scores (as assessed by the AMAS) among HIV+ Caribbean Latinx adults were positively associated with better global neuropsychological performance, processing speed, verbal fluency, and attention/working memory [51]. Higher Latinx acculturation was associated with better memory performance, whereas lower Latinx acculturation was associated with better executive function and learning [51]. An important implication of this study was that self-reported language competence still independently influenced performance in Latinx individuals – even among those highly acculturated to US culture, further supporting acculturation as a critical component of neuropsychological test performance in Latinx individuals.

Finally, it is imperative for clinicians and researchers alike to remember that contrary to previous popular thought, nonverbal measures are *not* "culture-free." In fact, nonverbal measures have been shown to be significantly associated with acculturation, which disputes the notion that nonverbal test performance is devoid of influence from cultural factors [51, 143]. This research suggests that dominant and non-dominant cultures differentially affect neuropsychological test performance and that acculturation should be taken into consideration in the interpre-

Table 3.3 Overview of sociocultural instruments for use with African American (AA), Asian/Asian-American (Asian), and Latinx populations

Sociocultural instruments	AA	Asian	Latinx
Acculturation Rating Scale for Mexican Americans (ARSMA) [144]			X
African American Acculturation Scale Short Form (AAAS-SF) [145]	X		
Asian American Multidimensional Accultural Scale (AAMAS) [146]		X	
Bicultural Self-Efficacy (BISE) [147]			X
Short Acculturation Scale (SAS) [132]			X
Suinn-Lew Asian Self Identity Acculturation Scale (SL-ASIA) [148]		X	
The Abbreviated Multidimensional Acculturation Scale (AMAS) [134]			X
The Multigroup Ethnic Identity Measure (MEIM) [149]	X	X	X

tation of both verbal and nonverbal neuropsychological measures. Thus, a multidimensional measure of acculturation can be an extremely useful tool to enhance both empirically supported practice and the clinical utility of an evaluation. In working with Latinx populations, the AMAS is a particularly useful to assess acculturation to both the dominant and non-dominant cultures.

Table 3.3 provides a list of several unidirectional and bidirectional measures of acculturation that have been designed for or adapted for use with culturally diverse individuals. Some of these instruments may be appropriate for assessing degree of acculturation to dominant and/or non-dominant culture for several culturally diverse populations of older adults, including African American, Asian/Asian-American, and Latinx individuals. Of note, this is not a comprehensive list, and only a subset of sociocultural instruments for the largest URM populations in the USA is included.

Quality of Education (QoE)

A growing body of literature suggests that demographic corrections for educational attainment using years of education may be inadequate in neuropsychological evaluations. Many studies suggest that the QoE a person receives is equally, if not more, important to neuropsychological functioning [45, 150–153]. This is particularly salient in the assessment of ethnic/racial minorities and/or individuals from low SES backgrounds [8, 153]. In cases where an individual is from disadvantaged areas in the USA or non-Western or less-industrialized countries, using years of education to determine expected performance level may overestimate the individual's expected performance on Westernized neuropsychological tests, increasing the likelihood of misdiagnosis [151, 154].

Crowe et al. [155] found an interaction between QoE and years of education, such that QoE predicted cognitive performance in individuals who completed ≤12 years of education, but not in those who completed at least 1 year of postsecondary school. These findings suggest that education inequality may be more pronounced in primary and secondary school, but this gap may be attenuated in individuals who attend some postsecondary school. Nevertheless, these findings are important because URM populations have historically been less likely to complete education beyond high school (except Asian-Americans) [156]; therefore, lower scores on neuropsychological tests that result from poor QoE may be more pronounced in older URM patients. However, the generalizability of this study, especially to non-native English speakers, warrants further exploration, as this sample was primarily comprised of native English speakers who were educated in the southern USA.

The Wide Range Achievement Test (WRAT) [157] Reading Recognition subtest or the

Wechsler Test of Adult Reading (WTAR) [158], which provide estimates of reading level, are commonly used as quantifiable proxies for QoE [45]. Emerging research demonstrates that QoE is significantly correlated with performance on WRAT, even after accounting for years of education, race/ethnicity, and SES [155, 159]. Furthermore, the WRAT demonstrated similarly high test-retest reliability across HIV+ non-Hispanic white, African American, and Latinx groups [160], providing further support for the cultural utility of the measure. Other measures of reading level, such as the North American Adult Reading Test (NAART) [161], may be used to approximate QoE [151], although the WRAT and WTAR appear to have the most support for this in the existing literature.

In assessing QoE, the examiner may also find it beneficial to obtain qualitative information about QoE during the interview process. This information may include self-perceived educational quality, student-teacher ratio, geographical setting (rural, suburban, or urban school), degree of school integration, duration of the school year, and perception of relationships with teachers [155, 159, 162].

When total years of education and QoE (i.e., grade-equivalent reading level) vary significantly, this should be clearly noted as a limitation and considered when examining performance on neuropsychological tests that are normatively corrected for education. In such instances, it will be important to ensure that the reading materials used during testing are written at an appropriate educational level so that the patient can reasonably be expected to understand them. Furthermore, when large discrepancies between education and reading level (QoE) exist, utilizing Dotson et al.'s [163] battery and the corresponding age- and literacy-based norms may be a useful option for patients who are up to age 64, African American, and of predominantly low SES background.

Working with Linguistic Minorities: Non-English-Speaking and Bilingual Older Adults

Issues related to the assessment of linguistic minorities (i.e., non-English speakers and bilingual clients) represent one of the most common ethical challenges that neuropsychologists face. Ideally, bilingual neuropsychologists and psychometrists should work with linguistic minority patients. An interpreter should only be used in assessing non-English speakers when outside referral is not feasible (e.g., in some rural areas). Ethical mandates of our profession should take precedence over local administrative demands (i.e., an organization or hospital tries to pressure a neuropsychologist to see a patient with an interpreter rather than refer out when this is a feasible local option). For those working in more densely populated regions, referral to a competent bilingual neuropsychologist may be more feasible, and certain neuropsychology organizations may also serve as helpful resources in identifying bilingual neuropsychology referrals (e.g., HNS, AACN Relevance 2050 Committee).

When evaluating a bilingual older patient, test selection also involves several specific considerations. Factors that should be considered include (1) which language is the individual's first or native language, or did they learn both languages simultaneously? If they did not, at what age was the second language acquired? (2) Which language is currently their primary language? What is their degree of bilingualism (e.g., balanced bilingual, English-dominant bilingual, Spanish-dominant bilingual)? A patient's lack of fluency in English may impact performance on neuropsychological assessments; therefore, it is important to assess the patients' degree of fluency in English prior to test selection and evaluation [164]. It may also be important to consider how many years of formal education the individual completed in

their primary language. Rivera Mindt et al. [4] should be consulted for further discussion of these issues. Briefly, individuals should typically be tested in their most competent (e.g., strongest or primary) language whenever possible and appropriate. Bilingual older adults with mild cognitive impairment generally experience loss of the second language before the loss of the first language [165]. Therefore, it is important to assess the patient in the appropriate and strongest language in order to ensure the most accurate results. In addition to level of proficiency, consideration should be given to the context and level of proficiency in which a particular language is used to determine whether it is used primarily at home, at work, or with specific family members [166]. Ideally, language competency should be determined on the basis of both objective language measurement and subjective report, although it is also important to note that older individuals are more likely to underestimate their language fluency [4, 167]. Some objective measures for assessing Spanish–English language dominance include the Woodcock-Muñoz Language Survey-Revised and examination of the difference in performance between the English and Spanish versions of verbal fluency or naming measures [4, 126]. Care should be taken to select tests that have been standardized and normed with the population and language of interest, whenever possible.

Awareness of the bilingualism literature will aid in interpreting the neuropsychological test performance of bilingual older adults, especially given the lack of normative data for this population. Research has generally shown a robust bilingual disadvantage in terms of performance on verbal measures when compared with monolinguals (who can be viewed as *hyperproficient* in their language) [167, 168]. Specifically, bilinguals may perform worse in expressive vocabulary [169], receptive vocabulary (including response latency times) [170], and verbal fluency (particularly semantic) [171, 172]. In contrast, research has been equivocal on potential subtle bilingual advantages on measures of attention/executive functioning, particularly cognitive control, and these advantages may confer some neuroprotection in the face of normal cognitive aging and AD [173], and some research has not found a neuroprotective effect [53, 174]. Of note, the measures conventionally used in neuropsychological assessment are not as sensitive to milder cognitive changes for bilingual individuals [175]. Many of the tests rely heavily on verbal ability, which is generally an area of weakness for bilingual older adults. Yet worse performance on verbal measures and better executive functioning ability, along with a slower rate of decline on these tests may obscure signs of cognitive impairment for bilingual elders [175]. Moreover, potential sample differences in SES, country of origin, and cultural attitudes about bilinguals depending on the geographic location of the study (e.g., USA, Canada) may limit the generalizability of some of this research, and more research is needed to better understand these associations. Ultimately, the disadvantages and potential advantages of bilingualism should be considered when interpreting test data of bilingual older adults and should be explicitly discussed in reports. For a thorough review of the neuropsychological implications of bilingualism, see Rivera Mindt et al. [4].

Qualitative Information

A process approach may be useful for estimating level of neuropsychological abilities for some URM patients for whom a standard evaluation may not be appropriate because of linguistic or other sociocultural considerations [176, 177]. This provides qualitative information by examining the types of errors the patient makes, their approach to the tests, and their response to testing limits. For example, one may allow a patient to continue past the standard time limit on a test, such as *Block Design*. Although points would not be awarded for a response given after the specified amount of time, this would allow the examiner to assess whether or not the patient's difficulty is due to time constraints. Further,

asking questions of the patient regarding how they approached a given test (after it was administered) can also be a useful tool to better understand the data.

Post-Evaluation Considerations

Upon completion of the neuropsychological evaluation, which has been conducted in a culturally competent manner, using the best available tests, the results must be examined and interpreted. There are several factors that must be considered, including which norms to apply to tests and caveats that limit test interpretation.

Typically, when evaluating an African American or Latinx older adult, the application of ethnicity-specific normative data will yield the most accurate estimation of their cognitive status [106]. However, other factors, such as the nature of the referral question, may lead to the decision to use generalized normative data sets. For example, as Brickman et al. [67] point out, "comparing test scores from a highly educated African American man from New York City to an African American normative data set collected in the rural South might not be appropriate." Additionally, one should consider whether the goal of the referral question is to determine how well the individual is likely to be functioning in their environment, or whether the goal is to determine whether decline is suspected relative to peers. In the first instance, race–ethnicity-based norms would likely be inappropriate, while in the second instance, they may be more appropriate [178].

Next, neuropsychologists must incorporate and synthesize the sociocultural information collected during the clinical interview, history, and throughout the evaluation into the test interpretation and case conceptualization. This can be accomplished utilizing an empirically based, hypothesis testing approach grounded in the quantitative and qualitative data gathered during the evaluation. How does this converging evidence point to a particular conclusion and how does this fit (or not fit) with the existing empirical literature? Equally important, it is recommended that neuropsychologists explicitly discuss in the report how the sociocultural data from the evaluation and the empirical literature factored into the test interpretation, case conceptualization, diagnosis, and recommendations.

Careful consideration should also be taken to avoid overinterpreting low performance that may be attributed, at least in part, to sociocultural factors. For example, if a test has been shown to have cultural biases, but is administered because a more appropriate alternative does not exist, the neuropsychologist should be sure to include this information in the report and to limit any conclusions drawn from these scores. For bilingual patients, Ardila et al. [179] recommend explicitly noting in the report the language the patient was tested in, formal documentation of the patient's degree of bilingualism, and whether or not an interpreter was used. In terms of differential diagnosis and the recommendations for culturally/linguistically diverse older adults, it is also especially important to consider the possible influence of other factors (i.e., comorbid medical or psychiatric conditions, SES, access to care, etc.). In bringing together all of the information, including the sociocultural information, it is hoped that neuropsychologists will be better able to improve diagnostic accuracy and develop more relevant, culturally tailored recommendations for their culturally/linguistically older patients.

Finally, in terms of providing feedback, attention to the same sociocultural norms and communication issues (clear, jargon-free language) also apply to this "final" aspect of the neuropsychological evaluation (see section "Establishing and Maintaining Rapport"). The critical goals of the feedback session are (1) that the patient, or her/his family member, or caregiver understands the pertinent test findings and follow-up recommendations; (2) that the neuropsychologist confirms that these recommendations are appropriate and feasible for the patient; and/or (3) that the neuropsychologist maintains a stance of respect, flexibility, creativity, and advocacy to modify the

recommendations if needed and to help advocate on behalf of the patient, if necessary, to ensure appropriate follow-up. For a more thorough discussion regarding the provision of feedback, the reader is referred elsewhere [180, 181].

Conclusion

This chapter reviewed sociocultural issues germane to culturally/linguistically diverse URM older adults and discussed considerations for the culturally competent and responsive evaluation of this population. Overall, a number of factors must be considered to provide a competent neuropsychological evaluation with URM individuals, and neuropsychologists are reminded to maintain a "sociocultural lens" throughout each step of the evaluation. It is also important to avoid overgeneralizing the information herein as each client's unique constellation of sociocultural issues (e.g., immigration history, level of acculturation) and intersecting identities (i.e., gender, sexual orientation, SES, religion, etc.) should be considered as this information is tailored to each individual client.

Specifically, neuropsychologists must first consider whether or not they have the appropriate training and experience to conduct a competent evaluation with a given culturally/linguistically diverse older adult. Neuropsychologists should consider the influence that cultural factors may play in the patient self-report, informant report, and expression of neuropsychiatric symptoms. The neuropsychologist should be culturally sensitive during the evaluation, including in the selection of appropriate tests and norms, and in the manner in which they interact with the patient and her/his family members or caregivers from the clinical interview until the feedback session. Importantly, transparency in the management of cultural/linguistic influences is encouraged. While the focus of this chapter has been culturally/linguistically diverse URM older adults in the USA, much of this information will also be relevant for nontraditional, older non-Hispanic white populations, such as those from rural or low socioeconomic backgrounds.

Clinical Pearls

- Remember to maintain a "sociocultural lens" and to be mindful of potential sociocultural norms throughout the evaluation, from the clinical interview to the feedback session.
- In working with informants of culturally/linguistically diverse older adults, be cognizant that there may be hesitance to report the cognitive or functional decline of a loved one, despite having observed such declines. Such reticence may be reduced through taking the time to establish solid rapport.
- Utilize the best available neuropsychological instruments and norms and acknowledge the potential limitations in the interpretation section of your neuropsychological report.
- Consult literature regularly for recent developments in measures and norms.
- Carefully evaluate the psychometric appropriateness of tests under consideration, particularly if the patient is bilingual.
- Consider the purpose of the evaluation (diagnostic or descriptive) and whether race-/ethnicity-corrected norms are indicated.
- Gather as much sociocultural information as possible (i.e., acculturation, quality of education, linguistic background, etc.) to best contextualize the neuropsychological findings.
- For non-English speakers or those from other cultural/linguistic groups for which the neuropsychologist does not feel competent to examine, refer to a neuropsychologist who has expertise with the population or consult with such a neuropsychologist when referring out is not feasible.
- Only use an interpreter when outside referral is not feasible (e.g., rural area). Ethical mandates of our profession should take precedence over local administrative demands.
- When interpreters must be utilized, only use professional interpreters who are trained in the unique communication demands of standardized testing (not children of patients, hospital staff, or other nonprofessionals) [4].
- Consider psychometric characteristics to determine how "low" scores should be interpreted

to avoid misdiagnosis and mismanagement of neurocognitive disorders.
- Suggest longitudinal assessments to better disentangle the impact of sociocultural factors versus neurodegenerative processes.
- Explicitly state the normative data sets used within the report, if different from the manual, and discuss any limitations to the interpretability of the data based on these norms.
- Be careful *not* to erroneously attribute problems to cultural or linguistic issues.
- Consider the whole person, including their sociocultural context, in the development and communication of recommendations.
- Become actively involved in advancing your own cultural competence, as well as that of our field (see Rivera Mindt et al. [10] for resources).

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4 Assessment of Depression and Anxiety in Older Adults

Dimitris N. Kiosses and Patricia Marino

Epidemiology of Late-Life Depression

The prevalence of late-life depression increases as we move from the community to medical settings, home care, and nursing homes. Three percent of older adults in the community, 5–8% of medical outpatients, 11% of medical inpatients, approximately 12% of nursing home residents, and 14% of home-care recipients have major depression [1–3]. The percentages are even greater in milder forms of depression including dysthymia.

Despite its detrimental consequences, late-life depression is underdiagnosed and undertreated. Factors which contribute to underdiagnosis and undertreatment of geriatric depression likely include the following:

(a) Similarities of depression symptoms with those of medical illnesses.
(b) Many older depressed adults do not report depressed mood but rather lack of interest or pleasure in activities.
(c) Aging stereotypes.
(d) Primary care settings, where most of the depressed older adults are treated, are busy and emphasize medical rather than mental health problems [4]. In primary care, almost half of high utilizers receive no antidepressant treatment, and 1/3 receive inadequate treatment [4, 5]. Even when antidepressants are prescribed, adherence rates are discouraging, ranging from 25% to 60% [5].

Suicide

Suicide is devastating for the victim's families, friends, and communities. Suicide rates have increased in the past 10 years, with white older men (85 year old or older) at greatest risk. Although there has been a decrease in suicide rates in older adults in recent years, rates may significantly rise again because of the aging of baby boomers, a cohort with increased suicide rates [6]. When compared with suicide attempts of young adults, attempts of older adults are more determined and use more lethal means, including the use of firearms or hanging. Psychiatric illnesses in general, but mood disorders and major depression in particular, are the most prominent risk factors for suicide. Other risk factors include poor physical health, disability, recent loss, and lack of social connectedness [7–9]. Assessment of these risk factors is important during the assessment of depression.

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Epidemiology of Late-Life Anxiety

Late-life anxiety contributes to decreased sense of well-being, reduced satisfaction, and increased disability [10]. Even though reported prevalence rates of diagnosable anxiety in older adults vary greatly in the community (2–19%), the best estimate is about 10%, while this rate increases in medically ill populations [10]. Comorbid anxiety is common in late-life depression, with reports estimating its prevalence up to 65% [10], and it is associated with lower response to antidepressant medication treatment, longer time to response or remission, and shorter time to recurrence once remission is achieved [11–15].

Diagnosis of Clinical Depression and Anxiety

Diagnosis of Clinical Depression

There are different types of clinical depression highlighted in the DSM-5 [16], some of them are updated from the DSM-4. Major depressive disorder (MDD), dysthymic disorder, depressive disorder NOS, and adjustment disorder of depressed mood and anxiety are the most common diagnoses of clinical unipolar depression. Differential diagnosis is based on the severity and duration of symptoms as well as on the precipitants of the onset of depression. As we review the symptoms of different types of depression, it is evident that MDD is the most severe. In the following section, the most common depressive and anxiety disorders will be described, and certain diagnostic considerations will be highlighted. Updates with reference to the DSM-5 (released in May 2013) are provided.

Major Depressive Disorder

MDD is characterized by the presence of one or more major depressive episodes (MDEs) and the absence of any hypomanic or manic episode. A MDE is diagnosed when either depressed mood or loss of interest or pleasure (anhedonia) is present for at least 2 weeks, every day, most of the day [16]. In addition, the patient may experience five or more of the following symptoms: (a) depressed mood, (b) lack of interest or pleasure in activities, (c) significant weight loss or weight gain or appetite disturbances (in older adults, most commonly weight loss and decreased appetite), (d) sleep disturbances, i.e., insomnia or hypersomnia, (e) psychomotor agitation or retardation, (f) fatigue or loss of energy, (g) feelings of worthlessness or excessive or inappropriate guilt, (h) concentration difficulties or indecisiveness, and (i) recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide (DSM-5) [16]. To diagnose an episode of major depression, clinically significant distress or impairment in social, occupational, or other important areas of functioning is required [16]. Within the diagnosis of MDD, there are different degrees of severity denoted in the last digit of the DSM-5 diagnosis [16]. Specifically, (1) refers to mild severity, (2) to moderate, (3) to severe without psychotic features, (4) to severe with psychotic features, whereas (5) and (6) refer to partial or full remission. The DSM 5 [16] now indicates two additional specifiers. The coexistence within a major depressive episode of at least three manic symptoms (insufficient to meet criteria for a manic episode) is now acknowledged by a specifier "with mixed features." Additionally a new specifier of "with anxious distress" has been added to rate the severity of anxious distress in all individuals with depressive disorders (DSM 5). Bereavement is no longer an exclusion in the DSM 5 for a major depressive disorder.

Psychotic Depression

Major depression with psychotic features is a severe disorder, which is characterized by delusions or hallucinations and is associated with slow recovery, poor outcomes, and increased disability and mortality [17–19]. Delusions are more frequent than hallucinations, and compared to delusions in dementia, delusions in psychotic depression are systematized and mood congruent [4]. Usual delusional themes include guilt, persecution, hypochondriasis, nihilism, and jealousy.

Persistent Depressive Disorder or Dysthymia

Dysthymic disorder is a chronic depression of milder intensity than major depression. Specifically, depressed mood is present for most of the day, not every day but for most days than not, for at least 2 years and should not be absent for longer than 2 months [16]. Contrary to the diagnosis of major depression, lack of interest or pleasure is not a cardinal symptom of dysthymia. In addition to depressed mood, the patient may experience two or more of the following symptoms: (a) poor appetite or overeating (in older adults, most commonly poor appetite), (b) insomnia or hypersomnia, (c) low energy or fatigue, (d) low self-esteem, (e) poor concentration or difficulty making decisions, and (f) feelings of hopelessness [16]. Once again, clinically significant distress or impairment in social, occupational, or other important areas of functioning is required for diagnosis [16].

A close examination of the symptoms of major depression and dysthymia may explain why late-life depression is underdiagnosed. First, fatigue, loss of energy, concentration difficulties, weight loss, and sleep disturbances may be symptoms of other medical illnesses. As older adults frequently suffer from medical illnesses, it may be difficult to differentiate whether these symptoms are features of depression or other medical illnesses. Second, due to aging stereotypes, lack of interest or pleasure may be incorrectly perceived as a normal part of aging. This is a very critical issue as many depressed older adults do not exhibit or report depressed mood, but rather lack of interest or pleasure.

Adjustment Disorder with Anxiety and/or Depressed Mood

Adjustment disorder refers to the development of emotional and behavioral symptoms as a response to a stressor occurring within 3 months of the onset of the symptoms [16]. Usual stressors of adjustment disorder in older adults include poor physical health and disability, socioeconomic deprivation, and placement to a long-term care facility [4, 20]. Based on DSM-5 [16], the symptoms are clinically significant and may cause marked distress (more than expected from the exposure to that stressor) and significant impairment in social or occupational functioning. Adjustment disorder may occur with anxiety, depressed mood, or both.

Cognitive Deficits Associated with Depression

As mentioned above, late-life depression may be accompanied by cognitive difficulties. Poor concentration is a common symptom of depression. Moreover, nondemented depressed elders may present with disturbances in processing speed and executive functioning [21, 22]. To evaluate the etiology of cognitive difficulties in late-life depression, a thorough neuropsychological examination is strongly recommended.

Some older adults display symptoms of dementia that are due to depression. As soon as depression remits, their cognitive functioning may reach their premorbid functioning. This clinical picture is referred as "pseudodementia" or "reversible dementia." The causes of "pseudodementia" are not clearly understood; in some cases, depression may contribute to cognitive impairment, whereas in others, cognitive deficits may be the result of a progressive subclinical dementia that is exacerbated by depression [4, 23]. Despite their return to almost normal cognitive functioning, older adults with "pseudodementia" may develop irreversible dementia at a rate of 9–25% per year (approximately 40% within 3 years) [4, 23]. Further research is needed to understand "pseudodementia" and its consequences.

Depression in Alzheimer's Disease

Some depressive symptoms may be similar to symptoms of Alzheimer's disease (AD). For example, diminished social activity and lack of interest, which are symptoms of depression, are prevalent in AD. The overlap of symptoms

between depression and AD may complicate the diagnosis of depression in AD [24]. Further, research suggests that depression in AD may be different from other depressive disorders [24].

In 2002, the NIMH organized a workshop with a group of investigators of depression and AD to facilitate the development of provisional diagnostic criteria for depression of AD [24, 25]. The goals of the development of these criteria were to assist clinicians in diagnosing depression in AD and to provide a target for research on the mechanism and treatment of depression and AD [25]. The criteria required three (or more) of the following symptoms to be present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) decreased positive affect or pleasure. The symptoms were (a) clinically significant depressed mood; (b) decreased positive affect or pleasure; (c) social isolation or withdrawal; (d) disruption in appetite; (e) disruption in sleep; (f) psychomotor changes (agitation or retardation); (g) irritability; (h) fatigue or loss of energy; (i) feelings of worthlessness, hopelessness, or excessive or inappropriate guilt; and (j) recurrent thoughts of death, suicidal ideation, and plan or attempt [24, 25]. These criteria must be present in an individual diagnosed with dementia of the Alzheimer's type, and the symptoms are believed to cause clinically significant distress or disruption in functioning [25].

The provisional diagnostic criteria for depression of AD mainly differ from DSM-5 criteria of MDD in the following ways: (a) the duration of cardinal symptoms (in DSM-5, the symptoms must be there nearly every day, most of the day, while in provisional criteria, the symptoms may have shorter duration), (b) the number of symptoms required for the diagnosis (five in DSM-5 vs. three in provisional criteria), and (c) description of anhedonia ("lack of pleasure in DSM-5" vs. "decreased positive affect or pleasure in response to social contacts or activities" in provisional criteria) [24, 25].

Diagnosis of Anxiety

In a review of cognitive therapy of anxiety disorders, Clark and Beck highlight the following definitions of fear and anxiety: "Fear is a primitive automatic neuropsychological state of alarm involving the cognitive appraisal of imminent threat or danger to the safety and security of an individual," whereas "Anxiety is a complex cognitive, affective, physiological, and behavioral response system (i.e., threat mode) that is activated when anticipated events or circumstances are deemed to be highly aversive because they are perceived to be unpredictable, uncontrollable events that could potentially threaten the vital interests of an individual" [26]. Therefore, fear and anxiety have a protective value of helping us deal with actual threats. However, in anxiety disorders, the patient's perceived threats may not be accurate, last longer than expected, while the threshold for perceived threats is lowered, and, therefore, the patient becomes hypersensitive to external stimuli. As a result, the response could be excessive compared to the severity of the perceived threat, while anxiety feels uncontrollable and significantly impairs functioning. Therefore, in the assessment of anxiety, the clinician has to evaluate the evidence for a realistic threat and the appropriateness and excessiveness of the patient's response to the perceived threat.

Generalized anxiety disorder (GAD) and phobias are the most common anxiety disorders in older adults [10, 27, 28], even though a number of older adults may experience clinically significant anxiety without any specific diagnosis [10]. The following section highlights the diagnoses of GAD, phobias, and panic disorder.

Generalized Anxiety Disorder

The critical features of GAD as described in DSM-5 [16] are (a) excessive and difficult to control anxiety or worry (apprehensive expectation), for more days than not, for at least 6 months, and (b) at least three or more of the following symptoms: (1) restlessness, (2) being

easily fatigued, (3) concentration difficulties, (4) irritability, (5) muscle tension, and (6) sleep disturbances [16]. Similar to other diagnoses in DSM-5, the symptoms must be severe enough to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning [16].

Specific Phobia

Specific phobia is characterized by "marked and persistent fear that is excessive and unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood)" [16]. The patient recognizes that his or her fear is excessive and unreasonable and avoids the phobic situation, as the exposure of the stimulus "almost invariably provokes an immediate anxiety response" [16].

Panic Disorder

As described in DSM-5, panic disorder is characterized by recurrent unexpected panic attacks; one of the attacks has been followed by at least 1 month of persistent concern about having additional attacks, worry about the implications or consequences of the attack, or a significant change in behavior related to the attacks [16]. Panic attacks are defined as "an intense period of fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 min: (a) palpitations, pounding heart, or accelerated heart rate; (b) sweating, (c) trembling or shaking, (d) sensations of shortness of breath or smothering, (e) feeling of choking, (f) chest pain or discomfort, (g) nausea or abdominal stress, (h) feeling dizzy, unsteady, lightheaded, or faint, (i) derealization (feelings of unreality) or depersonalization (being detached from oneself), (j) fear of losing control or going crazy, (k) fear of dying, (l) paresthesias (numbness or tingling sensations), and (m) chills or hot flushes" [16].

Agoraphobia

The DSM 5 now has separate diagnosis of panic disorder and agoraphobia, each with separate criteria. Agoraphobia is characterized by a fear of open spaces and avoidance of places or situations. The core symptoms require fear about multiple situations from across at least two distinct domains in which escape might be difficult (DSM 5) [16].

Diagnostic Considerations

Rule Out Other Diagnoses

The clinician needs to evaluate whether other mental disorders exist. For example, ruling out bipolar I and II disorders is critical because the pharmacological or psychological treatment of bipolar depression differs from that of unipolar depression. Geriatric bipolar disorder is relatively rare in the community, and its point prevalence rate is less than 0.5% [29]. However, 17% of older adults in psychiatric emergency rooms have bipolar disorder [29, 30]. Compared to young adults, fewer older bipolar patients have a diagnosis of substance abuse, and more have a cognitive disorder diagnosis (i.e., dementia, amnesia, and cognitive disorder NOS) [28].

Bipolar I is characterized by the occurrence of manic episodes, with or without MDEs [16]. However, bipolar I older patients usually have had one or more MDEs. Manic episode is defined as "a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)" [16]. During this period, the patient experiences three or more of the following symptoms (four if mood is only irritable): (a) inflated self-esteem or grandiosity, (b) decreased need for sleep (e.g., patient feels rested after only 3 h of sleep), (c) more talkative than usual or pressured speech, (d) flights of ideas or racing thoughts, (e) distractibility, (f) psychomotor agitation or increase in goal-directed activities, and (g) excessive involvement in pleasurable activities that

have a high potential for painful consequences (e.g., buying sprees, sexual indiscretions, or foolish business investments) [16]. The patient has significant impairment in occupational, interpersonal, or social functioning [16] that may require hospitalization. Because of the severity of the manic episodes, early-onset bipolar I disorder has been usually diagnosed before an older adult presents with psychiatric problems, while late-onset bipolar I disorder occurs only in a small minority of geriatric bipolar cases [31].

Bipolar II is characterized by the occurrence of MDEs and at least one hypomanic episode [16]. Hypomanic episode is of lesser severity and duration than a manic episode and is defined as "a distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood" [16]. During this period, the patient experiences three or more of the same symptoms described in the manic episode (four if mood is only irritable) [16]. According to the DSM-5 criteria, the hypomanic episode does not include psychotic features and is not severe enough to cause significant impairment in occupational, interpersonal, or social functioning or to necessitate hospitalization [16].

Substance Abuse

The use of alcohol, drug, or prescription medication needs to be evaluated. The clinician shall evaluate the amount and frequency of alcohol consumption and the use of possible illicit drugs and prescription medication. Special attention must be placed on the possible abuse of prescription medications as some of them may be addictive (e.g., medications for the treatment of anxiety or pain).

Evaluation of Medical Conditions and Medications

Certain medical conditions and medications may cause depression. Specifically, medical conditions, including thyroid abnormalities, deficiency of vitamin B12, lymphomas, and pancreatic cancer, are often associated with depression [4]. Moreover, steroids, anti-Parkinsonian drugs, and benzodiazepines may cause depression [4]. As noted in DSM-5, the symptoms of depression must not be "due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)." Treatment recommendations highlight that the medical condition may need to be treated first; however, there are cases that depression may not remit unless antidepressant medication treatment is prescribed [4].

Assessment of Depression and Anxiety

Accurate Diagnosis of Depression

During the first interview with the depressed older adult, the clinician must obtain the following information: present history of depression, onset of the current episode, precipitants of the current episode, past history of depression, current or past suicidal ideation, family history of depression and suicide attempts, history of antidepressant medication and psychotherapeutic treatments and outcomes, medical history, and list of psychiatric and nonpsychiatric medications.

The clinician needs to evaluate the onset of current and past depression episodes, explore any events that preceded these episodes, and evaluate the coping mechanisms that the patient used to deal with potential stressors. Helpful questions include: What were the precipitants of the episodes of depression? What were the most critical stressors that the patient experienced before the onset of depression? What were the coping mechanisms that the patient utilized? Which coping mechanisms were successful or unsuccessful?

As the clinician explores past and current depressive episodes, he or she needs to evaluate the patient's previous response to antidepressants or psychotherapies. The patient should also be asked to produce a list of all antidepressant medi-

cations (i.e., highest dosages, duration, and treatment response for each medication), a list of previous and current psychotherapeutic treatment (i.e., type of treatment, e.g., cognitive behavioral therapy, behavioral therapy, or problem-solving therapy; frequency and duration of treatment; and treatment response), and a list of any other treatments (e.g., electroconvulsive therapy). These lists may help the clinician to determine adequacy and response to antidepressant treatment. Finally, psychiatric hospitalizations, reasons for admissions, inpatient psychiatric treatments, and follow-up treatments should be discussed in detail.

Sometimes the patient's depression may not be easily recognized. Loss of interest and pleasure or depressed mood is cardinal symptoms of clinical depression. At least one of these two symptoms is required for the diagnosis of major depression. Therefore, a patient may suffer from depression even though he or she does not report depressed mood. In fact, many older adults report loss of interest or pleasure, as well as physical symptoms, in the absence of depressed mood. It is also important to recognize that depressed older adults may not necessarily use the words "depressed" or "sad," but rather "blue," "helpless," "hopeless," "apathetic," "disinterested," or "unmotivated." The clinician needs to evaluate the patient's words carefully and assess whether these words reflect clinical depression.

Assessment of Past or Present Suicide Ideation

The assessment of suicide ideation in older adults is critical as older adults have high suicide rates and use more lethal means to attempt suicide than younger adults. Older adults also suffer from increased disability, physical and functional impairment, pain, and interpersonal losses, all of which are risk factors for suicide. Because some older adults may not readily report psychiatric symptoms, the clinician needs to ask thorough questions to evaluate suicide risk.

Suicide ideation may be expressed in different ways, including passive (e.g., I wish I were dead) or active (e.g., I have thoughts of killing myself). Suicidal ideation usually covers a wide spectrum of thoughts and feeling, such as feelings that life is not worth living, wishes of being dead, thoughts of killing oneself but without intent or plan, thoughts of killing oneself with intent or plan, and thoughts of killing oneself with intent and plan. The stronger the degree of suicidal ideation, the higher the risk of suicide is.

Since hopelessness is associated with suicide ideation, the clinician should evaluate the degree of hopelessness and suicide ideation in past and current episodes of depression. Important questions include: What makes you feel hopeless? Have you recently felt (or have you ever felt) that life is not worth living? What parts of life are not worth living? What parts of life are worth living? How strong is your wish to live? Have you ever wished you were dead? Describe recent events that made you feel that life was not worth living or that you wished you were dead? Any specific event or stressor that precipitated these feelings? What went through your mind? Have you ever thought of hurting or killing yourself? If yes, have you thought about a specific plan? What kept you from doing anything to harm or kill yourself? Has there been a family history of suicide attempts?

The clinician needs to gather detailed information about past and recent suicide attempts. The patient may describe the sequence of events, as well as severity and duration of the suicide ideation that contributed to the suicide attempt. The goal of the clinician is to understand risky situations, to illuminate the hopeless thoughts that contributed to suicide ideation or suicide attempts, and to explore potential positive thoughts that have prevented the patient from harming or killing himself or herself. Access to firearms or to other potential lethal means (e.g., lethal doses of medication) must be evaluated during the interview of a patient at risk of suicide. In certain cases, to avoid risky access to firearms, the clinician may propose that firearms be removed from the patient's residence. Finally, the clinician may decide to hospitalize the patient if, after the evaluation, the clinician believes that the patient is a threat to himself or herself. In addition to suicide ideation, the clinician should also

evaluate whether the patient is a threat to hurt others or whether there is a history of violent outbursts and physical abuse.

Depression Versus Normal Fluctuation of Mood

Clinical depression is different from the normal "ups and downs" of everyday life in severity, duration, and its effect on the patient's functioning. Normal fluctuation of mood is usually not prolonged, is not as severe, and does not significantly impair functioning. Impairment in functioning is required for the diagnosis of clinical depression. Signs and symptoms of hopelessness, worthlessness, or excessive guilt are associated with clinical depression and are not typically part of normal mood fluctuations.

Complicated Grief

One of the most difficult situations in assessing depression and recommending treatment is when the sadness is associated with grief. In general, if the older adult's functioning is significantly impaired, psychotherapeutic or medication treatment is recommended. Because of the stigma attached to mental illness, the clinician needs to address the issue tactfully, recognizing that it is expected to experience sadness after the loss of a loved one. Grief-stricken patients may also experience an exaggerated sense of guilt when they feel pleasure, which may reinforce the vicious cycle of depression.

Accurate Diagnosis of Anxiety Disorders: Productive Anxiety Versus Unnecessary Worrying

Patients with anxiety disorders often present for the treatment of anxiety with the expectation of complete elimination of their anxiety symptoms. The clinician needs to discuss the potential benefit of anxiety to help the patient recognize that the goal of treatment may not be the elimination of anxiety per se, but rather learning techniques to effectively deal with excessive and uncontrollable anxiety or worrying. Moderate levels of anxiety may also be a motivating factor and become a productive force.

The interview may illuminate areas of worrying, degree and duration of worrying, and its impact on the patient's functioning. It is important for the clinician to understand the patient's fears and explore his or her "catastrophic" predictions that are the basis for their anxiety or worrying. Finally, patients with anxiety may either avoid situations that produce anxiety (e.g., a patient may avoid going out because he is concerned that he may have an anxiety attack) or focus extensively (obsess) on situations that trigger anxiety (e.g., a patient is obsessively worried about her health).

Differentiating Obsessive Anxiety and Overvalued Ideas from Delusions

The clinician needs to assess whether the patient's obsessive concerns, anxiety, or overvalued ideas are reaching psychotic proportions. For example, a patient believes that she has cancer in the absence of any medical data to support her conviction. Questions that may help the clinician make the differential diagnosis include: (a) How convinced are you that you have cancer? (b) Do you feel relieved that the physicians have confirmed that there is no evidence of cancer? (c) Do you see any alternative explanation for your pain other than cancer? Nondelusional depressed patients usually recognize that their thoughts are exaggerated, but they may not be able to reduce its effect [4]. In addition to astute questioning, the Delusional Assessment Scale for psychotic depression may help the clinician measure the intensity of delusional beliefs [32].

The Use of Formal Measures in the Assessment of Depression and Anxiety

Certain questionnaires may be helpful in identifying symptoms of depression and anxiety. These measures are not necessarily used to diagnose

clinical depression but rather help the clinician identify symptoms of depression and assess their severity. Both clinician-administered and self-report measures may be administered. Clinician-administered rating scales include Hamilton Rating Scale for Depression and Montgomery-Asberg Depression Rating Scale [33]; both may be used for patients with mild cognitive impairment. Depression in patients with dementia may be evaluated with the Cornell Scale for Depression in Dementia [34], a measure which calculates a composite score based on reports from both the patients and their caregivers. Self-report questionnaires include the Beck Depression Inventory [35] and Geriatric Depression Scale [36]. Measures that may capture anxiety symptoms also include self-report (e.g., Beck Anxiety Inventory [37]) or clinician administered (e.g., Hamilton Scale for Anxiety [38]).

Involvement of Caregiver

The clinician should encourage the participation of an available and willing caregiver in the assessment process. The caregiver may be a spouse, partner, child, sibling, other family member, or an aide. If the patient does not think that the involvement of caregiver is necessary or helpful, the therapist may try to understand the reasons for the patient's reluctance (e.g., beliefs that this may be burdensome to the caregiver, tension between the patient and the caregiver, caregiver is not involved significantly in the patient's care, etc.). The clinician may explore whether these reasons may contribute to or affect patient's depression.

Caregiver participation in the assessment process may prove to be important and at times necessary. The caregiver may help in identifying periods of depression, illuminate the patient's behavior when he or she is depressed, and highlight patient's cognitive, physical, and functional limitations. This is particularly important in patients with cognitive impairment, as obtaining information from a collateral source is necessary when patients are not good historians, have advanced cognitive impairment, or may lack insight into their difficulties.

Assessment of Disability

Depression may contribute to disability, and disability may precipitate the onset of depression. Furthermore, improving functioning and reducing disability may mediate reduction in depression [39]. Because of the reciprocal relationship of depression and disability, a careful assessment of patient's depression, disability, and everyday functioning is strongly recommended. Specifically, the clinician needs to evaluate the patient's physical and functional limitations and assess their performance in activities of daily living. Activities of daily living may be divided into instrumental activities of daily living (e.g., taking medication, walking a short distance, shopping for groceries, using the telephone, paying bills, doing housework and handyman work, doing laundry, preparing meals) or basic activities of daily living (e.g., bathing, eating, combing hair). The clinician may explore whether the patient was performing these activities before the onset of their depression, whether depression has affected the patient's performance in activities of daily living, or whether the patient *is able* to perform these activities with or without help. In addition to careful questioning, the clinician may administer instruments that evaluate a patient's functioning and disability such as the Philadelphia Multiphasic Assessment Instrument (MAI) [40] or the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [41].

Clinical Pearls

- Clinical depression is different from the normal fluctuation of depressed mood in the severity of symptoms, their duration, and most importantly, the patient's impairment in his or her everyday functioning.
- Depressed older adults may exhibit lack of interest or pleasure and physical symptoms rather than depressed mood. This is one of the reasons late-life depression is underrecognized.
- The clinician should be aware that the patient may not report sadness or depression per se, but

may report "discouragement," "lack of energy," "blue feeling," or "lack of motivation."

- Depressed elders may display "dementing" symptoms during their depression; sometimes, these symptoms subside when the depression remits. This phenomenon is called "pseudodementia" or "reversible dementia." Depression may also be a prodromal state of dementia.
- A thorough neuropsychological examination is recommended for depressed elders who present with cognitive difficulties.
- Treatment for complicated grief is recommended when the patient's functioning is significantly impaired.
- The clinician needs to thoroughly evaluate hopelessness given its strong correlation with suicide risk, past and present suicide ideation and attempts, and family history of suicide. Risky access to firearms or to other potential lethal means must be evaluated during the interview of a patient at risk of suicide.
- In the assessment of anxiety, the clinician has to evaluate the evidence for a realistic threat and the appropriateness and excessiveness of the patient's response to the perceived threat.

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The Assessment of Change: Serial Assessments in Dementia Evaluations

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Gordon J. Chelune and Kevin Duff

The Assessment of Change: Serial Assessments in Dementia Evaluations

As a multidisciplinary area of scientific inquiry, *neuropsychology* is often defined as the study of brain–behavior relationships. However, as an area of psychological practice, *clinical neuropsychology* has been described as the application of neuropsychological principles of brain–behavior relationships to the assessment, diagnosis, and rehabilitation of *changes* in human behavior that arise across the lifespan from known or suspected illnesses or injuries affecting the brain [1]. To this definition, we can also add the assessment of cognitive changes associated with medical interventions (e.g., open-heart surgery, epilepsy surgery) and treatments (e.g., deep brain stimulation, pharmacologic treatments). Whether the focus is on changes in cognition induced by abnormal medical conditions or those in response to treatments and interventions, the focus of the clinical neuropsychologist in everyday practice is on *change*.

The assessment of meaningful neurocognitive change is particularly relevant for the evaluation of older adults suspected of having underlying neurodegenerative disorders. Because the diagnosis of dementia as well as mild cognitive impairment (MCI) requires evidence of cognitive decline over time [2], it is critical to distinguish between age-related decrements in cognition (e.g., memory, processing speed, executive functions) believed to be part of "normal" aging [3–5] and those early clinical changes that are pathological and disease-related (e.g., neurodegenerative disorders, cerebrovascular disease, stroke, diabetes, etc.). Traditional single-point evaluations are limited in this context as they only capture a picture of the patient's current abilities at a single point in time. Unless the patient's performances deviate markedly from an *inferred* premorbid baseline, it is difficult for the practitioner to know whether these point estimates of a patient's abilities are meaningfully different from expectation [6]. To overcome the limitations of single-point assessments, clinicians increasingly are turning to serial assessments to determine whether patients' *observed* trajectories of change over time significantly deviate from those seen in normal aging [7, 8]. Unlike single-point assessments where the clinician must infer a premorbid baseline, the patient's initial scores serve as their *observed* baseline. Armed with an appropriate conceptual framework and some simple tools, serial assessments provide the informed practitioner a powerful means for assessing diagnostically meaningful change.

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In this chapter, we will briefly discuss the clinical use of norm-referenced neuropsychological tests, contrasting two underlying approaches to interpreting these norms in traditional single-point assessments. With this as a backdrop, we will then turn our attention to the use of serial assessments to objectively monitor and assess cognitive changes over time, discussing the unique advantages and challenges of serial assessments. An overview and distillation of reliable change methods will be presented and applied to a case example, demonstrating how these methods can be used as effective tools to inform the clinical evaluation of the individual patient. In the end, we hope to leave the reader with an appreciation that *change* is a unique variable with its own inherent statistical properties and clinical meaning.

Norms and How We Use Them in Single-Point Assessments

In clinical practice, when we see a patient for the first time, we use norm-referenced tests so that we can compare the performances of the individual patient to an external reference group. The norms simply describe the distribution of scores on a given test obtained by a reference group, which can be a sample from the general population, a well-screened group of healthy community-living individuals (i.e., robust norms), or a patient group with a specific condition of interest. To infer meaning from our patient's scores, we can take two very distinct approaches to answer different clinical questions [6]. The first approach is *descriptive*, that is, *where* does my patient's score fall with respect to the reference population along a standardized metric (e.g., standard scores, *z*-scores, percentile ranks)? We often apply descriptive labels such as "above average" or "below average" for ranges of scores in relation to the mean of the sample, and using standardized measures of the distribution of scores, we can assign percentile ranks that tell us how common or uncommon the specific score is *within* the reference population.

While the descriptive approach is useful in identifying where our patient's scores fall within a reference population, it does not address whether our patient's scores are impaired or not. To do this, we must take a *diagnostic* approach where we ask the question "does my patient's score *deviate* from premorbid expectations (i.e., where I expect the score to have been in the absence of an intervening illness or injury), and if so, by how much?" The reference standard is now the individual's premorbid status, *not* the mean of the reference population. In the absence of having baseline information, the clinician must infer this and often relies on demographic information [9] and performance on crystallized ability measures such as oral reading derived from normative reference groups (e.g., the Test of Premorbid Functioning [10]). Deviations from this *individual comparison standard* can also be placed on a standardized metric (e.g., *T*-scores, *z*-scores), and percentile ranks assigned to the deviations *if* we know the characteristics of the *distribution of the deviation scores* between the premorbid estimate and observed performance on a given test. Note that the focus is on the distribution of the deviation scores, *not* the distribution of either the premorbid estimates or the observed scores on a given test.

While the diagnostic approach allows us to quantify whether an individual's current performance deviates from estimates of his or her demographically predicted premorbid ability level, we are still constrained to describing the deviation in terms of base rates—how common or uncommon the deviation is for our patient relative to premorbid expectations. To be diagnostically useful, the clinician must further establish validity evidence. As neuropsychologists move more concertedly toward evidence-based practice [11], it is no longer sufficient to simply rely on personal case records, unsystematic observations, or general knowledge as validity [12]. Increasingly, clinicians must become skilled in performing evidence-based reviews of the literature [13] that allow the integration of "…best research derived from the study of populations to inform clinical decisions about individuals within the context of the provider's expertise and individual patient values with the goal of maximizing clinical outcomes and quality of life…" (Chelune, 2017,

p 160). Our interpretation that discrepancies of a certain magnitude are statistically more frequent in populations that have a specific condition of interest, such as amnesic MCI, than would be expected at this level of discrepancy in a normal population should be founded on empirical evidence.

To illustrate the points above, let us consider the example of super clinician, Dr. Bob, who works in a memory disorders clinic and uses the test MegaMemory to evaluate memory complaints. Knowing that a patient's memory score on MegaMemory is one standard deviation below the estimated premorbid level informs Dr. Bob that the base rate of deviations of this magnitude occurs in only 16% of cases where there is an absence of an intervening illness or injury. However, after carefully reading the chapter on validity in the test manual for MegaMemory, Dr. Bob finds that the publisher conducted a case-controlled study using MegaMemory that compared equal numbers of patients with amnesic MCI and normal controls, a prevalence rate similar to what Dr. Bob sees in his clinic. The manual reports that individual deviations of one standard deviation or more from estimated premorbid levels occurred in 64% of cases with amnesic MCI compared to only 16% of controls. Performing a Bayesian analysis of the base rates between the two groups [13] yielded an odds ratio of 9.3 and a likelihood ratio of 4.0. Based on this empirical evidence, Dr. Bob now feels he can interpret a deviation score of one standard deviation or more on MegaMemory as not only relatively uncommon among healthy older adults but also as being "impaired" since deviations of this magnitude are four times more likely to occur in patients with amnesic MCI than in healthy controls, and among patients with amnesic MCI, deviations of this magnitude are nine times more likely to occur than deviations of lesser magnitude.

Using Serial Assessments to Identify Meaningful Change

Although neuropsychological tests are generally designed to assess the current state or capacity of an individual, repeated assessments are increasingly common in neuropsychological practice and outcomes research [14, 15]. This has become especially true in geriatric settings where the determination of meaningful changes in cognition over time is essential for both the diagnosis of dementia and for planning therapeutic provisions and long-term care for patients and caregivers [6, 16]. Serial observations and longitudinal comparisons are classic tools in science, and their use in clinical practice requires clinicians to understand test–retest change scores as unique cognitive variables with their own statistical and clinical properties that are different from the test measures from which they were derived [17].

Like single-point diagnostic assessments discussed above, serial assessments share (a) a focus on *change* between two points in time (albeit one observed and the other inferred); (b) estimates of change based on *individual comparison standards* rather than population standards; (c) a focus on the psychometric properties of the discrepancy or change scores rather than on the test scores themselves (i.e., the properties of the distribution of change scores); (d) use of base-rate information to determine whether a change or discrepancy score is common or uncommon; and (e) *impairment* inferred on the basis of validity studies that demonstrate that large and relatively rare change scores are statistically more common in patient groups with a known condition of interest than would be expected among the reference population.

Although serial assessments share much in common with single-point assessments, they also pose unique interpretative challenges because two or more sets of scores are involved. Under ideal test–retest conditions, a patient's retest performance should be the same as that observed at baseline, and any change or deviation from baseline would be clinically relevant. However, in the absence of perfect test stability and reliability, the clinician must deal with the residuals of these statistical properties, namely, bias and error.

Bias Bias represents a systematic change in performance. The most important source of systematic bias in clinical practice is the variable of interest, that is, the effect of disease progression over time,

the impact of a surgical or pharmacological intervention, or the effect of rehabilitation. However, second only to the variable of interest, the most common source of bias in serial cognitive assessment is a positive *practice effect* in which performance is enhanced by previous test exposure, although negative biases can also occur such as those seen in aging [18]. For example, in a meta-analysis on practice effects on commonly used neuropsychological tests, Calamia et al. (2012) reported a mean practice effect of approximately +0.24 standard deviation units but noted that age decreased practice effects by approximately 0.004 per year after the age of 40 [19]. Other forms of systematic bias on retest performance are education, gender, clinical condition, baseline level of performance, and retest interval [19–22]. Where large, positive practice effects are expected, the absence of change may actually reflect a decrement in performance. To make accurate diagnoses, the clinician must separate the effects of the variable of interest from other sources of bias.

Error In addition to systematic biases, tests themselves are imperfect tools and can introduce an element of random error. For our purposes here, we will only consider two sources of error affecting serial assessment, both of which are inversely related to the test's reliability. The first is *measurement error* or the fidelity of the test, and it refers to the theoretical distribution of random variations in observed test scores around an individual's true score, which is characterized by the *standard error of measurement* (*SEM*). Because the *SEM* is inversely related to a test's reliability, tests with low reliability (<0.70) have large *SEM*s surrounding a person's true score at both baseline and on retest, and large test–retest differences can occur simply as random fluctuations in measurement. Conversely, small test–retest changes can be reliable and clinically meaningful for tests with high reliability (>0.90). Test–retest reliabilities of 0.70 or greater are often considered to be the minimum acceptable standard for psychological tests in outcome studies [23], and practitioners should be wary when interpreting cognitive change scores on tests that have lower reliabilities.

The second source of error affecting change scores is *regression to the mean*, which refers to the susceptibility of retest scores to regress toward the mean of the scores at baseline. The more a score deviates from the population mean at baseline, the more likely it will regress back toward the mean on retest. How much a score regresses depends on the reliability of the test. Again, scores on tests with high reliability show less susceptibility to regression to the mean than those on tests with lower reliability. The bottom line for clinicians when planning to perform serial assessments and faced with two tests purported to assess the same cognitive construct—choose the one with the better reliability!

Alternate forms Alternate forms are often touted as an effective means for avoiding or minimizing practice effects due to test familiarity. Carefully constructed alternative forms may attenuate the effects of content-specific practice for some measures [24]. However, research demonstrates that alternate forms used in serial assessments still show significant practice effects [25]. While alternate forms may dampen practice effects due to content familiarity, they do not control for procedural learning and other factors that contribute to the overall practice effect. More importantly, rote use of alternate forms in serial assessment ignores other factors that impact interpretation of test–retest change scores, namely, reliability and error [17].

Reliable Change in Serial Assessments with Older Adults

It should be clear that the interpretation of test–retest change scores is not a straightforward matter, and making accurate diagnostic judgments about whether an older adult has shown significant deterioration (or improvement) in cognitive status over a retest interval requires us to consider the role of bias and error in our measurements. Bias and error are problems only to the degree that they are unknowns and not taken into account when interpreting change scores. In this section, we will discuss *reliable change methods*, a family of related

statistical procedures that attempt to take into account the impact of differential practice effects and other systematic biases, measurement error, and regression to the mean on the interpretation of change scores. We do not intend to do a comprehensive or in-depth review of these procedures, and the interested reader is directed to other sources for more complete coverage [15, 17, 21, 22, 26–28]. Rather, we wish to distil the essential features of reliable change methods and demonstrate how these tools can be used diagnostically to evaluate meaningful cognitive change in older adults.

Reliable Change: A Statistical Approach to Meaningful Change

To understand the concept of reliable change, we need to distinguish between what is statistically significant at a group level and what is clinically meaningful at the individual level. Repeated measure tests of statistical significance tell us whether the mean difference between two groups of a given magnitude is a reliable difference that would not be expected to occur by chance at some predefined probability level (e.g., $p < 0.05$). However, the base rates of such differences at the level of the individual may actually occur with some regularity even when no real behavioral difference. For this reason, Matarazzo and Herman have urged clinicians to routinely consider base-rate data in their clinical interpretation of test–retest evaluations [29].

Reliable Change: The Basic Model

Reliable change methods all fundamentally strive to evaluate the base rates of difference scores in a population and to determine whether the difference between scores for an individual is statistically rare and cannot be accounted for by various sources of bias (e.g., practice) or error (e.g., measurement error and regression to the mean). Like a ruler or yardstick that measures *change* from point A to point B along a standard metric (inches/yards), the basic form for any reliable change method is a ratio: reliable change (RC) = (*change score*)/(*standard error*), *where the standard error describes the dispersion of change scores that would be expected if no actual change had occurred* [30]. This is simply the distribution of test–retest scores one would see in a reference population. RC is typically expressed as a standardized *z*-score under the unit curve that has a mean of 0 and a standard deviation of 1.0. The base rate of a given RC value being equal to the percentile associated with the *z*-score, for example, a *z*-score or RC of −1.64, falls at the bottom fifth percentile. The various reliable change methods reported in the literature primarily vary along two dimensions: whether the *change score* in the numerator is a simple-difference or a predicted-difference score and whether the *standard error* in the denominator represents a measure of dispersion (observed or estimated) around the mean of difference scores or around a regression line.

Simple versus predicted-difference change scores For the *change score* component of the RC ratio, when we do follow-up evaluations on a patient, we generally look at the retest scores and compare them with the baseline score (retest−baseline) to see if the difference is positive or negative. This is the simple-difference approach. When no difference is expected over the retest interval (perfect stability), the simple-difference change score reflects the patient's individual deviation from a population mean difference score of 0 or no expected change. However, as we have noted earlier, there are many sources of bias affecting retest scores, with practice often exerting a strong positive bias. As a result, the actual population mean of the test–retest *change scores* is positive and has led to the development of a practice-adjusted simple-difference approach [31]. For example, the mean retest performance on the Wechsler Memory Scale-III (WMS-III) Immediate Memory Index is 13.4 points higher than at baseline when readministered several weeks later [32]. If our 68-year-old male patient that we are following for suspected dementia has a baseline score of 97 and a retest score of 100, has he actually shown an improvement of 3 points when the average retest *change score* is 13.4 or a

decrement of −10.4 points (13.4 − 3 = −10.4) from expected change? To adjust for expected practice effects, Chelune and colleagues have suggested centering the *change score* component of the RC deviations around the mean of the expected practice effect and calculating the *change score* discrepancy from this mean [31].

The second approach to calculating the *change score* component of the RC ratio is the predicted-difference method. This is a regression-based approach that uses a patient's baseline performance to predict what his/or her retest score is expected to be at retest, with the regression equation being one derived from an appropriate reference sample. The discrepancy between the patient's actual observed retest score and the predicted retest score ($Y - Y'$) constitutes the *change score* discrepancy. Entering the baseline score as a predictor of the retest score into the regression equation allows practice effects to be modeled as a function of baseline performance (rather than as a constant) while also accounting for regression to the mean [33], two aspects not accounted for by the simple-difference approach. As in any regression approach, the equation can be univariate, using only the baseline score as the sole predictor, or multivariate, using additional information from other potential sources of bias as predictors, such as age, education, gender, and retest interval. In the example above of the 68-year-old male patient suspected of dementia, a regression-based equation using baseline WMS-III Immediate Memory Index scores and age was computed for the WMS-III test–retest standardization sample [17]. Given a baseline score of 97 for a 68-year-old normal individual, the predicted retest score would be 108.8. Our patient's predicted *change score* deviation is −8.8 points (observed retest score of 100 minus the predicted test score of 108.8). The reader will note that the −8.8-point predicted *change score* discrepancy is smaller than the −10.4-point simple-difference *change score*. The reason for this is that the regression-based predicted *change score* modeled not only practice effects (a positive bias) but also age (a negative bias), which dampened the expected practice effect, resulting in a smaller (although perhaps more accurate) expected retest score.

Measures of dispersion for the simple-difference method Once the individual's *change score* discrepancy has been computed, we have a measure of *change* but do not know whether the change is large or small without having a standard metric to evaluate the dispersion of *change scores* that would occur in the absence of real change (i.e., changes simply due to error). This is reflected in the denominator of the RC ratio, and the choice of the measure of dispersion has been the subject of much debate and refinement in the reliable change literature [15, 17, 22, 26, 27, 34]. The simplest version of the *standard error* component of the RC ratio is simply the *standard deviation* of the observed *change score* discrepancies. In our dementia case example with the WMS-III, the mean test–retest *change score* obtained from the WAIS-III/WMS-III Technical Manual is 13.4 [32]. However, like many test manuals and normative studies that report the means and standard deviations of the test and retest scores, the *standard deviation* of difference (change) scores was not reported. With permission from the test publisher, Chelune calculated the actual *standard deviation* of *change scores* for the WMS-III Immediate Memory Index from the retest sample and found it to be 10.2 [17]. With this measure of dispersion, we can calculate the RC magnitude of our patient's change score by dividing the observed practice-adjusted simple-difference score (−10.4) by the standard deviation of differences (10.2) and obtain an RC *z*-score of −1.02. A *z*-score of this magnitude would be expected to occur in only about 15% of cases when no real change has occurred. Is this sufficiently rare to classify our patient's *change score* as meaningful? Most studies of reliable change invoke a 90% RC confidence interval (*z*-score ± 1.64), in which only 5% of cases would be above or below this level of change. For our patient's change score to reach this level of decline, he would have needed a retest score between 93 and 94. It is worth emphasizing that a seemingly minor decrement in performance (e.g., 3–4 standard score points in this case), a change that many clinicians might call "within the range of the test's variability," actually reflects a reliable change when corrected for expected practice effects and measurement error.

In the absence of having the actual *standard deviation* of difference scores, it is possible to estimate it in one of several ways. Jacobsen and Truax initially introduced the Reliable Change Index (RCI) as a means for calculating RC with only knowledge of the simple-difference *change score* and the *standard error of the difference* scores (S_{diff}), a measure of dispersion derived from *SEM* for the test at baseline [35]. Chelune and colleagues later adapted the RCI by adjusting for the mean practice effect [31]. In a further refinement, Iverson suggested a modified RCI that used the *SEM* at both baseline and at retest to calculate the S_{diff} [36]. Comparison of the two versions of the S_{diff} suggests that Iverson's method produces a closer estimate of the actual dispersion of *change scores* than that of Jacobsen and Truax. In the case of our WMS-III Immediate Memory example, the Iverson method produces a S_{diff} of 9.9 compared to 8.8 for the Jacobson and Truax method, where the actual *standard deviation* of differences was 10.2. A final common estimate of the observed dispersion of *change scores* is the *standard error of prediction*, which represents the standard error of a retest score predicted from a baseline score in a regression equation where the test reliability coefficient is the standardized beta coefficient [17]. In our WMS-III example, the *standard error of prediction* for the Immediate Memory Index is 10.1, very close to the observed standard deviation of actual change scores, namely, 10.2.

Standardized regression-based (SRB) approach. As noted in our discussion of the simple versus predicted methods of calculating the *change score* discrepancy in the RC ratio, the predicted-difference method generates predicted retest scores (Y') for individuals based on their specific baseline performances (X) using linear regression and then subtracts this from their observed retest scores (Y) to obtain their personal *change score* discrepancy ($Y - Y'$). Additional sources of potential bias (e.g., age, education, gender) can be added to the regression equation in a multivariate manner [33]. As noted earlier, this approach allows practice effects to be modeled as a function of individual baseline performance as well as accounting for regression to the mean. This might be particularly important as these two variables interact (e.g., the practice effects may be attenuated by regression to the mean for someone with a high baseline score, whereas practice effects are enhanced by regression to the mean for an individual with a low initial baseline score). However, unlike the simple-difference approach where the standard error term in the denominator of the RC ratio reflects the dispersion of change scores around the mean of the *change scores*, the predicted-difference approach typically uses the *standard error of the estimate* (*SEE*) for the regression equation in the denominator of the RC ratio to reflect the dispersion of scores around the regression line. In our case example with the WMS-III Immediate Memory Index [17], the regression equation for predicting retest scores was given as:

$$Y' = (\text{Baseline score} * 1.00) + (\text{Age} * -0.097) + 18.45, \text{with an } SEE \text{ of } 10.24$$

The first part of this equation gives us an individual's predicted retest score that can be used to calculate the *change-score* discrepancy component of the RC ratio, whereas the *SEE* gives us the standard error term for the denominator. The reader will note that the *SEE* for the regression line is the same as the observed *standard deviation* of the simple-difference *change scores*.

While several authors have noted that the various RC methods produce relatively similar results [22, 30], the SRB RC-approach has generally become the preferred method for individual prediction, provided that the clinician has access to prediction equations derived from reference samples appropriate to their patients. While there is a growing body of such SRB equations for a variety of tests commonly used with older adults [8, 9, 16, 20, 37, 38], and some tests such as the fourth edition of the Wechsler Adult Intelligence and Memory Scales have incorporated RC algorithms into their scoring software [10], there is still a paucity of published longitudinal SRB data. Fortunately, as will be seen in the next section, John Crawford and Paul Garthwaite have developed a simple but powerful tool for building

regression equations from summary data that can be applied to the individual case [39].

Regression models of reliable change derived from summary data As noted by Crawford and Garthwaite [39], not all neuropsychologists are aware that it is possible to construct regression equations for predicting an individual's retest performance from their baseline performance simply using sample summary data, for which there is a potential wealth of clinically useful information available in test manuals and the published literature. To build univariate regression equations from summary data alone, one only needs the means and standard deviations for test and retest scores, the size of the sample, and the test–retest reliability coefficient (or alternately the *t*-value from a pair-samples *t* test). In their 2007 paper, Crawford and Garthwaite delineate the statistical steps necessary to build such regression equations, as well as the further steps needed to compute the associated statistics for drawing inferences concerning the individual case. Recognizing that the computations involved are tedious and prone to error, Crawford and Garthwaite also developed a compiled calculator that is available for download at no cost from the following web address: http://www.abdn.ac.uk/~psy086/dept/regbuild.htm

To use this calculator, one only need input the sample summary data and the patient-specific test–retest scores. Using the summary data from Chelune [17], Table 5.1 illustrates the output generated for our hypothetical 68-year-old patient whose baseline Immediate Memory Index was 97 at baseline and 100 on retest. The output is remarkably similar to that presented in previous sections for our patient example using various RC methods. Generally, the various approaches would predict our patient to have a retest score of 109–110 given his baseline score of 97. His observed retest score of 100 is 9–10 points below expectations (RC *z*-score deviation of about −1.0), which would likely occur in only about 15% of a sample for which there were no significant intervening events affecting cognition.

Although the Crawford and Garthwaite's regression calculator presented here is univariate [39], it has recently been expanded to handle multiple predictors, and this executable calculator is also available for download online at

Table 5.1 Output from Crawford and Garthwaite's [39] calculator to build regression equations from sample summary data for a hypothetical patient with test–retest scores of 97 and 100 on the Wechsler Memory Scale-III Immediate Memory Index

Inputs
Mean for predictor variable (*X*) in sample used to build the equation = 100.2
Standard deviation for predictor variable (*X*) in sample = 15.9
Mean for the criterion variable (*Y*) in sample = 113.7
Standard deviation for the criterion variable (*Y*) in sample = 19.2
Correlation between predictor and criterion variable = 0.85
Sample size = 297
Individual's score on the predictor (*X*) variable = 97
Individual's obtained score on *Y* = 100
Outputs
Regression equation built from the summary data: *Y* = 10.8532 + (1.0264 * *X*)
Standard error of estimate for regression equation = 10.1314
Analysis of the individual case
Individual's predicted score from regression equation = 110.4155
Discrepancy (obtained minus predicted) between individual's obtained and predicted scores = −10.4155
Standardized discrepancy between individual's obtained and predicted scores = −1.0262
Significance test (*t*) on the standardized discrepancy between individual's obtained and predicted scores: One-tailed probability = 0.1528
Estimated percentage of population obtaining a discrepancy more extreme than individual = 15.280799%

http://www.abdn.ac.uk/~psy086/dept/RegBuild_MR.htm [40].

Advanced concepts and models of reliable change The various RC methods we have described so far only consider measuring change as a discrete event across two points in time. However, there are many clinical situations where individuals are assessed serially across multiple time points, and change may be better described in terms of *trajectories of change* and intraindividual *rates of cognitive decline*. Early attempts to assess reliable change across multiple time points either averaged reliability coefficients and measures of dispersion between the various time points to arrive at composite indices of RC [41] or computed separate RC indices between each pair of time points [38]. Recently, more innovative approaches have been employed to model *change* as a trajectory or slope across multiple time points.

It is beyond the scope of this chapter to do more than alert the reader to some of these innovative approaches and to provide exemplars. Some investigators are using regression models that attempt to predict an individual's performance at time point$_{2+n}$ by entering into regression formula not only baseline performance but the practice effects between previous time points. For example, Duff and associates [8] developed multivariate SRB equations for several neuropsychological tests widely used with older adults that used baseline performance, demographic variables, and short-term practice effects (baseline to 1 week) in predicting retest scores 1 year later. Attix and colleagues [42] developed SRB normative neuropsychological trajectories for a variety of test measures administered five times at 6-month intervals by entering in successive performances at each time point as predictors of subsequent performance at the next time point. Other investigators have focused on developing regression models that compare an individual's slope of performance across multiple time points to that of a control sample [43, 44]. Still others are using variations of longitudinal linear mixed models to estimate age-adjusted mean slopes and confidence intervals of change to identify individuals whose performances begin to deviate from expectation [7, 45]. Growth mixture modeling has also been applied to longitudinal data sets to identify subgroups of individuals who show different cognitive trajectories over time [46–49]. Clearly, we are on the verge of seeing a new generation of RC methods to assess reliable change in patients' performances over time.

A Case Example: Application of Reliable Change Methods in Clinical Practice

The accumulation of pathophysiological changes characteristic of Alzheimer's disease (AD) is believed to develop years, if not decades, before the clinical expression of frank memory loss and general cognitive decline [50]. To maximize the efficacy of emerging disease-modifying therapies and to support continued functional independence, early detection of Alzheimer's disease (AD) and other neurodegenerative disorders is paramount [46, 51]. Descriptive clinical states such as *cognitive impairment but not dementia* (CIND) and MCI have been introduced to describe abnormal cognitive states that place individuals at increased risk for progressing to AD [52]. However, these clinical states describe individuals who are already symptomatic. One does not wake up one day with dementia or MCI. Rather, cognitive decline, like neurodegenerative disease, is a dynamic process that evolves over time. Hence, serial neuropsychological evaluations have come to play an important role in documenting cognitive decline in geriatric settings.

Let us consider a case example of a 63-year-old, right-handed man with a Ph.D. Our patient is a successful professor of sociology at a major university and a married father of three children. His past medical history is significant for depression and some cardiac issues, both currently well controlled. He has been stable on his medications for many years, and they are not thought be an issue with respect to cognition. Our patient has noticed insidious and progressive memory difficulties for about 2 years and presents to our cognitive disorders

clinic for evaluation. His neurologist obtains a Mini-Mental State Exam score of 30/30 but on further bedside testing notes some subtle memory difficulties. The neurologist decides to refer the patient to us for comprehensive neuropsychological evaluation. We perform our evaluation and find that the patient has a relatively circumscribed pattern of memory deficit within the context of otherwise normal findings (see baseline scores in Table 5.2). Our impression is that this patient has amnesic MCI. We know from the research literature that patients with MCI have an increased risk of showing further decline and developing a frank dementia. However, we also know that some of these individuals revert back to "normal" when seen in follow-up [53, 54]. We share these observations with our referring neurologist and recommend that the patient be referred for a follow-up evaluation in 1 year to assess whether there has been any evidence of significant interval change in his neurocognitive status. Seeing the wisdom in our recommendations, the neurologist agrees and orders repeat testing in a year.

The patient returns 12 months later, and we repeat his evaluation. As we can see from the test–retest data summarized in Table 5.2, some of our patient's scores have gotten worse and some have gotten better. To understand which of these changes are reliable and meaningful given the different psychometric properties of the tests in our battery and to place them on a common metric, we turned to RC methods. For our purposes here, we computed reliable change information using the predicted-difference method. Using the test–retest data presented in the manuals for the tests or from longitudinal research studies with samples of healthy older adults, we entered the sample summary data into Crawford and Garthwaite's regression calculator [39] along with our patient's baseline and retest scores. In the right-hand columns of Table 5.2, we present the patient's predicted retest scores given his baseline performances, the observed–predicted discrepancy ($Y - Y'$), and the associated z-scores and population percentiles associated with the predicted-difference discrepancies. From these data, we can see that the patient's memory has continued to significantly deteriorate. We also note that his global mental status on the Mattis Dementia Rating Scale [55] and on the WAIS-III verbal comprehension index [32] shows signs of notable deterioration. At this point, we can confidently say that the patient's current test results reflect some further deterioration in his capacity to learn and remember new information as well as some increased difficulties with verbal intellectual abilities. While he is still likely to meet the criteria for MCI rather than dementia, his increased difficulties with verbal skills are worrisome for a neurodegenerative disorder such as Alzheimer's disease.

Future Directions: Change as a Neurocognitive Biomarker

As noted earlier, practice effects are defined as improvements in test scores due to repeated exposure to the testing materials. Traditionally, practice effects have been viewed as error variance that need to be controlled, managed, or otherwise accounted for in our interpretation of change. However, practice effects, like cognitive change in general, seem to be a unique variable that can potentially provide clinically useful information about diagnosis, prognosis, presence of brain pathology, and treatment recommendations for our patients [59]. Over the past several years, we have been prospectively examining practice effects as a neurocognitive biomarker in the development of dementia in older adults.

In an initial study examining practice effects in community-dwelling seniors with MCI, we observed two subgroups: those that benefited from practice across 1 week and those that did not [60]. Those that showed significant gains after repeat testing could no longer be classified as MCI, as they now appeared intact. These MCI participants might reflect "accidental" MCI [53, 54]. Conversely, the MCI participants that did not benefit from practice retained their original diagnostic classification, and these participants more likely demonstrate the construct of MCI. In this way, short-term practice effects provide diagnostic information that was not available with baseline

Table 5.2 Clinical case example of test–retest scores and reliable change (RC) information based on data in bold using Crawford and Garthwaite's [39] approach to derive RC regression equation from sample summary data

	Baseline scores			Follow-up scores			Reliable change (RC) information			
Test	Raw	Standard score	*T*-score	Raw	Standard score	*T*-score	Predicted retest score	Discrepancy ($Y - Y'$)	RC *z*-score	Population percentile
Global mental status										
Mini-mental state exam[a]	**29**			**28**			28.57	−0.58	−0.33	37
Mattis Dementia Rating Scale: Total[b]	**140**	11		**133**	8		135.5	−6.36	−1.48	7
Wechsler tests										
Test of premorbid functioning[c]		**125**			**118**		124.25	−6.25	−1.13	13
WAIS-III Adult Intelligence Scale[d]										
General ability index	82	126	58	77	119	43				
Verbal comprehension	46	**131**	61	40	**118**	49	130.43	−12.43	−3.07	<1
Perceptual organization	36	**111**	47	37	**114**	50	115.11	−1.11	−0.19	43
Processing speed	19	**96**	41	20	**99**	43	100.14	−1.14	−0.17	43
Memory measures										
WMS-III memory[e]										
Logical memory-immediate	30	**8**	35	20	**4**	21	9.88	−5.88	−3.14	<1
Logical memory-delayed	14	**8**	37	4	**3**	18	10.61	−7.61	−3.87	<1
Digit span[d]	20	**13**	53	21	**13**	53	13.26	−0.26	−0.20	42
Hopkins Verbal Learning Test[f]										
Total trials 1–3	**22**		37	**17**		28	23.36	−6.36	−1.35	9
Delay	**0**		<20	**0**		<20	2.61	−2.61	−0.95	17
Brief Visuospatial Memory Test[f]										
Trials 1–3	**12**		31	**2**		<20	13.46	−11.46	−2.21	<1
Delay	**0**		<20	**0**		<20	2.25	−2.25	−1.01	16
Language										
Boston Naming Test[g]	**58**	13		**58**	13		57.72	0.28	0.12	55
Controlled Oral Word Association[f]	**46**	13		**49**	13		45.32	3.68	0.41	66
Visuospatial functions										
Judgment of line orientation[h]	**30**	16		**28**	14		23.48	4.52	0.83	79
KBNA complex figure and clock drawing total[i]	54	**12**		55	**14**		10.98	3.02	1.21	88
Executive functions										
Trail-making A time[f]	**38**	8		**33**	10		39.39	−6.93	0.44	67
Trail-making B time[f]	**63**	11		**97**	8		70.89	26.12	−0.51	30
KBNA practical problem and conceptual shifting total[i]	29	**13**		29	**13**		11.53	1.47	0.58	70

Notes: Sources of normative data used in developing RC prediction equations
[a]Tombaugh [38]
[b]Pedraza et al. [55]
[c]Holdnack and Drozdick [10]
[d]The Psychological Corporation [32]; Table 3.8
[e]The Psychological Corporation [32]; Table 3.11
[f]Duff et al. [8]
[g]Duff et al. [56]
[h]Duff et al. [57]
[i]Darby et al. [58]

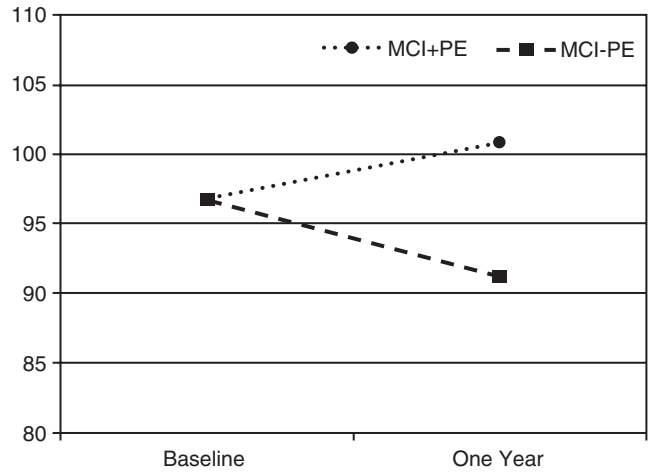

Fig. 5.1 Cognitive change across 1 year in patients with differential practice effects. Note MCI+PE=individuals with mild cognitive impairment who showed large practice effects across 1 week; MCI−PE=individuals with mild cognitive impairment who showed minimal practice effects across 1 week; *y*-axis=age-corrected standard score ($M=100$, SD=15) on total scale score of the Repeatable Battery for the Assessment of Neuropsychological Status

data. Others also have found practice effects to be diagnostically useful in MCI [61].

Prognostically, the presence of practice effects suggests a better outcome, whereas the absence of practice effects suggests a poorer outcome. In two independent samples of individuals with MCI, we have observed that practice effects predict future cognition, above and beyond baseline cognition [8, 62]. As seen in Fig. 5.1, when we followed our two MCI subgroups across 1 year, those that benefitted from practice across 1 week tended to remain cognitively stable across 1 year, and those that did not show the expected practice effects across 1 week tended to decline across 1 year [63].

In a sample of 25 older adults without dementia (some intact, some with MCI), we observed that practice effects across 1 week were negatively associated with amyloid deposition using F-18 flutemetamol positron-emission tomography (PET) imaging [64]. As seen in Fig. 5.2, smaller than expected practice effects (i.e., lower values on the *x*-axis) were seen in subjects with greater amyloid deposition (i.e., greater values on the *y*-axis). In this same cohort, we also noted that smaller practice effects across 1 week were associated with brain metabolism on fluorodeoxyglucose (FDG) PET imaging, such that smaller practice effects were associated with brain hypometabolism [65].

Lastly, we have examined the utility of practice effects in predicting treatment response. In a small sample of community-dwelling and cognitively intact older adults, within-session practice effects predicted response to a memory training course: those that showed practice effects displayed larger gains related to the cognitive intervention than those that did not show robust practice effects [66]. Although these findings need to be replicated, practice effects appear to contribute to a clinician's decision about diagnosis, prognosis, brain pathology, and treatment response, especially in older adults with memory difficulties.

Conclusion

The assessment of cognitive change lies at the very heart of clinical neuropsychology. Understanding change and how we assess it with our various test measures is complex and challenging, yet given an appropriate conceptual framework and some simple statistical tools, it is something that neuropsychologists can do uniquely well. Test–retest practice effects

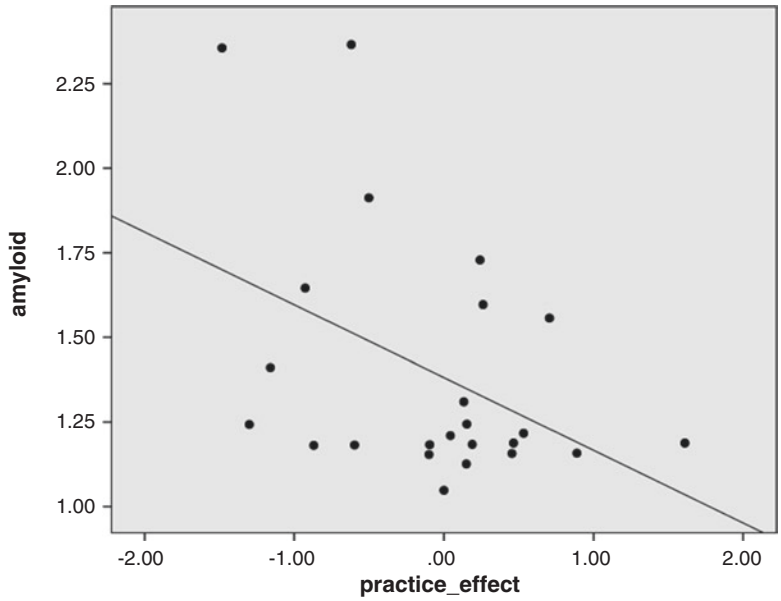

Fig. 5.2 Practice effect across 1 week is associated with amyloid deposition in non-demented older adults. On the *x*-axis, lower values reflect smaller than expected practice effects. On the *y*-axis, greater values reflect more amyloid deposits

are not simply statistical artifacts and something to be suppressed but rather something to be understood. Especially among older adults, the capacity to learn and benefit from exposures to new experiences to potentially guide future behavior has adaptive value and may be a biological marker of neural integrity that has diagnostic significance.

Clinical Pearls

- Patients deserve empirically based clinical decisions and recommendations.
- Test–retest change scores are unique variables with their own statistical and clinical properties that are different from the test measures from which they were derived.
- Where large positive practice effects are expected, the absence of change may actually reflect a decrement in performance.
- When planning to perform serial assessments and faced with two tests purported to assess the same cognitive construct, choose the one with the better reliability.
- Use of alternate forms in serial assessment may attenuate, but not eliminate, practice effects and do not address other factors that affect the interpretation of change scores, namely, bias and error.
- Test–retest reliabilities of 0.70 or greater are often considered to be the minimum acceptable standard for psychological tests in outcome studies, and practitioners should be wary when interpreting cognitive change scores on tests that have lower reliabilities.
- The basic form for any reliable change method is a ratio: reliable change (RC) = (*change score*)/(*standard error*), *where the standard error describes the dispersion of change scores that would be expected if no actual change had occurred*.
- The various reliable change methods reported in the literature primarily vary along two dimensions: (a) whether the *change score* in the numerator is a simple-difference or a predicted-difference score and (b) whether the *standard error* in the denominator represents a measure of dispersion (observed or estimated)

around the mean of difference scores or around a regression line.

- Not all neuropsychologists are aware that it is possible to construct regression equations for predicting an individual's retest performance from his/her baseline performance by simply using sample summary data, for which there is a potential wealth of clinically useful information available in test manuals and the published literature.
- For computing regression equations using sample summary data for individual cases, see Crawford and Garthwaite's univariate online calculator, and enter your patient-specific test–retest scores: http://www.abdn.ac.uk/~psy086/dept/regbuild.htm. For multivariate data, see the website at http://www.abdn.ac.uk/~psy086/dept/RegBuild_MR.htm.
- Although traditionally viewed as a source of bias, practice effects may provide valuable information about a patient's diagnosis, prognosis, brain pathology, and treatment response, especially for older adults with memory difficulties.

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6 Performance Validity Testing in an Older Adult Population: Considerations for Clinical Practice

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To make valid inferences regarding the meaning of test scores, neuropsychologists must verify that the patient exerted credible performance during the evaluation. Performance validity tests (PVTs) are routinely employed to determine whether test data reflect genuine cognitive ability or response bias (i.e., malingering or noncredible performance) [28, 35]. Historically, most research concerning the application of PVTs has been conducted on populations with clear external incentives, such as individuals with mild traumatic brain injury involved in civil lawsuits [23]. However, neuropsychologists commonly administer PVTs in clinical practice, so their use is not restricted to forensic contexts [8, 21]. For example, PVTs have been studied for use in pain, psychiatric conditions, intellectually disabled, and pediatric populations [11], in addition to older adults. This chapter will focus on concepts and research relating to PVT use with older adults and illustrate these issues with two contrasting case vignettes.

Diagnostic validity refers to how well classification decisions can be made and is largely concerned with two essential characteristics. Accuracy of a test is usually described as *sensitivity*, which is the ability of a test to correctly identify whether an individual actually manifests a criterion of interest. In the context of PVTs, sensitivity refers to the ability of the test to detect invalid or poor performance and is related to the percentage of "true positives" identified by a given test. Its counterpart, *specificity*, refers to the ability of a test to correctly classify the proportion of individuals who do *not* meet the criterion of interest (in this case, invalid or noncredible performance on formal testing) and is related to the proportion of identified "true negatives." Whereas sensitivity is important, it has been argued that PVTs should prioritize specificity [18]. In a clinical setting, false positive errors on PVTs have potentially serious or dangerous implications, as examinees may be erroneously identified as malingering, thereby jeopardizing their access to treatment or resources. To lower the risk of erroneously identifying an examinee as exerting noncredible performance, most investigators assert that PVTs should have a false positive rate of no higher than 10% (i.e., a specificity rate of 90%) [4].

A combination of so-called "stand-alone" and "embedded" measures of performance validity allows neuropsychologists to sample the examinee's pattern of responding throughout the course of an evaluation and affords multiple data sources to facilitate conclusions regarding the quality of test responses. Stand-alone PVTs are those that have been designed to provide an indicator of an

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examinee's response validity on cognitive tasks. Some of the most commonly utilized [28] standalone PVTs include the Test of Memory Malingering (TOMM; [42]), the Word Memory Test (WMT; [13]), the Medical Symptom Validity Test (MSVT; [14]), the Dot Counting Test [6], and the Rey 15-Item Test [31]. Embedded PVTs are derived from pre-existing measures (e.g., Reliable Digit Span; [17]) or combinations of measures [44] and have been empirically demonstrated to differentiate between valid and invalid performances.

Heilbronner et al. [21] concluded that with increasing numbers of failures on PVTs, a clinician can more confidently determine whether an examinee had noncredible performance during testing. Further, recent research has supported the use of at least two measures of performance validity in a clinical battery [24], yet there is no clinical standard for number of PVTs in an evaluation. There is some controversy as to whether or not the number of PVTs administered is positively correlated with false positive error rates [1, 3, 25]. Thus, neuropsychologists must be aware of the strengths and potential limitations of PVT data and must appropriately synthesize these and other sources of information in order to arrive at sound clinical judgment regarding whether a cognitive profile should be considered valid.

The possibility of unacceptably high false positive rates may be exacerbated in some populations. For example, among the elderly, especially those with dementia, poor performance on PVTs may reflect severe cognitive impairment rather than noncredible responding [11]. Thus, there is a risk of erroneously misclassifying performance of elderly patients as invalid, potentially leading to an incorrect diagnosis or no diagnosis. The repercussions of neuropsychologists making such a false positive error are potentially grave, as examinee's falsely classified may fail to receive therapeutic interventions (e.g., pharmacological intervention and cognitive rehabilitation) or neuroimaging (e.g., fMRI or FDG-PET) that might assist in the differential diagnosis and treatment of cognitive disorders. Incorrectly classified older adults may also fail to receive much needed accommodations, such as assistance with activities of daily living. Furthermore, elderly individuals erroneously identified as malingering may be presumed competent for medical, financial, or legal decisions, ultimately increasing their risk of exploitation by others. Preventing such false positive errors from occurring, or at least mitigating them as much as possible, is therefore a crucial consideration when evaluating older adults, especially those with possible dementia.

Application of validity testing in a population with significant cognitive impairment is complicated and challenges the presumption that PVTs are insensitive to genuine cognitive dysfunction. Consequently, use of PVTs in such a population assumes that elevated scores occur only in response to noncredible performance. If this is not the case, to maintain specificity (a low false positive rate), sensitivity may have to be sacrificed to the point where the test is not useful. These challenges are heightened by the practice of routinely administering PVTs, given the risks of invalid performance and contemporary practice guidelines in neuropsychology [8, 21].

The next section will provide brief comments and observations in the context of neuropsychological evaluation of older adults for some of the more well-established PVTs, as well as examples of some relatively novel embedded PVTs.

Extant Literature on PVT Use Relevant to Older Adult Populations

The following is by no means an exhaustive discussion of available PVTs. In order to provide a concise, salient commentary, we will highlight a selection of more commonly used PVTs in this section.

Stand-Alone Performance Validity Tests

The Test of Memory Malingering (TOMM) [43] has been shown to elicit false positive rates of 9.61% and 21.41% in individuals diagnosed

with mild cognitive impairment (MCI) and moderate to severe dementia, respectively. The authors suggest that the TOMM should be used with caution when moderate to severe dementia is among the differential diagnoses. Teichner and Wagner [41] also found that published TOMM cutoffs led to higher rates of false positive errors in classification among patients with dementia.

Boone et al. [5] investigated the sensitivity and specificity of a version of the Dot Counting Test (DCT), described in Lezak [26], in detecting noncredible performance among a group of patients with suspected effort (personal injury/disability or prison hospital) and a clinical sample. The clinical group was comprised of a variety of diagnoses including depression, schizophrenia, learning disability, traumatic brain injury, cerebrovascular accident, and dementia (i.e., probable dementia of Alzheimer's type). Individuals in the dementia group were further categorized as "mild" (MMSE score > 20) or "moderate" (MMSE score = 10 to 20). The data showed that the DCT had high specificity (≥85%) among groups, except for individuals with moderate dementia. In patients with moderate dementia, the DCT yielded poor specificity rates across all variables. This study suggests that the DCT is useful as a measure of performance validity among individuals with mild cognitive impairment (MCI) or mild dementia but is less appropriate for use among those with suspected moderate to severe dementia.

Similarly, Dean et al. [9] showed that a DCT error cutoff score of <17 had unacceptably poor specificity (50%) in a population of older adults with dementia. The authors also demonstrated poor sensitivity rates for two variables from the Rey 15-Item Test (Rey-15): free recall had a sensitivity of 26% and recognition sensitivity of 14% when the authors adjusted cutoff scores on this PVT when specificity was set to 90% or better specificity. To achieve adequate specificity, sensitivity rates became unacceptably low in dementia patients.

Rudman et al. [33] found similar results with other PVTs in a sample of older adults with various subtypes of dementia. In this sample, more severe levels of cognitive dysfunction (as measured by a brief cognitive screening tool) were associated with significantly lower scores on the DCT, Medical Symptom Validity Test (MSVT), Nonverbal Medical Symptom Validity Test (NV-MSVT), TOMM, and Rey-15. The authors of this study observed that individuals classified as having mild dementia demonstrated better scores on these PVTs compared to those with moderate/severe dementia. With the exception of the DCT, none of the PVTs examined, including TOMM, Rey 15-Item Test, MSVT, or NV-MSVT, showed adequate levels of specificity in the overall dementia sample.

Recognizing that cognitive impairment may compromise performance on traditional validity tests, several PVTs including the Word Memory Test, Medical Symptom Validity Test, and Nonverbal MSVT (NV-MSVT; [15]) include methods to increase specificity in genuinely impaired cognitive individuals. Specifically, the genuine memory impairment profile (GMIP; [13]) utilizes a so-called dementia profile that incorporates the difference in scores between initial "easy" trials and subsequent "hard" trials. Singhal et al. [37] compared the specificity of the MSVT and NV-MSVT when using the GMIP between patients with dementia and a healthy comparison group asked to simulate memory impairment. Both measures had 100% specificity in sparing true dementia patients from being flagged as having provided noncredible performance. However, individual sensitivity rates for the MSVT in this study were fairly weak, as four out of ten coached simulators were identified as meeting criteria of the dementia profile. Rienstra et al. [32] explored the ability of the dementia profile of the WMT to predict decline in performance on neuropsychological testing. Participants who obtained a positive dementia profile were more likely to show lower scores on cognitive testing compared to healthy controls and at baseline and 2-year follow-up. The authors concluded that the dementia profile of the WMT is capable of correctly predicting whether patients would go on to show true declines on neuropsychological test performances. Several other studies have demonstrated high specificity using

"dementia" profiles from the WMT, MSVT, WMT, and NV-MSVT [16, 22].

Embedded Performance Validity Tests

Reliable Digit Span (RDS; [17]), an indicator originally derived from the Digit Span subtest of the WAIS-III, has been extensively researched as an embedded PVT [40, 45]. In an exploration of multiple stand-alone and embedded measures of performance validity in patients with dementia, Dean et al. [9] reported that a cutoff of ≤6 on RDS was associated with an unacceptably low 70% specificity rate, and this pattern was exacerbated by severity of impairment. In particular, RDS specificity decreased in direct relationship to lower MMSE scores. Only when the RDS cutoff score was set at ≤4 was acceptable specificity (95%) achieved, which in turn resulted in unacceptably low sensitivity.

Loring et al. [27] found similar results, in that average RDS score was significantly lower for patients with early Alzheimer's dementia compared to patients with mild cognitive impairment (MCI), amnestic type. In this study, significant group differences were found between early Alzheimer's dementia and MCI groups at RDS cutoffs of ≤7 and ≤6. These authors also noted that, for individuals diagnosed with early Alzheimer's dementia, RDS cutoff scores of ≤7 and ≤6 were associated with false positive rates of 34% and 13%, respectively. Only when a cutoff score of RDS ≤5 was implemented did false positive error rates drop to 3%. Schroeder et al. [34], in their extensive review on RDS research, caution that an RDS cutoff of ≤6 is generally associated with inadequate specificity for patients with dementia.

Two relatively newer embedded PVTs derived from subtest scores within the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; [30]) include the effort index (EI; [36]) and the effort scale (ES; [29]). The EI is composed of weighted scores from the Digit Span and List Recognition subtests, which when combined produce an effort index score ranging from 0 to a possible 12 points total, with a published cutoff of >3 suggestive of noncredible performance. Novitski and colleagues reported that the EI yielded high false positive classification errors in adults with dementia. Consequently, these authors developed the ES to mitigate poor specificity in a "true amnestic" population. The ES is calculated using raw scores from the List Recognition, List Recall, Story Recall, Figure Span, and Digit Span subtests of the RBANS. The developers of the ES suggest that a cutoff score of <12 reflects invalid performance.

Dunham et al. [12] examined both EI and ES in a sample of individuals previously diagnosed with genuine memory impairment. These authors contended that ES showed higher specificity (81%) compared to EI (41%). When classified by severity of overall cognitive impairment, EI demonstrated much higher specificity for individuals classified as average or mildly impaired (RBANS total score ≥70), whereas ES showed higher specificity at more severe levels of impairment (RBANS total score <54). The authors concluded that these embedded PVTs may have clinical utility, depending on the overall level of suspected cognitive impairment for a particular patient.

These results were replicated by Burton et al. [7], who demonstrated that the EI tended to misclassify individuals with dementia as having provided noncredible performance, regardless of etiology (i.e., Alzheimer's vs. non-Alzheimer's dementia). For the subgroup of participants classified under Alzheimer's dementia, the ES false positive error rate was 4% using the standard cutoff of <12 and 0% with a modified cutoff of <7. However, the authors cautioned that ES did not fare as well in the non-Alzheimer's dementia group and demonstrated unacceptably high levels of false positive errors for these individuals. In keeping with the theoretical underpinnings of the ES, this measure has proven to work well in a population of older adults with amnestic memory impairment. The EI may also be helpful in cases where very mild cognitive dysfunction is suspected but not for more severely cognitively impaired patients.

Table 6.1 A selection of commonly utilized performance validity tests and considerations for their use in an older adult population

Test name	Traditional cut scores	Specificity/false positive issues with MCI/dementia	Special considerations
Test of Memory Malingering (TOMM)	Five or more errors on trial 2 or retention	90% specificity in MCI/mild dementia[a] 78% specificity in moderate to severe dementia[b]	Adults with moderate to severe dementia are more likely to score below cutoff and result in false positive finding
Word Memory Test (WMT)	<82.5% on IR, DR, or CNS	Use of GMIP is recommended to reduce false positive identification of PVT failure	"Profile analysis" affords much higher rate of specificity and minimization of false positive risk
Medical Symptom Validity Test (MSVT) And Nonverbal Medical Symptom Inventory (NV-MSVT)	≤85 on IR, DR, or CNS	100% specificity when using the GMIP in dementia patients, but low sensitivity	As with WMT, profile analysis affords high accuracy in identifying true cognitive impairment (i.e., dementia)
Dot Counting Test (DCT)	≥17 combination score (mean ungrouped time + mean grouped time)	>85% specificity in all groups except for moderate dementia[a] 50% specificity in moderate dementia[b]	Adequate specificity for mild dementia; inadequate specificity in adults with moderate to severe dementia
Rey 15-Item Test	Free-recall trial Recognition trial	Sensitivity = 26% when specificity = 90%[b] Sensitivity = 14% when specificity = 90%[b]	When cutoffs adjusted for dementia patients, sensitivity is too low
Reliable Digit Span (RDS)	≤7 ≤6	70% specificity[b] 95% specificity[a]	Widely used cutoff scores yield inadequate specificity rates for patients with dementia
RBANS effort index (EI)	>3	41% specificity[b]	Tends to misclassify individuals with dementia, regardless of etiology
RBANS effort scale (ES)	<12 <7	95% specificity in amnestic disorders[a] 100% specificity in amnestic disorders[a]	More appropriate for amnestic memory impairment; false positive rates high in patients with non-amnestic dementia subtypes

PVT performance validity test; *GMIP* genuine memory impairment profile; *IR* immediate recall; *DR* delayed recall; *CNS* consistency; *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status
Note: [a]Adequate specificity or sensitivity
[b]inadequate specificity or sensitivity

Table 6.1 provides a summary of the critical information provided in this section, particularly about the specificity of the selected PVTs in dementia populations. The table also provides some special considerations for clinicians when considering PVTs in individuals with significant cognitive impairment.

In summary, many PVTs have demonstrated good clinical utility (i.e., acceptable sensitivity and specificity) in older adults with suspected mild cognitive deficits. Nonetheless, the validity of standalone and embedded PVTs is much more limited among older adults with severe cognitive impairment. This conclusion notwithstanding the generalizability of these empirical findings to clinical care environments is complicated by an uncertain base rate of noncredible effort among elderly demented patients. In the existing literature, investigations included older adults with known impairment. Yet, the utility of PVTs in elderly examinees with an undetermined presence of dementia has not been studied to the best of our knowledge. Consider a scenario in which an older adult with self-reported cognitive decline

demonstrates significant impairment on neuropsychological testing and also fails one or more PVTs. According to the literature, the odds of this individual manifesting a false positive error on validity testing are high. Consequently, the neuropsychologist is obligated to use caution in exercising clinical judgment to determine whether poor PVT performance suggests genuine neurocognitive impairment, noncredible performance, or some combination of both.

As is the case for every interpretation of neuropsychological data that involves validity testing, no diagnosis or conclusion should be based on the results of one measure alone or even a group of measures. Careful consideration should be brought to bear when selecting appropriate tests, particularly with regard to a population of older adults. Other sources of data, including behavioral observations, self-report of functional impairments, and collateral reporting are critical components of the neuropsychological evaluation, and we discuss their role in the assessment process in the subsequent section. The next section and the vignettes later in the chapter describe factors to consider in making diagnostic determinations in these cases.

Beyond Formal Testing: Additional Sources of Data

In the event that a clinician suspects their patient has provided noncredible performances on neuropsychological tests, examining other data points will be necessary in order to determine whether the patient's test performance is consistent with the signs and symptoms of a cognitive disorder. Such data comes from review of available medical records, directly observed behaviors, patient self-report, and collateral report. Part of the clinician's job is to detect what, if any, discrepancies exist among the many possible combinations of these data. For example, does the patient report specific symptoms that are highly incongruent with their health history? Do they report profound impairments with anterograde memory, despite providing an organized, linear, and specific account of events occurring during the past 6 months? It is worth pointing out that the mere presence of a discrepancy is not itself indicative of invalid reporting. Consider the individual with anosognosia who may deny any problems or concerns with cognition, a report that may prove largely inconsonant with low performance on neuropsychological testing.

One final note that needs to be emphasized is that a diagnosis of "malingering" must *NOT* be made dismissively or carelessly. Malingering is a clinical diagnosis that is reached after careful consideration of multiple factors, of which *PVT* failure is but one. Many factors besides malingering may lead patients to produce poor performance on *PVT*s. Further, it is important to recognize that patients may have genuine cognitive impairments *and* exaggerate performance deficits on formal testing procedures. One empirically supported approach to this issue is a critical analysis of discrepant findings or "compelling inconsistencies" in psychometric, behavioral, and collateral data, first proposed by Bianchini et al. [2] and central to findings of Slick et al. [38] and Slick and Sherman [39] regarding discerning credible from noncredible performance.

These considerations notwithstanding the "Slick criteria" for malingered neurocognitive dysfunction are widely used, and clinicians would do well to keep these criteria in mind as they attempt to understand the degrees of complexity inherent in these types of evaluations. These guidelines codify the importance of evaluating for discrepancies between clinical interview, collateral interview, behavioral observations, formal neuropsychological testing, and medical record review. Rather than exhaust all the possible ways in which contradictory information might present itself, we instead present two real-world clinical cases that illustrate the thesis of this chapter.

Case Examples

Case #1

The first case involves an 82-year-old widowed woman with 16 years of education who was referred by her primary care provider due to memory complaints and concerns of possible

dementia. The patient was a retired elementary school teacher who had lived alone in her house since her husband's death 3 years prior to the evaluation. She retired from teaching at age 65 and worked as a part-time volunteer (12 h/week) at a local hospital. She stated that her supervisors liked her quite well and had no concerns about her ability to perform this role.

Medical history was significant for bilateral cataracts which were surgically removed 2 years prior, right-sided hip replacement surgery 4 years previously, and breast cancer that was treated surgically 12 years ago without recurrence or complication. There was no history of traumatic brain injury, neurological disorders, heart disease, diabetes, hypertension, hypothyroidism, hyperlipidemia, liver disease, or kidney disease. An MRI scan of the brain revealed "isolated periventricular white matter changes" but was deemed normal for her age.

The patient was accompanied by her oldest daughter to the appointment. The patient expressed considerable concern about her declining episodic memory and provided several examples, which were confirmed by her daughter. For example, the patient reported that she would forget peoples' names, misplaced items, and forget why she walked into a room. The patient was able to provide some specific information about these incidents (e.g., "just last Tuesday I misplaced my keys and it took me 20 minutes to find them."). The daughter expressed concern with the patient's forgetfulness and her ability to live alone. The daughter broached the idea of her mother moving in with her and her family. The patient said that she has driven and has not gotten lost or had and moving violations or traffic accidents or other incidents. The patient also said that she manages her own finances but will ask her daughter for help with major financial decisions. The patient and her daughter both agreed she is able to accurately keep track of her money and balance her checkbook.

On examination, the patient was well oriented to personal information, place, circumstances, and time. There were no indications of hallucinations or delusions, and her thought processes were logical and goal directed. There was no evidence of tangential or circumstantial speech. Her speech was appropriate in rate, tone, and volume. Her affect was generally appropriate and her mood was euthymic. She asked several questions to clarify directions, but generally did not require repetition or reminders of test instructions.

The formal neuropsychological testing was conducted by a practicum student who also participated in the interview and easily established rapport with the patient. Estimates of her premorbid functioning based on single-word reading was in the high average range, and this was consistent with her educational and occupational history. On the California Verbal Learning Test, 2nd Edition (CVLT-II; [10]), she demonstrated very severely impaired performance, including several unrelated intrusions (e.g., "candy bar" and "opera"). Delayed recall was impaired, and she only had two correct and ten false positives on recognition testing. Similarly, poor recall and recognition were observed on the Logical Memory subtest from the Wechsler Memory Scale-IV, indicating poor acquisition and retention of new memories. On the Rey-Osterrieth complex figure, the patient recalled almost no information after a 3-min delay despite displaying normal ability to copy the figure (35 out of 36 raw score points).

At this point, the student expressed concerns to the neuropsychologist about the patient's memory and possible dementia. Admittedly the neuropsychologist was surprised as well. The initial clinical hypotheses included a psychological etiology or mild cognitive impairment, based on the reported complaints and imaging. The student added the TOMM and the CVLT-II forced choice to the standard dementia battery. Reliable Digit Span was also calculated. The TOMM raw scores were well below published cutoffs on Trial 2 and Retention. On the CVLT-II forced choice, the patient obtained a raw score of 7 out of 16. In terms of embedded measures, Reliable Digit Span (RDS) was 5.

The graduate student expressed considerable surprise that this patient failed several PVTs and said she could not believe that "this sweet little lady could be malingering."

This case illustrates several salient points. First, it was explained to the student that PVT

failures are not synonymous with malingering, because malingering is a clinical diagnosis that requires examination of multiple data points in different domains and insufficient evidence supported this diagnosis. Further, there was no evidence for an external incentive such as a lawsuit. In fact, in many of these cases, the patient wants to perform as well as possible due to threats to their independence and autonomy (e.g., not able to live alone, losing driving privileges, having a guardian). Additionally, the student's surprise that this particular patient could fail PVTs points to the need to not rely entirely on our clinical intuition and the interview, because clinical judgment alone is insufficient in predicting noncredible performance [19, 20]. In fact, it was pointed out to the student that there were a number of inconsistencies between the patient's self-report and the testing data. Specifically, while the patient complained of numerous instances of memory problems, she was able to provide very specific details about these incidents, an observation that is typically not expected in an individual diagnosed with a dementia.

During the feedback session with the patient and her daughter, the issue of the PVT failure was brought up. The daughter in particular was upset and stated that the neuropsychologist was implying that the patient was malingering. After discussing the inconsistencies in the data and the observations, the patient eventually acknowledged that while she had some small concerns about losing objects, she generally felt that her memory was adequate compared to her peers. However, the patient elaborated that she had been feeling increasingly lonely and isolated because her daughter started a new job that left little time for the daughter to visit the mother, which they had done frequently in the first few years following the husband's death. The patient then said that after she mentioned her minor concerns about memory, the daughter began to spend more time with the patient and expressed more concern about the patient's well-being. In essence, the patient was using memory issues as a vehicle to connect emotionally with her daughter and receive more attention from the daughter. In strictly technical terms, this could be considered a diagnosis of a factitious disorder, but a clinical decision was made that no useful clinical purpose would be accomplished by including this diagnosis and the neuropsychologist simply related the facts of the case in the report and included no diagnosis. The patient and her daughter were referred to family counseling to assist them in their relationship.

This case illustrates a scenario in which the use of PVTs, in combination with other sources of data and observations, was very helpful in understanding the patient's presentation. Without data from multiple PVTs, this patient may have been diagnosed with a cognitive disorder and referred for neurological consultation and treatment, which would have incurred a considerable expense to the healthcare system. However, there was evidence of inconsistencies even during the interview between the patient's extensive reported memory concerns and her ability to accurately report many details. When the PVTs were included in the battery, there was evidence that the patient exerted noncredible performance. Additionally, without a clear external financial incentive, it was also very unlikely that a malingering diagnosis was appropriate. In many cases, it is not possible to determine the patient's specific motivation, and the neuropsychologist is left with simply saying that the data was not interpretable due to "non-cognitive factors."

Although this case illustrates how PVT true positive results can be helpful in understanding a case and not misdiagnosing an older adult, neuropsychologists also need to keep in mind that false positive results on PVT in moderate to severe dementia occur and should not be overinterpreted. The key is to evaluate the entire individual and assess for consistency of results between tests and other types of data (observations, self-report, observer reports, records).

Case #2

Similar to the first case, the second case is an 82 year-old woman with 10 years of education who previously worked as a homemaker. She was referred from her primary care physician

due to her family's concern about memory problems and her ability to live independently. The records noted that she wanted to remain living independently and "felt fine." Her history was significant for chronic obstructive pulmonary disease (COPD), hysterectomy, appendectomy, and breast cancer (treated surgically 5 years earlier without complication or recurrence). She had no history of traumatic brain injury or other neurological illness. Despite COPD, the patient continued to smoke two packs of cigarettes per day, but she denied significant alcohol consumption or use of drugs. Although she was prescribed an inhaler, family reported she inconsistently used it.

This patient was accompanied to the interview with her son who had observed increasing memory difficulties that reportedly began 1 year earlier. Forgetfulness seemed to have worsened over time, particularly recently. For example, the son noted she forgot that he had visited within 30 min of the visit. The son noted that the patient's long-term memory was intact, however.

The patient denied any problems with her memory or attention and stated that she did not see the need to attend this appointment. Rather, she was "humoring" her children. The patient reported that she worked with a psychotherapist in the 1980s for depression and again following her husband's death 15 years previously, but she denied any current or recent mood problems. She has four children who are supportive and see her frequently. She completed the 10th grade and characterized herself as an "average" student in school. She reported that she continues to cook and clean her house, but the son noted that the patient has left burn marks on furniture; she had apparently neglected to tend to burning cigarettes.

Behavioral observations from the psychometrist indicated that the patient frequently asked for testing directions to be repeated, particularly if they were lengthy. There were no indications of hallucinations, delusions, or unusual thought processes. The patient was generally oriented to personal information, place, and time. She reported a euthymic mood, and her affect was appropriate.

Performance on immediate verbal memory measures was considered to be at the lower end of expected limits (e.g., approximately 0.5 to 1.0 standard deviations below the mean), although delayed recall measures were impaired (over 2.0 standard deviations below the mean). On all verbal delayed measures (free and cued delayed recall of the CVLT-II and Logical Memory II from the WMS-IV), she could not recall any details. Recognition memory was likewise impaired, with forced choice recognition from the CVLT-II being 12/16. Delayed recall and recognition on the Rey-Osterrieth complex figure test were also impaired with almost no recall or recognition of the figure, despite displaying normal ability to copy the figure (33 out of 36 points). On the TOMM, her performance was below the published cutoff on Trial 2 and Retention Trial. Reliable Digit Span was 6. There was also evidence for deficits in attention, executive functioning, expressive language, and processing speed, but visual spatial abilities were intact.

In this case, after referral to neurology and neuroimaging, Alzheimer's disease was established as the most likely etiology of her cognitive deficits. Interestingly, a follow-up evaluation 1 year later indicated that her TOMM performance improved to the lower end of expected limits, but her performance on all memory measures was in the severely impaired range with global deficits in encoding and storing information.

While these two cases share similarities in demographics (82-year-old women who live alone but have children nearby), presenting complaints (e.g., memory concerns), and performance validity test failure, the interpretation of the formal testing results is very different. The difference in interpretation is not due to performance on any specific test, but due to a careful evaluation of the history and observations. Patient #2 demonstrated anosognosia, and this patient's lack of awareness of memory deficits is frequently observed in patients with severe cognitive dysfunction. Patient #1, in contrast, was able to report significant and apparently accurate details of various incidents of forgetting. This strongly suggests that the patient's memory is

more intact than her presentation. This is a critical issue all neuropsychologists (not just those working with older adults) need to keep in mind. The understanding of an individual case comes from integration of multiple data sources including interview, collateral sources, records, observations, and formal test results. When noncredible performance occurs, it is particularly incumbent upon the neuropsychologist to carefully evaluate all data sources for consistency of findings.

In the second case, the data from the PVTs were consistent with the clinical history and observations and suggested that the impaired performance on the TOMM was related to actual neurocognitive deficits in a moderate to severe dementia case. In contrast, in the first case, the PVT failure in combination with very impaired memory test performance was inconsistent with the reported history of mild difficulties (e.g., misplaced keys) but an intact ability to relate details of these events. The level of consistency between test findings and other data sources was the key difference in interpreting the PVT failures in these two similar cases.

As the clinical pearls noted below emphasize, neuropsychologists must treat PVTs like other formal tests—they are tools that help us to understand an individual and determine what we can (and cannot) say about their cognitive functioning. However, PVTs can never be interpreted in isolation but rather as part of the greater biopsychosocial context of the individual.

Clinical Pearls

- When dementia is among the differential diagnoses, minimizing false positive errors is especially important.
- PVTs may not provide useful information in cases with more moderate to severe dementia, and false positive errors could lead to misdiagnosis.
- If a neuropsychologist feels that a PVT is necessary when evaluating an adult with suspected moderate to severe dementia, consider one that utilizes profile analysis (e.g., Word Memory Test) or one that was normed on an appropriate population (e.g., RBANS effort scale).
- PVTs should not be evaluated in isolation. Neuropsychologists should develop a coherent conceptualization based on multiple contextual factors.
- Look for inconsistency among the sources of data, including self-report, collateral report, records, and formal test data.
- External incentives may be present within an older adult population, although they may not take the form of financial compensation.
- With any patient, malingering is a clinical diagnosis that is not made on the basis of PVT failure alone. Use of empirically supported criteria, such as Slick et al.'s [38] malingered neurocognitive dysfunction, is strongly recommended if a neuropsychologist is considering a malingering diagnosis.

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Inpatient Neuropsychological Assessment in Older Adults

7

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Introduction to Inpatient Evaluations

Neuropsychologists are often called upon to assess the cognitive and behavioral status of older adults within the context of an inpatient setting. Yet, published information about inpatient neuropsychology assessment remains limited. Descriptions from the early days of neuropsychology rarely make explicit reference to the setting in which patients were evaluated [1–3]. Classic neuropsychology papers on patients with stroke, head injury, and seizure disorders typically describe patients who are months or years after a medical event or are in the chronic stages of the disorder, when many were no longer in an inpatient setting. Some prominent neuropsychology textbooks include the caution that "formal assessment" should not be performed until several months after a neurological event, so as to avoid confounds from fatigue and recovery [4, 5]. However, inpatient acute rehabilitation programs routinely include neuropsychologists as part of the assessment team, where patients are evaluated in the early stages after injury.

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Some authors have tackled the challenges of inpatient neuropsychological exams; Kessler describes factors that may interfere with the exam (e.g., fatigue, side effects from surgery) and provides a detailed discussion of the types of tests that may be used at the bedside [6]. Schnider gives suggestions for assessment measures with an emphasis on non-standardized tests particularly well suited to the inpatient setting [7]. Both of these chapters, however, describe fairly lengthy exams that would be challenging to administer when available time is limited. While not focused exclusively on inpatient assessment, Heilman and colleagues provide a useful overview of the various components of a neuropsychiatric exam, many of which are relevant to inpatient assessment [8].

The referral questions that generate inpatient neuropsychology consultations are varied but may include issues of differential diagnosis, need for supervision upon discharge, clarification of degree of cognitive deficit, and "baseline" assessment to be used in comparison to future exams. The cognitive impairment that prompts referral for inpatient exam may result from any medical or psychiatric condition including, but not limited to, dementia, stroke, seizure disorder, organ failure, metabolic disorder, infection, malignancies, normal pressure hydrocephalus, and psychiatric disturbance (including factitious disorders). Questions of delirium may not be raised explicitly in the referral question but should always be considered, particularly when working with elderly

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patients. Neuropsychologists are particularly adept at identifying delirium by virtue of experience in combining information from the medical history, the neuropsychological exam, and reports from various members of the medical team (via interview or record review). In particular, evidence of alterations in arousal (either hypoarousal or agitation, especially with acute onset), variability in presentation ("waxing-waning" disturbances), visual hallucinations/delusions, and inattention/confusion should alert the neuropsychologist to the possibility of delirium. Somnolent delirium may be less likely to come to attention, at least until discharge planning is actively underway, because the drowsy patients are not usually a management problem (except when being treated on an inpatient rehabilitation unit). For detailed discussions of delirium presentation and diagnosis, the interested reader is referred to the work of Inouye and colleagues [9–11]. If delirium is suspected, the source of delirium (e.g., infection, medication side effect, metabolic disarray) should be worked up by the medical team. The neuropsychologist can play a vital role in prompting the search for the source of the delirium and recommending treatments (e.g., reductions of sedating medications, improved treatment for pain, moving bed near a window, increasing mobility, minimizing excess stimulation). Repeated assessment of sleep-wake cycle, orientation/mental status, and agitation episodes can be very useful in evaluating treatment outcomes [12–14] .

Mental Status Exams at the Bedside

Mental status exams are often the foundation of inpatient cognitive assessments. These tests are designed to tap a broad range of cognitive domains within a brief time frame (e.g., 15 min). Specifically, a mental status exam is comprised of a structured observation and interview to examine orientation, attention, memory, language, reasoning, visual spatial skills, and behavior; the bedside assessment may include some or all of these components [8]. When the assessment is limited to a mental status exam, the work of a neuropsychologist blurs with that of a knowledgeable psychiatrist, clinical psychologist, or behavioral neurologist, although the neuropsychologist has the unique perspective of interpreting the performance through comparisons to normative samples. Moreover, neuropsychologists arguably have a better appreciation of the various cognitive domains, how they interact and influence each other, and how to parse this out. As with any test, there are pros and cons to mental status exams—what is gained in speed and ease will result in loss of detail and subtlety. Nevertheless, used appropriately, a mental status exam can provide important information in contexts that do not allow for more comprehensive testing, such as acute care hospital settings. See any of Lezak's texts for detailed reviews of various mental status exam measures as well as useful suggestions [4]. The various editions of textbooks by Strauss and Spreen also touch on mental status exams and a small number of brief measures [5]. Entire texts have been devoted to the topic of the mental status examination such as the well-known work of Straub and Black [15].

There are many different types of mental status exams. The Mini-Mental Status Exam (aka, MMSE or Folstein) is one of the best known and continues to be widely used [16]. Different versions of the MMSE exist, and a test publisher has claimed copyright for one of the versions. The original version has seen many modifications, formal and informal. One of the modified versions of the MMSE is known as the modified MMSE or the 3MS [17]. The 3MS adds items to the MMSE (date/place of birth, word fluency, verbal reasoning, and delayed recall of words) allowing a score to be derived for the longer version (3MS) and/or the shorter version (MMSE). Methods of evaluating change over time with the MMSE and 3MS have been reported [18, 19]. The Montreal Cognitive Assessment (MoCA) is an increasingly popular alternative to the MMSE [20] (http://www.mocatest.org/) and has been shown to detect milder impairment than the MMSE [21]. A strength of the MoCA is that it has been translated into many languages, has multiple forms for repeat testing, and has been studied in a range of medical conditions including stroke [22, 23] and dementias [24–27]. A short-form

version of the MoCA showed some utility in identifying dementia [28].

Specialized measures have been developed for the assessment of the mental status in traumatic brain injury (TBI) patients. TBI assessment is not unique to the elderly, but, as our society ages, older patients are expected to represent an increasing proportion of TBI cases, largely due to falls, with high rates of morbidity and mortality [29, 30]. The Galveston Orientation and Amnesia Test (GOAT) is a well-known measure of post-traumatic amnesia (PTA) in traumatic brain injury (TBI) [31]. The GOAT consists of questions regarding orientation to self, place, date, and events immediately preceding and following the injury. A score of 75 or more is seen as evidence of emergence from PTA, and the time span between the last memory recalled before the injury and the first memory after the injury provides information about the length of amnesia surrounding the accident. The Orientation Log and Cognitive Log represent an alternative to the GOAT with a two-step approach, one measure for detailed assessment of orientation (Orientation Log) [12] and a companion measure for more general mental status, with a focus on memory and executive function (Cognitive Log) [32, 33]. Descriptions of these and many other useful scales for bedside exams are available on the website for the Center for Outcome Measurement in Brain Injury (COMBI, http://www.tbims.org/combi/). The Orientation Log and the Cognitive Log may be used for patients with any type of disorder, unlike the GOAT, which was tailored for use with TBI patients. The GOAT, Orientation Log, and Cognitive Log are designed for daily, repeated assessment at the bedside to track changes in cognition.

If there is sufficient time and patient cooperation, a mental status exam may be supplemented by other brief, more specialized measures such as the Frontal Assessment Battery (FAB) [34], clock drawing [35], and Commands/Complex Ideational Material subtests from the Boston Diagnostic Aphasia Exam [36] or by assessment of the patient's emotional state. The Mississippi Aphasia Screening Test (MAST) was developed as a repeatable measure for patients with significant language deficits and may be used in isolation or in combination with other brief measures of cognition [37].

The brevity of mental status exams may sacrifice accuracy [38]. A large-scale review of the MMSE cautioned that it should not be used alone to confirm or exclude dementia [39]. Reviews of the MoCA highlight limitations in clinical utility for dementia diagnosis [25]. The commonly used MoCA cutoff score of 26 may be inappropriate for some demographic groups [40, 41]. The MoCA may underestimate degree of cognitive impairment in acute stroke patients [42], and neither the MoCA nor the MMSE were adequate in discriminating mild cognitive impairment from normal cognition in a study of Parkinson's patients [43]. The GOAT and Orientation Log measures are useful only for assessment of orientation, and the Cognitive Log has undergone minimal study of diagnostic accuracy. When selecting a mental status exam, the neuropsychologist is advised to consider the quality of the psychometric data and need for/availability of demographic corrections.

Brief Neuropsychological Tests

In response to some of the limitations of mental status exams, tests have been developed to provide more detailed information about cognition without demand for hours of assessment. Examples include the Dementia Rating Scale (DRS) [44], the Cognistat [45], and the increasingly popular Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [46]. These measures offer the ability to assess specific subdomains of cognition within a brief administration time. They are designed to require less than an hour to administer—a lengthy assessment by acute care standards but far briefer than the typical outpatient neuropsychology exam.

The DRS, now in its second edition, was designed for the assessment of patients with suspected or known dementia with emphasis on the memory and executive function deficits [44]. The DRS has been demonstrated to be sensitive to cognitive impairment in a variety of dementia types [47–50]. It is a well-researched instrument

with the advantage of having normative data published from the Mayo Older Americans Normative Studies (MOANS) [51] and Mayo African American Normative Studies (MOAANS) [52] projects. Scores on the DRS have been associated with functional status [53–55].

The Cognistat, also known as the Neurobehavioral Cognitive Status Examination (NCSE), provides brief tests of attention, language, visuoconstruction, memory, and reasoning skills [56] (cognistat.com). Normative data are available from the manual and published studies [57–59], and score adjustment for some demographic groups may be needed [60]. The Cognistat has been studied in TBI [61], dementia [62], ALS [63], and stroke [23, 64], and results have been associated with functional status [65–67].

The RBANS is well suited to the inpatient setting and includes tests of memory, attention, language, and visuospatial skills. A recent publication proposed a method of calculating an executive function scale [68]. Duff and colleagues have published extensive normative information [69–71]. Factor analytic studies suggest two to five factors [72–74]. Regression-based formulas are available for evaluating change [75, 76]. The RBANS has been studied in a range of patient populations including Alzheimer's dementia [77–80], stroke [81–83], brain tumor [84], and Parkinson's disease [85, 86]. RBANS performance has been found to be associated with functional impairment [87–90].

While these extended screening measures offer slightly greater detail about cognition, the intrepid neuropsychologist may want to supplement these tests with additional assessments depending on the referral question, time constraints, and the extent of cognitive impairment. For example, the RBANS does not include assessment of orientation nor executive function, per se. The DRS, for all its strengths, does not include tests of language. The Cognistat includes several cognitive subscales, but the validity of the individual subscales is questionable [91]. The degree of supplementation will depend on the time available, the patient's ability to tolerate additional testing, and specifics of the presentation or referral question.

Inpatient Neuropsychological Exams

Illustrative examples of testing batteries are provided below, with a focus on brief assessments (30–60 min). These examples do not include time required for record review, consultations with medical staff and/or family (if available), scoring, or report writing. In considering the amount of testing to perform, the examiner must balance the desire for detail and comprehensiveness with the need for rapid results in a time-constrained environment. The best neuropsychological report will be worthless if it is completed after the patient has left the hospital. Similarly, attempting to pursue a lengthy exam with a drowsy patient will result in a frustrating, futile experience for everyone involved.

If the neuropsychologist expects to have an *hour* to test a patient, the exam might include:

- Interview for basic demographic information (educational background, occupational background, marital status, home situation) (~5–10 min)
- Orientation Log (~5 min)
- RBANS (~30 min)
- Trail Making Test (Part A & B) (~5 min)
- Complex Ideational Material (~5 min)
- Clock drawing (~3 min)
- Screening interview for depression, anxiety, and adjustment issues (~5 min)

If only *45 min* are available, the exam may be limited to:

- Interview for basic demographic information (5 min)
- Orientation Log (~5 min)
- RBANS (~30 min)

If only *30 min* are available or for a patient who may require repeated assessment during the

course of the hospitalization, the following example is provided:

- Interview for basic demographic information (5 min)
- Orientation Log (~5 min)
- Cognitive Log/MMSE/MoCA/3MS (~15 min)

Special Considerations for the Inpatient Environment

Beyond decisions about which tests to administer, the inpatient exam requires consideration of the setting. Contrary to exams in an outpatient office, the inpatient exam may not be a perfectly standardized assessment in a quiet room. The inpatient exam will proceed much more smoothly if the neuropsychologist can make adaptations to the approach and expectations for the assessment. Some of the unique aspects of the inpatient setting include the fact that the patient often has no advance warning of the exam. Whereas the outpatient exam involves a prearranged agreement for cognitive assessment, the inpatient exam may come as an unwelcome surprise to the patient—this may reduce cooperation with the exam. Some patients react with resentment, anxiety, or suspicion about the motives of the examiner, e.g., "Are you here to see if I'm crazy?" For other patients, the unexpected neuropsychology exam may represent yet another invasion of privacy or demand on time and comfort. This is especially true if the examiner arrives during a mealtime or a visit with family. Alternatively, the request for a neuropsychological exam may be perceived by the patient as a challenge to their intellect and judgment. If the patient is not adequately cooperative with the assessment, the results may be uninterpretable and a waste of everyone's time. Patient cooperation may be improved by providing a brief explanation for the exam, e.g., "Your medical team wants to ensure there have been no changes in your thinking as a result of (medical diagnosis)"; "We want to ensure that you get the help you need when you leave the hospital." For those patients who remain resistant to the exam after an explanation, it may be effective to give the patient the opportunity to refuse the exam. After all, patients have the right to refuse procedures and treatments. This conversation should note what information is lost if the patient refuses the exam. For some patients, having the opportunity to refuse, if they so wish, is enough for them to agree to the exam; the chance to exercise some control over the situation will be enough for them to agree to be examined, if grudgingly. If, after several minutes of explanation and encouragement to participate, the patient continues to object to the exam, it is likely pointless to attempt any testing. Even if results are obtained, an angry and resentful patient is unlikely to provide valid responses.

Related to the issue of the patient's agreement to participate is the subject of visitors. In an outpatient setting, it is generally understood that family/friends are not present during the testing portion of the exam, so as to remove sources of distraction and interference. This holds true for the inpatient exam as well—it is recommended that visitors leave the room for the exam although family may provide useful background information during the history interview for those patients who are confused. The absence of "third-party observers" is clearly advised in a medicolegal examination, but, even in those cases, exceptions may be reasonable if the neuropsychologist believes that the presence of a family member/caregiver may calm the patient and improve the quality of the exam [92]. This may also be a reasonable solution for dealing with those patients and families who are distrustful of the methods or motives of the exam/examiner. The examiner should, however, never agree to any recording or other documentation of the exam. In the end, deciding whether to allow a visitor to remain may make the difference as to whether the patient agrees to the exam or not—the neuropsychologist must decide which considerations take priority.

Practical Recommendations

In addition to the suggestions above, the inpatient assessment may proceed more smoothly with use of the following recommendations. The neuropsychologist is advised to:

- Notify nursing staff of the plan to perform cognitive assessment. Inquiries should be made as to whether the patient is scheduled to receive medication or undergo any tests during your exam time. Advance planning may be effective in avoiding these interruptions. Notifying the nursing staff about the exam will also allow staff to redirect visitors, other consultants, etc.
- Ask nursing staff whether they have observed any signs of cognitive or behavioral disturbance. In addition to enriching the neuropsychologists' understanding of the patient, these conversations can aid in building relationships on the acute care unit and improve the chances that recommendations will be implemented.
- Inform the nursing staff and patient of the plan to close the room door to reduce noise. Placing a sign on the door that an exam is in progress will not guarantee freedom from interruptions, but lack of a sign will not help these efforts.
- Arrange a tray table in front of the patient, if possible. Permission should be requested from the patient before moving items. Items should be replaced at the session end. A quick wipe with a paper towel and hand sanitizer will reduce the chance that test forms will stick to the table surface.
- Pull the privacy curtain to separate the patient from a roommate, as needed.
- Request permission from the patient to turn off the television.
- Request permission to raise window blinds or turn on room lights.
- Request visitors leave the room (see above for remarks on visitors who request to stay). Provide an estimate of when visitors can return.
- Request a roommate turn down their television (as needed). Request a roommate with visitors to take the visit out of the room, if possible, or lower their voices during the exam.
- Know the institution policies regarding patients in isolation rooms. Discuss with the infection control staff what steps may be taken to address the particular needs of a neuropsychologist. For example, is it permissible to take stimulus sheets in plastic covers into a contact isolation room and to wipe the sheets with disinfectant prior to leaving the room? If no papers can be removed from the room, could the examiner use the room phone to leave a message on the examiner's office phone with the raw scores from the exam?

Report Writing

The report generated from an inpatient exam should contain the same type of information included in an outpatient exam—medical history (including current medications), demographic history, behavioral observations, test names, exam findings, and interpretations/recommendations [93]. The medical history need not be lengthy and exhaustive—this information is documented elsewhere—but should focus on the most relevant diagnoses and test results. Similarly, the demographic history should contain the most pertinent, basic information such as educational background, occupational background, relevant psychiatric background, and marital/family characteristics. Inclusion of the pre-hospital living situation and post-discharge housing/assistance plan may be relevant. Behavioral observations may contain information about challenges to standardized assessment and validity (e.g., noise, interruptions, patient irritability, poor arousal), evidence of possible language barrier for nonnative English speakers, adequacy of patient insight, vision/hearing problems, and any other observations that may influence the case conceptualization; in some cases, the behavioral observations contain some of the most important information. The sections for test findings must be concise. Inclusion of percentile scores may be informative for the medical team [94]. Organizing the test results by cognitive domain may not be necessary, especially for very

brief exams, and may not be meaningful to referral sources [94]. The impressions section should be brief and concrete with clear statements of test findings, relevant behavioral observations, findings regarding mood and adjustment, and diagnostic impressions. If more than one diagnosis is possible, or can be ruled out, this should be noted with supporting rationale. Caveats about any limitations of the interpretability or validity of the exam should be clear. Recommendations should be concrete and focused on what can be accomplished during the hospitalization or shortly thereafter; bulleting or numbering of recommendations will maximize clarity. Placing the impressions and recommendations sections at the top of the report may be appreciated by referral sources and increases the chance that recommendations will be reviewed. Perhaps most importantly, the report should be completed and available in the patient's chart within a day of the assessment and, when possible, on the same day. Lengthy delays in producing the findings will undermine the likelihood that the neuropsychology exam will contribute to the conceptualization or management of the patient. Consultation requests will likely cease if the neuropsychology exam is not perceived to be useful during the hospitalization. If the neuropsychologist has doubt about ability to produce findings in a timely fashion, this should be made clear, and the option of referral for outpatient exam should be offered, if feasible.

Case Examples

Case examples are provided below to illustrate different referral questions. The first case example demonstrates a request for information about why a patient is failing to learn management of a cardiac device. The patient was examined during admission to the cardiology unit of a hospital. The concerns of the occupational therapist were especially influential in the consultation request. Recommendations are focused on suggestions for maximizing the patient's ability to learn the device.

Case 1

O.C. is a 68-year-old, African-American, right-handed gentleman with a complicated cardiac history who underwent placement of a left ventricular assist device (LVAD). During the course of inpatient treatment, his inpatient occupational and physical therapists voiced concerns about poor recall across daily treatment sessions, including inability to recall steps for managing his LVAD. Neuropsychology consultation was requested to inform the treatment team about the patient's cognitive abilities and assistance needs. The patient completed a bachelor's degree and retired 3 years previously from a large city agency.

Behavioral Observations

O.C. was initially alert and cooperative, but the session was abbreviated due to complaints of fatigue after 40 min. Social skills were good. He denied deficits in vision or hearing. Speech was fluent, and he was talkative, but speech content was tangential and somewhat empty. He benefitted from follow-up questioning to clarify answers during the history interview. Attention to task appeared good despite frequent noise in the room (4-bed step-down unit). Insight into cognitive deficits appeared poor. These results are believed to reasonably reflect cognition although performance may have been reduced somewhat by fatigue and noise in the environment.

Tests Administered

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A); Orientation Log; Complex Ideational Material subtest of the Boston Diagnostic Aphasia Exam (BDAE); Trail Making Test Part A & B (TMT Part A & B).

Test Results

RBANS subtest score (compared to similar age/education norms)	Percentile	Performance range
List learning	*3–5%ile*	*Borderline impaired*

RBANS subtest score (compared to similar age/education norms)	Percentile	Performance range
Story memory	*3–5%ile*	*Borderline impaired*
Figure copy	*3–5%ile*	*Borderline impaired*
Line orientation	*3–5%ile*	*Borderline impaired*
Picture naming	41–59%ile	Average
Semantic fluency	19–28%ile	Low average-average
Digit span	*3–5%ile*	*Borderline impaired*
Coding	*1%ile*	*Extremely low*
List recall	19–28%ile	Low average-average
List recognition	*3–5%ile*	*Borderline impaired*
Story recall	*2%ile*	*Extremely low*
Figure recall	*3–5%ile*	*Borderline impaired*

Deficits were found on many tests of memory. Low scores were also found on tests of visuospatial and attention skills. Scores were within normal limits on tests of naming, verbal fluency, and free recall for a word list.

Additional findings within normal limits Simple visuomotor speed was in the low average range (TMT Part A = 51 s, 10%ile).

Additional findings below expectation O.C. showed deficits in orientation to date and event with some benefit from cuing (Orientation Log = 23/30). Comprehension of complex language was reduced (Complex Ideational Material = 8/12, <1%ile). He discontinued a complex test of visuomotor sequencing skill (TMT Part B = discontinued at 139 secs @ letter G).

Impressions and Recommendations

Scores in the impaired range were found on several tests of memory, attention, visuospatial, and language comprehension skill. Behavioral observations were notable for limited endurance for testing and tangential speech with reduced meaningful content. There was some noise in the room. O.C. showed poor insight into his cognitive deficits. These results indicate substantial cognitive impairment and are consistent with reports from occupational therapy regarding poor functional memory. O.C. is expected to require full support to manage his LVAD and other complex tasks. Improvement may occur in the coming months.

Ability to learn LVAD management will be maximized by:

1. Teaching only one step at a time. No new steps should be added until the preceding step(s) is mastered. This may slow the pace of teaching but should improve retention and accuracy.
2. Teaching periods should be frequent and brief.
3. Teaching should be provided in a quiet environment.
4. Instruction should be provided the same way across all staff.
5. Instruction should be provided in concrete, simple language.
6. Guessing should be discouraged. Cues and prompts should be used to facilitate memory.
7. Visual aids should be incorporated as appropriate (e.g., colored tape on coordinating device parts).
8. Reevaluation of cognition in 6 months is recommended to assess for recovery.

The next case example demonstrates a repeat exam for a patient with significant language disturbance. The exam was conducted on an inpatient rehabilitation unit. Because the patient was not a native English speaker and was unable to recite the alphabet in English, the Color Trails Test was substituted for Trail Making Test.

Case 2

T.E. is a 74-year-old, French neurologist with history of stroke in 2003 (residual left-sided weakness and paresthesia), HTN, HLD, AF on Coumadin, s/p AICD placement who presented

with acute onset of aphasia and right hemiplegia s/p mechanical thrombectomy with recanalization (not a tPA candidate due to Coumadin). Head CT showed evidence of the old right hemisphere stroke (right anterior temporal, right subinsular, right centrum semiovale) but no sign of new, large acute infarct. He is being treated for UTI. He was admitted for inpatient rehabilitation for treatment of deficits in strength, balance, and language. Neuropsychological exam 1 week prior found deficit in language comprehension as well as poor insight, impulsivity, hyperverbosity, and perseveration of topic. T.E. was born and raised in France and moved to the USA in 1967. He reported equal fluency in English and French. He has worked as a neurologist since 1973. He returned to work after the stroke in 2003 and is currently on medical leave. He has voiced a strong desire to return to work. He lives with his wife.

Behavioral Observations

T.E. was alert, calm, and fully cooperative. Social skills were good. Speech was fluent with a French accent. He was verbose and mildly difficult to redirect. Mild impulsivity and perseveration of speech topic was noted. Insight into his language and physical deficits was limited with minor benefit from prompting. Performance on a test of automatic speech appeared to be influenced by language barrier.

Tests Administered

Orientation Log; Mississippi Aphasia Screening Test (MAST); Complex Ideational Material subtest of the Boston Diagnostic Aphasia Exam (BDAE); Color Trails Test (CTT Part 1 & 2); mood interview.

Test Results

MAST:
Expressive index:
Naming = 8/10
Automatic speech = 2/10 (possible language barrier)
Repetition = 8/10
Writing = 8/10
Verbal fluency = 10/10
Expressive subscale total = 36/50 (6 points lost due to suspected language barrier); improved compared to prior exam (prior score = 30)
Receptive index:
Yes/no accuracy = 16/20
Object recognition = 10/10
Following instructions = 8/10
Reading instructions = 8/10
Receptive subscale total = 42/50; improved compared to prior exam (prior score = 38)

Additional assessment found continued deficit in comprehension of complex language (Complex Ideational Material = 3/12, <1%ile, score 1 week prior = 0/12). Orientation improved to the normal range (Orientation Log = 29/30, score 1 week prior = 24/30). Simple visuomotor sequencing speed improved to the low average range (CTT Part 1 = 12%ile, score 1 week prior = <1%ile). Complex visuomotor sequencing speed improved to the borderline impaired range (CTT Part 2 = 8%ile, score 1 week prior = <1%ile).

Psychiatric Interview

In an interview, T.E. endorsed sadness related to his desire to be home and returning to work. He reported some reduced sleep in the hospital due to noise. He denied disturbances in appetite, concentration, self-esteem, energy, and hope for the future. He denied suicidal ideation. He endorsed restlessness but denied significant worry or irritability/muscle tension.

Impressions and Recommendations

Brief reassessment found improvements in language and visuomotor speed/flexibility. Language skills, however, remained impaired. He denied depression and anxiety although, given his language deficits, results of the psychiatric assessment must be viewed with caution. Behavioral observations were notable for impulsivity, hyperverbosity, perseveration of topic, and very limited insight. The profile is consistent with interval recovery from recent left MCA territory stroke, possibly exacerbated by the old right MCA territory stroke. Continued recovery is expected in the coming weeks.

1. Supervision is recommended for all complex activities (e.g., treatment planning, discharge planning, finances, medications).
2. T.E. is advised to postpone return to work. Responsibilities should continue to be delegated.
3. T.E. may benefit from continued emphasis of nonverbal/procedural treatment approaches in therapy (e.g., minimization of speech, maximal use of visual and hand-over-hand demonstration, increased practice of new techniques). Verbal cues, when needed, should be brief and concrete. Social conversation is encouraged at the start and end of therapy sessions and during rest breaks in treatment.
4. Reevaluation of cognition is recommended in 3 months.

In the next example, the medical team asked for clarification of cognitive abilities and insights into patient's capacity to direct the discharge plan. The patient was examined while admitted to the neurology unit of a hospital. As an example of an alternate report style, the impressions and recommendations are provided first.

Case 3

Name: D.B.
Referral question: clarification of cognition in context of confusional episodes prompting hospitalization

Impressions and Recommendations

Deficits were found on tests of visuoconstruction/visual memory, semantic fluency, visual scanning speed, complex language comprehension, and mental sequencing skill. Relatively normal scores were found on tests of verbal memory, naming, and simple oral speed. D.B. reported sadness and worry about her daughter but denied most other symptoms of depression and anxiety. Behavioral observations were notable for grossly normal speed, good social skills and range of affect, tangentiality in responses, and difficulty maintaining mental set. She reported reduced visual skills that were not improved by glasses (although she was able to discern small font numbers). She denied any safety concerns about discharge to home.

The presentation is suggestive of a dementing condition. The profile is not strongly suggestive of Alzheimer's dementia (relatively spared verbal memory and naming) or subcortical dementia (grossly normal speed, good range of affect). The cognitive profile is more consistent with diffuse Lewy body dementia; frontotemporal dementia and vascular dementia are other possibilities. The acute clinical fluctuations and findings on MRI do not support an NPH diagnosis. In light of the patient's poor ability to recognize the functional consequences of her cognitive deficits, she does not appear to have capacity to make decisions regarding her discharge plans.

1. Supervision is recommended for all complex activities (treatment decisions, discharge planning, finances, medications, meals, appointments).
2. D.B.'s preferences regarding discharge planning should be honored as much as possible, without sacrificing safety.
3. D.B. is advised to not drive.
4. Additional medical work-up is recommended to clarify the dementia diagnosis.
5. Reevaluation of cognition in 6 months is recommended to assess for interim change.

Please see below for full report

D.B. is an 89-year-old, Caucasian, right-handed woman with history of HTN and mild cognitive impairment who was admitted after showing increased confusion during outpatient follow-up with her neurologist. History is significant for an episode 2 months prior in which she drove throughout her state and a neighboring state for hours and was found to be confused and incontinent of bowel and bladder when discovered by police. Work-up was unrevealing for infection or acute stroke. Neurology exam in the hospital is significant for decreased short-term memory, bilateral cogwheel rigidity, and retropulsion. Brain MRI found moderate cerebral parenchymal volume loss, chronic microvascular ischemic

changes with old right centrum semiovale white matter infarcts and bilateral small cerebellar infarcts, and right pontine enhancement that may represent capillary telangiectasia or cavernous malformation. She was seen by the psychiatry service who found the presentation consistent with dementia. Current differential diagnosis includes Alzheimer's disease, diffuse Lewy body disease, and normal pressure hydrocephalus.

D.B. had difficulty providing coherent, logical information about her background thus this demographic information may not be accurate. She reported completing high school and many college classes but did not achieve a college degree. She worked for a small business owned by her husband. She has one daughter, was divorced 40 years ago, and lives alone. She reported some memory deficits, "I feel that my memory is not strong" but stated that her memory impairment did not present any challenge to a safe discharge home.

Behavioral Observations

D.B. was found asleep but easily awakened and remained fully alert for the session. Affect showed range and social skills were good. Response speed was grossly normal. Speech was fluent but tangential with reduced meaningful content at times. She required cuing to clarify responses to questions. Some perseveration of topic was noted. She had difficulty maintaining mental set. She complained of poor vision that was not improved with eye glasses (although was able to accurately identify small font numbers without glasses). Insight appeared limited. These results are believed to reasonably reflect cognition.

Tests Administered

Orientation Log; Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A); Complex Ideational Material subtest of the Boston Diagnostic Aphasia Exam (BDAE); Trail Making Test Part A & B (TMT Part A & B); Oral Trail Making Test Part A & B (Oral TMT); Clock drawing; Similarities subtest of the Wechsler Adult Intelligence Scale-IV; mood interview.

Test Results

RBANS subtest score (compared to similar age/educ/gender norms)	Percentile	Performance range
List learning	19–28%ile	Low average-average
Story memory	72–81%ile	Average-high average
Figure copy	*6–10%ile*	*Borderline impaired-low average*
Line orientation	41–59%ile	Average
Picture naming	90–94%ile	Superior
Semantic fluency	*6–10%ile*	*Borderline impaired-low average*
Digit span	19–28%ile	Low average-average
Coding	*<1%ile*	*Extremely low*
List recall	11–18%ile	Low average
List recognition	11–18%ile	Low average
Story recall	29–40%ile	Average
Figure recall	*3–5%ile*	*Borderline impaired*

Impairments were found on tests of visuoconstruction/visual memory, visuomotor coding skill, and semantic fluency. Normal scores were found for tests of verbal memory (better with prose format), naming, and ability to judge line angles.

Additional findings within normal limits Verbal reasoning was in the low average range (Similarities = 16%ile). Simple oral speed was in the average range (Oral TMT Part A = 40%ile).

Additional findings below expectation D.B. was disoriented to date (year and date of month) and event (Orientation Log = 20/30). Comprehension of complex language was poor (Complex Ideational Material = <1%ile). Clock drawing was deficient (5/10, <1%ile, extra numbers, spatial errors, misplacement of hands). Visuomotor scanning speed was severely slow and Ms. B. was unable to learn the more complex

version (TMT Part A = 202 s, <1%ile; Part B = discontinued at sample). Complex oral sequencing speed was discontinued due to perseverative errors (Oral TMT Part B = discontinued at 21 s @ letter D).

Mood interview D.B. denied sadness. She reported reductions in concentration and, recently, energy. She denied disturbances in appetite, sleep, ability to experience pleasure, self-esteem, and denied suicidal ideation. She reported worry about her daughter's welfare.

Feedback

Preliminary results were provided to D.B. at the session end. She was advised to not drive and to have supervision for all complex activities. She agreed with the information.

Clinical Pearls

- Delirium should always be considered in the differential diagnosis, especially for elderly patients.
- When selecting which mental status test to use, the quality of the psychometric data and need for/availability of demographic corrections should be considered.
- The length of the exam should be adapted according to patient's ability to tolerate the assessment. Scheduling constraints may also influence the duration.
- Even a brief exam can provide useful information when performed by a knowledgeable examiner.
- The inpatient environment may not allow for the degree of control and standardization achieved in the outpatient setting and may require adaptations to approach and expectations.
- Improvements in standardized assessment in the inpatient setting can be made by closing doors, pulling curtains, turning off the television, and asking nursing staff, other patients, and visitors for their help in minimizing noise and interruptions.
- Specific policies regarding contact isolation may vary across institutions. The inpatient neuropsychologist is advised to discuss with the infection control staff what steps may be taken to address the needs of the inpatient exam.
- Unlike the outpatient setting, inpatients are often unaware (or have forgotten) that they have been referred for neuropsychological assessment. Negative reactions or resistance may be overcome by taking time to explain the rationale and procedures for the testing and allowing the patient to have some control over the situation. This may include respecting the patient's request to shorten the exam or to allow a friend/family member to remain present.
- Results should be provided within 24 h of completion of the exam and, whenever possible, on the same day.
- Reports should be brief with concrete recommendations that can be accomplished during the hospitalization or shortly thereafter.

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8 Clinical Neuropsychology Practice and the Medicare Patient

Edward A. Peck III and Lucien W. Roberts III

In 1965, President Johnson signed HR 6675 to establish Medicare for the elderly in Missouri. President Truman was the first to enroll in Medicare [1].

Fast-forward a few years, the President of the United States, in his annual message to Congress, complained about the rising cost of health-care costs, the variations in access to health care, and the variation in the quality of health care across social and income groups. He recommended a more "level playing field" approach to national health-care reform that would rely on current market forces to bring change to the US health-care system. Congress voted to deny the President what he wanted. A familiar story? The President was Richard Nixon, and the date of the annual speech to Congress was 1972. The concern was how much the then current federal programs contributed to "this growing investment in health" as a portion of national expenditures [2].

Fast-forward to the early 1980s, at that time there were relatively few nationally identified federal health-care sponsors besides CHAMPUS and Medicare or multistate private insurance carriers such as Blue Cross/Blue Shield (aka Anthem/aka WellPoint). However, the mid- to late 1980s saw the first sparks leading to the now recognized baby boomer explosion of aging in the US population. Suddenly, mental health services were confronted with the expansion of the managed care system and the resulting attempts by employers to limit the costs of medical care, while simultaneously trying to continue to offer a comprehensive insurance plan to their employees. For a much more detailed review of this period of health-care change, the reader is directed to the Managed Care Museum website [3].

Health maintenance organizations (HMOs), the predominant managed care "cost control" strategy of the 1980s, offered an all-or-nothing option: typically, only care provided by providers in a network HMOs was covered. Through much of this period and even today, mental health has been something of an afterthought for insurance payors. HMOs evolved and preferred provider organizations (PPOs) were established to counter the "all-or-nothing" nature of restrictive HMO networks. These plans still had gatekeepers to access, but they also offered patients various financial and/or easier access to specified providers. In turn, these providers had to agree to work within the limitations in practice and the fees ordained by the PPO. Eventually, more costly point of service (POS) plans were developed to offer patients an opportunity to circumvent the more negative aspects of the gatekeeper provisions to their plans. In recent years, we have seen other efforts to control health-care costs by putting more of the responsibility for care on the

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patient. Plans such as health savings accounts, flexible spending accounts, high-deductible health plans, and tiered-pricing formularies are all examples of this effort to control health-care costs by involving the patient in the responsibility for their care.

The federal and state governments have continued to attempt to control Medicare and Medicaid expenditures. None of these attempts at managing health-care costs have been particularly effective in tempering the rising costs of health care significantly. Nonetheless, we expect that there will continue to be a migration toward some form of managed care alternative to traditional Part B Medicare, combined with reduced payments, in Medicare. The clinical neuropsychologist cannot ignore Medicare HMOs and other limitations on Medicare and simply hope that they will go away. Many Medicare managed care plans generally pay close to standard Medicare but may present the patient and the provider with additional constraints (e.g., arduous preauthorization processes or fewer testing units permitted). It is incumbent upon each Medicare provider and/or professional practice group to understand the cost and hassle factor of doing business with each plan, so that they can make informed financial decisions with regard to participation in such plans.

Fast-forward to today, a hot July day in the summer of 2017, the efforts of new President Trump and the Republican Party to repeal and replace the Affordable Care Act of 2010 enacted by President Obama and the Democratic Party have failed. Trump and Republicans instead are attempting to repeal the Affordable Care Act (aka Obamacare) outright. It's a difficult time to write a chapter on the future of the business side of health care. Still, the core tenets of the business of neuropsychology remain. Without a margin, there can be no mission. We therefore review many of the tenets of a successful neuropsychology practice that we shared in the first edition of this book.

The same superlative factors remain in play: an unfettered federal deficit, an aging population, a large portion of the US population either uninsured or underinsured, health-care expenses as a percent of federal and state budgets continuing to grow (albeit at a slower rate), and no easy solutions. Both primary political parties have chosen the blame game rather than work together; this is not a political statement but a political reality. The US health-care system of today cannot be sustained, period, and the failures of the primary political parties to work together put more pressure on tomorrow's generations.

Relevance

Neuropsychology must remain relevant. We as individuals and as professionals must demonstrate that our work (1) impacts patient care, (2) improves quality, and (3) is a good business investment for health-care purchasers. We want to emphasize this point before we proceed. Psychologists and neuropsychologists are excluded from the first 2 years of the Merit-Based Incentive Payment System (MIPS), the quality/cost program promulgated in 2017 to replace Meaningful Use (MU), and the Physician Quality Reporting System (PQRS) [4]. Exclusion is a bad thing: if we are not at the table, we are on the menu. Funding decisions will be made in our collective absence, increasing the likelihood that neuropsychology will be further marginalized. Therefore, as you review the following primer on understanding your cost drivers, focus too on the value of what we do in bending the cost curve for Medicare and other payors.

Purpose of the Current Chapter

This chapter is designed to provide practical information concerning the business aspects of providing clinical neuropsychological care to Medicare patients under current (and projected) access and funding parameters. The specific focus is on Medicare reimbursement as it relates to practice management issues in clinical neuropsychology.

Medicare is not going away. It comprised about 15% of the population of our nation in 2011 and 17% in 2015. Medicare enrollment

grew nearly 19% between 2000 and 2010, from 39.6 million enrollees to 47.1 million enrollees; it surpassed 55 million in 2015. The first baby boomers (those born between 1946 and 1964) became Medicare eligible on January 1, 2011, and will contribute to an expected *doubling* of Medicare enrollment by 2030. The existing health-care infrastructure and Medicare reserves are not prepared. As a side note, Medicaid enrollment grew nearly 60% between 2000 and 2010, further stressing federal and state funding [5, 6].

There will be increasing pressure on providers to do more with less and to cope with increasing constraints on utilization and reimbursement. In response, it is incumbent upon every neuropsychological practice to understand its internal revenue and cost drivers and to be as efficient—with time and resources—as practically possible.

Good business is good business, and many of the matters we discuss in this chapter are applicable to your entire clinical practice and not just to your Medicare patient services. At the end of the work day, the difference between the dollars which your practice collects and what your practice pays out in expenses is critical. A practice cannot thrive—much less survive—if it focuses on revenues while ignoring expenses or vice versa. The successful neuropsychology practice must keep an eye on both revenues and expenses.

In this chapter, we emphasize a proactive response to the management of your professional practice, whether it is in a private or institutional setting. We believe that by being proactive in your business planning and management, you can avoid many patient- and insurance-related problems. This is far more reasonable than trying to resolve a situation which has already gotten out of control.

This chapter is comprised of three sections:

1. Understanding Your Cost of Practice and Living Within Your Means
2. Addressing Common Medicare Scenarios: Examples and Forms
3. Medicare and Neuropsychology: A Look Forward to the Abyss or to Eden? What Will Our Business Management Practices Look Like in the Future?

The first section offers insight into the business management of your practice. We urge our readers to use this section as a building block upon which to improve the financial operation of their practices.

Understanding Your Cost of Practice and Living Within Your Means

Let us start with a basic point for the private practitioner or institutional practitioner. For the private practitioner, the point is how much your practice brings in per month is not as important as how much you actually spend per month to pay all the bills. You need to know the extent of your financial overhead in order to meet your responsibilities. For the institutional provider, the point is to understand and appreciate what your administrator is setting as your minimum RVU or cost recovery value per time unit for a specific time period (quarterly, yearly, and so forth). You need to know to understand what you (or the institution) have to spend to keep your practice open.

Our goal is to help you calculate what it actually costs your practice to operate. Knowing this cost is essential to managing your expenses and improving your operating margins. The first thing you should do is to have your accountant or office manager develop a financial spreadsheet which lists all of the expense categories paid during each month and each year. Table 8.1 is an example of a practice income statement; it lists many of the cost categories which should be included in such a spreadsheet [7].

The sum of your expenses is your total cost of practice. To make a profit, you must recoup more than this amount. Once you have calculated the total expense for your office, you can calculate "what if" scenarios relating to profit and loss. It is also helpful to look at a 3-year period when possible to trend/forecast changes. You should plan to calculate cost escalations for each of these line items, e.g., salaries and fringe benefits, as part of projecting expenses for the coming 3 years.

Once you have an annual total cost of operation, you can calculate your average total cost per

Table 8.1 A sample financial report

		Sample financial report	
Revenues	Current month October	Current year to date 10 months	Prior year to date 10 months
Fees received	46484.87	350875.00	320897.50
Other income	2490.00	30115.00	18737.00
Interest earned	30.39	429.00	190.00
Total revenue	49005.26	381419.00	339824.50
Cost of practice			
Accounting	300.00	3000.00	2800.00
Advertising	50.00	500.00	425.00
Bank charges	17.81	581.79	500.00
Co. car loan	350.00	3500.00	0.00
Co. car expenses	65.00	650.00	639.00
Charity contributions	100.00	225.00	200.00
Continuing education	120.00	250.00	250.00
Dues and subscriptions	400.00	2805.00	3000.00
Employee benefits	660.00	6660.00	5000.00
Equipment—capital	0.00	2000.00	1000.00
Equipment—other	125.00	300.00	500.00
Insurance—malpractice	100.00	900.00	900.00
Insurance—Co. car	90.00	900.00	860.00
Insurance—other	140.00	1140.00	1000.00
Interest—loans	43.49	825.74	0.00
Legal fees	125.00	350.00	675.00
Licenses	100.00	450.00	450.00
Maintenance—equipment	475.00	2900.00	2500.00
Miscellaneous	50.00	2400.00	700.00
Office expense	239.00	3100.00	3000.00
Postage	135.00	1650.00	250.00
Refunds	50.50	1117.00	1750.00
Registrations—meeting	180.00	450.00	400.00
Rent—office	2000.00	20000.00	17000.00
Repairs	0.00	1000.00	800.00
Supplies—office	54.00	1334.75	1000.00
Supplies—test	125.25	375.00	350.00
Taxes—payroll	4800.00	48000.00	39000.00
Taxes—other	0.00	375.00	375.00
Telephone	210.24	2848.90	2500.00
Telephone ans. service	90.00	900.00	800.00
Travel	616.00	3300.00	1000.00
Meals and entertainment	75.00	590.00	200.00
Wages	8711.52	77810.64	74508.97
Total expenses	20597.81	193188.82	164332.97
Net income/loss	28407.45	188230.18	175491.53

Co. is company, *ans*. is answering

hour of practice. For example, an office which is open 8 h a day, 5 days a week, has 2080 operating hours per year, less holidays, vacations, bad weather closings, and the like. Dividing your annual total cost by your total operating hours will calculate your practice's average cost per hour of operation. Simply stated, if your practice is not bringing in at least this much per hour of operation (e.g., per week or per month), it is losing money.

It is possible to take a more detailed look at how much it costs you to provide an hour of testing or an hour of therapy. For example, you can set up a spreadsheet which incorporates cost items such as (1) technician salary and fringe benefits, (2) cost of test equipment, (3) cost of room space rent, (4) cost of front office (scheduling to billing), and (5) your salary and benefits. However, this is secondary to getting a solid handle on your overall average cost per hour of operation. Once you have a good feel for such data, you can dig deeper and look at individual financial facets of your practice.

This juncture is a good time to review your expenses at a "line item" basis. Be critical. We urge you to focus on expenses because a dollar saved is a dollar earned, whereas a dollar charged often results in receipts of less than half that.

Some axioms for consideration: A mere 30 min of overtime a day for a technician earning $20 an hour will cost your practice $3900 per year ($20/h times 0.50 h/day times 5 days/week times 52 weeks/year times, at time-and-a-half). Add in matching tax obligations of 7.65%, and your cost exceeds $4000 per year.

If you have a 5-year lease for 2500 square feet at $20 per square foot, a 4% escalation clause will cost you $5359 more than a 3% escalation clause over the term of the lease ($20/square foot times 2500 square feet is $50,000 in rent in year 1; in year 5, you will be paying $58,493 with a 4% escalation clause or $56,275 with a 3% escalation clause).

By avoiding the overtime and higher rent escalation in these two examples, you would save more than $26,000 over 5 years. Savings equals income.

Review annual service agreements for copiers, faxes, credit card processing, and postage meters. Ask your vendors for better deals if you will renew for 24 months instead of 12 months. Talk with other medical practices to ensure that your staff wages and annual increases are not too far above or below the average range for your geographic area. Ask the practices next door and across the hall if they would like to bid out janitorial or some other service together to get a better price.

The checklist provided as Table 8.2 offers a road map for managing your practice better.

Clearly, Table 8.2 goes into more detail than we can discuss in the space of this chapter. However, we felt its inclusion would provide readers a good checklist of areas where the cost of your practice operations might be improved. In this regard, while it is possible for your practice to take a more detailed look at how much it costs you to provide an hour of testing or an hour of therapy is only part of getting a solid handle on your total average cost per hour of business operation.

Having gotten a grasp on your expenses, you should develop a spreadsheet that lists the actual reimbursement amount paid by each insurance carrier, for each service you provide. Table 8.3 presents such a spreadsheet, and it lists (for the purposes of this chapter) sample allowed payment rates for CPT codes 96118 and 90806 (and its successor code, 90834) for Medicare Region 3 and for several other (unidentified) plans. For the record, the other insurance plans are not named due to confidentiality requirements. Many insurance plans have subplans or carve-outs to their plan, which may pay at different rates. This includes Medicare HMO and PPO plans. The spreadsheet that you develop should have the information organized so that each insurance plan can be viewed and compared for the CPT codes actually used in your office. Such a spreadsheet will serve several purposes, including allowing you to evaluate which insurance plans pay a better fee for a particular CPT code unit of service. Table 8.4 provides a comparison of CPT allowed payments from different insurer sources.

The following instances warrant consideration of contract termination or negotiation with the insurance company:

- If a payor pays relatively less than others or less than what it costs your practice to provide a service. As noted in the chart above, there is tremendous variation among payors even at the CPT code level.
- If you and your office staff consistently spend so much time getting testing units or evaluations preapproved, or after providing the ser-

Table 8.2 Practice operations checklist

	2014	2015	2016	2017	2018
Budgets					
Operating budget used to track performance?					
Operating budget includes prior year (PY) comparison?					
Capital budget established?					
Expenses compared to PY, budget, benchmarks?					
Retirement plans					
Service agreements (basis points) renegotiated?					
Expenses allocated to participants vs. borne by practice?					
Former employees removed if costing practice $$?					
Contributions balanced with operating cash?					
Timing/cost of plan valuations reviewed?					
Housekeeping					
Cost per square foot compared to other practices?					
Bid out or renegotiated alone or with other practices?					
Right sized frequency of service for satellite/nonclinical areas?					
Backed out square footage for space that will not be cleaned (e.g., samples closet, electrical/server closet, extra rooms)?					
Shredding					
Quarterly check of bins for nonpatient content?					
Bid out or renegotiated?					
Eliminated junk faxes?					
Checked for duplicate office notes, etc., and rooted out causes?					
Overtime/wage management					
Given wage increases only when warranted?					
Compared wages/benefits to those of other practices?					
Tracked overtime hours as a percent of worked hours?					
Reviewed schedules for smart scheduling?					
Tracked provider start time vs. scheduled start time?					
Avoided scheduling of “same sex” at end of day?					
Avoided scheduling of procedures at end of day?					
Ensured staff has exam rooms ready at start of day?					
Kept unwarranted overtime at a minimum?					
Employee retention					
Trended turnover rate vs. PY? By office/dept?					
Maintained undesired turnover at <5%?					
Engaged employees per the Gallup Q 12 Survey?					
Employees know what is expected of them?					
Employees have what they need to do their jobs?					
Employees have a chance to do their best everyday?					
Employees recognized/thanked every week?					
Employee development encouraged?					
Employee input requested and used?					
Equipment purchases and leases					
Obtained multiple bids?					
Bid out with other practices if buying common/same items?					
Asked finalists for better pricing/terms?					
Shopped for best interest rates?					
Negotiated caps or free years on equipment maintenance?					
For operating leases, defined “fair market value” before signing?					

(continued)

Table 8.2 (continued)

	2014	2015	2016	2017	2018
Locked in pricing on future purchases before signing?					
Looked for leases/loans with no personal guarantees?					
Negotiated supplies purchasing with future caps?					
Evaluated refinancing of existing leases?					
Credit card processing					
Obtained multiple bids? Compared all costs/rates?					
Considered Internet-based processing services?					
Considered dual purpose "swipe" readers?					
Copiers/printers/scanners/faxes					
Inventoried existing units/leases/maintenance agreements?					
Determined cost per copy of existing units?					
Bid out with other practices?					
Asked for free consolidation audits/bids from vendors?					
Reviewed ways to reduce unnecessary/duplicate copies?					
Eliminated high-cost and duplicative units?					
Reviewed processes for document retention (scan vs. print)?					
Copiers/printers/scanners/faxes					
Compared current pricing discounted plans?					
Compared current pricing to other professional organization vendors?					
Solicited others in local community or same specialty to join in group purchasing?					
When purchasing the following, look at volume buying with others					
Copiers/faxes					
Housekeeping					
Shredding					
Supplies/equipment					
Payroll/accounting					
Legal advice					
*Contract review					
Electronic medical records and practice management systems					
Employee benefits/insurance options					
Office supplies					
Kitchen/coffee service and supplies					
If you buy it, bid it…					
Revisit provider schedules					
Provider Time Off policies reviewed for impact on schedule?					
Provider Time Off policies reviewed for carryover limits?					
Provider Time Off truly and fairly tracked?					
Reviewed schedules to make sure schedulers are optimizing?					
Looked for possible scheduling inequities?					
Determine relative value unit (RVU)/hour worked for each doctor/office?					
Provider compensation agreements					
Reviewed compensation relative to collections and overhead?					
Incentives and formulas understood by providers?					
Buy-in from providers on incentives and formulas?					
At least 50% of compensation to production incentives?					
Communications					
Evaluated elimination of pagers via cell phone use?					
Considered foregoing insurance on units if pagers are retained?					
Reviewed monthly answering service invoices?					

(continued)

Table 8.2 (continued)

	2014	2015	2016	2017	2018
Negotiated better rates and eliminated extraneous charges?					
Considered group bidding?					
Reviewed existing cell phone agreements?					
Considered foregoing maintenance insurance?					
Bid out agreement?					
Evaluated "family" vs. "corporate" plans?					
Looked at size of bucket of minutes vs. usage?					
Looked at cost of data messaging options?					
Completion of patient forms					
Asked patients to fill in nonclinical parts before appt.?					
Had providers/support staff fill out remainder during appt.?					
Reviewed charge(s) for form completion?					
Increased charge for time-consuming forms?					
Ensured form collection fees are collected up front?					
Patient registration forms					
Posted online or e-mailing to reduce copying/postage expenses?					
If making copies, farmed out to minimize cost per copy?					
The rent					
Negotiated cap on common area maintenance increases?					
Negotiated annual rent increase limits?					
Obtained guaranteed construction timeline in writing?					
Analyzed financing options and rates?					
Locked in renewal terms, including $$$ for refurbishment?					
Included "no-trade" provisions in lease to protect against involuntary relocation?					
Asked landlord to pay for all construction, architectural, and space planning drawings?					
Refinanced existing loans?					
Insurance benefits					
Medical malpractice					
Right sized limits to state caps?					
Bid out to ensure rates are competitive?					
Secured "tail" coverage for retiring docs at no cost?					
Ensured provider employment agreements are clear on tail coverage?					
Health/dental/disability/Section 125					
Bid out to ensure rates are competitive?					
Ensured all alternatives considered have the key providers in network that your staff, your docs, and their families use?					
Considered alternatives along a continuum of co-pays, deductibles, and drug plans?					
Offered multiple options (PPO, HMO, HAS)?					
Set practice's contribution to employee premiums as a fixed dollar amount rather than a percentage?					
Evaluated a Section 125 plan for employee premiums?					
Asked for group billing discounts for individual long-term disability (LTD) policies?					
Looked to American Psychological Association (APA) and others for discounts?					
Updated asset schedules for tax and business insurance calculations?					
Deleted unused assets?					
Used good descriptions/serial numbers for new assets?					
Most costs are fixed, so…					
Evaluated adding one patient/provider/day or/half-day?					

(continued)

Table 8.2 (continued)

	2014	2015	2016	2017	2018
Evaluated scheduling for efficient filling of schedules?					
Evaluated scheduling for potential creation of overtime?					
Ensured electronic remittance is in place and working?					
Looked to limit your nonrevenue-producing task producers?					
Credentialing?					
Mail review (and other distractions)?					
Patient/family phone calls?					
Exam room turnover?					
Ensured exam/testing rooms are stocked and ready?					
Shared "best kept" secrets with referrers to help them?					
Evaluated/reduced avoidable "no shows"?					
Looked at space utilization/efficiency/alternative uses?					
Subleasing?					
Shared satellite offices?					
Optimized coding and documentation?					
Most costs are fixed, so…					
Bell curve analyses vs. national norms and PY?					
Audited coding and documentation for problems/opportunities?					
Reviewed denial rates and trends by payor?					
Payor contracts					
Calculated operating expense and total expense per RVU?					
Compared payments for top 15–20 high dollar and high-volume codes by payor to operating and total expense for same?					
Eliminated or renegotiated money-losing and marginal agreements?					
Actively managed "% of Medicare" contracts to ensure proper payment?					
Established base Medicare year for contracts to protect against cuts?					
Asked for annual fee schedule increases?					
Asked for relevant fee schedules (not sample fee schedule)?					
Completed a strengths, weaknesses/limitations, opportunities, and threats (SWOT) analysis to assess negotiating strategy?					
Asked your providers and staff to complete payor report cards?					
Asked for carve-outs for certain services or codes?					
Loaded updated fee schedules in practice management system?					
Audited payments on signed contracts?					
If giving notice, considered 45 + 45 strategy?					
Co-pays, deductibles					
Ensured patients know what they owe before visit?					
Offered multiple payment options?					
Tracked collection of co-pays, deducts by site, by employee?					
Reminded staff what it costs to collect a co-pay after the fact?					
Ensured eligibility and deductible status are being checked previsit?					
Reminded providers that downcoding for friends only helps the payor?					
No shows					
Tracked "no show" excuses for patterns, noncompliance?					
Established "no show" fees not to anger but to deter?					
Empowered your front office to make decisions on excuse validity?					
After the fact collections					
Using lockbox services?					
Wasting $$ by sending pre-explanation of benefit (EOB) patient statements?					

(continued)

Table 8.2 (continued)

	2014	2015	2016	2017	2018
Considering collections placement after two statements?					
After the fact collections					
Looked at service charges for second/third statements?					
Looked at service charges for statements for co-pays?					
Accounts payable					
Verifying all nonrecurring invoices?					
Reviewed renewing contracts for onerous "evergreen" clauses?					
Tracking and managing inventory?					
Considered online bill pay?					
Used a "rewards" credit card for paying bills where possible?					

Table 8.3 Comparison of Medicare allowed payments for CPT codes 96118 and 90806 (90834)

Year	CPT code	
	96118	90806/90834
2007	$111.79	$87.71 (90806)
2011	$95.74	$87.97 (90806)
2017	$97.92	$84.91 (90834)

vice, having to file and refile the claim for payment, that the cost of doing business with that company is not worth the payment received. Remember, this is an overhead expense. It may not be worth it to spend that time refiling the claim. It may be better that you terminate that contract.

- If the patients of a particular payor are more likely to miss appointments without sufficient notice (e.g., the "no show" or "late cancelation"), therefore leaving your schedule with holes where you are paying staff but not getting offsetting revenues.

While fee negotiation with Medicare is not possible, it is possible to negotiate with Medicare managed plans offered by regional and national payors. This is particularly true when they need your specialty services due to local service supply shortages. It is better to walk away from an agreement that costs you more to provide the service than to provide the service for that plan.

There are many good automated appointment reminder systems on the market. Such systems use e-mail and text messaging in addition to standard phone messages. Because reminders can be sent at any time and repeated (e.g., an e-mail reminder 4 days out and a text message the evening before an appointment), many practices have found them to be both effective and cost-effective.

This is also a time to review your commercial payor contracts and ensure you are being paid what you are due. Surprise, surprise, some payors have been known to pay less than what they have told you they will pay you! Medicare claims are generally paid accurately in terms of the number of units allowed and billed. However, you must stay current with what are the published approved/allowed payment rates. We advocate meeting or having periodic calls with your key payors, even if you are being paid correctly. These "touches" give you an opportunity to help payors understand what neuropsychology is and to discuss the value of neuropsychology in bending the cost curve. Again, it helps us remain relevant.

If your current approved/allowed fee schedules have not been loaded into your practice management software system, make this a priority. This should be carried out for each insurance company and plan you bill. Updated and current fee schedules in your practice management system are the *best way* of tracking whether your practice is being paid the correct amount per unit of each plan contract. Make sure your billing staff is cognizant of what you should be paid when they are posting payments. We cannot overemphasize this point. Your billing staff should know how much is paid per unit and when there is a deviation from the expected payment amount. They need to know that you want to know when problems in reimbursement arise.

Other spreadsheets can be prepared which calculate various ratios of actual payment versus the average length of time it takes to receive payment

Table 8.4 Comparison of CPT allowed payments from different insurer sources

		Ins 1	Ins 2	Ins 3	Ins 4	Ins 5	Ins 6	Ins 7	Ins 8	Ins 9	Ins 10
		HMO	PPO	Medicaid	Commercial	Commercial	Medicare	Medicare	Medicaid	Commercial	Medicare
				Commercial			Region 3	Commercial 1			Commercial 2
90791	DI Int	120.00	120.00	107.63	85.00	75.00	131.23	135.00	87.84	99.62	97.75
90834	Therapy	90.00	90.00	67.49	65.00	75.00	84.91	82.00	83.55	83.55	79.68
96101	Psy test	90.00.37	90.00	58.65	75.00	72.00	78.32	78.32	74.98	91.05	88.75
96102	PT	93.00	93.00	37.48	75.00	72.00	61.87	61.87	74.98	91.05	88.75
96118	Np test	98.00	98.00	71.14	75.00	127.85	78.32		123.96	123.96	121.80
96119	NT	81.37	81.45	47.94	75.00	62.88	61.87		61.13	61.13	122.98
96120	NT	81.37	81.45	51.52	75.00	62.88	61.87		0.00	46.13	88.75

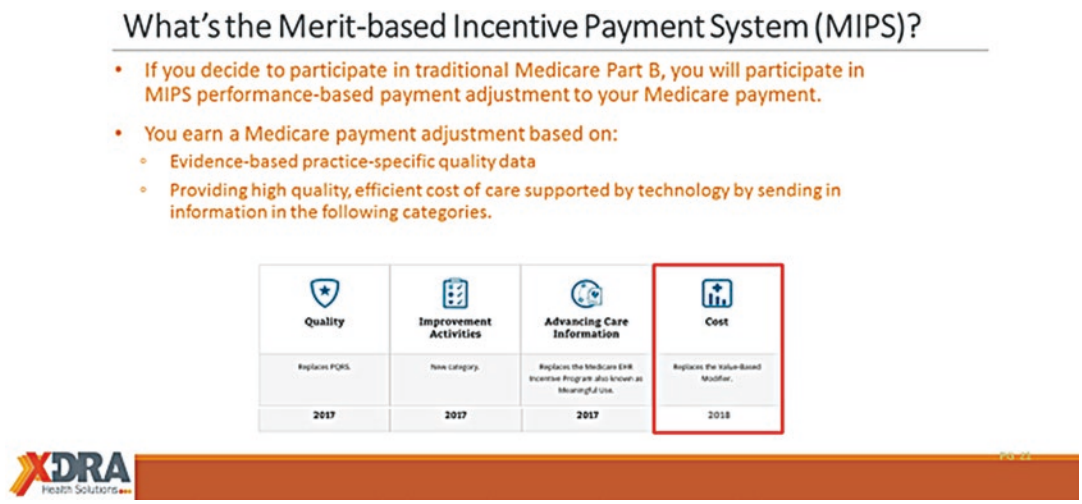
once your claim is submitted; number of first submissions (called "clean claims") leading to payment versus multiple submission/resubmissions of claims; and frequency of other problems leading to delay in payment and/or refusal of payment by the insurance company. Many of these spreadsheets are premade as part of commercial software billing programs.

Over time, you will determine that some insurance companies pay a lower fee per unit of service but that they actually cost less in terms of the actual cost to your practice. This is because they have a very high rate of clean claims, thereby lowering your claims processing costs. In turn, others may promise a high rate of payment but cost more to service the claim (or, as noted earlier, cost you so much more in staff and doctor time getting preauthorizations than your actual reimbursement per hour or per unit due to having to resubmit claims and so forth).

In the prior edition of this book, we discussed the sustainable growth rate (SGR), a formula used by the Center for Medicare and Medicaid Services (CMS) to attempt to control rising health-care expenditures. SGR was eliminated by the Medicare Access and Chip Reauthorization Act of 2015 (MACRA), the act that established the Merit-Based Incentive Payment System (MIPS). We do not discuss SGR in this update because it is no longer relevant [4].

Most of the above applies to Medicare as well as other federal, private, and commercial insurance plans. Earlier, we summarized key factors putting immense pressure on health-care costs. We mentioned MIPS, the payment system introduced in 2017 to combine prior payment systems.

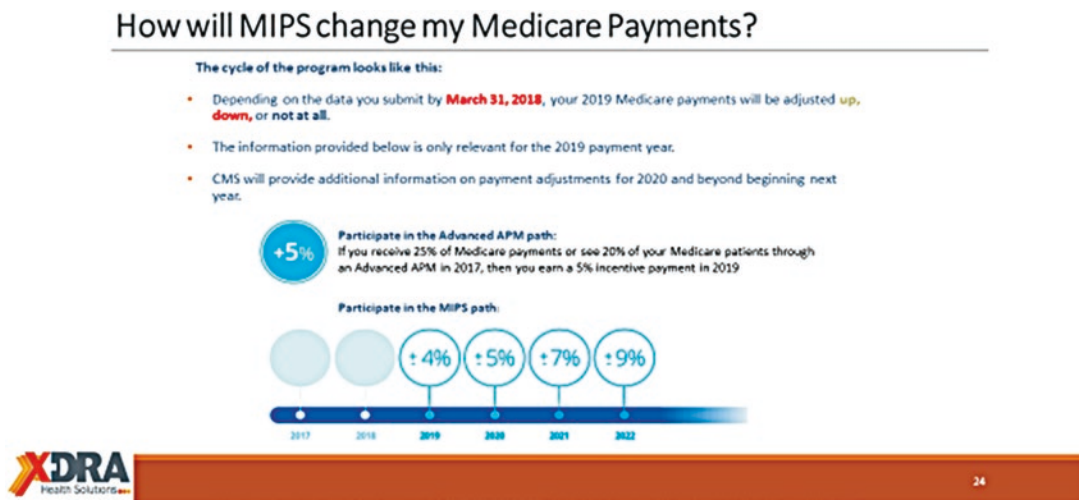
MIPS continues the trend established by Meaningful Use (MU) and the Physician Quality Reporting System (PQRS) of penalizing providers who do not participate. MIPS expands on this concept, though. It is a zero-sum program in which participants will be rewarded—or penalized—based upon their cost and quality performance. The following charts provide a good summary of MIPS.



Note the shift in MIPS toward demonstrating high-quality, cost-effective care. MIPS moves beyond its predecessors where the focus was on reporting data. MIPS also places an emphasis on technology, or more aptly, seamless and transparent cost and quality reporting.

MIPS is the payment system of Medicare's future, and other payors are following lockstep. We review it in this chapter because we believe neuropsychology *must* find a way to be part of MIPS. The risks of being marginalized by not participating are just too great.

MIPS payments are adjusted on a 2-year lag. Therefore, efforts in 2018 will result in either a payment increase or payment decrease in 2020. As noted in the following chart, the rewards and penalties increase significantly in the next few years.



As the chart shows, there will be a rapid escalation of opportunities to be paid significantly more—or less—than what one is paid today. Note: the Advanced APM path mentioned on the preceding chart is an option under MIPS for providers to accept downside risk in a specific model (e.g., comprehensive end-stage renal disease care) in exchange for the opportunity to make even more by meeting defined quality and cost performance metrics. Advanced APMs are not discussed further in this chapter.

So, why should you be concerned? All you want is to keep a full practice and pay your bills and earn your salary? Well, how are you going to know if your practice is going to (a) make a profit, (b) break even, or (c) operate at a loss on Medicare services such as psychotherapy or testing if you do not know what the amount of fee reimbursement is going to be a month, 3 months, or a year from today. You *have* to think about the basic cost of delivering your professional service to the public from a business management point of view.

Table 8.3 presents the hard reality of the decline in Medicare allowed payment (the actual amount you are paid) over the past 5 years. As you can see, the actual CPT 96118 fee in Region 3 has declined from a 2007 level of $111.79 to a 2017 level of 97.92 (12.4%). Without a doubt, your overhead has continued to increase during this time period. Can you afford to see Medicare patients for these rates? Where can you make up the difference in lost revenue?

At the institutional level, the same situation regarding Medicare reimbursement is going to direct how the institution will allocate resources for patient care and professional salaries. Most of us have heard the real stories from our peers who have been told bluntly by their hospital administrator to balance their department budget (including their continued salary and other overhead) by increasing actual cash receipts (not just billable hours to indigent patients) to a level which covers salary and other expenses, or their position would be canceled.

Here is a basic example using CPT 96118. If your office cost of service is $150.00 per hour and you currently receive $150.00 per unit of 96118, then you are breaking even, with no profit or loss. Now, if the amount you receive is the our current Medicare reimbursement rate of $97.92 for each unit of 96118 provided to a Medicare patient, that is a loss of 52.08 per unit. Thus, an 8-h service with 96118 leads to a loss of $416.64. Where will you make up this loss? Have you calculated the total number of Medicare-based CPT units of service billed by your practice in the past 12 months? Please take a minute or two and calculate this amount versus your actual overhead. Knowing your margins by payor and by service is critical. This is only one of the many reasons why large numbers of physicians and psycholo-

gists are considering whether they can afford to continue to provide services to Medicare patients.

Let us add an additional level of payment impediment to the above scenario. This example reflects a Virginia Medicare (primary insurer) patient with Standard Virginia Medicaid (secondary insurer). Using the per figure of $97.92 per unit of 96118, Medicare will pay 80% ($78.33) per unit, and the remaining 20% ($19.59) per unit is passed on to Medicaid for payment. However, Medicaid will not pay the remaining $19.59 per unit because Medicaid has determined that the amount by Medicare is greater than what Medicaid would pay—and so will pay $0.00. As a Medicare provider, you are not allowed to "balance bill" under most circumstances. As a Medicaid provider, you are not allowed to balance bill the Medicaid patient. If, for some reason, you are allowed to legally "balance bill" this Medicaid provider, do you really expect to collect that $19.59 per unit (or, $156.72 for 8 units) and recoup the cost of that collection as well—if you could balance bill the patient? Again, the greater the number of service units provided at a per unit loss, the greater the loss on your bottom line. Typically, working for only 80% of the Medicare rate will reflect a significant dollar loss per unit for your business. How do you balance appropriate professional service delivery versus being able to afford to stay in business to provide continued care?

How you spend your professional time is a decision based upon multiple issues. Having an accurate picture of your office's financial status and how it can be affected by seeing patients who lead to financial profit or loss for your practice is critical to your business decision-making. Once you actually analyze your costs for carrying out a neuropsychological evaluation to a patient with a specific insurance plan, is continued service to patients with that plan justified from a business perspective?

Another concern that drives up office costs is the matter of patient "no shows." These are the instances in which patients do not show for their scheduled appointments. "No shows" cost your practice money since they represent unproductive "no income" time in which you still have the cost associated with running a practice. Virtually all insurance companies (Medicaid is a notable exception in most states) permit neuropsychologists and other providers to charge patients who fail to show for their appointments. While "no show" charges do not offset all the lost revenue from a "no show," they can provide an incentive to patients to keep their appointments.

As of October 1, 2007, Medicare allows the clinical neuropsychologist to charge patients a "no show" fee, provided the following conditions are met [8]:

1. The "no show" charge must be applied consistently to all patient insurance groups (Medicaid being an allowed exception) and not just to Medicare patients.
2. Patients must be informed in advance of the "no show" charge (we recommend that you inform patients at the time appointments are made, at the time appointments are confirmed, and in your patient registration material).
3. The charge must be reasonable (there is no guideline for "reasonable," though we are aware of $25–50 being common for "no show" charges per hour in our community). A simple method to find out what is the common charge in your community is to call *your* personal physician's office and ask what they charge for a "no show." Just remember, most PCP visits are much shorter that the typically 1-h minimal unit of time you set aside for a patient.
4. "No show" charges are billed directly to patients as a "noncovered" service; they *cannot* be billed to Medicare or other insurance companies.

Medicare Participation Options

Neuropsychologists and other providers are not required to see Medicare patients. Three options exist for contracting with Medicare: (1) participating (PAR), (2) nonparticipating (NON-PAR), and (3) opting out/private contracting (OPT-OUT) [9].

As a general rule, Medicare contractors send letters to providers in mid-November of each year, informing them of the upcoming calendar year's payment rates and offering them an opportunity to change their participation status. Providers then have until December 31 of that year to make their participation decisions. Unless CMS reopens this "open enrollment period," participation is binding for the entire calendar year.

1. PAR: When a neuropsychologist agrees to "participate" in Medicare, they agree to accept Medicare's reimbursement rates as payment in full for the calendar year in question. Medicare reimburses participating providers at 100% of the approved payment rate and pays them more rapidly than nonparticipating providers. Generally speaking, 80% of the payment comes from Medicare, with the balance coming from the patient.
2. NON-PAR: If a neuropsychologist elects not to participate in Medicare, they have the option whether or not to "accept assignment." If the NON-PAR provider accepts assignment, Medicare pays claims at 95% of the participating provider amount, with 80% of that amount coming from the contractor and 20% from the patient. If the NON-PAR provider decides not to accept assignment, they must fill out a Medicare beneficiary's claim form and submit the claim directly to Medicare. Medicare then pays the patient directly, leaving the physician to bill the patient for services rendered. Physicians cannot charge Medicare patients for filing their claims, but by refusing assignment, NON-PAR providers can balance bill patients up to the "limiting charge" (federal law restricts Medicare nonparticipating providers from balance billing more than 115% of the Medicare nonparticipating reimbursement rate. This is called the "limiting charge." The potential reimbursement rate for NON-PAR providers is 115% of the Medicare NON-PAR reimbursement rate, which is 109.25% of the participating provider reimbursement rate). Of course, as a NON-PAR provider, the onus is on your practice to bill and collect from your patients. For many practices, the cost of billing Medicare on behalf of their patients, then billing the patients to collect what Medicare paid directly to them, and then attempting to collect from these patients is not worth it.
3. OPT-OUT: Neuropsychologists also may elect to opt out of the Medicare system entirely. To do so, one agrees to not participate in the Medicare program for 2 years and privately contracts with Medicare beneficiaries for services rendered. Neuropsychologists can then bill patients directly for their services at rates agreed to between the patient and neuropsychologist. To meet the legal requirements for the opt-out option, one must sign and file an affidavit in which they agree not to bill or receive payment from Medicare for at least 2 years.

The affidavit of participation status must be completed at least 30 days before the first day of the next calendar quarter; there is a 90-day window for rescinding the affidavit. The opted-out neuropsychologist and Medicare patient must sign a written contract *before* any service is rendered. The contract must clearly state that, by signing the contract, the patient (1) declines all Medicare payments for services rendered by the neuropsychologist, (2) is liable for all charges without Medicare balance billing limitations *or* assistance from Medigap or other supplemental insurance, and (3) acknowledges that the patient has the right to receive services from other medical providers.

Where a neuropsychologist opts out and is a member of a group practice or otherwise reassigns his or her rights to Medicare payment to an organization, the organization may no longer bill Medicare or be paid by Medicare for services that the neuropsychologist furnishes to Medicare beneficiaries. However, if the neuropsychologist continues to grant the organization the right to bill and be paid for the services he furnishes to patients, the organization may bill and be paid by the Medicare patient for the services that are provided under the private contract. The decision of an individual provider to opt out of Medicare does not affect the ability of the group practice or

organization to bill Medicare for the services of those and practitioners who continue in a participating or nonparticipating status with Medicare.

Some Common Medicare Patient Request Situations: What Is the Appropriate Response?

These responses are based upon a review of the current APA ethics code as well as our years of clinical and business-related experience. Our responses should be viewed as guidelines to be considered by the reader. You may develop other responses to these situations that are also appropriate or, perhaps, even more appropriate than what is noted below. The main thrust of each response deals with (a) making a priori service delivery decisions about the contractual arrangements you set up with the patient and (b) using your understanding of how the patient's insurance approval and reimbursement system works.

Situation A The patient who wants you to carry out a comprehensive, attorney-requested or court-ordered, forensic examination, which is to be billed in its entirety to Medicare. The purpose of this evaluation is for a forensic opinion(s) to be developed and used in a legal matter.

Response Do not accept the referral with the proviso of billing Medicare for a forensic (administrative) service. This is not a medically necessary service. You may be in violation of several ethical rules as well as run the risk of committing fraud in terms of your contractual relationship with the insurance payor. Ask yourself the question, "Is the referral question and the resultant testing medically necessary as they relate to the making of a diagnosis or alleviating a medical or mental problem? Would the testing be necessary if there was no active litigation?"

Medicare specifically states The services of CPs are not covered if the service is otherwise excluded from Medicare coverage even though a clinical psychologist is authorized by state law to perform them. For example, the Social Security Act (Section 1862(a)(1)(A)) excludes from coverage services that are not "reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member." Therefore, even though the services are authorized by state law, the services of a CP that are determined to be not reasonable and necessary are not covered [10].

Situation B The patient has always wondered if they could have a learning disability, and now they want to be tested under Medicare for that service. They want educational testing to identify a diagnosis of a learning disability, and the patient wants you to bill the services to Medicare. They are not complaining of any other form of medical, neurological illness or injury or mental health problem that may be causally associated with such an educational condition.

Response It is our understanding that Medicare does not cover testing for educational purposes, such as to identify a learning disability, as it does not meet the criteria for medical necessity/covered service.

Situation C The patient asks or demands that you waive either their co-pay, their deductible, or both.

Response Do not waive the co-pay or deductible. Not only are you providing a service well below your cost basis, but you may find that you have violated the law! The Centers for Medicare and Medicaid Services (CMS) has mandated that physicians and other providers of health care *must* collect co-pays and deductibles [11].

The reasoning behind this is as follows: If you (the neuropsychologist) waive the co-pay or deductible, you are, in effect, giving the patient a discount. Therefore, if you are willing to "sell" your service to the patient at a discount, you should also give a discount to the insurer. A sec-

ond (and lesser) reason for requiring co-pays and deductibles is to cause the patient to have a share in the cost of their health care, thereby reducing unnecessary consumption of covered services.

A Review of Some Sample Forms for a Private Practice in Clinical Neuropsychology

The items that follow are examples of the types of forms that we have developed to address common situations which occur in management of our practice. Please feel free to adapt them to your presented elsewhere [7].

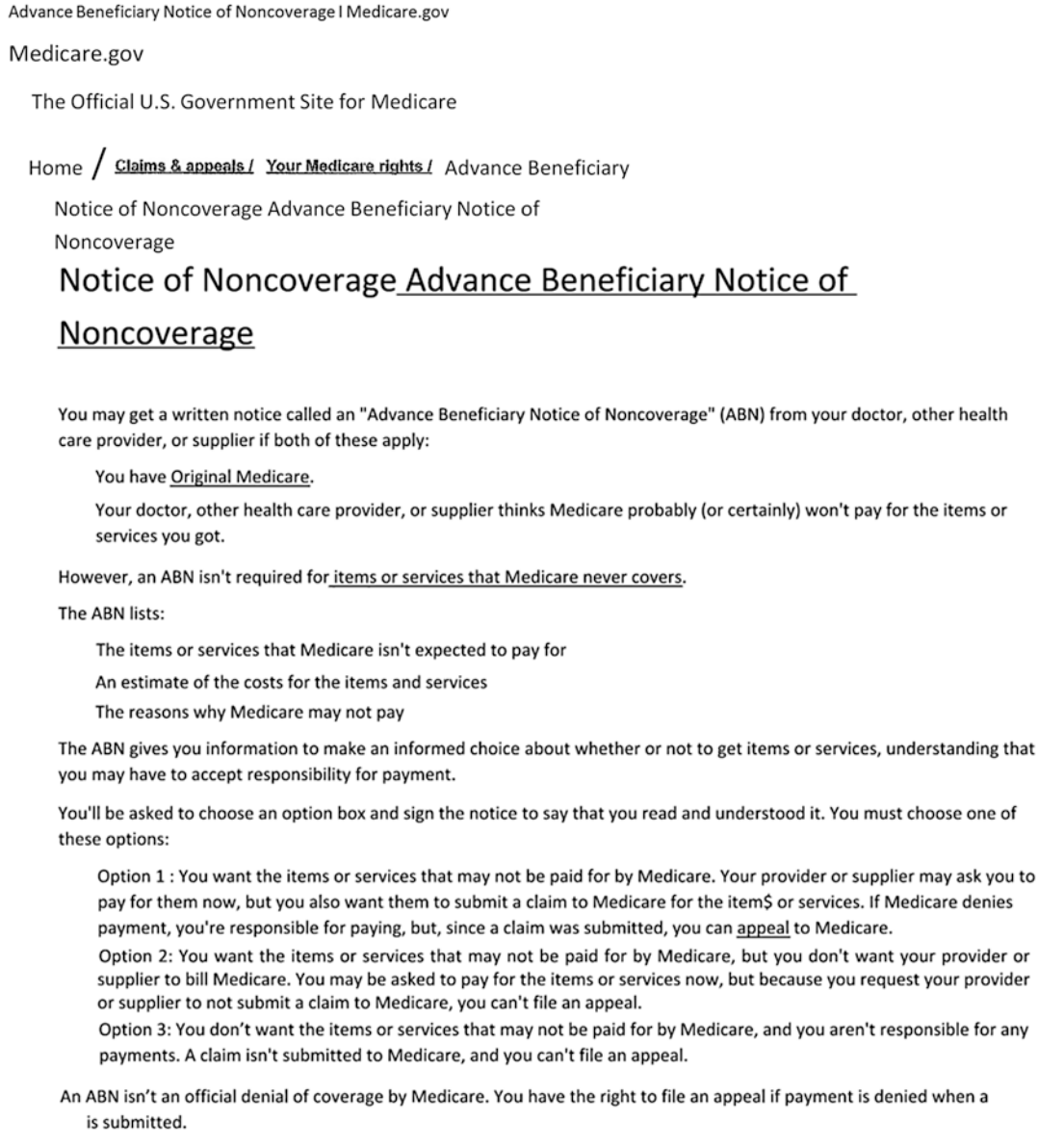
Please note the following caveats. Many of the forms have been reviewed by our company attorney for acceptable legal standards according to the laws of the Commonwealth of Virginia. You will need to determine whether the wording in these forms is legally valid in your jurisdiction. Also, we feel that these forms reflect an appropriate professional standard of practice according to current APA ethics standards. Please do not try to interpret these documents out of context. Our office will change these forms whenever it is deemed necessary so as to maintain acceptable legal and ethical standards. Finally, each of these forms is designed to be completed on an a priori service delivery basis. This issue is critical in many of the circumstances relevant to these forms.

(a) Referral form (Fig. 8.1): This intake form is typically completed as part of a telephone call from either the referral source or the patient/patient's family. Please note that it also prompts for secondary and tertiary insurance information. Some patients have Medicare plans that may require a preauthorization for services. You do not want to have to try to get a preauthorization, while the patient is waiting at the registration window and waiting for their appointment.
(b) Registration form (Fig. 8.2): Page 1 asks for the typical information. Page 2 addresses a number of specific issues. Without going into a line by line annotation, please note several items of particular interest: first, that the time for testing includes administration, scoring, and report preparation as well as report discussion and, second, that the cost of responding to medical legal matters requires time and that fees will be charged for these services; page 3 deals with documenting the Medicare no show policy and other general insurance matters.
(c) Waiver of insurance (Fig. 8.3): This form is a copy of the standard Medicare "Advance Notice for Medically Unnecessary Services—Waiver of Medical Necessity" form [12, 13]. This form should be used in those situations where you have a Medicare enrollee who is requesting services which, in their specific situation, are not likely to be deemed medically necessary by Medicare. In many situations, federal rules still require the provider to submit the claim, even though they have good reason to believe in advance that the service, e.g., forensic issues, is not going to meet the accepted standard of medical necessity. This signed waiver allows the provider to bill the enrollee for the service instead of having to write off the claim. For further information regarding this complex issue, please refer to the website of your state's Medicare Part B carrier.

This form is valid as of July 26, 2017, and the Medicare website states (taken verbatim as public information):

Medicare and Neuropsychology: A Look Forward to the Abyss or to Eden? What Will Our Business Management Practices Look Like in the Future?

(a) We see opportunities for reimbursement increases if our profession is successful in advocating for inclusion in MIPS and other quality/cost programs. However, we expect to see per unit reimbursement levels continue to decline over the next 10 years if our



Advance Beneficiary Notice of Noncoverage I Medicare.gov

Medicare.gov

The Official U.S. Government Site for Medicare

Home / Claims & appeals / Your Medicare rights / Advance Beneficiary

Notice of Noncoverage Advance Beneficiary Notice of Noncoverage

Notice of Noncoverage Advance Beneficiary Notice of Noncoverage

You may get a written notice called an "Advance Beneficiary Notice of Noncoverage" (ABN) from your doctor, other health care provider, or supplier if both of these apply:

You have Original Medicare.

Your doctor, other health care provider, or supplier thinks Medicare probably (or certainly) won't pay for the items or services you got.

However, an ABN isn't required for items or services that Medicare never covers.

The ABN lists:

The items or services that Medicare isn't expected to pay for

An estimate of the costs for the items and services

The reasons why Medicare may not pay

The ABN gives you information to make an informed choice about whether or not to get items or services, understanding that you may have to accept responsibility for payment.

You'll be asked to choose an option box and sign the notice to say that you read and understood it. You must choose one of these options:

Option 1 : You want the items or services that may not be paid for by Medicare. Your provider or supplier may ask you to pay for them now, but you also want them to submit a claim to Medicare for the item$ or services. If Medicare denies payment, you're responsible for paying, but, since a claim was submitted, you can appeal to Medicare.

Option 2: You want the items or services that may not be paid for by Medicare, but you don't want your provider or supplier to bill Medicare. You may be asked to pay for the items or services now, but because you request your provider or supplier to not submit a claim to Medicare, you can't file an appeal.

Option 3: You don't want the items or services that may not be paid for by Medicare, and you aren't responsible for any payments. A claim isn't submitted to Medicare, and you can't file an appeal.

An ABN isn't an official denial of coverage by Medicare. You have the right to file an appeal if payment is denied when a is submitted.

Fig. 8.1 Referral form

profession does not advocate effectively. We are moving away from per unit fees to global service fees. We still expect to see the upper limit of allowable testing units decline as Medicare and other payors increase the demand for computerized testing *and* decrease funding for our services.

(b) These changes will result in an even greater reliance on forensic and other professional services where fee structures are less regulated. This will also "make up" some of the lost revenue for those who continue to see Medicare patients.

(c) We also envision more neuropsychologists choosing to "opt out" of Medicare and work solely on a private contract arrangement with patients. The rise in "concierge neuropsychology" services is already a reality.

(d) Many of the "a la carte" options typically offered to patients for free, or little cost will

Neuropsychological Services Of Virginia
Intake Form

Referred To: _____ Referred By: _____ Date: _____

Referral Called In By: _____ Phone No: _____ Fax No: _____

Client Name: _____ DOB: _____ Age: _____

Address: _____ City/State: _____ Zip: _____

Home Phone: _____ Work Phone: _____ Cell Phone: _____

Preferred Phone: [Circle] Home - Work - Cell Email Address: _____

Responsible Party: _____ Relationship To Patient: _____

Responsible Party Contact Info: _____ Employer: _____

Reason For Referral: _____

_____

_____

_____

NT _____ PT _____ Therapy _____ EducT _____ DOA: _____ LOC [ ] Yes [ ] No

Outpatient: _____ Inpatient: _____ Room #: _____ Records Req?: [ ] Yes [ ] No

Accident?: [ ] Yes [ ] NO - DOI: _____ WC?: [ ] Yes [ ] NO - DOA: _____ Attorney: _____

Primary Insurance: _____ ID: _____ Phone #: _____

Address: _____ Contact: _____

Mental Health Carrier (If Different): _____ Phone#: _____

Mental Health Carrier Address: _____ Effective Date: _____

Policy Holder Name: _____ Rel to Pt: _____ Group#: _____

Policy Holder D. O. B. _____ Policy Holder Other Info _____

Deduct: _____ Met?: _____ Copay/Coinsurance.: _____ Preauth Req?: _____ OTR Req?: _____

Preauth # DI: _____ Preauth # Test: _____ Preauth # Therapy: _____

Notes: _____

_____

_____

Secondary Insurance: _____ ID: _____ Phone #: _____

Address: _____ Contact: _____

Mental Health Carrier (If Different): _____ Phone#: _____

Policy Holder Name: _____ Effective Date: _____

Deduct: _____ Met?: _____ Copay Visit/Unit: _____ PreAuth Req?: _____ OTR Req?: _____

Preauth # DI: _____ Preauth # Test: _____ Preauth # Ther.: _____

Appointment Date: _____ Confirmed Appt w/__ _____ on_____by _____

Appointment Date: _____ Confirmed Appt w/_____on _____by_____

Appointment Date: _____ Confirmed Appt w/_____on _____by_____

Client Informed: Copay Amount: _____ 48-hr Notice: _____ Glasses/Med List: _____ D/E Q_____ Rev. 6/26/10

Fig. 8.1 (continued)

NEUROPSYCHOLOGICAL SERVICES OF VIRGINIA, INC.

PATIENT REGISTRATION

First Name:_____ **Middle:**_____ **Last Name:**_____

Address:_____ **City:**_____ **State:**_____ **ZIP:**_____

Home Phone: (_____**)**_____**-**_____ **SSN:**_____/_____/_____ **Sex: [ ] Male [ ] Female**

DOB:_____/_____/_____ **AGE:**_____ **Referred by:**_____

Were you injured while working? (Workers' Comp) [ ] NO [ ] YES-->Date of Injury: _____/_____/_____

Accident? [ ] NO [ ] YES-->Motor Vehicle? [ ] YES [ ] Other _____ **Date of Accident** _____/_____/_____

Are you represented by an attorney? [ ] NO [ ] YES-->Attorney Name _____

Have you been seen at NSV previously? [ ] YES [ ] NO Are you here on an emergency basis? [ ] YES [ ] NO

Are you covered by insurance health plan(s)? [ ] YES [ ] NO If YES, we need to make a copy of your insurance card(s).

Primary Ins. _____ **Secondary Ins.** _____

Vocational Status:

[ ] full-time student
[ ] part-time student
[ ] homemaker
[ ] retired
[ ] full-time employed
[ ] part-time employed
[ ] unemployed
[ ] disabled
[ ] other _____

Education:_____**Years Completed Degree:**_____

Handedness: [ ] right [ ] left [ ] ambidextrous

Occupation:_____
Employer:_____
Work Phone:_____
Cell Phone:_____

Marital Status: [ ] Single [ ] Separated [ ] Divorced [ ] Married [ ] Widowed

Medication	Dosage (mg)	# per day	Medication	Dosage (mg)	# per day
1)			4)		
2)			5)		
3)			6)		

Responsible Party, if other than patient: (who is responsible for payment of all costs incurred)

First Name:_____ **Middle:**_____ **Last Name:**_____

Address:_____ **City:**_____ **State:**_____ **ZIP:**_____

Home Phone: (_____**)**_____**-**_____
Employer:_____ **Work Phone: (**_____**)**_____**-**_____

Responsible party's relationship to patient: [ ] Spouse [ ] Child [ ] Parent Other _____

Note: Fees are posted at the receptionist's window.

Fig. 8.2 Patient registration form

need to become full fee expenses, so as to be able to operate at a profit vs. loss for the time, talent, and effort involved. These items include (1) forms that the patient wants completed and (2) letters to document some element of care or diagnosis, as well as other services which may not be billed to Medicare.

(e) Once Medicare and other insurance companies allow for services where the professional is not actually physically present on-site with the patient, the entire question of in-office testing will become moot. The patient will not have to come to the neuropsychologist's office if they can go to another site such as the PCP's office and be interviewed and then

Neuropsychological Services of Virginia, Inc.

GUARANTEE OF PAYMENT AND ASSIGNMENT OF INSURANCE BENEFITS: For value received, the undersigned guarantor and/or patient (hereinafter the "Responsible Party") promises to pay to Neuropsychological Services of Virginia, Inc. (hereinafter "NSV") all charges incurred for services rendered to the Responsible Party. The Responsible Party understands that NSV will process the paperwork to complete insurance claim(s) but only as a courtesy to the Responsible Party, and the Responsible Party authorizes NSV to release any and all medical information necessary to complete insurance claim(s) and assigns any monies due and owing under the insurance contract to NSV. **It is, however, understood and agreed that the Responsible Party is responsible for all monies due and owing for services rendered by NSV in the event insurance does not pay for these services.** It is acknowledged that the ultimate completing and following-up of any insurance claims is the responsibility of the Responsible Party. It is further agreed by the Responsible Party, that in the event any monies received by NSV from the insurance carrier which are at any time after their receipt withdrawn from NSV by the insurance carrier, the Responsible Party will be responsible for those monies then due and owing, and waives any defense for payment the Responsible Party may have against NSV. In the event this account is turned over to an attorney for collection, the Responsible Party hereby agrees to pay all costs of collection including, but not limited to, court costs and 33 1/3% attorney's fees. The Responsible Party authorizes use of this form on all insurance claim submissions. Release of records to referral sources is also authorized. The Responsible Party agrees to be bound by the terms and conditions of this account with NSV.

A minimum of 48 hours weekday / 2 business days notice is required for cancellation of appointments. If this notice is not received, the Responsible Party may be charged a fee for the amount of time which was reserved for the appointment at the rates posted in the offices of NSV. See page 3 for details. This also applies to Medicare patients. Insurance will not be billed for missed/canceled appointments. Your copay is expected at the time of service. We will file the Responsible Party's initial insurance claim(s) and provide documentation necessary for insurance reimbursement. We do not, however, guarantee that each service will be covered or what percentage will be covered. The Responsible Party may incur extra charges for refiling of insurance claims.

In the event that the Patient's/Responsible Party's insurance does not cover our services (or any portion thereof), NSV will work with the Responsible Party regarding payment (e.g., setting up a payment plan). NSV expects full payment within thirty (30) days of the date of service. **The Responsible Party hereby agrees that accounts not paid within thirty (30) days will be charged a late fee of $15.00 and will accrue interest at the rate of 1.5% per month (18% A.P.R. - a minimum of $1.00 will apply).** The Responsible Party bears ultimate financial responsibility for all services rendered to the Patient/Responsible Party, including workers' compensation claims and personal injury cases, regardless of the outcome of litigation. In the event that coverage is denied under workers' compensation, the Responsible Party will pay any unpaid balance, notwithstanding any appeal of such denial. With respect to personal injury cases, the Responsible Party is responsible for fees incurred, NSV may not be able to seek payment from third parties, and NSV cannot wait on the outcome of pending litigation for payments. NSV does not accept contingency fee arrangements. If there is any remaining balance(s) due at the time of settlement, the Responsible Party hereby authorizes their attorney to clear the Responsible Party's outstanding accounts. In the event the Responsible Party has **"medpay"** available and health insurance, NSV considers medpay to be the primary insurer. The Responsible Party's signature also constitutes the irrevocable agreement to a waiver permitting payment of medpay insurance claims directly to NSV prior to claimant receiving such funds.

Responding to Forensic/Medical Legal requests, conferences and telephone calls with attorneys involve additional time and record keeping. The Responsible Party is responsible for all direct costs and expenses associated with NSV and its attorney responding to discovery requests (including depositions and subpoena duces tecum time and labor costs) and with conferences including, but not limited to court appearances, preparation of reports, photocopying, faxes, long-distance telephone calls, out of office travel, overnight delivery and courier services. These expenses are billed to the Responsible Party and to the Patient's/Responsible Party's Attorney. The Responsible party, however, remains responsible for payment of these charges if not paid in full within sixty (60) days. The above noted direct cost and expenses are understood and accepted to be in addition to any published federal and/or state statutes which may otherwise apply.

NOTE: Testing includes time for (1) administering and (2) scoring the tests, and (3) preparing the report. In nonforensic/nonmedical-legal cases, this will typically add 1-3 hours to the actual testing time. Forensic/medical-legal cases typically require even more time and may include record review and consultation(s) with attorney(s), etc. In certain cases (such as, but not limited to, medical-legal cases), a more comprehensive and time-consuming assessment may be needed than what may be approved under your insurance plan [for example, when an insurance plan covers up to 3 hours of testing/report preparation but your clinician feels that your case requires additional hours of testing/record review/report preparation/etc]. The responsible party as noted below accepts responsibility for these charges.

If you have any questions, please speak with a member of our Management team. Your signature indicates that you have read the above and agree to the terms contained therein. These agreements are irrevocable.

Signature: _____ Responsible Party: _____

Date: _____ Date: _____

****If patient is a minor, are you her/his legal guardian?** [ ] YES [ ] NO If **NO**, please notify our Management team regarding this matter.

Rev. 4/12/2011

Fig. 8.2 (continued)

Neuropsychological Services of Virginia, Inc.

Insurance & Appointment No Show Information Notice

From: The Clinicians & Staff at NSV

It has come to our attention that, despite every reasonable effort undertaken by *you* and by our clinicians and highly trained office staff to obtain specific and accurate information/confirmation from your insurance company regarding:

1. Whether our clinicians and/or NSV is an approved provider of services under your health care plan;
2. What are the insurance approved services requested in your case;
3. What is the time limited extent of services which may be provided per appointment;
4. What is the insurance company stated allowed amount of patient copay and/or the allowed amount of insurance payment to be made to NSV;
5. The specific preauthorization and preauthorization number for the requested services;
6. Other information which documents the insurance company's responsibility to pay the patient's claim.

Unfortunately, some insurance companies may provide NSV with the information needed to appropriately process and reimburse NSV for professional services rendered, but then (after we perform the requested services) they inform us that the insurance information which they gave us is incorrect and/or incomplete. Your insurance company then may inform the clinicians and NSV that they are not responsible for payment for the otherwise agreed upon services. Your insurance company may delay and/or defer their reimbursement for previously authorized services. The clinicians and NSV thereby inform the responsible party noted below that: first, this type of situation may develop in your situation despite your/our best efforts to prevent such an event; second, that the responsible party assumes responsibility for making the insurance company take appropriate responsibility for their actions; third, that the responsible party agrees to pay NSV the appropriate payment which is otherwise due from the insurance company while the responsible party seeks to make the insurance company live up to their agreed upon financial obligations to the patient.

7. *Missed/Broken appointments:* A minimum of 48 hours weekday/business days advance notice is required for the cancellation of appointments without incurring a missed/broken appointment penalty. This is strictly enforced. If this notice is not received, the Responsible Party may be charged:
   (a) $75.00 for a missed 1 hour Psychotherapy and or Office Feedback appointment and
   (b) $75.00 *per hour* for a missed Testing appointment. This may involve 3 – 8 hours of lost time.
   (c) $15.00 for a missed 10 minute Telephone Feedback/Conference appointments.
   (d) Please see the 2011 rate schedule posted in the office of NSV for further information.

If you have any questions, please speak with a member of our Management team. Your signature indicates that you have read the above and agree to the terms contained therein.

Signature: _____ Date: _____

Fig. 8.2 (continued)

accessed via Internet-based video connection (e.g., Skype-type service). This is already happening.

(f) As Medicare moves toward its uncertain future, Congress will explore other mechanisms to rein in the costs of caring for a growing Medicare population. We, as a profession, must work together to create a qualitative and quantitative value proposition. Neuropsychology can and should play a key role in caring for Medicare patients. If they are unable to make a strong case for such, we run the risk of neuropsychology being pushed to the sidelines of patient care. We make this point a second time because we believe being at the table beats being on the menu for the future of our profession.

(g) Now that electronic medical records have become more widespread, private practice neuropsychologists will adopt such technology in greater numbers. There will be many reasons, but simply being able to maintain

A. Notifier:

B. Patient Name: **C. Identification Number:**

Advance Beneficiary Notice of Noncoverage (ABN)

NOTE: If Medicare doesn't pay for **D.** _____ below, you may have to pay.

Medicare does not pay for everything, even some care that you or your health care provider have good reason to think you need. We expect Medicare may not pay for the **D.** _____ below.

D.	E. Reason Medicare May Not Pay:	F. Estimated Cost

WHAT YOU NEED TO DO NOW:

- Read this notice, so you can make an informed decision about your care.
- Ask us any questions that you may have after you finish reading.
- Choose an option below about whether to receive the **D.** _____ listed above.

  Note: If you choose Option **1** or 2, we may help you to use any other insurance that you might have, but Medicare cannot require us to do this.

G. OPTIONS: Check only one box. We cannot choose a box for you.

☐ **OPTION 1.** I want the **D.** _____ listed above. You may ask to be paid now, but I also want Medicare billed for an official decision on payment, which is sent to me on a Medicare Summary Notice (MSN). I understand that if Medicare doesn't pay, I am responsible for payment, but **I can appeal to Medicare** by following the directions on the MSN. If Medicare does pay, you will refund any payments I made to you, less co-pays or deductibles.

☐ **OPTION 2.** I want the **D.** _____ listed above, but do not bill Medicare. You may ask to be paid now as I am responsible for payment. **I cannot appeal if Medicare is not billed.**

☐ **OPTION 3.** I don't want the **D.** _____ listed above. I understand with this choice I am **not** responsible for payment, and **I cannot appeal to see if Medicare would pay.**

H. Additional Information:

This notice gives our opinion, not an official Medicare decision. If you have other questions on this notice or Medicare billing, call **1-800-MEDICARE** (1-800-633-4227/**TTY:** 1-877-486-2048).

Signing below means that you have received and understand this notice. You also receive a copy.

I. Signature:	J. Date:

Fig. 8.3 Medicare noncovered service form

record access from referral sources and to provide quick transmission and access of our reports to other sources will become more critical. If we do not stay on an EMR technology par with our MD referral sources, then the MD will see the cost of their office having to copy or fax records to us as a financial disincentive for a referral. Active use of an EMR will be critical for involvement in MIPS and other payment incentive models.

It is therefore incumbent to focus on the "value" of the services we offer. Even as many of our tests become computerized, we must continue to demonstrate the value of the personal interaction between neuropsychologist and patient. We must be able to demonstrate how the information we provide is better and more accurate than "shortcut" software-based neuropsychological testing being sold to (and used by) other medical professions who do not have our training and expertise. We must be able to show how our care creates better patient outcomes. To the extent we can do this, our future is much brighter.

Clinical Pearls

- Know what constitutes a medically necessary service and agree to bill Medicare for such service—and bill the patient for services that are not medically necessary according to Medicare.
- Play a role in making sure payors understand what neuropsychologists do and how our efforts have a positive impact on both patient outcomes and the overall delivery of cost-effective health care.
- Do not hesitate to educate the patient as to what is a medically necessary service and what is not medically necessary. The patient should have a say in their health-care delivery choices. This includes accepting financial responsibility for nonmedically necessary services.
- Document time and service provided to the patient properly the first time, according to documentation standards, and you will reduce the risk of audit problems in the future.
- Know what your cost of practice is and use that information properly in your clinical care decisions. This includes understanding the cost of unfilled time on your schedule when you are not receiving offsetting revenue.
- Do not forget the rules you knew yesterday may have changed overnight. Health-care reimbursement, quality measurement, and delivery have changed significantly since the first edition of this book a mere 5 years ago. Be a student and remain a student.
- Be clear and consistent with patients about collecting co-pays and deductibles.
- One cannot provide "Luxury car quality care at used car rates of reimbursement." Also, plan for the autonomous driving vehicle and don't be left at the curb.
- We enjoy helping people or we would not work in this field. We feel that our professional time has value and that the business arrangements that we make are reasonable and appropriate to providing care to our patients. We cannot provide quality services if we cannot meet our financial obligations.
- The next time you visit your doctor, read the sign next to the receptionist's window. Typically, it will state that "Co-pays are expected at time of service" and that "the patient is responsible for obtaining pre-authorization for requested services." *Treat your patients appropriately and in the same manner you are treated when you are the patient at the receptionist window.*

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9 The Multigenerational Family System in Dementia: Assessment and Feedback

Karen Postal

Mrs. Smith sits down in my consulting room with her husband and two grown daughters and answers my opening query with a steely look at her family. She suggests I ask them *why she is here today.*

Winnicott [1] famously noted that "There is no such thing as a baby…if you set out to describe a baby, you will find you are describing a baby and someone." His observation that humans exist and develop in the context of interpersonal relationships profoundly shifted the individual focus of early psychotherapy theories. Family systems theory stretched the focus even further away from the individual, declaring marital dyads, family of origin, and multigenerational family systems dynamics as primary to understanding and influencing the well-being of patients [2]. The lessons of object relations and family systems theory are particularly relevant for neuropsychologists as we assess and treat Alzheimer's and related dementias. In diseases marked by anosognosia, a neurologically based unawareness of deficit, and otherwise good health, there is often literally no complaint for doctors to address were it not for the observations and distress of the family system. Likewise, in the context of memory impairment and unawareness of the need for assistance, there is often no recommended intervention that will be carried out without the assistance of the family.

Because we rely on the family as a rich, ongoing source of clinical information to guide dementia diagnosis and as the primary avenue for carrying out recommendations over the course of the disease, our clinical focus necessarily includes the question, *what if this system fails?* The caregiving burden in Alzheimer's and related dementias is well established [3] with substantial numbers of caregivers experiencing clinically significant depression [4] and increased risk for physical health issues [5]. Supportive interactions of the larger family system have been associated with better caregiver mental and physical health [6], and family-based interventions, particularly those that strengthen the connection between immediate caregivers and their extended family, have been shown to significantly reduce caregiver depression [4] and avoid or delay patient institutionalization [7]. In this context, expanding one's clinical focus to the health of the family system is a necessary condition for carrying out our mandate to improve the health and well-being of the dementia patient.

Understanding the unique dynamics of each patient's family system is important as the composition, and roles of family members vary widely in this age category. Spouses may be well,

K. Postal (✉)
Harvard Medical School, Boston, MA, USA

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passed on, or in need of caregiving themselves. Grown children may live with the patient, be a frequent visitor with meals and assistance, depend on the patient for care of the grandchildren, or be attempting to contribute to the management of their parent from across the country. Grandchildren, siblings, and even very elderly parents of the patient may be in the picture as well with their own needs, caregiving responsibilities, and emotional dynamics.

How does one assess and manage a patient with dementia without expanding one's focus to understanding the relevant players in the patient's multigenerational family system? The answer is, not well. Given the lack of awareness of deficits and memory impairment interfering with adherence to recommendations, one might expect to assess and manage a patient who has dementia in isolation about as well as a pediatrician might assess and manage an infant she sees alone in her office. In a field that has narrowed our focus to the relationship between a single brain and its behavior, this shift to expanding focus to "brain and behavior in the context of multigenerational family systems" can take thought and practice. This chapter will address strategies for harnessing and nurturing the insight, observations, and caregiving network of the multigenerational family system in the initial clinical interview and feedback sessions to facilitate assessment and management of patients with dementia.

A Lot of People Are in My Office

I invite patients to bring their spouse, grown children, siblings, and any other relevant family stakeholders to the initial consultation and feedback sessions of the neuropsychological assessment. When things go well, there are a lot of people in my office.

The invitation to participate in the assessment occurs at telephone intake. Many initial dementia evaluation visits are arranged by a spouse, child, or other caregiver. I let that person know that when members of the multigenerational family system attend the initial assessment and feedback sessions, a better history can be gathered, family members will all be on the same page regarding their understanding of the diagnosis, the beginnings of a care plan can be discussed with all stakeholders in the room, and everyone will have a chance to have their questions answered.

The invitation itself represents a multigenerational family systems intervention. It is a strong message to the caregiver that the burden of providing information that often contradicts the patient's certainty that there is nothing wrong, the burden of hearing their worst fears about the patient confirmed, the burden of taking actions to insure the patient's safety (e.g., driving), and the burden of everyday caregiving are not theirs alone to shoulder. The intervention cannot fail. Should particular family members not accept the invitation to attend the assessment, important information is obtained that will be utilized in care planning.

Knowing who doesn't attend the initial session is often as instructive as who does attend. For example, it is always striking when a grown child brings their mother to a dementia assessment while the patient's husband of 50 years stays home. Why is Mrs. Ramirez' husband not present? Is he ill and in need of caregiving himself? If so, the assessment and care plan expands to address the safety of the current caregiving relationship. If he is not ill, asking for help to understand why he is not present opens the door to a rich discussion of the patient's family dynamics that will be utilized in the care planning process. Some family members may live far out of town or be unable to get time off. Offering the option of calling into the final meeting or attending via video conference will often secure their presence.

Conducting the Initial Interview

In addition to dragging more chairs into the consulting room, conducting an initial interview with a multigenerational family system requires clinicians to strategically manage multiple conversa-

tions, points of view, and the room's emotional temperature.

Directing the Flow of Information

Questions about daily living, doctors visited, medications, and educational and vocational history always serve two purposes in a neuropsychological interview. In addition to gathering the patient's history, the questions represent a highly personalized and ecologically valid recent and remote memory test. Family members will often jump in without thinking to help answer the questions, particularly when the patient habitually looks to them for cues and help remembering information in their daily interactions. A preemptive statement directed to the patient (and intended for the family members[1]) is usually sufficient, "Mr. Hsu, I am going to ask you some questions about your situation. It's great to have your family here. We can ask them as well for their input and perspectives, but I would like to start by asking you for your perspective."

As the patient blithely describes his driving as competent, his cooking as frequent, and his memory as about as good as most people his age, his spouse or children may begin to bounce in their chairs, clearly worried that only his perspective will be given attention. If I see pained expressions, or family members begin to cut off the patient, I make a point to ask the patient, "Mr. Hsu, your perspective is important to me. After I hear from you, is it ok if I ask your daughter for her opinion?"

Far from dreading a complicated history with five different perspectives from five different family members, disagreements about how well the patient functions are a valuable source of diagnostic information. For example, if I ask Mrs. O'Sullivan how well she does cooking these days and she tells me that she has no trouble making dinner for the family while her spouse looks at her incredulously and says, "but you haven't cooked dinner for 6 months!" this tells me about her cooking as well as her level of awareness of deficit. An adult child who lives in town may be able to provide very detailed information about the patient's daily needs. However, the perspective of their sibling who lives a 1000 miles away and only sees the patient once every 3 months will also be helpful in a different way. Their "stop motion" quarterly observations provide insight about rate of change in their parent that may not be as evident to their sibling who has daily contact.

Diagramming the Family System Early

As early as practical in the initial clinical interview, I ask the patient and family to help me understand their family. I pull out a fresh piece of paper and begin to draw their family genogram [8]. The genogram is a family tree that can be used to map the relationships between the members of the extended family: who lives with whom, which members of the family have similar dementia syndromes or other mental health conditions, and which family members are actively involved in in the patient's life. The genogram can be referred to throughout the interview as family members are asked to describe activities of daily living for the patient and which family member is offering assistance. It is important to ask specifically who lives in the patient's household, and if there are other important people in the family, even if they aren't blood relatives.

Family members who are important in the life of the patient but who have not come to the initial interview can be identified through the genogram process. When such members are identified, I always take a moment to say, "It sounds like Uncle Ted is an important person in your mother's life. He seems like a person who should be at the feedback session." As the interview progresses and family members offer information that suggests conflicts and alliances within the family, the genogram can be pulled out to con-

[1]Recall that all members of the family system are "listening in" when you speak directly to an individual family member in the room. The power of an overheard communication can be consciously utilized to send messages to other targeted family members without the friction of direct confrontation.

firm or refine the clinician's impression of the relationship dynamics and draw the data on the genogram, "It sounds like your oldest and youngest daughter have a lot of conflict."

Multicultural Factors in Obtaining a Clinical History

Norms for roles within families vary considerably by culture and also vary considerably within cultures based on (among other things) levels of acculturation, blended cultures within families, and generational status. Multicultural competence [9] is therefore based in part on the clinician's willingness to ask questions directly to family members, such as "How is this in your family?" and "How does this go in your culture?" Neuropsychologist Tony Wong, Ph.D., put it beautifully when he said, "Neuropsychologists are best able to pitch their message when they are open to engaging in a dialogue and asking questions about their patients' culture… When I am on people's turf, I ask about their turf." [10] Caregiving norms and roles likewise vary widely within and between cultures. Understanding the *actual* current caregiving roles in the context of the *expectations* for caregiving in a family and the expectations for caregiving in the family's larger culture will be helpful to understanding the dynamics playing out in the room. This is particularly relevant if the cultural or generational expectations conflict with the actual roles family members have taken on. An example of this is a grown daughter from an Armenian American family with strong expectations for her to take on a primary caregiving role for her dementing mother that conflicts with her role as a high-tech CFO (more in line with role expectations for her higher level of acculturation and generation).

Asking every family about cultural expectations for caregiving and whether there are conflicting expectations based on who is more acculturated and which generation is involved allows clinicians to enter the discussion about the family caregiving plan during the feedback session maximally equipped to assist family members in working toward a sustainable caregiving plan. While European Americans may feel questions regarding culture are for those from non-European American cultures, in fact, asking questions about culture almost always often opens up rich family stories reflecting role expectations (and cautionary tales for those who break expectations). Role strain and role conflict is common, particularly for children caring for one or more sets of parents while managing careers and their own family.

When Did the Problem Begin?

In addition to understanding caregiving roles, the extent to which early symptoms of dementia are considered symptoms versus normal aging is culturally dependent [11]. I will never forget the alarm that was raised in the tertiary care medical center memory disorders clinic during my fellowship when a family came in with a patient with severe dementia and reported that her symptoms had begun just a month prior. The presenting complaint was that the patient had begun to defecate in the large flower pots in her home. On exam, she was clearly severely demented, with a single digit Mini-Mental State Exam score. We immediately began to think about a rapidly progressive dementia such as Creutzfeldt-Jakob disease.

While it was true that she had begun defecating in flower pots only over the past month, careful questioning revealed she stopped driving 5 years earlier as she was getting lost, she stopped cooking 4 years prior as her once excellent meals tasted terrible, and she hadn't managed her medications or handled money in 3–4 years as well. Our team realized that by standard metrics, she had been dementing over a series of years. However, her decline occurred in the context of a family who did not view the symptoms as alarming for someone of her age. That is, her family system did not consider loss of the ability to drive, cook, and handle finances medically relevant symptoms. But defecating in the flower pot? We are bringing her in!

Of course, as clinicians we frequently also see the opposite. In many families, the first forgotten appointment or repeated story will earn a nor-

mally aging family member a trip to the neuropsychologist's office. In some cases, the hypervigilance toward possible symptoms of dementia stems from anxiety in the context of a family history of Alzheimer's or other dementia syndrome.

Because the answer to the question, "when did the symptoms begin?" can vary based on cultural and unique family systems perspectives, asking very specific questions about each activity of daily living is key to clearly eliciting an accurate understanding of the patient's clinical course. A vague question like, "Any problem with your mom's cooking?" is subject to interpretation. Mom may not be able to cook anything other than a peanut butter sandwich these days, but because she lives with other family members who have taken over most meals, there is no problem with her cooking identified by the family. Very specific questions better elicit patient's actual skills in each activity of daily living: "Do you make the same recipes as you used to?" "Do your recipes come out the same way as they used to?" "Do you need to look at cookbooks for recipes that you made for years?" "When was the last time you cooked a big family meal?"

Family Secrets Revealed

"I dropped out of high school to work." Three pairs of incredulous eyes are glued to Mrs. Jones as she drops the bombshell she no longer remembers to hide. "Oh, I never told you girls." All kinds of emotionally charged family secrets may be disclosed during the clinical interview. Disinhibition or loss of emotional concern (anosodiaphoria) is often the genesis for patients disclosing information they had kept secret for years. As misleading others about one's education level is common [12] and misleading neuropsychologists about one's education leads to less accurate diagnoses, I make it a point to uncover secrets about education. I do this by diving beyond the first answer to the question, "How far did you go in school?" When a patient reflexively says, "high school," I will ask them, did you stop before graduating? (pause) Or did you finish the 12th grade?"

When one of these truth-telling moments occur, particularly if the information regards long-held beliefs about family values, the emotional temperature in the room may rise. Normalizing the moment by letting grown children know how typical it is to tell children an idealized version of one's history and, if appropriate, reframing the "alternative facts" as common when parents want to help their children live a more idealized way than they were able to, is a way to be able to bring the emotional temperature of the room back down in order to continue the history gathering.

Modeling Simple Speech and Nonreactive Repetition of Information During Interview and Feedback

One of the most useful family systems interventions clinicians can offer in dementia assessments is modeling productive communication strategies. This provides each member of the family system with concrete tools they can easily use in their regular interactions with the patient. As dementia progresses, the patient's ability to process long, rapidly spoken sentences with multiple clauses significantly diminishes. Family members may not realize that the patient can no longer understand most of their communications. Without accurate comprehension, memory deficits are exacerbated. I make it a point to speak in short sentences using plain language when a family with a moderately dementing family member is in my office. At some point during the initial interview, if I notice that a family member's speech patterns may be hard for the patient to process, I will comment on my speech, "Mr. Cohen, I…speak...slowly. I…use…short sentences. It...is...easy... to…understand…me. Your …wife ...may ...understand ...more …when ... you ...speak ...this…way."

At all dementia stages, modeling nonreactive responses to memory loss gives exasperated caregiver tools that will lower the temperature of their

interactions with loved ones who have dementia at home. Most clinicians have had the frustrating experience of engaging the patient, his wife, and their children in a long, emotionally charged, often tearful conversation about a safety issue like driving. At the end of the conversation, the patient interjects, "Ok, but I still have a question. They are saying I can't drive. Do you think I have a problem driving?" A collective groan arises from everyone in the room. Mr. Rind has forgotten the conversation.

Rather than viewing the conversation as a waste of time, the clinician can more fruitfully view this as an opportunity to model nonreactive responses to patients asking the same questions over and over again. "Mr. Rind, that's a great question. The results of the testing show that it is not safe for you to drive. Your kids are going to arrange for a taxi service/ senior center van to pick you up for all of your scheduled activities. I have written this down on this piece of paper so if you have questions about it, it is all here for you."

Hallway Conversations and Pre-Appointment Phone Calls

Disclosing information about a loved one's decline in function is often a painful experience. Doing so in front of the loved one, particularly when the person in question has little awareness of their decline, is particularly painful. If Ms. McDonough genuinely feels like she is having no problems and her daughter sits in front of her and claims to her doctor that she can't cook or manage her house anymore, the disclosure may feel like a particularly bitter betrayal. Because disclosure is difficult, many spouses and children will attempt to provide information outside of the consultation room. Sometimes this comes in the form of a pre-appointment phone call, letter, or email. Other times the true nature of the patient's cooking abilities is disclosed in the hallway after the initial consultation has wrapped up as the family is walked back out to the waiting room.

My practice policy has always been to respectfully accept any information that is offered. I will slow my steps to give more physical distance and time for the hallway disclosure. I will also listen attentively to input via the phone. That said, I believe there is a benefit to having frank but sensitive conversations about the patient's function with the patient present. The neuropsychologist's office may be the first place where an open expression of the depth of the concerns of family members has occurred. Better to have the conversation in the doctor's office where most members of the family including the patient will be on their best behavior. The neuropsychologist has the opportunity to "make space" for various family member perspectives with phrases like, "Mr. Rao, I know you feel differently. Is it alright if I get your wife's perspective on this?" or "OK, I am going to ask your husband about your cooking, he isn't going to get in trouble for this after the visit is he!?" Injecting gentle humor to lighten the exchanges is often helpful.

Another benefit to airing serious concerns about their family member in the consulting room is the opportunity to see the clinician model nonreactive acceptance of the fact that patients may have dramatically different perspectives on their abilities than family members do. As a clinician, my goal is not to convince the person with Alzheimer's disease that they have a memory problem, because I know that the part of their brain that allows them to know their memory isn't working- isn't working any longer. When family members understand that I am not trying to convince their father he has a memory problem and I simply respectfully acknowledge that he has a different point of view, they often begin the process of letting go of their goal "to finally convince Dad there is something wrong with him."

Finally, while the patient may not recall the conversation about their emerging difficulties, family members have practiced sharing information that the patient can't agree with due to their neurologically based unawareness of their deficits. Such conversations will be necessary on an ongoing basis at home to maintain safety regarding issues such as driving, using the stove, and managing medications.

Multigenerational Considerations While Conducting the Testing

If extended family members contribute to the testing phase of the neuropsychological assessment process, it is typically through filling out formal behavior rating forms regarding the experiences and behaviors of the patient (e.g., the BEHAVE-AD [13]). Additionally asking family members to fill out instruments that measure their own well-being and caregiver burden sends a powerful message that caregiver's health and well-being matter. The Caregiver Reaction Assessment Scale [14] is an example of one of many available caregiver burden checklists. I use this particular instrument as it has questions addressing specific caregiving time and tasks, as well as perception of other family members involvement and positive/negative emotional effects of the caregiving experience.

It is important to hand (or email) caregiver checklist forms to every family member, not just the primary caregiver. Asking multiple family members to fill out forms regarding their caregiving experience invites the multigenerational family system to engage in a thought experiment. As family members fill out the form, knowing other members are doing the same, it is likely that they will be mentally comparing their answers to imagined answers of other family members. For example, as Ms. Jones' son fills out the form asking about the number of hours a week he spends caring for his father, whether he is able to get away for short periods of time to run errands for himself like get a haircut, whether his sleep is being disturbed, and about his feelings of anxiety and sadness, he will likely be imaging his mother and older sister's responses to the same form. When members of the extended family system are asked to fill out the caregiving inventory, the relative levels of caregiver responsibility and emotional burden of various family members are literally being placed on family members' radar screens. It is an opportunity for empathy and an invitation to imagine other family members stepping into caregiving roles.

Because issues of caregiver burden are not relevant in cases of mild cognitive impairment or in assessments of individuals who are anxious about the effects of normal aging, I often wait for the end of the initial clinical interview to determine whether the caregiver burden inventories should be handed out. I will refer to the multigenerational family genogram as I ask how the instruments can be best sent to family members who are not present.

Dementia Management: The Feedback Session

One is always conducting feedback sessions in the context of a multigenerational family system. The question is, how many of the family members are in the room or on speaker phone at the time the session is being conducted?

When important family stakeholders are missing from the feedback session, the work of communicating assessment results and negotiating a care plan still gets done eventually; the clinician is just not the one managing the interaction. Absent family members will be told about the findings, or the findings will be withheld from them. The communication will likely occur in the way important communications typically flow in the family, reinforcing alliances and estrangements. The content of the feedback session will be relayed accurately or inaccurately. If information is relayed inaccurately, this may be in error as occurs in the game of "telephone" or, purposefully, in order to soften blows or in some cases amplify need. One benefit of discussing the family genogram in the initial assessment is that clinicians will have an opportunity to comment on missing family members, discuss and predict issues with communicating, and therefore inoculate against unproductive flows of information. "You know, from talking with you during our initial session, it sounds like your sister plays a pretty big role in your life. I am surprised she isn't here [pause to discuss]. I wonder how she will hear about the news we are talking about today? [look to the family] Who is the person who usually shares things with Aunt Jo?"

Disclosing the Diagnosis

There is a considerable body of literature addressing disclosing the diagnosis of Alzheimer disease and related dementias [15]. Family beliefs about diagnosis disclosure are often influenced by culture [16] and generational status [17].

Family member's concern that their loved one will react to the news like they would have reacted prior to the onset of their dementia with emotional devastation, sadness, and anxiety may lead them to ask clinicians not to disclose the diagnosis [18]. This fear of emotionally harming the patient often leads to requests that the word "Alzheimer's" not be used or the patient not be present during the feedback session. At times, different family members within the multigenerational family system may have different views on diagnosis disclosure, with some requesting disclosure while others requesting the diagnosis be withheld. Levels of acculturation and generational status may play a role in shaping various family members' opinions about diagnosis disclosure.

As clinical care across all specialties has become more collaborative, a default stance on diagnosis disclosure in all medical conditions has become truth telling, with a consensus regarding the benefits of disclosure of Alzheimer's disease [19, 20]. My clinical policy when family members ask me not to disclose the diagnosis is to share my beliefs about the benefit of being open regarding an Alzheimer's diagnosis: (1) patients, particularly in the early stages of the disease, have the opportunity to collaborate on treatment and management decisions; (2) family members will have a shared historical moment to refer back to in future conversations with the patient, even if the patient does not fully remember the conversation, "Mom, do you remember when we were in Dr. Postal's office? Because of the Alzheimer's disease, it isn't safe for you to drive," and (3) due to problems with lack of awareness and changes in emotional processing, family members are often much more upset about the diagnosis than are patients.

That said, in situations where family members are adamant and particularly when the dementia is significantly progressed, I will respect their wishes. I will often say to them, "Is it alright if I discuss the problem using the phrase 'the type of memory problem that tends to get worse over time?'" Should family members have conflicting views about disclosure, I will honor the wish of the spouse first.

For specific strategies regarding what to say to patients and families when disclosing dementia in feedback sessions, readers may wish to refer to the chapter on dementia in *Feedback That Sticks: The Art of Effectively Communicating Neuropsychological Assessment Results* [21].

Family Politics of Caregiving

Which family member is dropping meals off at Mom's house every evening, taking her to medical appointments, building an in-law unit for her in their home, and fielding frantic calls in the middle of the night is typically multi-determined by both individual family dynamics and larger cultural forces. Burdens are often not equally shared across multiple members of the family system. As a clinician, beyond understanding who is playing which role, a question of intervention arises when burdens are not distributed evenly. My bias, based on my understanding that caregiver burnout leads to mental and physical health problems in caregivers and worse patient outcomes, is to intervene to more widely distribute the caregiving roles and to set up mechanisms for regular meetings to course correct and redistribute the caregiving activities as the disease progresses. I will share that bias with the family and explicitly collaborate with them to redistribute caregiving roles.

The place most families start is with a gender bias in caregiving roles. Daughters, sisters, wives, and daughters-in-law typically shoulder the largest caregiving burden [22] with wives and daughters estimated to provide two-thirds of all dementia care [23]. Commenting on this larger societal phenomenon to family members is a way of opening up the conversation about who is pulling their weight without blaming the specific people in the room. "It is easy to fall into gender

roles early on when the caregiving activities are light. But as time goes on, before everyone knows it, those minor roles have become really, really big! And it makes sense to take some time and say, ok, let's widen the circle of folks who are taking on caregiving roles." Reframing unbalanced caregiver burdens as having crept up without anyone realizing what was happening allows family members to more easily enter into conversations about sharing caregiver activities without blame and guilt.

Depending on cultural and specific family expectations, parents may feel uncomfortable asking children to participate in caregiving. In those cases, the burden of caregiving will fall entirely on the shoulders of the spouse. Grown children may not realize prior to the assessment the extent to which one parent is now caring for the other. They may understand that their parent needs help, and genuinely want to help, but unwittingly offer help in a way that forces their parent to reengage in the "moment of asking" over and over. I hear from adult children frequently, "Mom is so stressed. I keep telling her that she should call me whenever she needs some time off. But she won't." I will say to children, "It is really clear that you see your mother is stressed and needs some time to herself. I'm not a mind reader, but I will bet that your mom doesn't want to burden you. Here is an idea that might work. Why don't you sit down at the calendar with your mom and arrange a regular shift to be with your dad? It might be that every Tuesday afternoon from 1-4 you come by the house. She doesn't need to call and ask, you just show up. Ms. Pierce, when your daughter comes, you can go get your hair done, have lunch with a friend, or just take a walk."

As clinicians, we can transform vague offers of assistance into specific, scheduled commitments. As a homework assignment for the week after the feedback session, I will ask family members to all "take a shift." For example, daughter #1 now "owns" Friday afternoons so mom can have some free time. The son "owns" Saturday mornings when he will take dad out fishing, and Aunt June "owns" Thursday evenings where she will bring dinner and help mom and dad fill the weekly pill box. Daughter #2 who lives out of state will "own" Wednesday afternoons by paying for a caregiver to come into the home and give mom an extra afternoon of respite. Asking extended family members to plan to meet once a quarter via phone or in person to determine what needs the patient has, and who will take on which tasks, helps families to view their caregiver roles as necessarily evolving over time in the context of a progressive dementia.

Normalizing Common Painful Caregiving Dynamics

Some common family dynamics that arise when caregiving for patients with Alzheimer's disease are particularly painful for the caregivers. Sharing these common patterns with families normalizes the caregiver's experiences or inoculates them from personalizing the experiences should the patterns arise in their home.

Lack of awareness of memory deficit often leads patients with dementia to misinterpret lost items as stolen. In these cases, memory loss plus unawareness equals a cognitively based rather than psychiatrically based paranoia. For example, If I lost my handbag and I have no awareness that I am forgetful, a reasonable assumption is that someone stole it. If many of my personal items are missing on a regular basis, I might come to the conclusion that someone is purposefully hiding my things. Why would they do this? Malice? I don't know, but what else makes sense? If my daughter insists that I can't drive, when I have no awareness that there are changes in my brain, my conclusion is that she is unreasonably interfering in my life. Why? I couldn't tell you, but it makes me resent her. Unfortunately, the family member who spends most time caring for their loved one often receives the brunt of the suspicions, resentments, and anger. It is always hard to hear a patient sing the praises of a child who lives across the country while lowering her voice to confide about the constant problems she has with her son who comes by her house to bring dinner every night.

Reframing and normalizing suspicion, anger, and rejection of assistance as a perfect storm created by thinking problems, coupled with a lack of awareness of those thinking problems, helps reduce the temperature in patient/ caregiver interactions. It is also important to educate caregivers that resistance to help and lack of awareness of deficits will only get worse over time. Many family members assume that as Dad's deficits get worse and worse, he will *finally admit something is wrong* and then he will see why he needs someone to set up his pill box. This belief will typically lead to more frustration for family members as they attempt to help the patient through daily activities and also to lead to delay of conversations about important safety issues (such as driving).

Assisted Living and Nursing Home Placement

Guilt, sadness, financial burden, conflict, relief, and fatigue are all typical threads that run through discussions of placement of patients into nursing homes. Depending on the predilections and finances of patients and family members, decisions regarding assisted living may be more or less fraught. It is often helpful to contextualize the conversation about nursing homes and assisted living facilities with family members as an ongoing rather than single conversation that should occur with input of a financial advisor and the needs and desires of multiple family stakeholders. Many families are not aware of the continuum of services that are available in the community for patients not interested in assisted living and nursing care. I will open up the conversation by letting families know that there are many community-based services through agencies that can assist with tasks from shopping to cooking to bathing and medication management. I also like to talk about the social benefits of assisted living options. Clinicians should have contact information for state elder care agencies ready for families that are ready for more information about caregiving options.

Dysfunctional Family Systems

Of course, having a dysfunctional family where members do not have each other's best interests at heart does not protect members of that family from developing dementia. Long-standing dysfunctional family patterns will likely be exacerbated by the stress and caregiving burden of Alzheimer's disease and require clinical support and intervention.

Your patient may have been physically abusive to his wife and children. He may continue to utilize intimidation to maintain control over family members, or he may be pleasantly dementing with a personality change that other family members experience as an improvement. A child who was a target of abuse in a family system may have taken on the role of primary caretaker as an expression of a long-standing role of servitude in the family or in an attempt to finally have value in her parent's eyes. The advent of a dementia diagnosis may be a catalyst for estranged children, siblings, or even spouses returning to care for a dementing patient. Unfortunately, long-overdue conversations/confrontations regarding abuse are irrevocably now colored by the patient's deteriorating mental status. When family members bring up their desire to confront a patient as a condition of them participating in caregiving activities, I will often suggest that they process the planned communication with a psychotherapist who can assist them in developing appropriate content and managing their expectations and emotional needs. I offer to consult with the therapist regarding cognitive limitations and abilities of patients at the particular stage of their dementing family member.

Sadly, children, spouses, or other family members may adopt an abusive role toward the patient. Individuals with dementia are at greater risk for elder abuse than those in the general population [24]. This abuse may take the form of overcontrol and bullying, financial abuse, neglect, or physical abuse. In some cases, family members use the neuropsychological assessment as an instrument to gain power over the patient and may provide false or misleading information in service of that

goal. A moment may come in the initial clinical interview or feedback session when the feeling "something is not right" occurs to clinicians. In other cases, telephone calls from children not aware of or invited to the assessment will shed light on complex family dynamics that were glossed over or obscured during the initial clinical interview. Another advantage of constructing a family genogram and identifying adult children who are not at the initial clinical interview is the opportunity to ask not only, "Why do you think they couldn't be here?" but more specifically, "Did they know about the assessment and were they invited?"

When clinicians become aware of or suspect abuse is occurring, the clinical assessment process will include decision-making regarding appropriate reporting in order to protect the patient (see the chapter on elder abuse in this volume). Consultation with state laws and regulations regarding abuse reporting requirements is critical to appropriate management.

Engaging Families in Conversations about Safety

"How does your dad do on the road? Is he a safe driver?" *"I don't know! I sure won't drive with him!"*

Anosognosia on the part of the patient, psychologically based denial from spouses and grown children, and reluctance to overtly disrupt power structures within the multigenerational family system often all converge to keep family members with dementia engaging in activities that are no longer safe, such as driving and possession of firearms.

Driving

In some cases, test scores are such that a clear, authoritative directive that Mr. Jones should no longer drive must be made by the clinician. In other cases, test data are not as conclusive, and the appropriate directive is for the patient to have an on-road driving test prior to continuing to drive and follow-up road tests every 6 months as the dementia progresses.

In a discipline such as psychology with a tradition of "one down" or neutral stances regarding communication with patients, clinicians may find taking an authoritative stance particularly difficult. Even when clinicians feel comfortable with taking an authoritative stance, complex multigenerational family dynamics often result in difficulty engaging family members in these conversations. Obtaining one's driver's license is an American rite of passage into adulthood. Having that license taken away is not only experienced as diminishing for the patient, but it is also an overt rupture in the power dynamics within the family system. The child or spouse who must insist the patient stop driving is explicitly and publically breaking long established hierarchies in the family. While those hierarchies may have been quietly eroding over the course of a few years as a spouse or child takes on more responsibilities vis a vis the patient, the moment of taking the license away is often experienced as a time when family members must publically acknowledge that now things are changed within the family. It is often a moment of painful clarity.

Because of the painfulness of the moment and a desire to avoid what are often ugly confrontations with unaware patients, families may convince themselves that "compromises" regarding driving are reasonable. "*Dad only drives to the grocery store and back."* Explicitly acknowledging the difficulties and complexities of the emotional binds the family is experiencing regarding driving creates space for family members to consider alternatives to inaction. Reframing the driving test as a financial safety mechanism often motivates family members and eases past the patient's anosognosia. "If you get into a car accident Mr. Jones, even if it wasn't your fault, and they get the feeling you have a memory problem? Maybe because you are asking questions over and over at the accident scene? The other driver could sue you. And when they get ahold of your medical records showing you have a medical condition, dementia, that could interfere with your driving…and you don't have a test on file showing you are

safe, you could lose everything you ever worked for." [Look directly at the family] "Everything you have ever worked for." At this juncture, most grown children stop suggesting that short trips to the grocery store are not an issue and instead ask, "Where can he get that test?"

Guns

In a country where a third of households report gun ownership [25], the presence of guns are an important safety issue for neuropsychologists to address when working with patients who have dementia and their families. I first became aware of this issue as a postdoctoral fellow when one of our memory disorders clinic patients with reduplicative paramnesia became convinced that the neighbor's lawn was encroaching on his lawn. One night he took out his shotgun and shot up the neighbor's lawn. As clinic staff, the delusional misidentification of place wasn't the surprising part. A patient with moderate dementia having access to firearms was. We began asking patients and their families (1) do you keep guns in your house, (2) are they loaded, and (3) why are the guns present? What we found was dramatic [26]. Sixty percent of demented patients in our Southern US clinic lived in households with guns. Of those families who kept guns in the house, 83% reported that either the guns were kept loaded or the family was unsure if they were loaded or unloaded. Only 16.9% of families specifically kept the guns unloaded. The presence of guns and whether they were loaded was not correlated to level of dementia or level of behavioral disturbance, with moderately and severely demented individuals, and those severely behaviorally disturbed just as likely to have access to loaded guns. The number one reason families of demented patients kept loaded guns in the house? "Safety." The reflexive notion that guns protect family members was typically not reexamined in the context of profound impairment in judgment, the presence of agitation, and even an inability to recognize family members as familiar people.

In order to have a conversation about gun safety, clinicians must first ask patients and families if there are guns in the household. As gun ownership is often associated in this country with ideas about personal liberty, conversations about removing guns from the household typically involve similar family dynamics found during conversations about giving up a driver's license.

Conclusion

A thread that runs through many of the suggestions in this chapter is offering clinical attention and respect to the complex interactions of patients with dementia and the multigenerational family systems who care for them. During the assessment, I am conscious that the patient in front of me is battling to make sense of and maintain dignity in a world where their mental tools are slipping away. Family members are attempting to redefine family roles while grieving for the relationship with the patient they have known – typically while managing multiple conflicting needs of other family members and societal expectations. Understanding the pressures and strengths of the family dynamics is complicated for clinicians as changing societal expectations and the diversity inherent in different cultures and unique family dynamics result in an almost limitless variety of presentations. Clinicians must therefore design our assessments to specifically ask families about dynamics, preferably in person, and be prepared to utilize that understanding to improve diagnostic accuracy and support the multigenerational family system as care plans are developed and carried out.

Clinical Pearls

- Inviting members of the patient's extended family to attend the initial consultation and feedback sessions is a multigenerational family systems intervention. It is a strong message to the caregiver that the burden of providing

information that often contradicts the patient's certainty that there is nothing wrong, the burden of hearing their worst fears about the patient confirmed, the burden of taking actions to insure the patient's safety (e.g., driving), and the burden of everyday caregiving are not theirs alone to shoulder.

- Some family members may live far out of town or be unable to get time off. Offering the option of calling into the initial consultation or feedback session or attending via video conference will often secure their presence.
- As early as practical in the initial clinical interview, engage the family in drawing a genogram, a family tree that maps the relationships between the members of the extended family and provides insight into conflicts, alliances, and patterns of caregiving.
- Ask every family about cultural expectations for caregiving and whether there are conflicting expectations based on who is more acculturated and which generation is involved. Asking rather than assuming allows clinicians to enter the discussion about the family caregiving plan during the feedback session maximally equipped to assist family members in working toward a sustainable caregiving plan.
- Keep in mind that role strain and role conflict is common, particularly for children caring for one or more sets of parents while managing careers and their own family.
- Because the answer to the question, "when did the symptoms begin?" can vary based on cultural and unique family systems perspectives, asking very specific questions about each activity of daily living is key to clearly eliciting an accurate understanding of the patient's clinical course.
- At all dementia stages, modeling nonreactive responses to memory loss gives exasperated family members tools that will lower the temperature of their interactions with dementing loved ones at home.
- There is a benefit to having frank but sensitive conversations about patients' function with the patient present. Clinicians have the opportunity to "make space" for various family member perspectives with phrases like, "Mr. Rao, I know you feel differently. Is it alright if I get your wife's perspective on this?" or, "OK, I am going to ask your husband about your cooking, he isn't going to get in trouble for this after the visit is he!?" Injecting gentle humor to lighten the exchanges is often helpful.
- Asking multiple family members fill out forms regarding their caregiving experience invites the multigenerational family system to engage in a thought experiment. The relative levels of caregiver responsibility and emotional burden of various family members is literally being placed on family members' radar screens. It is an opportunity for empathy and an invitation to imagine other family members stepping into caregiving roles.
- Clinicians can collaborate with members of the family system to more widely distribute the caregiving roles and to set up mechanisms for regular meetings to course correct and redistribute the caregiving activities as the disease progresses.
- Grown children may not realize the extent to which one parent is now caring for the other. They may understand that their parent needs help, and genuinely want to help, but unwittingly offer help in a way that forces their parent to reengage in the "moment of asking" over and over. As clinicians, we can transform vague offers of assistance into specific, scheduled commitments.
- Reframing and normalizing suspicion, anger, and rejection of assistance as a perfect storm created by thinking problems, coupled with a lack of awareness of those thinking problems, helps reduce the temperature in patient/ family member interactions.
- Taking a driver's license away is often experienced as a moment of painful clarity within the extended family system, where eroded hierarchies must be acknowledged. Explicitly acknowledging the difficulties and complexities of the emotional binds the family is experiencing creates space for family members to consider alternatives to inaction. Reframing the driving test as a financial safety mechanism often motivates

family members and eases past the patient's anosognosia.

- Clinicians should ask family members whether there are guns in the patient's household. The reflexive notion that guns protect family members is not necessarily reexamined in the context of profound impairment in judgment, the presence of agitation, and even an inability to recognize family members as familiar people.

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Part II

Neuropsychological Assessment of Older Adults: Special Considerations/Common Issues

Medications and Cognition in Older Adults

10

Gregg L. Caporaso

Practicing clinicians cannot escape the irony that elderly patients are more predisposed to medication side effects (e.g., due to reduced renal clearance) and to cognitive disorders (e.g., Alzheimer's disease), and yet this same population is prescribed more medications, some of which may impair cognition. It is therefore incumbent upon the clinician to recognize when cognitive problems might be due to medications or combinations of medications, which medications are the most common offending agents, and how to treat these individuals optimally, by either substituting safer drugs or using non-pharmacological therapies. In addition to adverse motor effects such as impaired fine motor coordination and imbalance, many medications prescribed to elderly patients can produce adverse cognitive effects that impact attention, memory, and executive functions. The scope of this potential problem is immense, with upward of one-third of older adults taking psychotropic medications like antidepressants, anxiolytics, antipsychotics, and sedative-hypnotics [1]. Many more elderly patients are prescribed medications for non-neuropsychiatric conditions that can also negatively affect cognition (e.g., antihistamines).

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Clinical Assessment

History is always key in diagnosing the potential cause of cognitive decline. For example, progressive cognitive decline of insidious onset is typical for Alzheimer's disease, whereas forgetfulness after new treatment for hypertension might be due to beta-blocker use. It should be kept in mind that the addition of a new medication may unmask an underlying incipient cognitive disturbance such as neurodegenerative dementia or borderline cognitive function related to prior cerebrovascular disease. Indeed, preexisting dementia puts patients at 2–3 times the risk for developing delirium [2]. In obtaining a cognitive history, reports from a spouse, adult child, or caregiver are essential since cognitive impairment or behavioral changes may not be apparent to the patient. In this regard, a correlation between the addition of a new medication or change in dose of an existing medication can be important in identifying an offending agent.

Laboratory assessment should be directed at potential effects of medications on metabolism (e.g., hypokalemia related to diuretics or hypoalbuminemia resulting in higher circulating drug levels), serum levels of some medications (e.g., antiepileptic toxicity), or supervening medical conditions that can affect drug clearance or potentiate drug effects (e.g., complete blood counts and urinalysis to diagnose urinary tract infection). One must keep in mind that most

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elderly patients have reduced muscle mass and therefore lower serum creatinine values, so that a value within the normal laboratory range may actually represent impaired renal clearance in these individuals [3]. Consequently, most medications should be started at reduced doses in the elderly population, with upward titration proceeding slowly and cautiously ("start low, go slow").

Medications That Can Affect Cognition

Though many medications have the potential for affecting cognition, there are several classes of medications that are the most common offenders (Table 10.1). Rather than an exhaustive review of any potentially problematic drugs, this section will discuss those medications that the clinician is most likely to encounter in a typical hospital or office practice. In addition, toxic effects associated with drug overdose will not be discussed so that the focus will be on cognitive and behavioral problems that arise during normal prescribing practice. Cognition-enhancing drugs such as those used to treat Alzheimer's disease (e.g., donepezil, memantine) will be covered elsewhere in this volume. One convenient way to approach these various medications is by dividing them into neuropsychiatric drugs (i.e., drugs that are designed to act on the nervous system) and systemic drugs (i.e., drugs that primarily target tissues outside the nervous system).

Neuropsychiatric Drugs

Antidepressants

Depression can produce cognitive impairment, usually as attentional deficits that can resemble memory loss, so-called pseudodementia. It can also worsen cognition in patients with underlying cognitive impairment. Treatment of depression in patients with or without cognitive impairment may therefore have benefits on cognitive functioning in this group [4]. However, positive effects on cognition in the elderly can depend on the choice of antidepressant [5], and certain antidepressants have the potential to worsen cognition.

Tricyclic Antidepressants

As a group, tricyclic antidepressants (TCAs, e.g., amitriptyline, nortriptyline, imipramine, clomipramine, desipramine, doxepin) are effective antidepressants but have anticholinergic effects that can worsen memory functioning in the elderly. Given the cholinergic deficits seen in age-related illnesses such as Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies, it is not surprising that the elderly population may be especially sensitive to the negative cognitive effects of this class of medications [6]. Approximately 5–7% of geriatric inpatients who received a TCA may develop delirium [7, 8]. In a mouse model of memory and learning, the TCAs amitriptyline and imipramine worsened memory and potentiated the effects of the anticholinergic agent scopolamine, whereas the selective serotonin agent fluoxetine had no effect on memory and could reverse scopolamine's negative effects [9].

TCAs have been demonstrated to have negative effects in the elderly on measures of verbal memory [10–13]. In a randomized controlled crossover trial of patients with Alzheimer's disease, subjects receiving clomipramine had both greater acute and lasting improvements in depression compared to placebo but significantly lower cognitive scores [14]. However, low-dose imipramine (25 mg/day) was shown not to worsen memory in patients with Alzheimer's disease with or without depression [15]. In a large population-based study ($N = 1488$ patients), TCA use was not associated in the short or long term with cognitive deficits or memory impairment [16].

The atypical TCA tianeptine has fewer anticholinergic and cardiovascular side effects than older generation TCAs [17]. In a small study of elderly patients with depressive symptoms, tianeptine reduced depression significantly, as well as improved cognition [18]. In a larger trial

Table 10.1 Medications that can affect cognition (see text for discussion)

Medical condition	Drugs that might impair cognition	Safer drug alternatives	Non-pharmacological alternatives
Depression	Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin)	SSRIs (e.g., fluoxetine, paroxetine, sertraline, citalopram, escitalopram) SNRIs (e.g., venlafaxine, duloxetine) Tianeptine	Counseling Psychotherapy Group therapy Cognitive-behavioral therapy
Psychosis, agitation	High-potency antipsychotics (e.g., chlorpromazine, haloperidol)	Atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine) Aripiprazole?	Structured environment Regular daily routines Trained caregiver
Insomnia	Benzodiazepines (e.g., alprazolam, triazolam, temazepam, diazepam, lorazepam) Diphenhydramine	Z-drugs (e.g., zolpidem, zaleplon, eszopiclone) Chloral hydrate Melatonin Ramelteon Suvorexant?	Proper sleep hygiene (i.e., no late-day caffeine, no napping, regular exercise, fixed bed/awakening time) Cognitive-behavioral therapy
Parkinson's disease	Anticholinergics (e.g., trihexyphenidyl)	L-dopa Dopamine agonists (e.g., pramipexole, ropinirole) MAO-B inhibitors (e.g., selegiline, rasagiline) COMT inhibitors (e.g., tolcapone, entacapone)	Exercise Neurorehabilitation Deep brain stimulation
Epilepsy	Phenobarbital Primidone Topiramate	Carbamazepine Valproate Levetiracetam Lamotrigine	Vagus nerve stimulation
Pain	Opiates (e.g., morphine, codeine, oxycodone, hydrocodone)	Acetaminophen NSAIDs Tramadol Topical agents	Biofeedback Physical therapy Acupuncture Chiropractic therapy
Motion sickness, vertigo	Scopolamine	Meclizine[a] Dimenhydrinate[a]	Vestibular exercises
Hypertension	Beta-blockers[b]	Diuretics (e.g., hydrochlorothiazide) ACE inhibitors (e.g., captopril, lisinopril, ramipril) Angiotensin receptor antagonists (e.g., losartan)	Exercise Weight reduction
Urinary urge incontinence	Oxybutynin	M3 selective agents (e.g., tolterodine, trospium, solifenacin, darifenacin) Mirabegron?	Scheduled toileting Fluid restriction Caffeine avoidance

ACE angiotensin-converting enzyme, *COMT* catechol-*O*-methyltransferase, *M3* muscarinic receptor, *MAO-B* monoamine oxidase-B, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant

[a]There are abundant data for scopolamine's amnesic effects but less so for these other two agents listed

[b]Lipophilic beta-blockers such as propranolol or metoprolol are more likely to impair cognition compared to hydrophilic beta-blockers such as atenolol

comparing tianeptine with escitalopram in patients with major depressive disorder, there was greater improvement in multiple measures of cognitive function after controlling for changes in depression in the tianeptine group [19].

Selective Serotonin and Serotonin/Norepinephrine-Reuptake Inhibitors

Selective serotonin-reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, citalopram, escitalopram) and serotonin/norepinephrine-reuptake inhibitors (SNRIs, e.g., venlafaxine, duloxetine, desvenlafaxine) are the most commonly prescribed antidepressants. Fortunately, they do not seem to be associated with the negative cognitive effects seen with TCAs [20]. Escitalopram improved cognition as well as mood in depressed elderly patients with memory impairment [21]. Though sertraline seemed to provide greater cognitive benefits than fluoxetine in elderly patients with depression [5, 22, 23], the efficacy of fluoxetine appears to be comparable to that of paroxetine [24]. Fluoxetine may also provide some benefits for memory in non-depressed patients with mild cognitive impairment [25].

Duloxetine and venlafaxine do not affect histaminergic or cholinergic receptors and have been shown to improve certain cognitive measures in older depressed patients [26–28]. Given their apparent safety in patients susceptible to cognitive impairment and their potential for improving cognition, SSRIs and SNRIs should be considered preferred treatments for depression in older patients. The prescribing physician, though, should be aware of the risk, albeit small, of delirium induced by serotonin agents as part of the serotonin syndrome, which is also characterized by myoclonus, rigidity, hyperreflexia, tremors, and autonomic instability. The risk of this syndrome is increased when monoamine oxidase (MAO) inhibitors (and perhaps triptan migraine medications) are co-administered.

Other Antidepressants

Although selective MAO-B inhibitors are safely used to treat Parkinson's disease (e.g., rasagiline, selegiline), nonselective MAO inhibitors such as phenelzine and tranylcypromine are not routinely used to treat depression nowadays due to their risk in causing hypertensive crisis and lethal interactions with other medications. The norepinephrine-dopamine reuptake inhibitor bupropion is an effective antidepressant, often used in combination with SSRIs, as well as a useful aid for smoking cessation. However, bupropion can increase the risk of seizures and should be used with caution in elderly patients, especially those with Alzheimer's disease, who carry a two- to six-fold risk of seizures compared to age-matched control patients [29].

Antipsychotics

Antipsychotic drugs, or neuroleptics, are dopamine receptor antagonists used in the treatment of hallucinations or delusions that might occur in disorders such as schizophrenia or dementia. They are also used to treat affective diseases (e.g., bipolar disorder), Tourette's syndrome, and nausea. This group of medications carries the risk of extrapyramidal side effects (EPS) including parkinsonism (bradykinesia, rigidity, and tremors), dystonia, akathisia, and tardive dyskinesia. The first-generation "conventional" or "high-potency" antipsychotics (e.g., chlorpromazine, haloperidol) are less selective in their blockade of dopamine receptor subtypes and are associated with a greater risk of EPS. The second-generation "atypical" antipsychotics (e.g., risperidone, olanzapine, quetiapine) preferentially block serotonin 5-HT2A receptors more than dopamine D2 receptors and are believed to have a lower risk of EPS [30].

It should be noted that the use of either conventional or atypical antipsychotics in the elderly may be associated with increased mortality [31] and that the Food and Drug Administration has issued advisories that caution their use in this patient group [32]. The potential magnitude of this problem was highlighted by a recent study of the National Nursing Home Survey, which demonstrated that one quarter of nursing home residents are prescribed antipsychotics, and of these, perhaps 40% are prescribed antipsychotics inappropriately [33]. Though antipsychotics are commonly used in managing behavioral

problems in the elderly, their use cannot be endorsed in most patients. Indeed, many patients with Alzheimer's disease can experience substantial benefits in neuropsychiatric symptoms, as well as cognition and daily functioning, with treatment using approved dementia agents such as donepezil [34], rivastigmine [35], or memantine [36]. Furthermore, though many of the neuroleptics have been shown to improve cognition in patients with schizophrenia (e.g., executive function), there are fewer data on their effects in nonschizophrenic elderly patients.

Conventional Antipsychotics

The older neuroleptics such as chlorpromazine exhibit anticholinergic activity, so one might predict that they would detrimentally affect cognition in older individuals and in particular patients with Alzheimer's disease. The results of studies examining antipsychotic use in elderly demented patients have been mixed, with some studies showing no effect on cognition [37–39] and others demonstrating negative effects on cognition [40–42]. One should interpret these studies with caution, however, since dementia patients with psychotic symptoms or behavioral disturbances have a worse prognosis than patients without these problems and they tend to experience more rapid cognitive decline [43, 44].

Atypical Antipsychotics

The newer generation of antipsychotics seems to confer neuropsychiatric and sometimes cognitive benefits to elderly patients with psychosis, while being associated with fewer EPS [45]. However, the risk of EPS, as well as orthostatic hypotension and sedation, is not negligible, putting this group of patients at risk for falls and bone fractures.

Clozapine is a dibenzodiazepine with perhaps the lowest risk of EPS among neuroleptics. However, it carries a risk of agranulocytosis as high as 1% during the first several months (requiring weekly monitoring of blood counts) and roughly 0.01% after 1 year of use [46]. This agent also possesses anticholinergic activity, which can impair memory function, at least when studied in patients with schizophrenia [47]. Olanzapine has been shown to worsen cognition in patients with Alzheimer's disease, especially those with greater baseline impairment [48].

Compared with haloperidol, quetiapine had a wider range of benefits on psychiatric symptoms in patients with Alzheimer's disease and improved memory and daily functioning without producing significant EPS [49]. Quetiapine also showed neuropsychiatric benefits without cognition deterioration in an open-label pilot study of Alzheimer's patients [50]. Another small, open-label study using risperidone demonstrated improvement in psychosis, agitation, and aggression in patients with dementia without impacting cognition [51].

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study group randomized over 400 patients with Alzheimer's disease and psychosis or agitation to antipsychotic medications (risperidone, olanzapine, or quetiapine) or placebo [52]. When this group examined time to discontinuation as a primary study endpoint, they concluded that adverse effects offset any advantages on neurobehavioral symptoms of antipsychotics compared to placebo [53]. In a subsequent analysis of antipsychotic medication versus placebo, though, the authors indicated that treatment with olanzapine or risperidone (and perhaps quetiapine) improved certain behavioral symptoms but had neither positive nor negative effects on cognition. Similar benefits on behavioral symptoms without cognitive deterioration were seen with these three agents in another smaller study of outpatients with Alzheimer's disease [54]. A recent review of 69 studies in which quetiapine was used in older patients demonstrated that quetiapine worsened cognition, caused more falls, and resulted in higher mortality in patients with signs of parkinsonism [55]. However, these detrimental effects did not occur in patients with dementia. In addition, quetiapine was overall safer when compared to risperidone and olanzapine on measures of falls, stroke, and death.

Aripiprazole is a newer agent used in the treatment of schizophrenia, bipolar disorder, and as an adjunctive to antidepressants for major depression. Several recent placebo-controlled studies have demonstrated its efficacy in treating

hallucinations and delusions in patients with Alzheimer's disease with little negative impact on cognition or safety [56–58]. However, head-to-head studies with other antipsychotics will be needed to test whether it really is safer than older agents.

In summary, atypical antipsychotic agents may be useful in treating psychosis, agitation, and aggression in some patients with dementia without harming cognition, but the treatments must be individualized, and it would be prudent to start slowly with low doses to minimize the chance of adverse effects.

Sedative-Hypnotics and Anxiolytics

Insomnia occurs frequently in older patients and may have various causes. These include a consequence of aging, sleep apnea, restless leg syndrome, or various parasomnias, such as periodic leg movement disorder. Overnight sleep studies that monitor brain electrical activity, movements, and breathing are sometimes required for diagnosing sleep disorders. Depression and anxiety are among the most common causes of insomnia, so accurate diagnosis and directed therapy should be attempted before treating sleeplessness with more generalized sleep aids. Dementia is often associated with inverted sleep-wake cycles that result in daytime sleepiness and nighttime restlessness or wandering.

In managing insomnia, a trial of non-pharmacological therapy should be completed before prescribing hypnotics or sedatives. This includes counseling on good "sleep hygiene." The patient should be told to avoid caffeinated beverages in the afternoon and evening, refrain from napping, get regular exercise, set regular bedtime and awakening hours, and restrict the bed at night for sleeping and not watching television or reading. Cognitive-behavioral therapy has also been shown to improve sleep in elderly patients with chronic insomnia [59] and was shown in a randomized controlled trial to be superior to zopiclone in this patient population [60]. Such non-pharmacological interventions are underutilized despite their effectiveness [61]. When needed, sleep aids should be used judiciously (e.g., only 1–2 nights/week when a patient really needs to catch up on sleep) and should not be taken nightly.

Although they are still commonly prescribed for the treatment of anxiety, the use of short-acting benzodiazepines (e.g., estazolam, triazolam, temazepam) as sleep aids has largely been supplanted by the development of non-benzodiazepines or "Z-drugs" (i.e., zolpidem, zaleplon, eszopiclone) that also act as $GABA_A$ agonists but which are believed to have fewer side effects. It should be noted that the perceived safety vis-à-vis reduced daytime sleepiness of the latter group of medications might be due to the fact they have been unfairly compared to longer-acting benzodiazepines (e.g., nitrazepam) or inappropriate doses of short-acting agents such as temazepam [62].

Benzodiazepines are more potent in elderly patients due to target organ sensitivity, are cleared less efficiently due to reduced hepatic clearance and increased distribution volume, and can accumulate, resulting in cognitive impairment, psychomotor slowing, delirium, or sedation [3]. In the elderly, short-acting agents are preferred, and high-potency benzodiazepines (e.g., alprazolam) should be avoided due to increased risk of side effects, such as overuse and withdrawal symptoms upon discontinuation [63]. Two large epidemiological studies in older French men and women demonstrated an association between benzodiazepine use and cognitive decline [64, 65], whereas a third did not [66]. Benzodiazepines can impair reaction time, attention, and memory [67]. Longer-acting agents are more likely to produce impairment [68]. Whenever the clinician makes a decision to stop benzodiazepines, they should be withdrawn gradually (i.e., dose tapered over one to several weeks) to lessen the risk of delirium associated with drug withdrawal in the elderly [69].

When treating anxiety, SSRIs or SNRIs should be considered before prescribing benzodiazepines. In addition, buspirone has been shown to be at least as effective as sertraline in treating anxiety in the elderly without significant adverse effects [70]. In healthy older subjects, buspirone did not affect reaction time, psychomotor speed, or memory [71]. Nefazodone seems to be a safe

choice in treating elderly patients with anxiety and comorbid depression [72].

The so-called Z-drugs are the most commonly prescribed sleep aids in the elderly population. They are not without side effects and can produce hallucinations, delirium, and amnesia [73–75]. Most studies of these drugs have been conducted in younger individuals, with some showing cognitive impairment at commonly used doses [76] and others showing no significant effects [77–79]. Studies in the elderly have been limited. Following a single dose, zolpidem did not appear to affect attention or memory in healthy elderly individuals [80]. Weeklong administration of zolpidem also did not significantly impair psychomotor or cognitive functioning [81]. In contrast, another study demonstrated that older subjects experience memory impairment the day following dosing with zolpidem [82].

The antihistamine diphenhydramine is often prescribed as a sleep aid, especially by hospital staff, or taken by patients seeking over-the-counter remedies. It possesses anticholinergic activity and can induce delirium in elderly patients and can impair attention and memory [83–85]. Chloral hydrate can be an effective sleep aid in older patients that carries little risk of delirium but may increase the free concentrations of certain other drugs (e.g., warfarin) due to displacement from plasma proteins [3]. Although trazodone is commonly prescribed as a sleep aid in elderly patients due to its perception as a "safe" drug, a comprehensive review of the evidence for trazodone in insomnia identified few trials that were mostly performed in depressed patients. There was also evidence of possible tolerance and side effects that included daytime sedation, dizziness, and psychomotor impairment [86].

The orexin receptor antagonist suvorexant was recently approved for treating insomnia. The most common side effects of the medication include headaches, dry mouth, and excessive daytime sleepiness, and it should be used with caution in patients at risk for delirium [87]. In a meta-analysis of four clinical trials of the drug, suvorexant was demonstrated to be superior to placebo on subjective measures of time-to-sleep onset and total sleep time [88]. It remains to be determined whether the drug is safe and effective in patients with cognitive impairment or dementia.

Ramelteon is a selective melatonin receptor agonist that was recently approved by the FDA for treating insomnia. In one open-label study in subjects over age 65 with primary insomnia, ramelteon (8 mg) each night improved subjective measures of sleep latency and total sleep time over the course of 1 year [89]. This drug also appears to be safer and better tolerated than Z-drugs. In a placebo-controlled crossover study comparing ramelteon and zolpidem, older adults performed worse on middle-of-the-night balance tests and immediate recall tests when taking zolpidem, but there was no significant impairment when taking ramelteon [90].

Lastly, melatonin has been shown to improve sleep quality and possibly cognitive functioning in healthy elderly individuals [91]. It also appears to be an effective sleep aid in patients with dementia, reducing sleep latency and prolonging sleep duration, though long-term use may predispose to worsening affect [92]. In a randomized, crossover study comparing melatonin and zolpidem in healthy older individuals, a prolonged-release formulation of melatonin did not impact psychomotor functioning, memory, or driving skills, whereas zolpidem negatively affected all three measures [82].

Parkinson's Disease Medications

Multiple classes of medications are used in treating Parkinson's disease, including L-dopa, dopamine agonists (e.g., pramipexole, ropinirole), MAO-B (monoamine oxidase inhibitor, class B) and COMT (catechol-*O*-methyltransferase) enzyme inhibitors (which increase the bioavailability of dopamine), and anticholinergic agents (e.g., trihexyphenidyl). It should be kept in mind that cognitive dysfunction is common in patients with Parkinson's disease, either in the form of dementia with Lewy bodies, as a later complication of idiopathic Parkinson's disease, or due to depression, which occurs in more than half of Parkinson's patients during some point in their illness. As such, these patients may be particularly susceptible to untoward cognitive effects of medications described in this chapter. However,

drugs used specifically to treat Parkinson's disease might also have the potential for negatively impacting cognition.

L-dopa did not seem to impair cognition after 3 months of treatment in patients with Parkinson's disease with or without comorbid dementia [93]. The absence of negative cognitive effects of L-dopa seems to carry over into moderate or severe Parkinson's disease [94]. However, an earlier study failed to show any cognitive benefit of L-dopa in Parkinson's patients [95]. In patients with early Parkinson's disease, treatment either with L-dopa or the dopamine agonist bromocriptine improved cognition, whereas anticholinergic therapy worsened it [96]. Addition of the MAO-B inhibitor selegiline to L-dopa treatment may help improve cognition in Parkinson's patients without dementia [97]. The newer MAO-B inhibitor rasagiline does not seem to be associated with any significant cognitive or behavioral worsening [98].

In a randomized study of patients with early/mild Parkinson's disease, the D2/D3 dopamine agonist pramipexole significantly impaired verbal memory, attention, and executive function compared to L-dopa [99]. The same study group also showed that the D1/D2 dopamine agonist pergolide was comparable to L-dopa in its effects on cognition [100]. However, both pergolide and pramipexole might improve working memory in medically naïve Parkinson's patients [101]. It should be noted that dopamine agonists such as pramipexole or ropinirole have been linked to impulse control disorders in patients with Parkinson's disease (e.g., pathological gambling, compulsive sexual behavior, binge eating), the risk being perhaps 2–3 times higher than in patients not treated with dopamine agonists [102]. In a small study of patients with advanced Parkinson's disease, treatment with tolcapone, a COMT inhibitor, resulted in improved scores for attention, verbal and visual-spatial memory, and praxis [103].

The anticholinergic agent trihexyphenidyl is useful in treating tremors in Parkinson's disease [104, 105] and may also be of use in patients with tardive dyskinesia [106]. Trihexyphenidyl was shown to worsen executive function in patients with Parkinson's, an effect that is mediated by subcortical frontal circuits [107]. This medication was also demonstrated to impair cognitive shifting and memory [108]. In a crossover study of patients with drug-induced EPS, cognitive performance was better on the Parkinson's medication amantadine than in trihexyphenidyl [109]. Lastly, an uncontrolled study of elderly patients with schizophrenia demonstrated a dose-dependent correlation between global cognitive and memory impairment and chronic use of trihexyphenidyl [110].

Anticonvulsants

Anticonvulsants or antiepileptic drugs (AEDs) are used primarily in treating seizure disorders but also play an important role in the management of mood disorders, neuropathic pain syndromes (e.g., trigeminal neuralgia), and migraine headaches. Since these drugs function to reduce neuronal irritability, such as cortical seizure foci, vis-à-vis inhibiting neuronal excitability, they have the potential for impairing cognition, as well as other brain and spinal cord functions such as balance [111]. This is especially true in elderly patients, in whom the pharmacokinetics of AEDs may be different than in younger patients and who might be taking other medications that interact with AEDs [112]. Note also that the type of epilepsy (e.g., focal-onset versus primary generalized) may restrict the choice of appropriate AEDs. There should be a low threshold for seeking the guidance of an epileptologist when managing epilepsy in older patients who do not respond to monotherapy with first-line AEDs or who experience significant side effects.

At normal therapeutic doses, use of phenytoin, valproate, or carbamazepine did not seem to affect cognition significantly in most adult patients, though their safety in the elderly is less well established [113]. Carbamazepine seemed to produce fewer adverse effects on cognition compared to phenytoin, primidone, or phenobarbital in a large study of veterans [114], and a subsequent study in the same population showed no difference between carbamazepine and valproate [115].

In elderly patients on monotherapy for epilepsy (carbamazepine, phenytoin, or valproate), increasing the dose of their AED to a higher level within the normal dose range did not induce cognitive impairment or sedation [116]. A randomized study comparing valproate and phenytoin in elderly patients with new-onset epilepsy found no significant adverse cognitive effects and no difference between the two drugs [117]. However, a tolerability study of valproate in non-epileptic patients with Alzheimer's disease demonstrated cognitive worsening at a dose of 1500 mg/day, though doses less than 1000 mg/day might be safe [118]. Carbamazepine was shown to be superior to placebo in treating agitation and aggression in demented nursing home patients with no effects on cognition or functionality [119].

A large, randomized, double-blinded clinical trial comparing lamotrigine, gabapentin, and carbamazepine in geriatric patients with new-onset epilepsy showed similarly efficacy on seizure control among the three medications but significantly fewer adverse effects in the lamotrigine and gabapentin groups [120]. In a randomized, case-control study of Alzheimer's patients with seizures, levetiracetam improved attention and oral fluency and lamotrigine had a positive effect on mood, but phenobarbital caused persistent cognitive impairment [121]. Topiramate has been shown to impair cognitive speed, verbal fluency, and short-term memory in patients with epilepsy, whereas levetiracetam or lamotrigine seems to lack cognitive side effects [122, 123]. Other studies have demonstrated negative effects of topiramate on verbal fluency and attention in adults with migraines [124, 125]. In a small study of elderly patients with seizures comparing two different doses of topiramate (50 or 200 mg/day), approximately 13% of patients reported negative cognitive effects [126].

Vagus nerve stimulation (VNS) by means of an implanted electronic device is an approved therapy for medication-refractory forms of epilepsy and major depression. It has been shown to be effective in treating epilepsy in older adults and is associated with only mild, transient side effects [127]. Although only a small number of patients have been formally studied, patients with Alzheimer's disease who received VNS demonstrated improvement or stability at 1 year on several measures of cognition [128].

Opiates

The geriatric population is particularly susceptible to musculoskeletal and rheumatologic illnesses associated with pain. Although studies directly addressing this issue are lacking, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and topical agents (e.g., fentanyl patch or capsaicin lotion) are effective therapies that only rarely produce cognitive effects in elderly patients [129–132] (for some exceptions, see section on corticosteroids and NSAIDs).

For more severe or intractable pain, patients may be prescribed opiates (e.g., morphine, codeine, oxycodone) or combination medications (e.g., acetaminophen-hydrocodone). Though any opiate may of course produce sedation or cognitive impairment in patients of any age, one study of primary care patients with non-malignant pain found that problems with cognitive functioning were more likely related to psychological health and pain control than with specific opiate medications [133]. A review of postoperative pain management in elderly patients concluded that meperidine has consistently been shown to be associated with an increased risk of delirium, whereas this has not been shown for other commonly used opiates (e.g., morphine, fentanyl, hydromorphone) [134].

In using opiates, it should be kept in mind that tolerance for a dose administered chronically may subsequently be too high and result in delirium, sedation, or cognitive impairment following another intervention to reduce absolute pain levels (e.g., spinal nerve block, surgery). Also, given the substantial risk of abuse and addiction associated with opiates, physicians should attempt to substitute non-opiate analgesics or non-pharmacologic treatments (e.g., physical therapy) whenever possible.

Anti-Vertigo and Motion Sickness Agents

Anticholinergic and antihistaminergic agents are widely used to treat vertigo and motion sickness (e.g., seasickness). Dimenhydrinate and meclizine are antihistamines that are effective in relieving motion sickness and vertigo but which can produce psychometric slowing and sleepiness [135]. Although a case report noted memory loss and confusion in an elderly woman taking meclizine, there have been no studies specifically examining this drug's or dimenhydrinate's effects on cognition in older patients [136].

Scopolamine is an anticholinergic medication used to treat motion sickness and has been associated with memory impairment. In a blinded placebo-controlled study, it was shown to worsen cognition and behavior in a dose-dependent fashion in patients with Alzheimer's disease [137]. It has also been demonstrated to worsen memory in Parkinson's patients without pre-existing cognitive impairment [138]. In a comparison between healthy individuals of different ages, scopolamine impaired memory and constructional praxis in old but not young subjects [139].

Systemic Drugs

Cardiovascular Drugs

Hypertension is a common risk factor for carotid atherosclerosis and cerebrovascular disease. Ischemic changes in the brain may in themselves produce cognitive impairment or dementia (e.g., "subcortical dementia," Binswanger's disease) or contribute to the pathogenesis or potentiate the effects of other dementias (e.g., Alzheimer's disease). However, overaggressive lowering of blood pressure in treating hypertension can also cause cognitive changes. Elderly patients with a long history of hypertension might have cervical or cerebral blood arteries with poor compliance that require pressures greater than those considered normal in order to adequately perfuse the brain. Cerebral hypoperfusion can also occur with atrial fibrillation, congestive heart failure, myocardial infarction, or coronary artery bypass grafting (CABG) [140]. As such, it can sometimes be difficult to gauge the extent to which either underlying cardiovascular pathology versus therapies used to treat them may be contributing to cognitive worsening. With the possible exception of beta-blockers (see below), antihypertensives are not thought to affect cognition significantly. A review of several randomized, placebo-controlled studies and a meta-analysis examining the effects of antihypertension medications on dementia suggested that these medications, and angiotensin-converting enzyme (ACE) inhibitors and diuretics in particular, may help prevent or slow the progression of dementia [141, 142].

Beta-Blockers

Although propranolol is also used to treat essential tremor and prevent migraine headaches, the clinician is most likely to use beta-adrenergic antagonists, or beta-blockers, in elderly patients with hypertension or cardiac disease. Beta-blockers may exert biological effects in the CNS either specifically via activity at downstream receptors of central adrenergic pathways (e.g., projections from the locus coeruleus) or nonspecifically via neuronal membrane stabilization [143]. Lipophilic beta-blockers such as propranolol and metoprolol cross the blood-brain barrier and accumulate in brain tissue compared to hydrophilic agents like atenolol [144]. These differences in lipophilicity seem to correspond to the relative risk of CNS effects. Switching from a lipophilic beta-blocker to a less lipophilic agent was associated with improved sleep, concentration, and memory, and atenolol was less likely to produce sleep disturbances than metoprolol [145].

However, a comprehensive review of beta-blockers concluded they in general have minimal or absent effects on memory function, as well as in causing sleep disturbances, nightmares, or hallucinations [146]. A large, randomized, controlled study of antihypertensives in elderly women failed to find evidence of cognitive decline after 5 years of treatment with a diuretic and atenolol [147]. Elderly patients with hypertension randomized to the angiotensin receptor antagonist losartan experienced improved memory,

but those who received atenolol showed neither improved nor worse memory function [148]. Another study compared propranolol to placebo in young or middle-aged patients with hypertension and found little or no difference in performance on a battery of cognitive tests [149]. A small study in hypertensive veterans demonstrated no decline in cognitive performance with treatment using either propranolol or atenolol [150]. However, in a study of cognitively impaired elderly patients, use of beta-blockers was associated with a trend toward worsening memory [151].

Digoxin

Digoxin is a naturally occurring glycoside used to improve cardiac output in patients with congestive heart failure. Altered mental state and delirium can occur with toxic doses of digoxin [152] and have even been reported with so-called therapeutic serum concentrations [153]. However, at therapeutic dosages, digoxin may actually improve cognitive performance [154].

H2 Blockers and Proton-Pump Inhibitors

Histamine H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine) and proton-pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole) are widely prescribed for the treatment of acid-reflux disease and peptic ulcer disease and to help reduce the gastric side effects of medications such as aspirin. Both classes of drug inhibit acid secretion from gastric parietal cells. Stomach acid is necessary for the release of vitamin B12 from ingested food, and H2 blockers may reduce B12 absorption [155, 156]. Since vitamin B12 deficiency can cause cognitive impairment, dementia, or delirium, prolonged inhibition of gastric acid secretion may increase the risk of neurobehavioral symptoms [157].

A case-control study of elderly patients demonstrated an association between chronic use (at least 12 months) of H2 blockers or proton-pump inhibitors and vitamin B12 deficiency [158]. Another study showed that prolonged use of proton-pump inhibitors, but not H2 blockers, was associated with vitamin B12 deficiency in the elderly, though the consequences of this on cognition were not examined [159]. A longitudinal study of elderly African-Americans demonstrated that H2 blocker use doubled the risk of developing cognitive impairment [160]. Thus, it might be prudent to periodically check serum B12 levels (or sensitive surrogate markers such as methylmalonic acid and homocysteine) when using H2 blockers or proton-pump inhibitors in elderly patients.

There have been numerous case reports describing mental confusion in patients taking the H2 blockers cimetidine, ranitidine, or famotidine. However, a randomized, placebo-controlled, crossover of healthy elderly individuals showed no adverse effects of cimetidine on cognition, leading the authors to conclude that earlier case reports might have been due to specific patient sensitivities to this class of medications [161]. A large cohort study, in contrast, suggested that H2 blocker use was associated with higher risk of cognitive impairment or decline in cognitive functioning [162].

Urinary Antispasmodics

Urge urinary incontinence due to an overactive or spastic bladder may be treated with medications that have the potential to produce cognitive symptoms. Simple measures such as restricting fluid intake, avoiding caffeine, or scheduling frequent visits to the toilet can reduce the need for medical treatment in some patients. Others, though, may be prescribed anticholinergic medications directed against muscarinic M3 receptors that decrease bladder detrusor muscle activity (e.g., oxybutynin, tolterodine, trospium, solifenacin, darifenacin). As with any anticholinergics, these drugs can produce dry mouth, constipation, dizziness, and drowsiness. The risk for these agents to impair cognitive functioning is related to their ability to penetrate the brain and their interaction with muscarinic M1 receptors [163].

In a study of healthy elderly volunteers, solifenacin did not seem to affect cognition, whereas oxybutynin impaired several measures of cognition [165]. After 3 weeks of treatment, healthy elderly subjects experienced significant memory

impairment on oxybutynin in contrast to those on darifenacin, which showed no difference in memory compared to the placebo group [166]. Darifenacin was found to have no effects on cognition in another trial involving healthy elderly volunteers [167]. Tolterodine was demonstrated to produce reversible memory impairment in a single case report [168] but was found to have no effect on memory in a 3-week crossover study compared to oxybutynin [163].

Mirabegron is a beta-3 adrenergic agonist that causes relaxation of the detrusor muscle and was approved for use in the United States in 2012 for the treatment of overactive bladder. It does not have the anticholinergic effects of the older medications used for incontinence, but it is contraindicated in patients with poorly controlled hypertension and should be used with caution in those with other cardiovascular conditions [164]. No significant cognitive side effects have been reported to date, but this has not been studied addressed in the elderly population.

Corticosteroids and NSAIDs

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat various conditions associated with inflammation or pain (e.g., vasculitis, arthritis). Severe psychiatric symptoms, such as affective and psychotic conditions, may occur in upward of 5% of patients treated with corticosteroids [169]. Acute corticosteroid treatment, but not chronic treatment, seemed to induce memory impairment in patients with rheumatoid arthritis [170]. Steroid use has likewise been associated with reversible dementia [171, 172]. It should be noted that too rapid withdrawal of corticosteroid therapy can also affect the brain [173].

Though non-neurological side effects of NSAIDs are quite common (e.g., dyspepsia, renal impairment), they infrequently can cause aseptic meningitis, disorientation, hallucinations, and memory or attentional impairment, and the elderly may be at increased risk [174]. A large randomized, placebo-controlled study of patients with cardiovascular disease showed no difference in performance on multiple cognitive tasks with long-term low-dose aspirin therapy [175]. Aspirin failed to prevent cognitive decline in healthy older women participating in the Women's Health Study [176]. Neither naproxen nor celecoxib prevented cognitive decline compared to placebo in elderly non-demented subjects with a family history of Alzheimer's disease [177]. In contrast, a randomized, placebo-controlled study of patients with subjective memory impairment demonstrated improvements in executive functioning and memory, as well as increased cerebral metabolism on positron-emission tomography (PET) imaging with celecoxib treatment [178].

The effects of long-term NSAID use on reducing the risk of cognitive decline and dementia have been mixed [179], with most studies showing a possible protective effect [180–186] and others providing no evidence for such protection [187, 188] or demonstrating a potential detrimental effect [189, 190]. These diverse results likely reflect differences in patient or subject groups, types and doses of NSAIDs taken, age at first use, and length of therapy. Needless to say, a disappointment for those studying Alzheimer's disease is that no prospective clinical trial has yet shown that NSAID use prevents dementia.

Hormonal Therapy

There was initial enthusiasm that estrogen therapy might help prevent cognitive decline and dementia based on epidemiological studies of estrogen-replacement therapy in younger women. However, no benefits have been demonstrated in older, postmenopausal women [191, 192]. Indeed, the large Women's Health Initiative revealed that postmenopausal estrogen therapy was associated with significant risk of dementia (hazard ratio 1.76), as well as negative effects on selective cognitive measures such as verbal memory and lower brain volumes in the frontal lobe and hippocampus [193].

Testosterone levels in men decline with aging. Evidence suggests that this drop might contribute to parallel cognitive decline and that testosterone supplementation might prevent or be useful in

treating cognitive impairment, though neither the association nor the benefits have been strongly demonstrated in large-scale, rigorous trials [194–196]. Treatment of elderly men with low serum testosterone levels and no cognitive impairment with exogenous testosterone (either alone or in combination with the 5-alpha reductase inhibitor finasteride, which blocks conversion of testosterone to dihydrotestosterone) did not impact cognition [197]. Further, a 6-month randomized, placebo-controlled trial of testosterone in older men with low normal serum testosterone levels failed to show any effects on cognition [198].

The long-term effects of antihormonal treatments for breast or prostate cancers on cognition in the elderly are uncertain [199]. Treatment with the antiestrogen drug tamoxifen in women with breast cancer may be associated with cognitive difficulties later in life [200, 201]. However, the selective estrogen receptor modulator raloxifene, which is used to treat osteoporosis and reduce the risk of breast cancer in postmenopausal women, was shown to improve verbal memory versus placebo [202]. Androgen deprivation in men with prostate cancer seems to be associated with decline in some cognitive domains [203]. In elderly men being treated with androgen blockade for prostate cancer, no decline in cognition was noted after 12 weeks of therapy, and addition of estrogen failed to improve verbal memory compared to androgen blockade alone [204].

Cholesterol-Lowering Drugs

The 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase inhibitors commonly known as statins (e.g., lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin) are effective in lowering levels of total cholesterol and low-density lipoprotein (LDL) and have been important treatments in reducing the risk of coronary and cerebrovascular disease. Statin therapy in elderly non-demented women was associated with lower risk of cognitive impairment [205]. In the large Cardiovascular Health Study ($N = 3334$ patients), cognitive decline in the elderly was less in statin users, a finding that seemed to be in part independent of lowering cholesterol levels [206]. The most recent Cochrane review on the use of statins to prevent dementia concluded that there was no convincing evidence that statins prevent cognitive decline or dementia [207]. However, a more recent study examining statin prescriptions in Medicare recipients found that the incidence of Alzheimer's disease was reduced with certain statins and in specific demographics (e.g., pravastatin and rosuvastatin only reduced dementia risk in white women) and in particular found no significant risk reduction in black men with any of the statins [208]. Further research will be needed to confirm whether the benefits of statins in reducing risk of dementia is indeed gender- and race-specific.

Less is known about the cognitive effects of other cholesterol-lowering drugs on cognition. Treatment with gemfibrozil in elderly patients with hypertriglyceridemia and stroke risk factors improved cognitive scores and cerebral blood flow after several months compared to placebo [209]. Severe niacin deficiency can produce dementia (i.e., pellagra), and dietary niacin intake was found to be inversely related to risk of cognitive decline and Alzheimer's disease [210]. However, the effects on cognition in the elderly of high-dose niacin used to treat hypercholesterolemia (usually 500–2000 mg/day) have not been examined. Ezetimibe is a second-line cholesterol-lowering agent that inhibits cholesterol absorption from the gut. In a small study of elderly patients with atrial fibrillation, those who received atorvastatin plus ezetimibe demonstrated improvements in cognitive speed and memory as well as less medial temporal lobe atrophy at 1 year compared with the placebo group [211]. A follow-up examination by the same group showed reductions in multiple markers of serum inflammatory markers in the atorvastatin plus ezetimibe patients, suggesting a protective mechanism for preservation of hippocampal volume [212].

The clinician must be vigilant in identifying medications that can cause or contribute to cognitive impairment in the elderly. In this age of polypharmacy, the potential for inappropriate or overprescribing has burgeoned, yet the increasing

use of electronic medical records might help reverse this trend. Non-pharmacologic interventions (e.g., counseling, structured environment, group activities) should be considered in treating affective and behavioral disturbances, single agents should be used whenever possible, and drugs with potential anticholinergic (i.e., TCAs) or extrapyramidal (i.e., neuroleptics) side effects should be eschewed.

Clinical Pearls

- In prescribing any medications for elderly patients, follow the rule: "start low, go slow." Elderly patients may require lower doses of a given medication than younger patients, so by starting at the lowest possible dose and titrating upward slowly, you will be more likely to identify the least amount of medication required as well as minimize any potential side effects.
- Avoid polypharmacy and keep abreast of what medications are being prescribed by other physicians. Increasing adoption of electronic medical records, patient-centered medical home (in which the multiple needs of a patient are coordinated through a primary/personal physician), and electronic prescribing are ways to help reduce the number of medications for a given patient and prevent deleterious interactions and side effects.
- When possible, select medications that may be used to treat more than one of the patient's medical conditions in order to reduce the patient's number of medications. For example, the SNRI duloxetine can be used to treat depression as well as painful diabetic neuropathy, or propranolol might be a good choice of antihypertensive for a patient with essential tremor.
- Before prescribing sleep aids in elderly patients, especially those with cognitive impairment, try promoting healthy sleep habits, so-called good sleep hygiene. That is, instruct the patient or caregiver to set regular awakening and sleep times, avoid caffeine in the afternoon and evening, and restrict the bed for sleep and not reading or watching television. In addition, recommend that the patient avoid napping and that he or she get regular exercise.
- Every attempt should be made to manage behavioral problems in patients with dementia using non-pharmacological means. Simple measures such as a structured home environment (e.g., regular routines for meals, sleep, and social activities) can sometimes reduce the likelihood of behavioral outbursts or confrontations without having to resort to sedating medications.

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Sleep and Aging

11

Matthew R. Ebben

There is a general perception that degradation of sleep quality is a normal part of aging. In fact, practitioners who see geriatric patients on a regular basis often hear complaints of sleep difficulties in their patients. As we age, a number of age-related health problems are associated with difficulty sleeping. It is often difficult to differentiate sleep problems secondary to underlying health problems or medication effects from primary sleep disorders. This chapter will review the changes that occur in sleep quality as one ages and will address sleep disorders often seen in older adults. Some have argued that subjective or physiological age and time from death are more accurate ways of defining age; however, chronological age is the most consistent definition for aging. The data discussed within this chapter is almost exclusively based on defining age chronologically.

Changes in Sleep Architecture as We Age

A number of studies have been conducted to look at changes in sleep architecture over the life span. One of the most consistent age-related changes in sleep architecture is a decline in delta or slow-wave sleep (SWS). SWS is defined electrographically by low-frequency (0.5–2 Hz), high-amplitude (>75 μV) waveforms [1] and is primarily confined to the first half of the sleep period (as long as the person is not rebounding from a period of sleep deprivation). Behaviorally, SWS is distinct from other stages of sleep because of a higher arousal threshold. The decrease in SWS over the life span was originally described in the 1970s and has been confirmed by several studies since that time [2–6]. A recent comprehensive meta-analysis of 65 studies concluded that SWS declines at a rate of approximately 2% per decade of adult life and plateaus at approximately 60 years of age [7]. There appears to be a gender difference, with men showing a dramatic decrease in SWS. However, in women, delta sleep is preserved across the life span [8]. Generally, the EEG frequency of SWS is maintained in older adults, whereas the amplitude of the waveform decreases [2]. It is thought that this decrease in amplitude of SWS is a result of atrophy of brain tissue over time.

As the name implies, rapid eye movement (REM) sleep is defined by REMs, mixed frequency, low-voltage EEG (similar to the waking state), and muscle atonia [1]. REM sleep at one time was also called paradoxical sleep because it is electrographically similar to waking. The majority of REM sleep is typically present in the second half of the night. However, as we age,

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there tends to be a shift in REM sleep to earlier in the night, resulting in a slightly decreased latency to REM sleep [7, 9]. Also, a decrease of approximately 0.6% per decade in percentage of REM sleep [7, 8] has been reported [10], but this trend toward decreased REM percentage has not been found in all studies [9].

Stage 1 sleep (also referred to as N1 sleep) is a light, transitional stage of sleep between waking and stage 2 (N2) or REM sleep. It is defined by mixed frequency, low-voltage brain waves with slow rolling eye movements [1]. When awakened from N1 sleep, individuals often report that they were unaware that they were sleeping, which underlines the transitional nature of N1 sleep. An increased level of N1 sleep is often seen as a marker for fragmentation of the sleep architecture. Compared to the young, there is a mild to moderate increase in N1 sleep in the older adults, suggesting there is increased sleep fragmentation [7]. It is thought that the increase in N1 sleep may be, in part, due to the reduction in both REM sleep and SWS. However, like SWS sleep, the level of N1 sleep seems to be better preserved in woman than in men [8].

Stage 2 sleep (N2) is defined by an EEG signal that contains both K-complexes (negative to positive spikes with a duration of ≥0.5 s) and sleep spindles (periods of relatively fast, synchronous EEG activity that looks like a spindle of yarn and is generated by the thalamus). These two electrographic patterns are superimposed on a background of theta (4–7 Hz) activity [1]. N2 sleep makes up the majority of the sleep period throughout the life span. Although the relative percentage of N2 sleep changes very little over time, the landscape of this sleep stage undergoes significant changes. Sleep spindles and K-complexes become less numerous, and the frequency of the spindles becomes slower as we age (Table 11.1) [11].

Table 11.1 Changes in sleep variables with aging

Sleep variable	Change in % (or min)
N1	↑
N2	–
SWS	↓
REM	↓
SE	↓
WASO (min)	↑

Key: *N1* stage 1 sleep, *N2* stage 2 sleep, *SWS* slow-wave sleep, *REM* rapid eye movement sleep, *SE* sleep efficiency, and *WASO* wake after sleep onset. All variables are listed as a percentage of total sleep time, except WASO, which is in minutes, and SE, which is the total sleep time/time in bed.

Insomnia in Older Adults

Insomnia is one of the most prevalent health concerns worldwide. Current estimates indicate that 6–15% of the population suffers from insomnia [12]. According to the *International Classification of Sleep Disorders* [13], insomnia is defined as a complaint of difficulty initiating or maintaining sleep, waking up too early, or experiencing sleep that is consistently not refreshing. The sleeping difficulty should also be accompanied by daytime impairment, such as difficulty concentrating, memory difficulties, fatigue, stomach problems, irritability, or reduced motivation. Studies investigating the impact of chronic insomnia demonstrated reduced quality of life, higher absenteeism, impaired job performance, and higher healthcare utilization [14, 15].

In older adults, the prevalence of insomnia appears to be even higher than in the general population. In the mid-1990s, a large-scale epidemiological study was conducted that included nearly 7000 individuals aged 65 and older. Over half of those surveyed complained of frequent difficulty sleeping [16]. Nearly a quarter of participants reported symptoms consistent with insomnia. Surprisingly, less than 20% reported little or no complaint of difficulty sleeping. When sleep quality in older compared to young adults was objectively investigated, there was a decrease in total sleep time and an increase in wake time after sleep onset [7]. However, when mood and health problems were controlled for, the prevalence of insomnia was dramatically lower at 7%. Once health or mood problems dissipate, symptoms of insomnia are also likely to disappear [17]. This suggests that insomnia is commonly a symptom of concomitant health or mood problems and not vice versa.

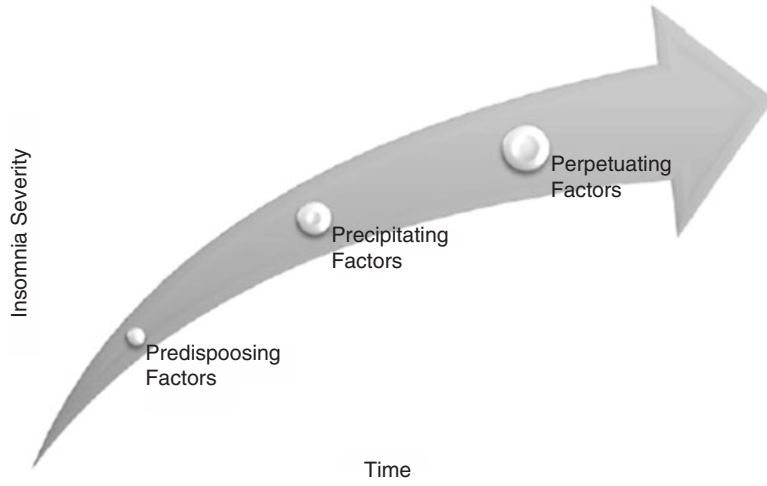

Fig. 11.1 The role of the 3Ps in the increase of insomnia severity over time. An illustration of the progression of insomnia over time. The severity of insomnia is an additive effect of each of the three factors (predisposing, precipitating, and perpetuating) described in the 3-P model. The relative importance of these factors changes over time

To better understand how insomnia progresses over time, it is helpful to discuss this condition within the framework of the 3-P model (see Fig. 11.1). The 3Ps in this model stand for predisposing, precipitating, and perpetuating factors of insomnia. *Predisposing characteristics* are genetic or underlying personality traits such as basal level of anxiety or hyperarousal. Individuals with high levels of anxiety or hyperarousal, for example, are at increased risk of developing insomnia regardless of age [18]. These factors are considered to be relatively stable over the life span and should not be dramatically increased with age. *Precipitating events* are events that stimulate the onset of insomnia. Baseline level of predisposing factors will determine the magnitude of a precipitating event necessary to cause the onset of insomnia. Precipitating events include factors such as health and emotional problems or death of friends or family members. Factors such as these can induce periods of difficulty sleeping [19]. As we age, we are more likely to be exposed to precipitating factors; therefore, the likelihood of developing acute insomnia increases. A *perpetuating event* is an event that causes the insomnia to continue even after the precipitating event has passed. Perpetuating activities commonly include maladaptive behaviors, such as prolonged time in bed, eating, using a computer or watching television in bed, and drinking alcohol in an effort to help promote sleep. Acute insomnia becomes chronic due to these perpetuating habits, practices, and worrying. Older adults may be at greater risk for engaging in some perpetuating activities like spending too much time in bed because they are often retired and have more flexible schedules.

Treatment Approaches

The first-line treatment considered for insomnia for the majority of Americans is typically pharmacotherapy [20]. Many of the benzodiazepines prescribed for insomnia increase risk for falls. This is particularly problematic for older adults because they are already at a heightened risk for falls. In addition, treating insomnia with medication is typically not as durable as non-pharmacological treatments, such as cognitive-behavioral therapy for insomnia (CBT-I) [21].

CBT-I is a general term that describes a host of treatments that have been shown empirically to improved quality of sleep. These commonly included sleep restriction therapy, stimulus control, cognitive therapy, and relaxation techniques. Sleep hygiene education is also commonly part of CBT-I treatment; however, it has not been shown to improve sleep quality when used in isolation of other techniques. Each of these

treatments will be briefly discussed below; for a more comprehensive review, please refer to Ebben and Spielman [22].

Sleep restriction therapy was originally developed by Spielman et al. [23]. It involves drastically reducing a patient's time in bed in order to help consolidate sleep. Typically, sleep logs are completed for a period of 2–4 weeks (see Fig. 11.2). Based on the time in bed and the total sleep time documented on the sleep log, a new sleep/wake schedule is calculated. This new schedule only provides enough time (or less) in bed to achieve the patient's current sleep time. Once the patient begins the new schedule, they typically accumulate a sleep debt, which presumably helps them consolidate their sleep. Once sleep is consolidated into this relatively short period of time, total sleep time is slowly extended to satisfy the patient's sleep need. Although this technique can be difficult for the patient to execute at first, if performed correctly, sleep restriction therapy can greatly improve sleep quality and daytime functioning.

Stimulus control therapy focuses on the role of conditioned wakefulness in maintaining insomnia. Often when individuals spend sleepless nights lying in bed, they condition themselves to expect wakefulness in their bedroom environment. Once this occurs, commonly the individual will begin to spend more time in bed hoping it will increase the likelihood that they will sleep more; however, frequently the opposite occurs. When this conditioning pattern has developed, it is not uncommon for the patient

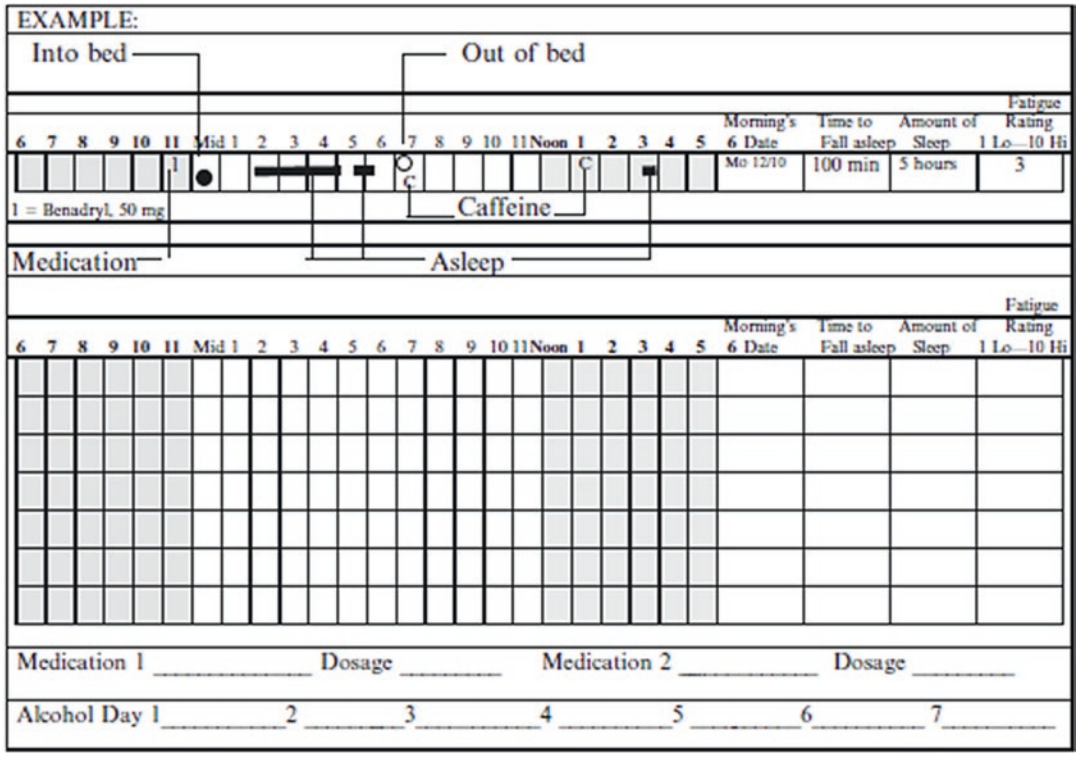

Fig. 11.2 A version of the City College of New York sleep log. Patients are instructed to complete this log upon awakening in the morning. The *black dot* indicates the time the patient got into bed, and the *black lines* represent periods of sleep. The *black circle* shows time out of bed. The number prior to the *black dot* indicates when medications were taken (if any were taken before bedtime). Medications taken at other times of the day are listed below the chart. *C* indicates time of caffeine consumption. Daily alcohol consumption for each day is listed below medications [22]

to report improved sleep away from home. Emphasizing this notion of conditioned insomnia is the fact that even during laboratory polysomnograms, which involve numerous pieces of bothersome apparatus, individuals with conditioned wakefulness can achieve improved sleep quality. Therefore, the goal of stimulus control therapy is to separate sleep from wakefulness activities. This is done by encouraging the patient to reserve the bedtime for only sleep and sexual activity. Activities such as watching TV or listening to the radio in bed should be eliminated.

The practice of *cognitive therapy* to treat insomnia differs little from its practice in treating other types of psychopathology. Often patients with insomnia develop erroneous associations between their difficulty sleeping and other problems they are experiencing. For example, some may begin to worry that without high-quality sleep, they will completely lose their ability to function during the day. However, most individuals with insomnia have maintained somewhat normal daytime schedules, even after several nights of poor-quality sleep. The goal of the cognitive therapist is to replace the patient's catastrophic thinking with more realistic thoughts. This process often takes longer than behavioral techniques because many thought patterns are more effectively approached indirectly (at least at first). Gaining permission from the patient to restructure their thought process requires a bond between the patient and therapist, which takes time to develop.

Relaxation techniques are treatments that focus on tension in the muscles. Progressive muscle relaxation (PMR) is the most common relaxation technique used for insomnia; however, EMG biofeedback is also occasionally used. PMR is typically used at bedtime and involves having the individual progressively tense and then relax muscles throughout the body starting with the head or toes. In general, this technique has been shown to improve quality of sleep [24]. Interestingly, some data show that if this technique is used in insomniacs without muscle tension, it can worsen their sleep [25].

Circadian Rhythms in Aging

The term circadian is derived from the Latin roots circa (meaning "about") and diem ("day"). A circadian rhythm is a rhythm that is approximately 24 h or 1 day long. The pacemaker, or master clock of mammalian circadian rhythms, is located in the suprachiasmatic nucleus above the optic chiasm [26]. Circadian rhythms are generally set or reset by daytime light exposure, which naturally entrains the rhythm of the clock to a 24-h day. The human endogenous circadian rhythm (in the absence of light) in young and middle-aged adults is typically longer than 24 h. Therefore, in controlled conditions that exclude light, an individual tends to fall asleep and wake up a bit later each day.

Studies in aged animals have shown a flattening and desynchronization of circadian rhythms, which can be restored by transplanting suprachiasmatic tissue from younger animals [27]. In humans, a reduction in period length and amplitude of circadian rhythms is seen in older adults compared to the young [28]. Clinically, it is not uncommon to hear complaints from older adults regarding falling asleep too early and waking up too early. This condition is referred to as advanced sleep phase syndrome (ASPS). It is easy to confuse this type of complaint with insomnia; however, it is important to differentiate circadian rhythm disorders from insomnia because the treatments for each disorder are different.

Differentiating ASPS from insomnia is done through a careful examination of the patient's sleep/wake pattern. For example, if a patient reports a long history (usually since childhood or adolescence) of difficulty both falling asleep at night and waking up in the morning, there is a very good chance they suffer from delayed sleep phase syndrome (DSPS). It is quite common for insomniacs to report difficulty falling asleep. However, it is much less common for insomnia sufferers to report difficulty waking up in the morning. This condition is frequently seen in teenagers and young adults, although it can also be present in older individuals. In other cases, the patient may report a history of falling asleep or getting sleepy early in the evening and then

waking up too early, unable to fall back to sleep. These individuals may be suffering from ASPS. This disorder has an estimated prevalence of approximately 1% overall but is more frequently seen in older adults, with an estimated prevalence of 7% in this age group [29]. It is not uncommon to hear patients with ASPS report bedtimes of 6 pm with wake times of 2 am. In addition to physiological changes in period length of circadian rhythms such as core body temperature and melatonin that occur with age, behavioral patterns such as less social activities in the evening and less light exposure in general may lead to the development of ASPS.

In both DSPS and ASPS, if the individual has an adequate opportunity to sleep at their preferred time, total sleep time is generally within normal limits and daytime sleepiness is usually not reported. However, particularly in cases of DSPS, daytime social activities can limit the person's ability to sleep into the late morning or early afternoon on a regular basis; as a result, they often report daytime sleepiness. Patients with ASPS are often bothered by the boredom of waking at a time when other friends and family members are still sleeping. In addition, the early bedtime limits their ability to take part in social activities in the evening. DSPS and ASPS are some of the most common circadian rhythm disorders in both young and older adults; however, numerous other circadian sleep disorders exist.

Generally, circadian rhythm disorders are treated with a combination of bright light, melatonin, and/or a customized sleep/wake schedule, not the typical cognitive-behavioral treatments reviewed previously in this chapter. A detailed review of the various treatment options for these disorders is beyond the scope of this chapter; for a thorough review on this topic, please refer to Zee [30].

Sleep–Disordered Breathing (Sleep Apnea)

Apnea is a Latin term that means "without breath." Sleep-disordered breathing (SDB) is a general name that includes two primary breathing disorders that occur during sleep. These two disorders are called obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA consists of a decrease or cessation in airflow secondary to a collapse in the upper airway. Another type of respiratory event included in the diagnosis of OSA is called hypopnea. This is a reduction in airflow accompanied by a decrease in blood oxygen saturation [1]. CSA, as the name implies, refers to cessation of airflow secondary to a lack of signaling to breathe from the higher brain areas or "central centers."

It is normal to have some respiratory events during sleep; however, having too many is problematic. The diagnosis of sleep apnea is determined by a sleep study or polysomnogram during which sleep stages and respiratory events are monitored. Apneas and hypopneas are typically grouped into one index called the apnea-hypopnea index or AHI, which is the total number of apneas and hypopneas divided by the total hours of sleep. The typical range of AHI severity is as follows: 5–15 is mild, 15–30 is moderate, and $\geq$ 30 is severe [31]. The decrease in oxygen saturation associated with the respiratory events also factors into the severity of SDB. Typically, respiratory events result in brief arousals from sleep, which can cause daytime sleepiness. In fact, the majority of adults with SDB complain of excessive daytime sleepiness [32].

OSA is a serious health problem and puts patients at greater risk for hypertension, congestive heart failure, cardiac arrhythmia and ischemia, and cerebrovascular disease [33]. The prevalence of SDB in American adults is 4% for males and 2% for females [34], and the prevalence of moderate to severe apnea increases dramatically with age. The Sleep Health Heart Study found a prevalence of SDB of 20% in adults over the age of 60 [35].

Treatment for SDB most commonly involves the use of continuous positive airway pressure (CPAP). CPAP is basically a medical quality air compressor that blows air into the patient's airway causing a pneumatic splint. Once the appropriate CPAP pressure is determined, the patient begins using the CPAP machine nightly during sleep. Use of CPAP typically causes a reduction

in clinical symptoms of OSA such as snoring and excessive daytime sleepiness. It is also thought to reduce the risk of the other disorders associated with sleep apnea mentioned above.

REM Behavior Disorder

REM behavior disorder (RBD) is a condition that is defined by increased motor activity during REM sleep. Dream mentation is thought to occur more frequently during periods of REM sleep. During REM, voluntary muscles are inhibited through the inhibition of spinal motor neurons [36], thereby preventing movement during dreaming episodes. However, in individuals with RBD, the inhibition of these muscles is absent or incomplete. This disinhibition presumably allows the person to act out their dreams. This may involve violent actions such as kicking, punching, or screaming (the type of movement that occurs, most likely, depends on the dream content). RBD is more common in older males with an estimated prevalence of approximately 0.5% in older adults [13]. In most cases, RBD develops after the age of 50.

There is growing evidence of the association between RBD and synucleinopathies such as Parkinson's disease, Lewy body disease, and multiple systems atrophy (MSA). In fact, one study found that 69% of patients with MSA also had RBD [37]. Another study found that 33% of patients with Parkinson's disease who underwent sleep studies were also found to have RBD. It appears that RBD can also be a prodrome of synucleinopathies. Estimates suggest there is a mean interval of approximately 10 years from the development of RBD to the diagnosis of a synucleinopathy [38]; however, RBD has been shown to precede the onset of clinical symptoms in Parkinson's disease by as long as five decades [38]. In one small study (n = 29), 38% of men originally diagnosed with idiopathic RBD developed Parkinson's disease later in life [39]. Withdrawal from alcohol or sedative medication, as well as the use of tricyclic antidepressants, has also been associated with the development of RBD [40].

Treatment for RBD generally involves the nightly use of a low dose of clonazepam, which has been found effective in eliminating or reducing RBD symptoms in 90% of cases [41]. However, once the medication is discontinued, the symptoms of RBD return. Other benzodiazepines are also occasionally used if the patient cannot tolerate the side effects of clonazepam.

Common Neurological Disorders that Affect Sleep

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is often associated with behavioral problems, particularly as the disease progresses. A common behavioral problem referred to as sundowning represents agitation and wandering that is often exacerbated after sundown. EEG findings in AD are typically an exacerbation of the progression normally seen in elderly patients. This includes a decrease in REM sleep and SWS, increased sleep fragmentation, and a flatting of phasic events such as K-complexes and sleep spindles normally seen in N2 sleep (reviewed in Petit et al. [42]).

Research investigating the relationship between AD and sleep has led to three theories about disease development. One theory posits that fragmentation of sleep for any reason results in increased wakefulness during the nighttime period. Consequently synaptic activity in the brain is also increased [43]. This results in increased beta-amyloid (Aβ) protein creation leading to increased plaque deposition. Another proposed hypothesis is that decreased sleep, particularly SWS, deduces that ability to clear Aβ from the brain due to decreased interstitial space [44]. A third proposed mechanism is that sleep fragmentation results in Aβ misfolding in the endoplasmic reticulum of neuron cells, leading to increased Aβ plaque accumulation [45].

Parkinson's disease (PD) is a neuromuscular disorder that causes tremors, rigidity, stiffness, bradykinesia, and coordination problems. In addition to the higher incidence of RBD described above, a significant percentage of PD patients complain of sleep problems. In a study of 149 PD

patients with age-matched controls, 42% were found to have sleep difficulty compared to only 12% in the control group [46]. The most common sleep problems reported were insomnia, nightmares, and excessive daytime sleepiness (EDS). It has been hypothesized that sleepiness in PD patients is partially related to the use of dopamine agonists. This theory is refuted by the Canadian Movement Disorder Group who found EDS was common in PD patients [47].

In summary, there are a host of reasons for changes in our sleep as we age. These include significant changes in sleep architecture, as well as an increased frequency of a number of sleep disorders, some of which can be attributed to underlying health or mood disorders. Age-related behavioral changes, such as a lack of a defined daily schedule (i.e., work schedule), also contribute to sleep disorders such as insomnia or circadian rhythm disorders. Disorders that result from behavioral changes can frequently be treated successfully with behavior modification and do not necessarily need pharmacological intervention. A list of practitioners trained in the use of cognitive-behavioral treatments for sleep disorders can be found on the website of the American Academy of Sleep Medicine. In situations where the sleep disorder is secondary to another condition, treatment of the primary disorder is recommended first before sleep symptoms are the target of intervention.

Clinical Pearls

- Deterioration of sleep quality is not necessarily a normal part of aging and is most often associated with physical or psychological maladies.
- Changes in sleep architecture as we age often include a decrease in SWS and a shift of REM sleep earlier in the night.
- Insomnia is commonly a symptom of concomitant health or mood problems and not vice versa.
- Use of hypnotic medication for the treatment of insomnia is often not recommended in older adults because of the increased risk of falls.
- The first-line treatment for insomnia in the elderly should be cognitive-behavioral therapy for insomnia (CBT-I).
- Older persons appear to be at greater risk for certain circadian rhythm disorders such as ASPS, which can and should be differentiated from insomnia because the treatments are different.
- REM behavior disorder (RBD) is a disorder that is most common in older adult men and may be a prodrome for synucleinopathies such as Parkinson's disease, Lewy body disease, and multiple systems atrophy.
- RBD can be effectively controlled in 90% of patients with the use of low-dose clonazepam.

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Differential Diagnosis of Depression and Dementia

12

Lauren L. Drag and Linas A. Bieliauskas

Depression in older adults has prevalence rates estimated to be between 3% and 14% in the community-dwelling population [1–3]. Approximately 1 in 15 older adults may experience major depression over the course of 1 year [2]. Late-life depression has been associated with negative outcomes such as functional impairment and disability, increased medical symptoms, negative rehabilitation outcomes, and increased utilization of health-care services [4–6]. Depression can also have significant economic costs. Due to unexplained somatic complaints and functional impairments, older adults with depression tend to use more medical services. Katon et al. [7] found that depressed older adults incurred approximately 50% higher medical costs than their non-depressed counterparts, even when taking chronic medical illness into account. Only a small part of these costs went to mental health care; the majority of costs were associated with primary care visits, diagnostic visits, emergency room visits, and pharmacy costs. A recent examination by Bock et al. [8] found that in individuals with multimorbidity, each endorsed item on the Geriatric Depression Scale increased an individual's health-care costs by 540 euros (approximately 610 US dollars) over a 6-month period. Thus, late-life depression can place a significant burden on patients, their caregivers, and the health-care system, illustrating the importance of adequately assessing, managing, and treating this disorder.

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Depression–Related Cognitive Impairment or "Pseudodementia"

In addition to negative clinical outcomes, late-life depression can be accompanied by significant cognitive impairments. These depression-related changes are often similar to those associated with dementia. Historically, a psychiatric illness that mimicked dementia symptoms was referred to as "pseudodementia." The cognitive symptoms of pseudodementia were assumed to be related to transient mood symptoms and therefore reversible with adequate psychiatric treatment. Therefore, the term "reversible dementia" was also used to describe depression-induced cognitive impairments.

Despite the initial popularity of "pseudodementia" among clinicians, there has been debate about the use of this term, and it has generally fallen out of favor in current practice. The term has been of historical importance in that it

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encouraged clinicians to evaluate every patient carefully and look for alternate causes of cognitive decline other than dementia. However, as Reifler [9] has pointed out, there are some drawbacks to using this term. Pseudodementia implies a mutually exclusive process, which can lead a clinician to focus on whether a patient is depressed or demented at the exclusion of the possibility that both conditions could be present. The term also implies complete reversibility and a lack of organic pathology without taking into account that there may be both reversible and irreversible components to the illness. Several more recent studies have confirmed that the cognitive deficits associated with "reversible dementias" may not actually be truly reversible as cognitive symptoms often persist despite improvement or even remission of depressive symptoms in older adults [10, 11]. For example, older adults with a history of depression, even in remission, can demonstrate lower performance across multiple cognitive domains, most notably in attention and processing speed, when compared to individuals without a history of depression [12]. Butters and colleagues [13] found that in some older adults with depression and cognitive impairment, executive functioning did improve following successful antidepressant treatment but failed to reach normal levels of performance. Similarly, Saczynski 2015 [14] demonstrated that use of antidepressants did not modify the course of cognitive decline in late-life depression. Finally, Alexopoulos and colleagues [15] followed older adults with depression who showed a pattern of "reversible dementia" as demonstrated by cognitive impairment at baseline followed by improvement in cognitive symptoms subsequent to treatment for their depression. However, at follow-up 1 year later, individuals with reversible dementia were five times more likely than depressed individuals without cognitive impairment to develop a true dementia syndrome. Thus, these data altogether suggest that a history of depression, even if adequately treated, increases the risk of persistent cognitive impairment in older adults, thus arguing against the concept of true "pseudodementia."

Relationships Between Depression and Dementia

Longitudinal studies have consistently demonstrated that depression confers an increased risk of developing subsequent dementia [16, 17]. This risk increases with a higher frequency and severity of depression [18]. For example, when following 639 participants over a 3-year period, Verdelho [19] found that depression at baseline was a predictor of mild cognitive impairment and dementia at follow-up, independent of multiple factors including white matter changes, medial temporal lobe atrophy, age, education, and baseline cognitive functioning. Among studies, adjusted hazard ratios have ranged from around 1.5–3.0 [17, 20]. For example, a retrospective longitudinal study examining data on nearly 50,000 older adults over a 10-year period found that depression led to a threefold increased risk of vascular dementia [21]. It has been shown that the presence of vascular disorders (e.g., stroke, hypertension) is a moderating factor in that it increases the influence of depression on subsequent dementia risk [22]. While the risk tends to be higher for vascular dementia compared to Alzheimer's disease (AD) [23], late-life depression is still associated with increased risk of all-cause dementia [24]. Thus, depressed individuals, compared to nondepressed individuals, can be up to three times more likely to develop a subsequent dementia. Despite these somewhat alarming findings, Ownby et al. [25] posited that from a clinical perspective, the absolute risk of AD conferred by a history of depression is small and should not be overemphasized in clinical work. Rather, it is suggested that depression be considered a modifiable risk factor.

Relatedly, older adults with cognitive impairment, namely, mild cognitive impairment and dementia, have higher rates of depression than cognitively intact individuals. High rates of depression and psychiatric symptoms in general are found across various neurodegenerative disorders, including AD, vascular dementia, Lewy body dementia, multiple system atrophy, and Parkinson's disease [26–31], and it has been

shown that individuals with dementia endorse more depressive symptoms than individuals without dementia [32]. Starkstein and colleagues [33] examined 670 patients with probable AD and found that approximately half of these individuals had significant symptoms of depression. Higher rates of depression can be seen even in mild cognitive impairment. For example, in a study by Snowden and colleagues [34], individuals with mild cognitive impairment without depression were over twice as likely to develop depression over a 2-year period compared to those without cognitive impairment. Not only is depression common in mild cognitive impairment and dementia, it has also been shown to accelerate rates of cognitive decline [35] with more severe depression associated with an increased rate of decline [36]. Depression also increases the risk of conversion from MCI to dementia [36, 37]. There has even been some suggestion that depression can have a greater influence on rate of cognitive decline than AD neuropathology [38].

Overall, it is clear that dementia accompanies depression and that depression accompanies dementia. Although a primary intent of this chapter is to assist with the differential diagnosis between depression and dementia, these are not orthogonal constructs. Much research has been directed on the nature of the relationship between depression and dementia, with some debate whether this relationship represents unidirectional, bidirectional, additive, or shared causality [39, 40]. For example, it may be that depression is simply an emotional reaction to cognitive impairment; some researchers have argued that depression accompanies cognitive decline rather than precedes it [41]. However, it is unlikely that depression can be attributed solely to a reaction to the disease itself as awareness of deficits has not clearly been linked to the development of depressive symptoms [42]. There has also not been strong support for an association between severity of dementia and depression; depressive symptoms have been shown to be equally prevalent across disease stages [43, 44], which would argue against this hypothesis. Conversely, it is possible that cognitive impairment is simply a by-product of depression although, as described above, the concept of a "pseudodementia" appears overly simplistic.

Other, more nuanced hypotheses have been proposed in attempts to elucidate this complex relationship. First, it may be that depression independently increases the risk of subsequent dementia [25]. For example, it has been proposed that inflammation or chronic glucocorticoid exposure (through overactive hypothalamic-pituitary-adrenal activity) can have toxic effects and thus increase vulnerability to dementia-related neuropathology in individuals with depression [45]. Relatedly, it may be possible that depression treatment in itself may confer an increased risk of dementia; for example, long-term use of anticholinergic medications (e.g., Paxil, Elavil) has been associated with an increased rate of dementia [46]. A second hypothesis, similar to the first, is that depression lowers the threshold for manifesting dementia in otherwise vulnerable or preclinical individuals.

Third, it has also been argued that depression represents the prodromal stage of dementia and thus reflects an early manifestation rather than risk factor for dementia [47]. Research has demonstrated that depressive symptoms may actually be an early sign of subsequent cognitive impairment and dementia [48]. Modrego and Ferrández [49] followed individuals with amnestic mild cognitive impairment over 3 years and found that those individuals with baseline depression were more than twice as likely to develop dementia compared to their nondepressed counterparts and were more likely to develop dementia earlier. Similarly, Rosenberg and colleagues [50] followed a large sample of 436 older women over a 9-year period and found that baseline depressive symptoms were associated with increased rates of incident impairments on cognitive tests across multiple domains. Thus, it may be that depression is simply an early symptom of an underlying, predetermined neurodegenerative condition.

Fourth and finally, the high comorbidity between depression and dementia may also reflect common risk factors, resulting in a high prevalence of both disorders in certain populations. For example, even in the absence of acute

stroke, vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia) are associated with both late-onset depression and vascular dementia secondary to changes in white matter integrity and disruptions in fronto-subcortical circuits (for review see Aizenstein et al. [51]). These structural and functional changes may predispose, precipitate, or perpetuate depressive symptoms in older adults and lead to typical symptoms of vascular dementia, including psychomotor slowing, executive dysfunction, and apathy. Even a seemingly innocuous disorder such as sleep apnea can be associated with depression and may induce cognitive dysfunction and underlying neurodegenerative changes through sleep fragmentation and intermittent hypoxia [52]. There are multiple excellent reviews that cover this relationship between depression and dementia in greater detail [18, 23, 53, 54].

Clinical Assessment

Neuropsychologists play an important role in the assessment and treatment of both depression and dementia. Various clinicians such as primary care practitioners, psychologists, psychiatrists, and neurologists often refer older adults for neuropsychological evaluation to better clarify a patient's cognitive and psychiatric complaints. Neuropsychological evaluation can have significant contributions to diagnosis, management, and treatment of these symptoms through an objective characterization of cognitive and psychiatric profiles, identification of areas of weakness that can lead to functional impairments or be addressed through interventions, and follow-up assessments that can track the extent to which symptoms improve, worsen, or remain stable in response to interventions or time [55]. As noted above, it is often not simply a question of whether a patient has dementia versus depression. Rather the clinician should focus on understanding how each of these disorders may be contributing to the patient's emotional, behavioral, and cognitive functioning in order to (1) educate the medical team, the patient, and the family, (2) inform prognosis when possible, and (3) provide recommendations for interventions to optimize functioning and quality of life.

Assessment of Geriatric Depression

An important part of a neuropsychological evaluation of a patient with depressive symptoms is to gain both a qualitative and quantitative understanding of these symptoms. However, depression is often difficult to assess in older adults for a number of reasons. Symptoms of depression are easily confounded by the effects of age and medical disorders. Changes in weight, appetite, and libido; psychomotor retardation or agitation; and a loss of interest in activities are common to medical illnesses, physical effects of aging, and age-related lifestyle changes, as well as depression. For instance, a patient may endorse a decline in social activities, but upon further prompting, clarify that he or she can no longer drive and does not have many friends or family members who live nearby. Similarly, it may be that a preference to stay home reflects fatigue related to medical conditions rather than a symptom such as anhedonia.

Older adults may also be more likely to underestimate their depressive symptoms. They may have lower functional expectations for themselves due to their increasing age (e.g., they may believe that their fatigue is a normal part of the aging process) and therefore dismiss their depressive symptoms as a common response to life stressors or normal aging. This is a common misconception; depression is not a normal part of aging. While older adults may be prone to depressive symptoms due to declining health and functioning, the aging process itself does not confer an increased risk for depression [56].

Further complicating matters, older adults are less likely to report dysphoric mood than their younger counterparts. Rather, they tend to present with vague symptoms such as sleep disturbances or fatigue [57]. Given that older adults may not endorse prominent dysphoria, clinicians need to be aware of the more subtle indicators of depression. These can include frequent office

visits or use of medical services, persistent reports of pain, fatigue, insomnia, headaches, changes in sleep or appetite, unexplained GI symptoms, social isolation, increased dependency, delayed recovery from medical or surgical procedures, and refusal of treatment [58].

Patients may be referred for a neuropsychological assessment for subjective cognitive complaints, and only after detailed questioning will evidence of possible depression emerge. Older adults with depression are more likely to initially present to their primary care physician rather than to a specialist such as a psychiatrist [59] and may report only vague physical symptoms. Therefore, depression may go undetected in some patients unless a careful evaluation is performed. This suggests that all older adults complaining of cognitive problems should be screened for depression, regardless of the referral question.

Several psychometric instruments have been developed to screen for depression (Table 12.1). Popular instruments include the Beck Depression Inventory-II (BDI-II) [60] and the Hamilton Depression Rating Scale (HDRS) [61]. The Geriatric Depression Scale (GDS) [62] specifically targets symptoms common to depression in older adults. Several rating scales have also been developed specifically for use in patients with dementia. Table 12.1 provides a list of psychometric instruments that are commonly used to assess depression in older adults. These inventories can be useful to quantify and monitor depressive symptoms over time, yet they should be used as a supplement to a clinical interview. Individuals with cognitive impairment may endorse depressive symptoms, but further prompting may be required to tease apart primary depression from possible secondary effects of cognitive symptoms. Cognitive impairment can limit a person's ability (but not necessarily desire) to be involved and engaged with activities. For example, individuals with cognitive impairment may be unable to drive or have difficulty keeping up with social activities (e.g., playing complex card games) like they used to. On questionnaires such as the GDS, which probes for symptoms such as a decrease in activities or boredom, further discussion is warranted to determine whether these symptoms reflect a true underlying depression rather than situational factors. Overall, a careful choice of depression inventories and a detailed clinical interview are important in individuals with cognitive impairment.

Table 12.1 Instruments commonly used to assess depression in older adults

For use in both adults and older adults
Beck Depression Inventory-II [62]
Center for Epidemiological Studies Depression Scale (CES-D) [134]
Zung Depression Rating Scale [135]
Hamilton Depression Rating Scale [61]
For use in older adults
Geriatric Depression Scale [62]
Geriatric Depression Scale (short form) [136]
For use in patients with dementia
Cornell Scale for Depression in Dementia [137]
Dementia Mood Assessment Scale [138]
Depression Sign Scale [79]
Neuropsychiatric Inventory [139]
CERAD Behavior Rating Scale [140]

Considerations for Differential Diagnosis

When a patient presents with reported changes in both mood and cognitive functioning, there are several potential diagnoses to consider. Table 12.2 provides a list of disorders that have been associated with both cognitive and psychiatric symptoms in older adults. Primary psychiatric disorders such as depression, anxiety, and bipolar disorder should be considered, although an initial onset of psychiatric symptoms in late adulthood is unusual. Psychiatric symptoms such as depression, irritability, and apathy are also common across many of the dementia subtypes, including AD, Lewy body dementia, frontotemporal dementia, and vascular dementia. Changes in mood and cognition can also be associated with strokes, particularly those affecting frontal regions or frontostriatal circuits. For example, it has been suggested that one-third to one-half of stroke survivors experience depression in the 5-year period following stroke [63, 64]. This may be due to both psychological factors

Table 12.2 Common differential diagnoses to consider for older adults with psychiatric symptoms and cognitive complaints

Dementias
Alzheimer's disease
Frontotemporal dementia
Lewy body dementia
Vascular dementia/stroke
Dementia associated with Parkinson's disease
Psychiatric disorders
Depression
Bipolar disorder
Anxiety
Other potential causes
Medication side effects (e.g., beta-blockers, calcium channel blockers, anticholinergics)
Sleep apnea
Vitamin deficiencies (e.g., vitamin D, vitamin B12, thiamine)
Hormonal conditions (e.g., hypothyroidism, menopause)
Substance abuse
Hypothyroidism

(e.g., social stressors, functional limitations) as well as physiological mechanisms (e.g., inflammatory processes, changes in glutamate neurotransmission, lesion location) [65, 66]. It has been shown that the risk of developing poststroke depression is reduced in individuals receiving active psychotropic treatment, however [65].

In addition, many medications commonly used to treat medical illness in older adults can cause depression-like symptoms and also cognitive changes [67]. For example, calcium channel blockers, beta-blockers, levodopa, corticosteroids, and even certain antibiotics can affect both mood and cognitive functioning (REF to Caporasso, Chap. 10 in this volume). Other medical conditions, such as hypothyroidism, vitamin deficiencies, and sleep apnea, should be considered.

Differences Between Depression and Dementia

Cognitive and psychiatric symptoms associated with a primary depression can differ from those associated with a dementia process. Depression is typically associated with a more acute onset of symptoms (e.g., days to weeks), whereas the impairments associated with dementia can progress over the course of years. Therefore, a gradual onset and progression of cognitive and mood symptoms is more likely to reflect an underlying dementing process, whereas a more acute onset is typically associated with depression. In addition, depression is often accompanied by significant subjective cognitive complaints [68, 69]. Older adults with depression are more likely to complain about their cognitive difficulties than individuals with dementia [70], and these cognitive complaints may be out of proportion to an individual's actual level of functioning. For example, a patient may complain of severe memory deficits yet continue to independently manage his or her medications and finances. In contrast, a lack of insight into symptoms is common in dementia, particularly AD, making these individuals more likely to minimize their cognitive difficulties.

The presence of apathetic symptoms can also have clinical indications when differentiating between depression and dementia. Apathy is typically defined as a loss of motivation and can manifest as diminished initiation, lack of interest, low social engagement, a blunted emotional response, and loss of goal-directed behaviors. While apathy can be a principal symptom of depression, it can also reflect an independent syndrome, distinct from the dysphoria typically associated with depression. Apathy is often characterized by indifference, whereas dysphoric symptoms are better characterized by sadness, guilt, self-criticism, hopelessness, and helplessness. Bieliauskas[71] suggested that true primary depression includes a significant loss of self-esteem and that, in the absence of this loss, depressive symptoms likely reflect neurological change.

Apathy is a prominent feature in various neurodegenerative disorders, including AD, frontotemporal dementia, and Parkinson's disease [72, 73]. In AD in particular, apathy symptoms are more prevalent than dysphoric symptoms [74, 75], and older adults who present with apathetic symptoms are more likely to develop AD than

those with either no depression or depression without apathy [76, 77]. This affirms that mood symptoms in the early stages of dementia are better characterized by an apathetic syndrome rather than dysphoric mood. Therefore, apathy, particularly in the context of cognitive changes, may be an early marker of preclinical AD, whereas dysphoric mood may be more indicative of a primary depressive disorder [64, 78, 79]. During clinical interview, it is important to go beyond simply asking about feelings of sadness or a depressed mood and inquire about how patients spend their time, what they look forward to, and what types of activities they initiate and engage in. Apathy can manifest in social withdrawal (e.g., a lack of participation in conversations, staying in the bedroom for most of the day), limited initiation of activities, declining activities that are offered, and a preference to stay at home. When assessing apathy in patients with cognitive impairments, it is important that clinicians focus on the behaviors for which a patient is still capable of performing, as cognitive impairments can limit a person's ability to engage with their environment independent of motivational factors. Structured measures have been designed to specifically measure symptoms of apathy, including the Neuropsychiatric Inventory [80] and the Apathy Evaluation Scale [81]. The Irritability/Apathy Scale has been used to measure apathy in patients with dementia [82]. In addition to apathy, depressive symptoms associated with dementia may be characterized by fewer and less prominent symptoms compared to a primary depression, with salient features of social withdrawal, irritability, loss of interest, and loneliness [83–86].

The age of onset of depressive symptoms should also be taken into consideration. There are significant differences both phenomenologically and etiologically between early-onset and late-onset depression, suggesting that these may be distinct psychiatric entities. The median age of onset in depression is 32 years of age with 50% of individuals reporting onset between ages 19 and 44 [87]. Late-onset depression is typically defined as depression with a first onset between 45 and 60 years of age. Compared to early-onset depression, depression that occurs for the first time in late life is more likely to be associated with an underlying organic etiology [88–91]. Bieliauskas [71] suggested that when older patients present cognitive difficulties associated with an initial onset of depression, these are most likely based on neurological disease. Lamberty and Bieliauskas [84] reviewed a number of studies showing high correlations between cognitive changes with depression and positive findings on neuroimaging. In a later review of neuroimaging findings, Kumar, Bilker Jin, and Udupa [92] suggest that atrophy and high-intensity lesions may represent relatively independent pathways to late-life major depression. The underlying neurological basis for depressive symptoms has been explored by Langenecker et al. [86], not only for depression with onset in late life but also for a neuroanatomical network impacted in the majority of individuals with mood disorders. As mentioned above, a common organic etiology of late-life depression is vascular disease. The prototypical "vascular depression" is characterized by a late onset, a high cardiovascular illness burden, poorer outcome, absence of a family history of depression, and higher risk for cognitive impairment (namely, executive dysfunction and psychomotor slowing) (see 49). Depression associated with vascular dementia also tends to be more treatment-resistant than that seen in AD [93].

Depression and dementia can also differ with regard to sleep, although the clinical utility sleep patterns in differential diagnosis is uncertain. AD is typically associated with poor sleep efficiency with frequent night awakenings. Phase delays are prominent, meaning that the onset of sleep is later and accompanied by difficulty awakening in the morning [94]. While older adults with depression also have frequent night awakenings, impaired sleep continuity, and difficulty falling asleep, early morning awakenings are a prominent feature of depression [95]. Individuals with depression have difficulty staying asleep in the morning, whereas those with dementia are more likely to have difficulty waking up. In addition,

when directly compared to individuals with AD, individuals with depression had a higher number of night awakenings [96]. Increased REM sleep may also be a specific to depression and helpful in distinguishing depression from dementia (which is associated with reduced REM); however, this type of detailed sleep data is typically not available to clinicians without requesting a formal sleep study [95].

Although much of the focus on differential diagnosis of dementia and depression focuses on more common dementia processes, such as AD and vascular dementia, behavioral variant frontotemporal dementia (FTD) can be accompanied by prominent emotional and behavioral changes that may mimic depression or even bipolar disorder. FTD can be accompanied by depressive-like symptoms, including a lack of interest, decreased motivation, and low energy levels. However, a sustained depressed mood, guilty ruminations, feelings of worthlessness, and suicidal thoughts are less common in FTD. In addition, while patients with FTD may experience apathy, this may be distinguished from the anhedonia typically accompanying a primary depression by the lack of accompanying distress or dysphoria [97]. Evidence of persistent and progressive cognitive difficulties, a positive family history of familial forms of dementia, a more focal cognitive profile, poor response to psychiatric treatment, and evidence of frontal/anterior temporal atrophy or abnormal perfusion on neuroimaging would also be more consistent with FTD. In contrast, a dysphoric mood, a positive family history of mood disorder, a history of multiple mood episodes, comorbid anxiety or substance use, suicidal ideation, complete or partial recovery of cognitive symptoms with psychiatric treatment, an earlier age of onset, and an improvement in cognitive functioning with psychotropic medications or psychotherapy would argue against FTD [97, 98].

In sum, the phenomenology of a depressive syndrome can differ between primary depression and dementia. Depression is associated with an earlier age of onset of symptoms; a higher level of subjective reporting of cognitive symptoms; an acute onset of cognitive deficits; the presence of dysphoria including loss of self-esteem, rather than apathy; and early morning awakenings. This contrasts with dementia-related symptoms that are associated with a later age of onset of symptoms, a lack of insight into cognitive symptoms, a gradual onset of cognitive deficits, more severe cognitive impairment, and the presence of apathy rather than dysphoria. Although these patterns can be useful as a heuristic in combination with other observations and objective testing, caution needs to be taken when applying findings using group differences to a single individual given the significant variability across individuals.

Neuropsychological Profiles of Depression and Dementia

Differences in symptom presentation between depression and dementia can be informative; however, a neuropsychologist's unique contribution to differential diagnosis is the ability to provide an objective assessment of cognitive functioning. As discussed previously, older adults with depression are more likely to report subjective cognitive difficulties than patients with dementia. However, these complaints are not always indicative of true impairments [99, 100], thus highlighting the importance of objective neuropsychological testing.

In general, the cognitive changes associated with dementia tend to be more severe than those associated with depression [101–103]. It has been our experience (and that of others [104]) that many depressed individuals report cognitive complaints but do not show cognitive impairment on formal testing. In fact, objective evidence of significant cognitive impairment in a depressed individual may actually be indicative of dementia or at least future conversion to dementia. For example, studies have shown that depressed individuals who later convert to dementia show greater cognitive impairment than depressed individuals who do not convert; this is particularly evident on measures of delayed memory (e.g., CERAD delayed recall and recognition,

Logical Memory Delayed Recall) and, to a lesser extent, executive functioning (e.g., Trails B) [105, 106]. For example, Rushing and colleagues [106] found that for every additional point earned on Logical Memory Delayed Recall, individuals were 0.806 times less likely to develop dementia after controlling for other variables. These authors suggested that performance falling more than one standard deviation below age and education-based norms should raise concerns for possible preclinical AD. Similarly, individuals with vascular depression can show greater cognitive impairment than individuals with nonvascular depression of the same age [51].

Severity of deficits in the memory domain can be particularly telling as low memory performance should be concerning for a poor cognitive prognosis [107]. For example, in a study of 1646 patients with various types of dementia, mild cognitive impairment, or major depression, it was found that verbal learning and memory scores were highest in individuals with depression and lowest in individuals with AD, with mild cognitive impairment falling in between. In other cognitive domains, however (e.g., visual learning and memory, visual attention, language), individuals with depression and individuals with MCI performed equivalently, both higher than individuals with AD [108]. This suggests that for domains outside of verbal learning, depression-related deficits are more in line with MCI as opposed to dementia, which speaks to the milder severity of difficulties to be expected in depression.

There are other qualitative distinctions that may help to differentiate typical cognitive patterns associated with depression versus dementia. Cognitive symptoms associated with neurodegenerative disorders are progressive, whereas cognitive deficits related to depression should generally stabilize (or improve in some cases) with adequate management of psychiatric symptoms. Thus, repeat neuropsychological evaluations can be helpful to monitor cognitive changes over time. In addition, the cognitive changes that accompany depression tend to be more generalized and non-specific, which can contrast with the more isolated amnestic deficits seen in AD.

In addition, late-life depression is associated more with a subcortical profile compared to the primarily amnestic profile seen in AD, and it has been suggested that the memory difficulties seen in depression are actually secondary to executive dysfunction [109; see [110] for review]. Thus, in addition to difficulties with memory recall, depression can also be associated with changes in processing speed, fluid cognitive abilities and reasoning, and verbal fluency [111–116]. In contrast, visuospatial functioning and orientation are typically intact. Depression-related cognitive symptoms are generally thought to reflect deficits in effortful processing, leading to difficulty on tasks that require a high degree of cognitive resources. According to this hypothesis, performance is generally adequate on tasks that are more automatic and require less effort to complete [103]. In contrast, the deficits found in dementia are associated with decrements in ability rather than effort, and therefore, impairments are apparent independent of the degree of effortful processing required [117]. While this effortful-automatic hypothesis can be a useful heuristic, it may be overly generalized and has not consistently been supported by research.

With regard to memory, although depression and dementia can both impact performance on immediate and delayed memory tasks, delayed retrieval tasks can be useful for differentiating between the groups [103]. AD is associated with rapid forgetting of information, which results in poor delayed recall and recognition performance. Therefore, patients with AD do not benefit significantly when given mnemonic support such as cues at retrieval, as information has not adequately been retained in memory. This difficulty with the retention of information in memory is not surprising given that AD pathology affects the hippocampus and surrounding regions and areas critical to memory encoding and storage. In contrast, depressed individuals may struggle with delayed recall, but performance can improve significantly when given cues. This is because in depression, memory difficulties are associated

with deficits in executive functioning and strategic processing. When there is a reduced demand on strategic processing, as is the case when cues or organization are already provided, memory abilities are better. For example, Elderkin-Thompson and colleagues [109] demonstrated that older adults with depression performed poorly on list learning tasks, but when given semantic cues, memory significantly improved to normal levels. Thus, it appears that depressed patients derive more benefit from cuing than AD patients. This is consistent with multiple studies comparing individuals with AD and depression that have found an AD-specific deficit in cued recall tasks [118–121]. This suggests that this cued recall tasks may be effective in distinguishing AD from depression. Suggestions for cued recall tasks that can be included in a neuropsychological battery include Verbal Paired Associates from the Wechsler Memory Scale-IV [122], Paired Associates Learning from the CANTAB [123], and Cued Recall from the California Verbal Learning Test-II [124].

Recognition performance can be another way to differentiate between memory difficulties associated with AD versus depression. Given that recognition tasks minimize the need for effortful and strategic retrieval, depressed individuals typically show adequate performance on these tasks. In contrast, patients with AD tend to show impairments given that information is often not encoded or retained in memory and therefore even recognition of this information is deficient. In addition, there are also differences in how individuals with depression and dementia approach recognition tasks. Whereas depressed individuals tend to take a more conservative approach, leading to "I don't know" answers and false-negative errors, individuals with AD tend to adopt a more liberal response bias, leading to a high number of false-positive errors [125]. Through our clinical experience, this heuristic can be helpful at the group level but not always diagnostic at the individual level. Recognition memory is still an easier task than recall and thus more specific than it is sensitive. It has been our experience that some individuals who go on to develop AD can still show intact recognition performance in the earlier stages (e.g., mild cognitive impairment). This is supported by research showing that recognition deficits in mild cognitive impairment are less severe than in AD [126]. Thus, while impaired recognition would lend support to consideration of incipient AD, intact recognition would certainly not rule this out. Suggestions for memory tasks with a recognition component include Logical Memory, Visual Reproduction, and Verbal Paired Associates from the Wechsler Memory Scale-IV, the Hopkins Verbal Learning Test-Revised [127], the California Verbal Learning Test-II, the Brief Visuospatial Memory Test-Revised [128], the Rey Auditory Verbal Learning Test [129], and the Recognition Memory Test [130].

Analysis of serial position effects can also be informative. Foldi [131] found that patients with AD showed poorer overall recall of a word list compared to depressed individuals. Moreover, AD was associated with an advantage of recency over primacy (i.e., individuals recalled words from the end of the list better than those at the beginning), which is consistent with difficulty retaining information in memory over time. In contrast, individuals with depression showed both a strong primacy and recency effect with poorer recall of words in the middle of the list. This poor middle-list performance distinguished depressed patients from healthy controls. Therefore, recall abilities in individuals with AD across a word list can reflect an upward-sloping line (with better performance at the end of the word list), whereas the performance of individuals with depression may be better characterized by a U-shaped function (with better performance at the beginning and end of the word list).

Patients with depression and AD can also differ on other nonmemory tasks. For example, Kaschel and colleagues [132] found that even when memory performance was equated, AD patients had more difficulty compared to depressed patients on tasks requiring dual-tasking. In addition, compared to depression, dementia is more associated with impairments on tasks of naming,

visuoperceptual processing, and ideomotor and ideational praxis [101, 102, 119]. With regard to language ability, impaired confrontation naming and semantic fluency can accompany AD but would be less common in depression. While depressed individuals can show weaknesses in verbal fluency, this is typically secondary to overall slowed processing as opposed to the semantic retrieval deficit seen in AD.

As discussed above, the cognitive profiles in depression versus AD can be distinct. However, it may be more difficult to differentiate between depression and other types of dementia, such as vascular dementia or FTD. While there is overlap in the cognitive profiles of depression and vascular depression (e.g., both show slowed processing speed and executive dysfunction), there is some evidence that executive functioning deficits are more prominent in individuals with vascular depression [133]. In addition, executive dysfunction in vascular depression has been associated with greater treatment resistance to antidepressants. In fact, it has been suggested that the efficacy of treatment in late-life depression can be dependent on the degree of underlying white matter pathology [133].

Although FTD and depression can both result in a dysexecutive profile on cognitive testing, the cognitive deficits associated with FTD tend to be more focal (e.g., specific to executive functioning, language, semantic memory) and progressive. In addition, while patients in the mild stage of FTD stage can perform comparably to individuals with depression with regard to severity of deficits, moderate FTD is associated with a higher level of impairment across all cognitive domains [109].

Overall, depression and dementia can differ in both the quantity and quality of cognitive deficits. The cognitive profile associated with AD is most reflective of a cortical dementia, typified by a prominent memory disturbance. In contrast, depression is better represented by a frontally mediated (or subcortical) pattern leading to executive functioning deficits that can affect other cognitive domains due to the lack of initiation of strategic or effortful processing. The cognitive difficulties associated with depression are less severe than those associated with dementia, and thus late-life depression accompanied by significant cognitive impairment, particularly in the memory domain, should be concerning for an organic etiology.

Conclusion

Depressive symptoms and cognitive complaints are common in older adults. While depressive symptoms may reflect a primary depressive disorder, they may also represent the early signs of a neurodegenerative or otherwise organic process. Dementia and depression are highly comorbid and are certainly not mutually exclusive. Depression and dementia can differ in terms of their cognitive profile as well as the phenomenology of the depressive symptoms. Table 12.3 presents differential features of depression and AD that can be used as a general guideline in clinical practice. Accurate differential diagnosis has significant clinical implications as treatment approaches and prognosis vary significantly depending on etiology. Neuropsychologists can play an important role in differential diagnosis by providing an objective assessment of an individual's cognitive and psychological functioning.

Clinical Pearls

- Depression and dementia should not be viewed as orthogonal entities but rather as possibly comorbid, additive, or even interactive factors. Clinically, trying to differentiate between depression versus dementia as a cause of cognitive impairment can be difficult and in some instances futile given the lack of mutual exclusivity.
- Depressive symptoms of apathy tend to be associated with neurologic disorders as compared to the dysphoria (especially with a loss of self-esteem) that is more often associated with primary depressive disorders.

Table 12.3 Differential features of depression and AD

	Depression	AD
Onset of depressive symptoms	Early	Late
Prior psychiatric history	Present	Absent
Family psychiatric history	Present	Absent
Sleep	Frequent night and morning awakenings; increased REM	Delayed sleep onset, difficulty waking in morning
Onset of cognitive symptoms	Acute	Gradual
Severity of cognitive symptoms	Less impaired	More impaired
Severity of mood symptoms	More severe	Less severe
Prominent mood symptom	Dysphoria	Apathy
Temporal relationship between cognitive and mood symptoms	Mood symptoms precede or concurrent with cognitive symptoms	Mood symptoms precede, equal to, or follow cognitive symptoms
Insight into cognitive deficits	Exaggerated complaints	Poor insight
Memory		
Serial position curve	Intact primacy and recency, reduced middle	Impaired primacy, intact recency
Cued recall	Intact	Impaired
Immediate recall	Impaired	Impaired
Delayed recall	Impaired	Substantially impaired
Recognition	Generally intact	Impaired
Language (naming)	Intact	Impaired
Response biases	"I don't know" answers False negatives	Prone to guessing False positives
Praxis	Intact	Impaired
Retention	Adequate	Rapid forgetting
Orientation	Adequate	Can be impaired
Copying	Intact	Impaired
Dual-tasking	Intact	Impaired
Effortful processing	Impaired	Depends on task
Automatic processing	Intact	Depends on task
Primary area of cognitive impairment	Executive functioning	Memory
Pattern of cognitive deficits	Subcortical	Cortical

- Significant subjective complaints, in particular those that are disproportionate to objective findings, are more often associated with primary depression rather than a neurologic etiology. Conversely, evidence of significant cognitive impairment on formal testing, particularly in the memory domain, should raise concern for a potential dementia process. In general, the cognitive deficits associated with a dementia (e.g., vascular dementia, AD) are more severe than those associated with a primary psychiatric etiology.
- If the onset is gradual, there is more likely an underlying neurological basis than an affective one.
- Depression associated with a vascular or neurodegenerative etiology will be less likely to respond to treatment. Similarly, treating depression in individuals with organic dementia is unlikely to have a significant benefit on cognitive functioning.
- Referring clinicians may sometimes delay a referral for neuropsychological testing to see if cognitive impairment may improve with adequate depression treatment. However, obtaining neuropsychological testing sooner rather than later can be helpful to identify warning signs of an incipient dementia process and to track progression over time (which can provide additional information for differential diagnosis).

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Elder Abuse Identification and Intervention

13

S. Duke Han, Bonnie J. Olsen, and Laura A. Mosqueda

Introduction

Elder abuse (otherwise known as elder mistreatment) is a devastating societal problem that can take many forms. The authors of this chapter use the terms *elder abuse* or *elder mistreatment* interchangeably to refer to the intentional action or lack of action that results in any physical, emotional, or financial harm of an older adult (see [11] for a review). Elder mistreatment has been associated with multiple poor health and well-being outcomes [2], including perhaps most consequentially, higher rates of mortality [1, 7], and this finding has even been replicated in cohorts outside of the United States [15]. Although 1 in 10 adults over age 60 experience abuse or exploitation, it is estimated that fewer than 10% of elder abuse cases are reported [12]. Neuropsychologists have a unique opportunity to address this devastating public health concern through the course of their clinical practice activities. To provide neuropsychologists with the background and tools necessary to properly address elder mistreatment that may occur their patients, this chapter has three sections. The first section is dedicated to educating the reader as to the different forms that elder abuse may take. This section is provided to make the clinical neuropsychologist reader aware of a multitude of possible scenarios that might present themselves as elder mistreatment. The second section is dedicated to providing concrete recommendations and suggestions for elder abuse screening during the clinical neuropsychology examination. The third and final section reviews recommendations for reporting and provides additional information that may be helpful to the neuropsychologist should a report become necessary.

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Types of Elder Mistreatment

Elder mistreatment may take many different forms. The Centers for Disease Control and Prevention recently developed uniform defini-

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tions of elder abuse [6] and consider five broad types of abuse of which to be cognizant as a clinical neuropsychologist. These are briefly described below.

Physical Abuse

Physical abuse of an older adult refers to when force is applied to the patient that results in physical or psychological harm. The actions that result in harm can range dramatically, including actions such as pushing, shoving, shaking, hitting, biting, scratching, burning, and choking. The harm may manifest in overt physical symptoms such as bruising or pain or may manifest in more psychological symptoms such as fear and distress. Included under this category are inappropriate use of medications to intend harm and inappropriate use of physical restraints. Often physical abuse occurs as a form of punishment inflicted by caregivers of an older adult.

Sexual Abuse

Sexual abuse is defined as forced or unwanted sexual actions committed against an older adult. Although forced touch of genitalia would clearly qualify as sexual abuse, unwanted touch over clothing or actions not involving touch at all (e.g., forced viewing of pornography, verbal sexual harassment) would also qualify as sexual abuse. Since sexual abuse is considered when there is a suspicion of coercion, any patient that is found to lack the ability to consent may be screened for potential sexual abuse or exploitation.

Emotional/Psychological Abuse

Emotional abuse is considered when a person in a trust relationship with the older adult behaves in such a way as to produce feelings of fear or distress. Actions committed by the abuser can be of a verbal nature, or may be of a nonverbal threatening nature, as in the example of holding a weapon in anger toward the patient. The behavior of the abuser may leave the patient feeling humiliated, threatened, harassed, fearful, or isolated in some way.

Neglect

Neglect is considered when someone in an established caretaking relationship with the patient fails to meet the medical or physical needs of the patient. An example of neglect may be a family member that does not ensure the patient eats meals regularly or that does not help the patient maintain basic hygiene such that they are in filthy conditions and develop pressure sores. The result of neglect is harm to the patient's health or safety.

Financial Abuse/Exploitation

Financial abuse has been described as one of the most common forms of elder mistreatment. As the number of older adults with substantial long-term high-yielding funds and life savings exponentially increases and as cognitive abilities decline in later life, financial exploitation of older adults can be viewed as a growing societal problem. Examples of financial abuse include depriving the patient information or access to his or her annuities or funds, misdirecting funds to the benefit of someone who is not the patient, forgery of documents using a patient's information, selling of commercial products or other services to an older adult without knowledge or understanding of the products or terms of services, coercion or undue influence in financial matters, or withholding care of the patient for financial gain.

Other Types of Abuse

Other types of abuse have been documented that may not readily fit within the categories provided above. For example, some earlier conceptualizations have included self-neglect as a form of elder abuse inflicted upon oneself. Within the context

of a nursing home, resident-to-resident abuse or aggression has also been noted. Abduction or imprisonment of older adults has also been discussed as abuses that may not readily fall within one of the above criteria. For more information on the different types of abuse, the reader is referred to the resources of the National Center on Elder Abuse (NCEA), which can be accessed at https://ncea.acl.gov/.

Recommendations for Screening

Neuropsychological evaluations offer a unique opportunity to screen for elder abuse given the longer clinical times and in-depth assessments providers commonly engage in. This section provides specific considerations and recommendations for elder mistreatment screening in the context of the clinical neuropsychological examination.

Clinical Interview

The best opportunity for a clinical neuropsychologist to screen for potential elder abuse is during the clinical interview portion of the neuropsychological examination. Bearing the typologies of elder abuse in mind, questions can be tailored to specifically illicit information that may be indicative or confirmatory of potential elder abuse or exploitation. To this end, a model framework of elder abuse may be useful to conceptualize potential risk factors for elder abuse.

The Abuse Intervention Model (AIM; [12]) conceptualizes the elder abuse experience as having three primary and interacting considerations: (1) the cognitively impaired older adult, (2) the caregiver or person who is in a trust relationship with the cognitively impaired older adult committing the abuse or exploitation, and (3) the social or environmental context in which the abuse may be occurring. Risk factors for elder abuse can be identified along any of these three axes. For example, in keeping with the first consideration, if an older adult is found to be cognitively impaired, then the risk for elder abuse and exploitation is greatly elevated [14]. If the insight of the patient is found to be poor, then the ability of the patient to report conditions or experiences that are abusive might be considered. If the patient is found to have multiple chronic medical conditions or other disabilities, then the patient's level of dependence may predispose the patient to a higher risk for abuse. Depression among older adults has been associated with elder abuse and thus is another potential risk factor or indicator [4].

Under the second consideration of the AIM, if the primary caregivers or loved ones closest to the patient have a criminal history or an untreated psychiatric disorder, then the risk of elder abuse of the patient should be elevated in the clinician's view, and this should be probed during the clinical interview. Similarly, if there is an adult child or acquaintance that has been living with the patient because of financial difficulties, then this should raise the possibility of financial exploitation of the patient in the clinician's mind. Pensions are common among men or women who have served in the military or other governmental positions. During the course of the interview, inquiries about how pension, annuity disbursements, or social security benefits are handled by the patient or his or her caregivers may lead to an assessment of exploitation risk.

The third consideration of the AIM refers to the contextual circumstances surrounding the patient, and this may highlight multiple risk factors for exploitation. For example, if the patient is recently widowed or had been living alone for some time, feelings of loneliness may lead the patient to establish relationships with persons who may not have the best intentions for the patient, particularly if the patient receives a regular annuity. If immediate family members of the patient have recently hit hard economic times, then the risk of financial exploitation might be elevated. If a patient has been diagnosed with a dementing illness, there is only one caregiver available to provide support to the patient, and there is very little social support for that caregiver, then burnout may be a risk, which in turn

may lead to abuse of the patient out of sheer exasperation of the caregiver. The assessment of the context of the patient may arguably yield the most pertinent information to assess the risk for elder abuse. Inquiries as to the stability of finances, current housing situation, level of social support for the patient and primary caregivers, and nature of primary relationships would highlight potential risk factors for abuse. Incidentally, interviewing of the patient apart from caretakers or family members is recommended to determine whether there is any undue influence or fear of retribution.

Neuropsychological Testing

The assessment portion of the neuropsychological examination is less likely to elicit signs of elder abuse, although based on the writers' clinical experience, this can still be screened through behavioral observations and approach to testing. For example, patients who show significant anxiety in response to testing may further be probed to determine whether the source of anxiety is rooted in any ongoing potential abuse or mistreatment by caregivers. Recent work has highlighted the identification of bruises, broken bones, or other injuries during medical visits as potential signs of elder abuse, mistreatment, or neglect [5]. These signs might be more clearly evident during the testing portion of the examination as patients are asked to complete psychomotor and other tasks. Finally, the testing portion of the examination allows for the patient to be interviewed separately from any accompanying caretakers. This separation should be utilized to determine if there was any additional information withheld during the formal interview portion of the examination.

There are many measures that have been developed to directly assess for symptoms of elder abuse and mistreatment. These measures vary greatly in terms of length and approach, and it is generally accepted that there is no one preferred approach to quantitatively assess for elder abuse. The 22-item Indicators of Abuse (IOA) tool, the 44-item Elder Assessment Instrument (EAI), and the 15-item Elder Abuse Screening Test (EAST) are some examples of measures that have been used in long-term care facilities [9]. These and other measures of elder abuse and exploitation have been reviewed and discussed in previous work [10]. Interest in financial exploitation among older adults has led to recent efforts to formally assess risk for impaired financial capacity. The Lichtenberg Financial Decision Rating Scale (LFDRS, [8]) and the corresponding screening measure (Lichtenberg Financial Decision Screening Scale (LFDSS)) are examples of tools that are currently available for practitioners. Well-validated measures of elder abuse and elder exploitation risk are much needed tools in the clinical neuropsychology arena.

Feedback and Follow-Up

Dementia and cognitive decline are arguably the most salient risk factors for elder abuse [3, 12]. Given this, any situation where an older patient is found to be cognitively impaired should be considered with respect to potential of elder abuse or mistreatment. The AIM framework is useful to assess for potential risk should a patient be newly diagnosed with cognitive impairment. If the social context was not sufficiently ascertained during the clinical interview, then the feedback session may be another opportunity to probe this for the protection of the older adult. If a patient is found to be cognitively impaired, then power of attorney may be discussed in the context of the feedback session. It is important to be cognizant of the risk of abuse and exploitation while considering holders of power of attorney, as there have been many unfortunate cases where abusers have been assigned power over patients' financial and health decision-making, resulting in great detriment to the patients. Related to this point, the clinical neuropsychologist should be aware of potential for abuse when the reason for referral is initiated by a family member to determine another family member's capacity to handle finances and health decisions.

Guidelines for Reporting

Licensed clinical neuropsychologists in the United States are ethically obligated to report or intervene when learning of potential abuse or harm toward their patients or others. This section provides recommendations and helpful information for elder abuse reporting.

Laws

State laws vary widely with respect to what is required in reporting, and it is the legal and ethical responsibility of every licensed clinical neuropsychologist to be familiar with the legal mandates within his or her jurisdiction of practice. Many of the state-specific statutes can be accessed through the NCEA website (https://ncea.acl.gov/whatwedo/policy/state.html). As of the submission of this chapter, there is no overarching federal law currently governing elder abuse, although most have instituted mandatory reporting of elder abuse. However, it is notable that states have been instituting different criteria for elder abuse and elder abuse reporting. For example, some states set a specific age as a criterion for elder abuse, with some using the age of 60 and others using the age of 65. Furthermore, some states have enacted different laws and protocols for the different types of elder abuse. For example, some enact harsher guidelines and penalties for elder financial exploitation than others.

While most of this chapter has been written from the perspective of having a patient at risk for elder abuse and exploitation, it should be acknowledged that as mandated reporters, clinical neuropsychologists also have an ethical responsibility to respond should it be discovered that a patient (of any age) may be abusing or exploiting an older adult. This duty to protect can be described as one of the limits to confidentiality before the evaluation begins, and the AIM framework may be used to assess potential of a patient to become an abuser or exploiter of vulnerable older adults.

Agencies

Many states have instituted Adult Protective Services (APS) or a similarly functioning entity as a community supportive service devoted to the protection of vulnerable adults. These services can be contacted via phone or online and provide the opportunity to report elder abuse anonymously. For more state-specific information or for assistance in making a state-specific report, the National Adult Protective Services Association website is a useful resource (http://www.napsa-now.org/). If an older adult is in immediate danger, the local police should be called. If elder abuse or exploitation is suspected in a nursing home context, then the Long-Term Care Ombudsman Program is the appropriate agency to contact as there is an ombudsman in every state in the United States. For state-specific information or for assistance in making a state-specific report relevant to a long-term care facility, the National Long-Term Care Ombudsman Resource Center (NORC) website can be accessed (http://ltcombudsman.org/). Finally, a new and exciting trend has been the establishment of Elder Abuse Forensic Centers. These are multi-disciplinary centers devoted to specifically addressing elder abuse and can include geropsychologists, neuropsychologists, medical doctors, law enforcement professionals, social workers, lawyers, and community representatives working in a coordinated effort [13].

Conclusion

Clinical neuropsychologists have a unique opportunity to address the abuse and exploitation of older adults through routine clinical assessment activities. Knowledge of the major characteristics of elder abuse [6] and a framework to consider potential risk factors for elder abuse (AIM, [12]) can assist with screening. Since elder abuse is associated with multiple negative health outcomes and mortality, the action or inaction of the clinical neuropsychologist with respect to elder abuse or exploitation may literally mean life or death for the patient.

Clinical Pearls

- Elder abuse can take many forms. The most common forms are physical, sexual, emotional, financial, and neglect. The clinical neuropsychologist should be mindful of the range of abuse types.
- Elder abuse can be effectively screened during all aspects of the neuropsychological evaluation; however, the clinical interview may offer the best opportunity to assess for abuse or exploitation.
- The Abuse Intervention Model (AIM; [12]) is a useful framework for assessment of elder abuse. AIM conceptualizes the elder abuse experience as having three primary and interacting considerations: (1) the cognitively impaired older adult, (2) the caregiver or person who is in a trust relationship with the cognitively impaired older adult committing the abuse or exploitation, and (3) the social or environmental context in which the abuse may be occurring. Risk factors for elder abuse can be identified along any of these three axes.
- Cognitive impairment of an older adult is one of the strongest risk factors for elder abuse. Anytime an older adult is found to be cognitively impaired, the clinical neuropsychologist should consider potential for abuse or exploitation.
- Laws vary greatly by state in regard to reporting requirements; however, the National Center on Elder Abuse website provides useful information on state-specific statutes (https://ncea.acl.gov/whatwedo/policy/state.html).
- If the older adult is believed to be in immediate danger, the local police should be contacted right away.
- The National Adult Protective Services Association website is a useful resource (http://www.napsa-now.org/) for assistance in making a state-specific report. If the patient is in a long-term care facility, then the National Long-Term Care Ombudsman Resource Center website (http://ltcombudsman.org/) is a useful resource for reporting.

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Prevention of Cognitive Decline

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Introduction

While we have made great strides toward achieving measurable gains in dementia prevention, efforts to prevent cognitive decline and dementia have failed to show consistent results. The significance of researching preventative measures stems from the impeding dementia epidemic that affects individuals, society, and global healthcare. As the older population continues to advance in age, both cognitive decline and dementia become increasingly prevalent and apparent. Accompanying advancing age is a decline of cognitive abilities including perceptual speed, reasoning, episodic memory, and working memory [1]. Cognitive decline covers a vast array of symptoms and may occur due to a variety of causes, ranging from mild, stable symptoms observed with normal aging to progressive symptoms as seen in dementia.

Dementia is characterized by the gradual loss of cognitive abilities, in multiple domains, severe enough to interfere with daily living [2]. Alzheimer's disease (AD), the most common form of dementia, occurs in approximately 10% of persons older than 65 years and up to 50% of those older than 85 years [3]. The risk of dementia nearly doubles with every 5 years of age. The US Medicare economic cost of caring for people with dementia in 2008 was 91 billion dollars and is predicted to double by 2015. By 2050, it is expected that the number of people diagnosed with AD will triple, leaving a great impact on global healthcare and families alike [4].

Over the years, countless modifiable and non-modifiable risk factors have been brought to light, suggesting a high potential for research of both non-pharmaceutical and pharmaceutical strategies for AD therapeutics. While this global problem of dementia is often associated with the elderly, many of the pathologic changes associated with AD may occur decades before symptom onset, leaving ample time for preventative measures. Earlier identification of at-risk individuals could lead to faster diagnoses, better stratification of patients, higher levels of enrollment in clinical trials, and ultimately more effective preventative treatments [5].

Preclinical Alzheimer's disease is the state of being cognitively normal but testing positive for the presence of cerebral amyloid [6]. Future dementia prevention trials focusing on patients with preclinical Alzheimer's disease will need to screen out up to 80% of potential participants, but the cost of scanning all potential participants for the presence of amyloid would be prohibitive. The use of noninvasive screening measures including web-based programs will become increasingly important to reduce the number of

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individuals who need to be scanned prior to enrollment in these trials [7]. Several risk indices are available for this purpose. Researchers have identified at least 11 risk factors and 4 protective factors for AD (age, sex, education, body mass index, diabetes, depression, serum cholesterol, traumatic brain injury, smoking, alcohol intake, social engagement, physical activity, cognitive activity, fish intake, and pesticide exposure) [8]. Studies with emphasis on genotype, lifestyle, and nutritional intake may serve to be an important consideration for neurodegenerative diagnosis and disease modification. As such, health authorities should focus on identifying high-risk individuals at an early stage, when intervention is more likely to help [9].

It should also be noted that because adult brain structure is primarily established in early life and young adulthood, childhood factors such as socioeconomic status and early life brain growth could also influence AD risk. Learning disabilities may predispose to atypical phenotypes of AD [10]. Interactions between these and other interrelated factors are difficult to detect. Early life brain development could render different brain regions selectively vulnerable to the onset, accumulation, or spread of AD-related pathology during later life. The adult life mechanisms by which early life factors exert influence on AD risk remain unknown.

While in past years, the concept of dementia prevention has been perceived by many clinicians as impossible, in 2014 a group of 109 scientists from 36 countries signed a statement detailing how dementia (including AD) can be prevented [9]. While there is no one "magic" pill or definitive single way to prevent dementia, the most recent projects have found that if indeed the known modifiable risk factors for AD are in the causal pathway to dementia, then one out of every three cases could potentially be prevented by addressing those factors [11]. It is currently unclear which specific interventions would be most effective, in which patients and during which life stages. Although the entire life course is relevant to dementia prevention, this review focuses on only those risk factors which are modifiable and which have been demonstrated in adults or the elderly.

Understanding Cognitive Decline

Normal cognition requires complex neural networks localized in different parts of the brain such as the medial temporal lobes including the hippocampus and the entorhinal cortex, as well as the frontoparietal cortices [12]. Memory, attention, executive function, perception, language, and psychomotor function are key components [13]. In relation to neurodegeneration, impairment of any of these components has a pathological substrate in a corresponding brain area, culpable for its processing. Different pathological changes correlate to the various form of dementia. Given that AD is the most prevalent neurodegenerative disease associated with dementia, it is the most studied and pertinent focus for many clinical trials. In practice, however, dementia due to coincident disease (mixed pathology) is more common than dementia due to pure AD [14].

In AD, deposition of amyloid beta (Aβ) protein aggregates and accumulation of tau protein in areas of the brain, such as the hippocampus and the entorhinal cortex, are associated with early disease-related changes in AD. These two proteins and their respective signaling pathways are thought to be important rate-limiting steps in AD pathology. The Aβ and tau aggregates gradually become widespread plaques and tangles in the brain of AD patients. Years of accumulation result in decreased synaptic function and neuronal atrophy, likely a significant driving force behind the cognitive deficit [12]. Oxidative damage, excessive glutaminergic activity, energy failure, inflammation, and apoptosis seem to be significant contributors to neuronal loss and progressive cognitive dysfunction [15]. The order in which these pathologic features occur is still being debated. Degeneration of certain brain regions results in deficiencies in neurotransmitters that serve essential roles in neuronal circuits dealing with cognition (e.g., degeneration of the basal forebrain is associated with decrements in acetylcholine-mediated neuronal activity involved in memory).

Multiple genetic, clinical, and environmental risk factors have been directly linked to the

occurrence of AD. Appearance of dementia later in life is believed to be a result of the combination of age-related changes in the brain, predominantly vascular changes, AD, and α-synuclein pathology [5]. Vascular risk factors like hypertension (HTN) and diabetes mellitus (DM) appeal to the interest of the public perspective on health due to their global prevalence, ease of administered treatment, and affiliation to diseases with similar risk factors. The magnitude of these risk factors appears to be directly proportional to the observed prevalence and intensity associated with the disease.

Evidence also suggests abnormalities in glucose metabolism, mitochondrial function, and oxidative stress are invariant features of AD and may occur decades before the onset of clinical symptoms (during the "preclinical AD" stage) in both genetic and nongenetic AD forms [5]. As one example, the presence of the apolipoprotein E ε4 (ApoE4) allele is a well-studied genetic risk factor for late-onset AD. In ApoE4-positive younger adults, cerebral glucose hypometabolism has been observed in asymptomatic individuals in the temporal, parietal, posterior cingulate, and prefrontal lobes decades before the expected development of AD (average age of 30.7) [16]. Mitochondrial dysfunction may also be a key link in AD pathogenesis. While it is not entirely clear whether amyloid and tau may lead to mitochondrial dysfunction, there is well-grounded scientific rationale that mitochondrial dysfunction may more likely lead to glucose hypometabolism and has been seen early in the brains of patients at risk for developing AD [17]. Mitochondrial dysfunction may lead to most of the mechanisms thought to impair brain function in AD, including oxidative stress, apoptosis, and inhibition of protein degradation and autophagy, potentially leading to the accumulation of amyloid and tau. Other changes such as alterations in calcium homeostasis also precede clinical symptoms, and abnormal glucose metabolism, mitochondrial dysfunction, and oxidative stress may promote plaques, tangles, and calcium abnormalities that accompany AD [18]. Therapies targeting mitochondrial function, glucose hypometabolism, and their associated distinctive metabolic requirements are under active investigation. This "mitocentric" view of the pathogenesis of AD offers some key theory behind why a myriad of the interventions discussed below may be practical options toward lowering dementia risk while also being generally low in risk [19].

Diet

The first suggestion that diet could offer protection against cognitive decline and dementia came from the Mediterranean region. A high dietary intake of fruit, whole grains, legumes, fish, and vegetables resulted in a lower occurrence of cognitive decline and brain-related diseases. Since then, several studies have investigated the "Mediterranean diet" (also referred to as MeDi) as well as other dietary patterns [20]. At least five high-quality, prospective cohort studies examining the MeDi with longitudinal cognitive follow-up of at least 1 year support the idea that among cognitively normal individuals, higher adherence to the MeDi is associated with a reduced risk of mild cognitive impairment (MCI), a dementia prodromal stage, and AD [21]. Randomized trials show that healthful diets can even show effects on cardiovascular disease markers and cognitive performance in as little as 4 weeks. A 4-week, low-saturated fat/low-glycemic index diet, compared to a high-saturated fat/high-glycemic index diet, modified cerebrospinal fluid (CSF) biomarkers and improved delayed visual memory for normal adults and adults with MCI [22]. A diet with high antioxidative capacity (fatty fish, rapeseed oil, oat, barley and rye foods, bread supplemented with guar gum, soybeans, and dry almonds), compared to a control, healthful diet devoid of the "active" components, significantly improved cardiovascular risk variables and also resulted in improved performance tests of selective attention and also auditory verbal learning [23]. A recent study found that normal subjects with higher adherence to the MeDi diet had less cortical thinning in the same brain regions as clinical AD patients [24]. These data suggested a protective effect against tissue loss and suggest that the MeDi diet may play a role in the prevention of AD.

In general, a healthy diet is attributed to having sufficient mineral, vitamin, and other elemental component intake, necessary for basic cellular functioning. These elements could reduce the risk of dementia and cognitive decline by interfering with pro-inflammatory responses in the brain [25]. Examples include neurodegenerative protection in the form of high supply of natural fish oil, vitamins, and polyphenols.

Several scores and outcome scales have been created to assess adherence to the Mediterranean diet [26]. In a recent prospective cohort study, a higher Mediterranean diet score was associated with better cognition. In this same cohort, a dose-response effect of Mediterranean diet was suggested based on the progressive lower risk for developing dementia or MCI in the middle and the upper score tertile when compared with the bottom tertile (21% and 47% risk reduction, respectively) [27, 28]. Another prospective cohort demonstrated that high adherence to the Mediterranean diet was associated with better cognitive output and episodic memory scores over time, but did not show any protective effect for the development of AD [29].

Variable information regarding education, geographic location, exercise, and less prevalent cardiovascular risk factors are reason for current debate over the final impact of the Mediterranean diet on cognition. Regardless of these discrepancies, it is generally assumed that early introduction of a healthy diet is beneficial for cognition and for various cardiovascular risks associated with contributing to the occurrence of AD and cognitive decline [20]. While there is insufficient randomized prospective data to prove the efficacy of Mediterranean diet vs. other dietary patterns, the Mediterranean diet still exemplifies the most commonly recommended potentially beneficial diet to overall brain health.

Gu and colleagues proposed a different approach to the evaluation of diet and the risk for cognitive decline/AD [30]. Given the potential for low prevalence of Mediterranean diet in local communities, statistical analyses assessed nutrients and dietary patterns in order to compartmentalize dietary elements associated with lower risk of AD development. Resulting data illustrated that greater intake of nuts, fish, poultry, fruits, and cruciferous and leafy vegetables is associated with a lower risk of AD and a negative correlation with red meat, high-fat dairy, and butter intake. Overall, evidence suggests a diet rich in fruits, vegetables, legumes, fish, nuts, and grains to be healthiest [1, 2, 4]. Regardless of these recommendations, the effect that any individual dietary component has on others remains in question.

Diet interventions may affect individuals in different ways, specifically with respect to ApoE4 allele carrier status [31]. In Yoruba populations in Nigeria, there is no association between ApoE4 status and AD as compared to genetically similar populations with a Western lifestyle and diet [32]. In older individuals, C-reactive protein (CRP) levels are associated with cognitive decline only in ApoE4-negative individuals [33]. Consumption of fatty fish more than twice per week was associated with a reduction in risk of dementia and AD only in ApoE4-negative subjects [34, 35]. Saturated fat intake was associated with an increased risk for dementia 20 years later but only among the ApoE4 carriers [36].

MIND and DASH Diets

The DASH (Dietary Intervention to Stop Hypertension) diet has been associated with an improvement in cognitive function [37]. Participants with hypertension who were randomized to follow the diet, which encourages a variety of foods rich in potassium, calcium, and magnesium, and places an emphasis on vegetables, fruits, and low-fat dairy, exhibited an improvement in psychomotor speed. The diet also includes moderate amounts of whole grains, fish, poultry, and nuts.

Combining aspects of the MeDi (discussed previously) with aspects of the DASH diet, a dietary pattern was devised called the MIND diet. The MIND diet considers individual foods which have been shown to bolster cognitive function and de-emphasizes those without strong "brain-specific" evidence [37]. For example, it de-emphasizes dairy and makes no specific recommendation for fruit other than berries, which

have been shown in both human and animal trials to improve cognition. In a large prospective study (the Nurses' Health Study), berry consumption was found to be associated with reduced cognitive aging [38].

In the initial MIND trial, both high and moderate adherence were associated with a slowed rate of cognitive decline when compared to either the DASH diet or MeDi diet alone. In a follow-up study involving 923 seniors followed over 4.5 years, individuals with moderate adherence to the MIND diet lowered their Alzheimer's risk by 35%, while those who adhered to it rigorously reduced risk by up to 53%.

FINGER Study

Considering the complexity of Alzheimer's disease and other forms of dementia, a multimodal approach may be most effective in terms of mitigating risk and slowing cognitive decline. Recently, the first long-term trial with a large sample size showed that multiple interventions are effective in delaying cognitive decline. The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) trial involved 1260 older non-demented adults at risk for cognitive decline. Participants were randomized to an intervention arm which included nutritional counseling, physical exercise, social support sessions, cognitive training, and management of metabolic and cardiovascular risk factors [39]. The control group received standard-of-care health advice on an as-needed basis. After the 2-year intervention, compared to controls, improvements were observed in executive functioning (83% higher) and processing speed (150% higher). There was a 27% improvement in overall cognition compared to the control group.

Nutritional Interventions and Dietary Supplements

Evidence on nutritional interventions for cognitive decline and dementia is in a constant state of growth. While the content below is a fairly broad and up-to-date summary for dementia, a recent initiative begun by the Alzheimer's Drug Discovery Foundation, called Cognitive Vitality, attempts to update the evidence for many of the topics below on an ongoing basis. For more information about this initiative, visit: http://www.cognitivevitality.org.

Garlic

Garlic is high in antioxidants and organosulfurs. An extract preparation has been associated with decreased cholesterol levels and blood pressure. Additionally, it is thought that garlic may be doubly beneficial in that it lowers cardiovascular risk factors and their impact on AD development as well as supplies antioxidants capable of counteracting the ongoing neurodegenerative process. It has been shown in animal models that garlic can reduce homocysteine [40]. In vitro studies demonstrated that garlic extract can inhibit Aβ and caspase enzymes that promote the deposition of amyloid [41]. Budoff and coworkers demonstrated garlic decreases levels of homocysteine in humans; however, it is unclear if this result was independent of the concurrent statin therapy subjects were receiving [42].

Ginkgo biloba

Flavonoids and terpenes contained in *Ginkgo biloba* have been linked to pleiotropic actions that can affect inflammation and oxidative processes in the human body [43]. It is approved in some European countries for the treatment of cerebrovascular insufficiency and cognitive decline, although in the United States it is sold as a supplement [1]. Short-term supplementation has provided conflicting results, with some studies showing marginal improvement in cognition while others fail to reproduce any significant effect [44]. One small, randomized controlled trial (RCT) showed that ginkgo extract was associated with marginal improvement in the Clinical Dementia Rating (CDR) Scale when adjusting for medication adherence [45]. However, the

clinical significance of this marginal improvement in cognitive testing, in conjunction with a higher incidence of cerebrovascular events in the treatment arm, could have confounded the results. While there has been a lot of uncertainty around the effect of *Ginkgo biloba* in AD treatment and prevention, definitive research has shown that this is not effective for the prevention of AD [46]. In fact, there are now several studies that show that this supplement is not effective in prevention of dementia nor cognitive decline, in general. While low doses are generally safe, most clinicians are hesitant to recommend it for use. However, a meta-analysis of nine trials using standardized formulation in the treatment of dementia showed statistically significant improvement in cognitive scales with no significant benefit in activities of daily living [47]. The high variability of study designs hampers the generalizability of these results.

Alcohol

Some observational studies have shown that low to moderate alcohol consumption may lower the risk of dementia [48]. There is speculation that alcohol exerts its benefit through lipid profile improvement, although the content of flavonoids in red wine could also contribute [15, 49]. A recent meta-analysis of 23 observational studies demonstrated that alcohol in small amounts can be protective against dementia and AD but did not impact the rate of cognitive decline or the incidence of vascular dementia [48]. Inconsistent results of the analysis prevent a firm conclusion to be made on the applicability of the findings. In another study, moderate alcohol consumption was linked with resistance to the effects of Aβ, which could reduce risks of developing dementia and cognitive decline [50]. Considering the evidence, many clinicians would support moderate alcohol intake (one drink in women, one to two drinks in men) for the potential risk reduction of dementia over time. Neafsey and Collins concluded that this amount may reduce the risk of dementia and cognitive decline [51], although further studies are warranted. Most clinicians advise against consumption of more than two servings per day, as this may lead to significant health consequences. In the United States, a "standard" drink contains about 0.6 fluid ounces or 14 g of "pure" alcohol. Typical servings of alcohol are as follows: 12 oz beer = 8–9 oz malt liquor = 5 oz wine = 3–4 oz fortified wine (e.g., sherry or port) = 1.5 oz hard liquor (i.e., "a shot").

Caffeine

Caffeine has been used by civilization since ancient times. Its popularity has granted it status as the more popular and most consumed behaviorally acting substance around the world [52]. Caffeine is an antagonist of adenosine receptors A_1 and A_{2A}, although it can also interact with other enzymes and receptors like $GABA_A$ or 5′-nucleotidase at higher levels [53]. In animal models, antagonist of A_{2A} receptors like caffeine decreased the levels in cerebrospinal fluid and serum of Aβ peptides and counteracted its noxious effects at the neuronal levels [54, 55]. Inhibition of phosphodiesterase is thought to be a potential mechanism to convey neuroprotection [56]. The activation of A_{2A} receptors has been associated with long-term potentiation in striatal and hippocampal synapses essential for memory processing. The excessive or insufficient activation of these receptors results in aberrant synaptic functioning [56–59]. Caffeine can act as normalizer of aberrant memory performance rather than enhancing this process, especially in conditions with excessive endogenous adenosine stimulation such as fatigue and stress [55–58].

In humans, caffeine reaches a peak in plasma 45–120 min after oral ingestion and has a half-life that ranges from 2.5 to 4.5 h [53]. Caffeine facilitates learning on tasks in which information is presented passively, but it has not proven effective for those tasks that involve intentional learning. The caffeine effect on memory tasks seems to have an inverted U-shaped curve, showing improvement during mild- to moderate-complexity tasks but impaired performance for high-complexity tasks [13]. Caffeine confers a boost for cognitive performance among fatigued individuals, and it might also improve cognitive functioning with chronic consumption, although

its acute effect is more evident in non-usual consumers [60]. The effects of caffeine appear to vary across the age span. Administration of caffeine in the older population is more effective for improving attention, psychomotor performance, and cognitive functioning, possibly offsetting the decline associated with age. A large part of these effects may be explained by counteracting age-related decreased arousal [61].

The relationship between AD and caffeine has been more difficult to understand. A retrospective cohort study suggested that caffeine intake at midlife has protective effects against the subsequent development of AD [62]. In prospective studies, Ritchie et al. showed a protective effect of caffeine in women consuming more than three cups of coffee per day [63], and van Gelder and colleagues [64] showed that men also benefitted from caffeine intake. In this prospective cohort, men who drank more than three coffee cups per day showed slower cognitive decline when compared with those drinking less than three cups per day and non-coffee drinkers. Another prospective cohort analysis showed that cognitive performance was strongly associated with caffeine intake, with no gender differences in its protective effects. However, caffeine intake was also strongly associated with age, IQ, and social class; thus, education confounding effects could not be ruled out [65]. Finally, Boxtel and coworkers were not able to reproduce any of the abovementioned findings and demonstrated no associations between long-time caffeine intake and cognitive performance [66]. Provided the variability of the studies and results of clinical outcomes, it is difficult to strongly recommend caffeine intake as an effective measure against cognitive decline; nevertheless, it seems safe to say that caffeine can provide a boost in cognitive ability and has been shown to be protective in some populations.

B Vitamins

B vitamins are organic compounds acquired through dietary intake. They are known for their major roles in cell metabolism and are associated with protective roles in cognition. Vitamin B1 (thiamine) and vitamin B2 (riboflavin) are found in a variety of foods, such as whole-grain cereals, organ meats, milk, and vegetables. Vitamin B6 (pyridoxine) and vitamin B12 (cobalamin) are typically from poultry, seafood, meat, and eggs and often in enriched cereals. The major source of folates is the green leafy vegetables [67]. Thiamine, riboflavin, and niacin function in major biochemical pathways in the metabolism of glucose, amino acids, and fatty acids, while the coenzymes of vitamin B12, folate, and vitamin B6 interact together in the metabolism of homocysteine, a risk factor for vascular disease and dementia [68, 69]. Investigating the antioxidant and anti-inflammatory properties of these vitamins, along with their contribution to nucleotide synthesis and nerve functions, is important in the context of cognition [67]. Interaction between vitamin B12, folate, and pyridoxine could prove influential to some effects in cognitive decline. These vitamins are key determinants of homocysteine levels, of which high levels can be destructive due to neurotoxic and vasotoxic effects on brain vasculature and normal cognitive functioning [70, 71]. Other studies have shown folate levels associated with varying degrees of cognitive decline independent of the homocysteine and vitamin B levels [72, 73]. To further clarify the interaction of B vitamins and folate supplementation, future studies should control for homocysteine levels. Trials of combined vitamin supplementation are difficult to interpret because of various covariates that make it challenging to isolate an effect [7, 67]. The strongest evidence to date studied the effect of a combination of B vitamins on cognitive functioning and clinical decline in MCI patients with elevated homocysteine. In this double-blind study, MCI patients (age 70 and above) with high homocysteine levels receiving 0.8 mg of folic acid, 0.5 mg of vitamin B12, and 20 mg of vitamin B6 each day show improved cognitive test scores on the Mini-Mental State Examination (MMSE) and a category fluency test. In this RCT, this specific B vitamin combination appeared to slow cognitive and clinical decline in people with MCI, as well as slow atrophy of the hippocampus. Further studies are warranted to determine whether these

vitamins may slow or prevent the progression from MCI to AD or delay or prevent the onset of MCI [74].

Vitamin B1 (Thiamine)

Animal models have shown that rats with low thiamine diet have impaired cognitive performance compared to controls fed with adequate thiamine supplementation, and repetitive episodes of thiamine deficiency can cause worsening of cognitive performance and severe brain damage [75, 76]. Thiamine deficiency has been associated with blood-brain barrier (BBB) dysfunction and intracellular edema in animal models, revealing pathological changes that could derail the normal functioning of the brain [67].

In a non-randomized controlled trial (RCT), Meador and colleagues found that older individuals supplemented 3–8 g/day of oral thiamine showed significant improvement in the ADAS in the initial months with slowing of the cognitive decline rate during 11–13 months after the trial stopped [77]. The small sample and open design are concerns in this trial. Mimori and colleagues showed that higher blood levels of thiamine after supplementation with an oral form were associated with improvement in scores on the MMSE in an open design trial [27]. Low thiamine levels have not been consistently associated with higher prevalence of AD [78], and there is currently not enough evidence at this point to recommend thiamine supplementation for the prevention of cognitive decline [2, 7, 28].

Vitamin B2 (Riboflavin)

Goodwin and colleagues showed that individuals at the bottom decile of riboflavin dietary intake had worse cognitive performance in some domains compared to the upper deciles [79], and Lee and coworkers [80] found that MMSE scores increased as riboflavin intake increased in women but not in men. Nevertheless, low riboflavin serum levels have not been linked with the presence of AD. There is no RCT specifically designed to assess the effects of riboflavin in cognitive decline or dementia. Riboflavin supplementation is not recommended for AD prevention [2, 7, 28, 81].

Vitamin B6 (Pyridoxine)

In rodents, the supplementation of pyridoxine did not improve cognition or learning functions. Low pyridoxine was associated with worse motor skills when analyzing the linear dose-response relationship [67]. In high-dose supplementation trials in humans,[14] pyridoxine was associated with improved long-term memory, but threats to validity make conclusions based on these trials uncertain. Mizrahi et al. found an association of low pyridoxine dietary intake with AD: however, the recall bias for dietary exposure among patients with dementia limits interpretation of this data [82]. Currently, there is evidence to support the use of pyridoxine in combination with folic acid and vitamin B12 for the prevention of cognitive decline in those MCI patients with elevated homocysteine [2, 7, 28, 74, 83].

Vitamin B12 (Cobalamin)

In rats with nucleus basalis magnocellularis lesions (mimicking a hypocholinergic state), cobalamin showed no effect on movements and did not improve memory [84]. In observational studies, high methylmalonic acid level, a more specific marker for vitamin B12 deficiency, was associated with faster rates of cognitive decline, especially in ApoE4 carriers [85]. The administration of cobalamin was associated with improvement on a 12-word list learning test at 15 min, and a trend was found for improvement on other cognitive measures in a RCT of cognitively impaired individuals with B12 deficiency [86, 87]. In uncontrolled trials, there is conflicting evidence on the effects of cobalamin supplementation in normal and cognitively impaired patients. In most of the studies where cobalamin supplementation was associated with cognitive improvement, the cobalamin was administered via parenteral route. Dietary intake of cobalamin has not been associated to the presence of AD in cross-sectional studies [67]. The heterogeneity of the trials, cognitive outcomes, and populations studied contributes to the inconsistency of the findings. The supplementation of cobalamin alone for the prevention of cognitive decline is not supported at this point; however, there is evidence to support the use of B12 in combination

with folic acid and pyridoxine for the prevention of cognitive decline in those patients with elevated homocysteine [2, 7, 28, 74, 83]. Additionally, vitamin B12 levels are part of the work-up for reversible causes of dementia as well as other neurological diseases, and deficiencies should be a target of clinical intervention.

Folate

In amyloid precursor protein (APP) mutant mice model, Kruman and colleagues [88] showed that the amount of deposition of Aβ amyloid did not differ among folate-deficient mice vs. a control group. However, the *cornu ammonis* (CA) 3 region of the hippocampus in folate-deficient mice had at least 20% fewer neurons compared to controls, suggesting susceptibility of this region to folate deficiency independent of Aβ production or deposition. Thought to be at increased susceptibility to oxidative damage, ApoE-deficient mice were fed a folate-free diet in one group and folate-supplemented diet in the other one. The folate-supplemented group showed significant decrement in the amount of oxidative by-products when challenged with iron, an oxidizing substance [67, 89]. These results suggest that the oxidative potential of ApoE deficiency could be alleviated with folate supplementation. In a diet-induced hyperhomocysteinemia rat model, investigators evaluated the impact of folate supplementation on the homocysteine-induced endothelial dysfunction [80]. Folate supplementation showed reduced endothelial nitric oxide synthetase activity and glucose transporter protein-1 activity, suggesting that folate supplementation could offset the oxidative potential of homocysteine at the endothelial level.

In regard to dietary intake of folate and the presence of AD, observational studies have shown conflicting data. Tucker et al. investigated the association of dietary intake and several vitamins and found that high dietary folate offered independent protection against cognitive decline [90]. In a study conducted by Morris et al., a faster rate of cognitive decline in a cohort of aging individuals was linked with high levels of folate from food or supplements [91]. Despite these conflicting findings, most of the cross-sectional and case-control studies suggest that lower levels of serum folate or higher prevalence of folate deficiency is found in patients with AD [67].

In human studies, one RCT showed cognitive benefit of folate supplementation in demented, cognitively impaired, and normal subjects, but no clinical benefit was reported [67]. Fioravanti and coworkers showed that folate supplementation improved cognitive scores in aged patients with cognitive impairment and low folate levels. Of interest, initial cognitive status did not correlate with initial folate levels [92]. Bryan and colleagues studied women of all ages without cognitive impairment and reported that folate supplementation improved cognition in the older women. Unfortunately, the dietary intake of these women could potentially be an interaction that was not controlled for, since dietary intake of folate and other vitamins was correlated with speed of processing, recall and recognition, and verbal ability [93]. In a small sample, Sommer and colleagues showed that very high doses of folate supplementation (20 mg/day) could be associated with worsening cognitive function [94]. While recent systematic reviews and meta-analyses do not support the use of folate with or without vitamin B supplements for the prevention of cognitive decline in the short term, the use of B12, folic acid, and pyridoxine for the prevention of cognitive decline in those patients with elevated homocysteine may be recommended [2, 7, 28, 74, 83, 95]. Long-term administration of folate supplements to healthy and cognitively impaired individuals has yet to be systematically studied.

Vitamin C and E

The protective factors of antioxidants are the proposed mechanism of action of vitamin C for the prevention of cognitive decline. It has been observed that higher levels of ascorbic acid (vitamin C) are associated with better cognitive performance in a cohort study [96]. Vitamin E is considered a powerful antioxidant available in oily food. In adults over 65 year of age,

individuals in the upper tertile of vitamin E consumption (data obtained by a food questionnaire) showed better cognitive performance than the lower tertile [97]. Wengreen et al. studied the dietary intake of vitamin C and E in individuals older than 65, followed on average for 7 years, and found that a higher intake of vitamin E and C was associated with higher MMSE scores. Moreover, a low intake of these vitamins and carotene was associated with a higher rate of decline in MMSE [98]. However, trials examining the combination of vitamins E and C supplementation have not consistently demonstrated significant improvements. At this time, there is no evidence to support the prescription of vitamin C and conflicting evidence regarding vitamin E. In fact, a recent study suggests that 2000 IU slows functional decline in mild to moderate AD [83, 99, 100].

Chromium

Insulin resistance and secondary hyperinsulinemia are associated with metabolic syndrome. The receptor for insulin transport across the BBB becomes saturated with the flush of plasmatic insulin, thus creating a hypoinsulinemic state in the brain. Hypoinsulinemia is associated with increased rate of Aβ aggregation. Peripheral hyperinsulinemia has also been associated with worse cognitive performance among AD and non-AD patients [101]. Inside the brain, abnormal distributions of transition metals can potentially serve as diagnostic markers for neurodegenerative diseases, including AD [102]. Chromium, an essential trace mineral used in insulin receptor signaling, is thought to amplify the insulin action [103]. Improved insulin resistance in diabetic patients has been shown at doses of 200–1000 mcg [104, 105]. Krikorian and colleagues [103] randomly assigned 26 patients to receive chromium supplementation vs. placebo and followed them for 12 weeks with examination on multiple cognitive tests. No effects were seen on fasting insulin or fasting glucose, but a reduced rate of intrusion errors was found in the active group. Functional magnetic resonance imaging (fMRI) data showed that individuals in the active arm had increased activation in multiple regions of the brain including the thalamus and the frontal cortex; however, areas of activation did not correspond to improved cognitive performance. These findings suggest that chromium may have functions independent of its effects on metabolism and should be further explored. Chromium supplementation shows promising results, but not enough to unequivocally determine an association with AD or cognitive decline [7]. In order to strengthen current evidence, a well-designed study using a larger sample size should be undertaken.

Polyphenolic Compounds (Flavonoids)

Polyphenols are the most prevalent component in our daily foods and represent the major portion of the phytochemicals found in plants. Polyphenols have received special attention because of their antioxidant capacity and ability to debilitate the pathological process seen in neurodegenerative disorders, such as AD [106]. Aβ-mediated neurodegeneration is one of the most well-studied hypothesis underlying AD causation. Several phenolic compounds, such as wine-related myricetin (MYR), curcumin, nordihydroguaiaretic acid (NDGA), and rosmarinic acid (RA), have shown to possess strong anti-Aβ aggregation properties in vitro and in vivo [49]. Flavonoids, a subclass of polyphenols, are a group of phytochemicals thought to have important antioxidative, antiviral, and anticarcinogenic properties [67]. They are ubiquitous in vegetables, and they provide the plant with its color that attracts pollinators and repels insect attacks [15]. They are found in high concentrations in berries, onions, dark chocolate, broccoli, apples, tea, red wine, purple grape juice, soybean, and tomatoes [107]. Below we will discuss the more conspicuous members of the phenolic family that have been studied to date.

Berries

Berries are thought to be rich in antioxidants, and their consumption is hypothesized to provide neuroprotection against the oxidative and inflammatory process associated with aging. Strawberries, blueberries, blackberries, cranberries, and raspberries are fruits with high antioxidant capacity due to the high content of anti-inflammatory anthocyanins and/or proanthocyanidins (flavonoid compounds) [67, 108, 109].

Anthocyanins can cross the BBB and block 5′-deiodinase activity and stimulate T3 transport into rat brains [110]. Histopathology and cognitive test results suggest a protective effect in blueberry-fed rats, compared with controls. Blueberry extract was associated with increased precursor cells (increased neurogenesis) in the dentate gyrus in rats that also performed better on cognitive testing [111]. In animal experiments, strawberry extract supplementation has been associated with improved biochemical markers in the brain suggestive of neuroprotection; however, an association with cognitive performance has not been reported [67]. In vitro studies suggest that various berry extracts can protect the deleterious effects of Aβ-induced oxidative damage [112]. A weekly minimum of two servings of blueberries and/or strawberries was linked with decreased rates of cognitive decline [5]. Randomized, prospective human studies are lacking to recommend berry extracts for the prevention of cognitive decline; nevertheless, inclusion of berries in the diet has a theoretical benefit and is recommended as part of a balanced diet.

Curcumin

Hamaguchi and colleagues showed that RA, CUR, and MYR inhibit the aggregation of Aβ monomers to Aβ oligomers and from oligomers to Aβ deposition [49]. Curcumin is a potent antioxidant and an effective anti-inflammatory compound. Curcumin can inhibit the formation of Aβ oligomers and fibrils, bind plaque, and reduce plaque burden [113]. In another animal model of dementia, curcumin (20 mg/kg po daily for 14 days) successfully attenuated streptozotocin (STZ)-induced memory deficits. Higher levels of brain AChE activity and oxidative stress were observed in STZ-treated animals, which were significantly attenuated by curcumin [114]. Other animal studies raise the possibility that curcumin may act as a metal chelator, have anti-apoptotic or immunomodulator properties, or promote neurogenesis [12].

Poor bioavailability of curcumin is one of the main challenges faced in human studies [115]. In a pilot study, a small RCT evaluated the pharmacokinetics and effects of curcumin supplementation in humans [116]. The preliminary results showed promising MMSE changes without major side effects, but the short period of follow-up and lack of cognitive decline in the placebo group limit interpretation of the data. The risks associated with the administration of curcumin are uncertain, and further studies are warranted in regard to safety and efficacy. In the trial by Baum et al., gastric, neurological, and pulmonary symptoms were reported at an equal rate among patients taking placebo and those on active treatment [116]. While there is no clinical trial evidence for AD prevention, studies have been performed in the area of AD treatment [116, 117]. A more recent study by Ringman and colleagues found that curcumin was generally well tolerated in a group of mild to moderate AD patients, although there was no clinical or biochemical effect over 24 weeks. The study helped us to understand why curcumin was not effective, and that was most likely related to the body not being able to absorb the curcumin. Thus, limitations in bioavailability likely led to the lack of effectiveness [51]. The risk/benefit ratio of curcumin supplementation should be discussed in detail with patients and caregivers.

Resveratrol

Resveratrol is an antioxidant that is most commonly known for being found in wine (from grapes), but it is also found in a variety of food sources like blueberries, peanuts, and cocoa powder. However, the highest concentration is

specifically contained in red grapes (in their skin) and as such high in red wine. The problem with resveratrol is that the actual amount in these sources is quite low – a person would have to drink several hundred glasses of red wine in order to get the same amount that is contained in one capsule of a resveratrol supplement. In these supplements, while some of the actual resveratrol may come from red grape skin, most commonly it is derived from Japanese knotweed. While studies in animals have shown that resveratrol may delay age-related cognitive decline, data are more limited when it comes to humans with AD, as well as for prevention. One recent study of 23 individuals without memory loss who took 200 mg per day found that supplementation improved memory function, as well as a host of metabolic markers, including glucose metabolism, and decreased body fat [118]. Using neuroimaging studies, researchers also found functional improvement in brain regions associated with memory. Further research is necessary to clarify the relationship between resveratrol and AD prevention and treatment.

Docosahexaenoic Acid (DHA)

DHA is a long-chain 22-carbon omega-3 polyunsaturated fatty acid with 6 double bonds. It is found abundantly in marine algae, fatty fish, and fish oil [12]. While there have been various discrepancies, many studies have shown that people with more of these fatty acids in their blood are less likely to develop AD [119]. The main proposed mechanism of action of DHA in the context of cognitive decline is the preservation of drebrin, a vital component for the adequate synaptic function. Other pleiotropic mechanisms in which DHA can affect the progression of cognitive decline are anti-inflammatory activity, neuroprotection, neurogenesis, antioxidant, metabolic enhancer, and weak amyloid aggregation inhibitor [12].

In animal models, depleting DHA from the system was associated with cognitive impairment, but replacing DHA prevented pathological changes similar to those seen in AD [120, 121]. In a small trial of MCI and AD, DHA was associated with a slower rate of cognitive decline [78, 122]. A recent randomized, double-blind, placebo-controlled study with 485 subjects (aged 55 and older) called the "Memory Improvement with Docosahexaenoic Acid Study" (MIDAS) aimed at evaluating the effects of 900 mg/day of algae-based DHA in healthy older adults with age-related cognitive decline [78, 122]. The study found that DHA taken over the course of 6 months improved memory and learning in healthy, older adults with mild memory complaints.

Recent systematic reviews of RCT and observational studies published for DHA supplementation have failed to identify unequivocal evidence suggestive of a protective effect of DHA on cognitive decline [7, 28, 83], although the association of DHA with slower cognitive decline seems to be somewhat consistent across studies [2]. Collectively, while data suggest that DHA supplementation does not help AD patients overall, further studies are warranted to clarify whether DHA supplementation could play a role in prevention of cognitive decline [123, 124]. Early supplementation, as well as the long-term effects of DHA, warrants further investigation.

Cardiovascular Risk Profile

Although age is the single most important risk factor for the development of dementia, cardiovascular risk factors appear strongly associated with cognitive decline and dementia and carry the great advantage of being modifiable. Traditional risk factors like hypertension, diabetes, dyslipidemia, and smoking are believed to convey risk for vascular disease. Vascular disease is associated with cerebral hypoperfusion, oxidative stress, neurodegeneration, and cognitive decline [125]. The clinical expression of vascular disease can manifest as either mild cognitive symptoms or full-blown dementia that may be attributable to an AD process, mixed AD/vascular pathology, or vascular disease alone [126]. There is general agreement that the pure cases of

AD account for less than 20% of all the cases and that AD with various components of vascular disease is much more common than AD alone [127–129]. The amount of AD pathology necessary to produce clinical dementia seems to be less when concurring with the presence of vascular risk factors [126]. The cumulative presence of vascular disease has a biological gradient in the severity of cognitive decline moderated by covariates like age, gender, and race [130–132]. This is difficult to disentangle, as it would be unethical to perform a RCT to evaluate the effects of controlling for risk factors in some, but not other subjects.

There is uncertainty regarding secondary prophylaxis with treatment of cardiovascular risk factors. Heterogeneous definitions of MCI and varying methodologies in conversion studies confound our understanding of the impact of these risk factors on the progression of MCI to dementia. Even with a stable and reproducible definition of MCI, no strong association has been found with the presence of cardiovascular risk factors [133]. To date, no strategy has been successful to halt the progression of MCI to dementia [127]. As mentioned above, general recommendations to engage in a healthy life should be applied to patients with MCI.

Hypertension and Hypercholesterolemia

It seems that a lifetime exposure to cardiovascular risk factors can be associated with higher odds of dementia, suggestive of a time period where exposure is more fundamental for subsequent risk. The interaction of the risk exposure and time of onset varies according to each risk factor. As an example, evidence has shown that higher levels of systolic pressure in midlife are associated with higher risk of dementia later in life, but lower levels of systolic pressure later in life can also be associated with dementia [134]. The same effect has been described for cholesterol levels [135]. Nevertheless, diminished vascular integrity of the blood-brain barrier is characteristic of hypertension and results in protein extravasation into brain tissue. As such, this can lead to cell damage or death and a reduction in synaptic function and may directly contribute to the beta-amyloid accumulation seen in AD pathology [136].

In primary prevention trials of cardiovascular disease, conflicting evidence exists about the effect of controlling risk factors on the incidence of dementia. While treatment of hypertension with calcium channel blockers and ACE inhibitors showed reduction in all cardiovascular outcomes and halved the risk to develop AD [137], other trials using diuretics and beta blockers or angiotensin receptor blockers did not reproduce similar findings [138, 139]. A Cochrane review including 14 clinical trials which tested nimodipine in patients with AD and/or cerebrovascular dementia found statistically significant benefit at 12 weeks on clinical global impression and cognitive function in the treatment of patients with features of dementia due to Alzheimer's disease, cerebrovascular disease, or mixed Alzheimer's and cerebrovascular disease [140]. Other meta-analyses have not found a significant effect for the treatment of hypertension and the subsequent risk of developing AD [7, 141, 142]. The SPRINT (Systolic Blood Pressure Intervention Trial) study, to be completed in 2018, may help to determine whether antihypertensive treatment can prevent cognitive decline (NCT01206062).

Trials and meta-analysis investigating the effects of cholesterol-lowering medications (statins) have failed to demonstrate protective effects on the subsequent risk of developing AD [7, 143–145]. Effect of statins may depend on baseline cholesterol, stage of AD, and ApoE4 carrier status [146]. Studies may have been underpowered, too short, too late in the life-span, or affected by selective dropout of participants with cognitive impairment. Also of note, polymorphisms affecting individual response to statins (KIF6 gene, HMGCR isoforms) have yet to be been taken into account. Cardiovascular risk factors should be aggressively treated in populations with or without cognitive decline to reduce cardiovascular mortality.

Diabetes and Insulin Resistance

Several investigators have claimed that insulin resistance is a risk factor for cognitive decline [127]. Insulin facilitates cognition when given concomitantly with glucose to support metabolism and may play a role in overcoming the decreased utilization and transport of glucose in AD patients [147]. Defects in insulin signaling are associated with increased deposition of Aβ and tau hypophosphorylation. Insulin-degrading enzyme (IDE) is a protease involved in the degradation of insulin and Aβ. In patients with hyperinsulinemia, insulin can saturate IDE and subsequently increase the AB serum levels [148]. Patients with diabetes have lower hippocampal and prefrontal volumes when compared with nondiabetic controls [149]. The progression of dementia in patients with stroke and diabetes was more prominent when compared to patients without stroke and diabetes [150]. Diagnosed and undiagnosed diabetes have been associated with lower MMSE scores in a population-based sample [151]. Although diabetes has been strongly associated with the presence of AD [152–154], less is known about its treatment and the effects on dementia incidence [151, 155]. The treatment of diabetes should be a priority in all patients for its multiple deleterious consequences.

Smoking

Initial observational studies suggested that smoking could be associated with lower risk for developing Alzheimer's disease in carriers of ApoE4 [156, 157]. Former smokers had a decreased risk for developing dementia with increasing numbers of pack-per-year smoked. This was suggestive of a dose-effect relationship of higher exposure to nicotine and a lower incidence of dementia [156, 158]. The interaction between ApoE4 status and smoking exposure has been a matter of debate and remains unclear. Nevertheless, it is generally accepted that smokers have higher risk of developing dementia and that there is a dose-effect gradient with higher odds for heavier smokers [159]. Additionally, smoking can accelerate atrophy and degenerative changes resulting from neuronal loss [160, 161]. In a recent meta-analysis of prospective studies, Anstey et al. showed that current smokers had an increased risk of Alzheimer's disease compared with former smokers at baseline. Current smokers also showed greater decline in cognitive abilities, but the groups were not different regarding risk of vascular dementia or other dementias. The authors concluded that elderly smokers have increased risks of dementia and cognitive decline [162]. A recent systematic review found low-quality evidence to unequivocally support the association of tobacco use and dementia, although it was categorized as a risk factor [7]. There is no question that all smokers should be encouraged to quit. In the case of patients with cognitive decline and dementia, it should be further emphasized.

Physical Exercise

Interventional studies have demonstrated that people who become physically active can improve their cognition and can slow down the rate of decline as early as 4 months after the intervention [163, 164]. Physical exercise is thought to exert its protective effects on cognition through the improvement of cardiovascular disease, as well as by decreasing amyloid throughout the brain (e.g., frontal lobes and hippocampus) [4, 165]. Additionally, exercise stimulates production of brain neurotrophic factors that are used in repair processes [4, 165]. In observational studies, there appears to be a lower prevalence of dementia in people who exercise regularly compared with those who do not [166, 167]. Promoting exercise should be part of a holistic strategy to promote healthy lifestyles and should be advised in patients with cognitive decline or AD, unless contraindicated or impractical. Tailoring of both physical activity type and routine to the patient's needs and capacities is advisable.

In summary, it would be unethical to advise against treating cardiovascular risk factors in the absence of evidence toward preventing cognitive

decline or dementia. The development of cerebrovascular disease is a well-known consequence of uncontrolled risk factors, and the incidence of stroke is strongly associated with cognitive problem or dementia [168–171]. It is safe to say that addressing the cardiovascular profile should be a priority in patients with cognitive dysfunction and dementia or those at risk of developing either.

Cognitive Engagement

Subjects with preclinical Alzheimer's disease who have higher levels of education demonstrate lower levels of functional connectivity by FDG-PET in areas affected by Alzheimer's disease, suggesting that there is indeed a compensatory role of education to maintain cognitive performance in preclinical AD [172]. The term "cognitive reserve" has been applied in the literature to describe this general idea that the greater number of neurons or advance neuropsychological competence (intelligence) can protect an individual from developing clinically evident cognitive decline or dementia [173]. A more comprehensive definition of cognitive reserve involves neurocomputational flexibility where the end goal is adaption. It suggests that high brain-reserve individuals have a larger repertoire of strategies to resolve complex tasks as well as redundant neuronal networks to carry out the same activities. As such, in the case of a particular network malfunction, other networks can be used to conduct the same strategy, or, if not possible, other strategies can be used to solve the same tasks [174]. Environmental enrichment has been associated with neurotrophic and nerve growth factors, increased synaptogenesis, and synaptic plasticity [173].

Cognitive Training

Cohort studies assessing the association of mental activities and the incidence of dementia have shown that engaging in highly complex mental activities is a protective factor against the development of dementia, with a dose-dependent effect observed in some studies [175, 176]. A systematic review of observational studies evaluated 22 population-based cohorts and showed that education attainment, cognitive lifestyle activities, and occupational complexity conferred protection against the subsequent development of dementia [177]. An earlier trial found that individuals who received cognitive training had a favorable influence on everyday coping and on memory performance [178].

The ACTIVE trial published in 2002 was a major study in this field that randomized 2832 patients to 4 groups and 3 intervention arms: 10-session group training for memory (verbal episodic memory; $n = 711$), reasoning (ability to solve problems that follow a serial pattern; $n = 705$), or speed of processing (visual search and identification; $n = 712$) or a no-contact control group ($n = 704$). The results showed significant improvement in 87% of processing speed, 74% of reasoning, and 26% of memory-trained participants and demonstrated reliable cognitive improvement immediately after the intervention period. Booster training significantly enhanced training gains in processing speed and reasoning interventions (speed booster, 92%; no booster, 68%; reasoning booster, 72%; no booster, 49%), which were maintained at the second year of follow-up. No training effects on everyday functioning were detected in the second year of follow-up [179]. A 5-year follow-up of the same population showed improved cognitive abilities, specific to the abilities trained, that persisted after the intervention was stopped compared with the control group [180].

A computer-based cognitive training RCT, with a focus on improving aural language processing, was linked to improvement in targeted cognition and non-trained cognitive function in the active group compared to controls [181]. In individuals with MCI, unimodal memory training might not be enough [182, 183]. A small study indicated that multimodal intervention might be more effective in patients with MCI [184]. Encouraging results have come with using the multi-domain cognitive training approach in patients with dementia [182]. However, longer follow-up is needed to investigate whether the

effects of cognitive training are sustained. Based on previous results, it seems advisable for individuals at risk for developing dementia to engage in cognitive training programs as part of a formal multimodal therapeutic approach.

Social Engagement

It has been well documented that individuals with reduced social networks are at greater risk for developing cognitive decline compared to those who have broader social interactions. Activities that exposed the individual to interact with others and create bonds are considered protective against cognitive decline [4]. A few critics have challenged the notion that this is a predictive association, suggesting that retraction from social networks might precede the onset of cognitive symptoms during midlife and could be a sign of premature non-cognition symptoms of neurodegeneration [185]. Other difficulties in isolating social engagement effects on the risk of dementia have been the multiple covariates associated with both, such as exercise and cognitive reserve. It seems reasonable to advise engagement in social activities as tolerated to promote healthy aging.

Depression

One of the reversible causes of cognitive impairment that adults of all ages with cognitive complaints should be evaluated for is depression. In older adults it can be difficult to isolate depression from dementia, since patients with dementia have a higher prevalence of depression than non-demented populations, and sometimes depression could be a prodromal sign of dementia [4]. A recent meta-analysis of observational studies showed that depression doubles the risk of developing dementia in later life. Findings of increased risk were robust to sensitivity analyses. Interval between diagnoses of depression and AD was positively related to increased risk of developing AD, suggesting that rather than a prodrome, depression might be a risk factor for AD [186]. Even if the overall evidence quality is low, patients with cognitive complaints should be screened for depression and treated when indicated. New-onset depression in an adult with no prior history could be one of the earliest signs of brain changes due to AD. By contrast, lifelong depression in someone with cognitive complaints is a risk factor for dementia with Lewy bodies.

Pharmacological Strategies

Hormones

Hippocampal atrophy is a major pathological change seen in patients with MCI or AD. Shrinkage of the hippocampus can start in early adulthood and accelerate with age; losses of 0.3–2.1% per year are reported, with slower rate of progression reported in women compared with men [187, 188]. The apparent slower degeneration in women in early adulthood reverses in the postmenopausal stage, with greater odds of dementia for women when compared with men [189]. As a result, multiple studies evaluating the role of estrogens and other gonadal hormones as neuroprotectors have taken place.

Estrogens are known to influence verbal fluency and memory, performance on spatial tasks, and fine motor skills [190]. They can mediate neuroprotection provided their ability to mediate the oxidative processes in the brain, besides altering the potassium conductance, apoptosis, and transcriptional factor regulation [189]. The aging process is associated with decreases in memory abilities, focusing attention efficiently, and the speed of processing information. However, women tend to have smaller hippocampal volumes, decreased glucose metabolism in areas concerned with cognition, and greater age-adjusted prevalence of dementia [191]. Observational studies have suggested that memory problems are often associated with menopause, although healthy postmenopausal women do not have significant memory problems, as measured by standard psychological testing [192, 193]. Blood levels of estrogenic hormones are not consistently associated with differential cognitive performance [194].

Another explanation for the excess of AD cases in women seen in observational designs has been attributed to longer survival of women compared to men [195].

Several clinical trials and longitudinal studies have attempted to solve this puzzle. Researchers observing a longitudinal cohort reported an association with hormone replacement therapy (HRT) and better performance on psychological testing [196] although another group with a different cohort failed to reproduce this claim [197]. Two recent meta-analyses found a 29–34% risk reduction for women using HRT vs. nonusers [194, 198]. The Women's Health Initiative Memory Study (WHIMS) used a sample from a large, population-based prospective cohort to enroll in a RCT to test the hypothesis that HRT with estrogen with progestin could reduce the risk of MCI or dementia. They enrolled 4532 patients, who were randomized to active and control arms, and followed up around 13 months. The study failed to show that estrogen in combination with progesterone offers protective effects against cognitive decline in the form of MCI or probable dementia. On the contrary, they found an elevated risk of developing either MCI or dementia in patients using the HRT, nearly doubling the risk for those not using it [3]. This is the largest and best-structured RCT to test the hypothesis behind the possible cognitive benefits provided by hormonal supplements. The possibility of hormonal replacement at earlier stages of gonadal hormone withdrawal in perimenopausal women has not been explored, and some believe that larger periods of estrogen deprivation can lead to irreversible damage to some brain structures [195, 199, 200]. This remains to be settled with future RCT specifically designed to test this hypothesis. Currently, there is no evidence to recommend hormonal supplementation in postmenopausal women to prevent or treat cognitive decline [2, 7].

The role of dehydroepiandrosterone (DHEA) has also been explored in the context of cognitive decline. They are the most abundant circulating hormones in young adults and the major precursors of androgens and estrogens in the central nervous system [201], especially in the postmenopausal stage in aged individuals where the gonadal production of sex hormones drops [202]. Some observational studies have suggested that the DHEA drop seen with aging may account for some of the cognitive difficulties associated with age, partially due to the unopposed deleterious effect of cortisol on the oxidative stress balance [203, 204]. Although DHEA supplementation may be an appealing as a way to prevent cognitive decline, human results have failed to prove significant improvement in chronic supplementation of the hormones, and few have shown negative effects. As theorized with HRT, the timing of supplementation is thought important, and future trials should explore early supplementation after the drop of "youthful" levels of the hormones [205]. The age-associated decrement in enzymatic activity necessary to convert the hormones into their active metabolites, as well as individuals with advanced disease, is another explanation for the lack of positive results. There is no evidence at this point to recommend the supplementation of DHEA for the prevention or treatment of cognitive decline.

Piracetam and Piracetam–Like Drugs

Piracetams are nootropic compounds ("nootrope" comes from ancient Greek meaning "for or toward the mind") [206]. The mechanisms of action of these medications are related to their effects as GABA-mimetic, antioxidants, modulators of intracellular calcium, as well as facilitators of cholinergic transmission in the hippocampal area [207]. Due to their facilitation of cognitive processes, some members of this family are known as cognitive enhancers.

Piracetam is the most studied cognitive enhancing compound. It has been used to evaluate protection against cognitive decline in numerous clinical settings such as traumatic brain injury, cerebrovascular insufficiency, cardiac bypass cognitive deficit, and MCI with promising results [207]. Part of its efficacy can be attributed to the offset of depressive symptoms. Conflicting evidence has been produced by

meta-analysis [208, 209], and thus far, no large-scale trial has demonstrated the effects of this compound in patients with MCI and dementia [208, 209]. Oxiracetam, aniracetam, and pramiracetam are less-studied nootropic compounds. Overall, the level of evidence currently available is not enough to systematically recommend piracetam or any nootropic drugs for the prevention of cognitive decline.

Conclusion

Effective strategies to prevent cognitive decline in the context of normal aging, mild cognitive impairment, and dementia are imperative to face the oncoming epidemic of dementia and cognitive disease in our society. Evidence-based recommendations are imperative to avoid unnecessary expenses and the creation of false expectation in patients and their families. Methodological difficulties and biases plague several good-intentioned trials. Existing studies have provided some clues into the puzzle of prevention of cognitive decline, yet it is rare that the evidence is unquestionable. The issue of studying a complex process like cognition represents challenges that researchers must be aware of. The presence of multiple factors and covariates that can bias the results presents a major hurdle in the design stage as well as in the statistical analysis, especially in small sample studies. However, from a practical clinical perspective, a good rule of thumb would be to keep expectations metered and to always balance existing evidence with safety, as low-risk interventions are of paramount importance.

When evaluating diet components, the major difficulty is in isolating the effect that a nutrient or diet component has on cognition or the evolution of dementia. The fact that isolated vitamins, minerals, and other components have failed to demonstrate a reliable association does not mean that the intake of these is not beneficial. There is a possibility that the combination of multiple components is what makes the difference. Additionally, trying to adhere to healthy lifestyle recommendations including a diet rich in essential nutrients, smoking abstinence, regular exercise, as well as adequate cardiovascular profile is by all means a goal in any patient. Challenging the brain with new information and new experiences seems to be advisable, especially in those who already have early cognitive complains.

Clinical Pearls

- A Mediterranean-style diet rich in vegetables, fruits, nuts, and fish is advisable for patients at risk of developing cognitive decline or Alzheimer's or vascular dementia.
- What is good for the heart is good for the brain; paying attention to CV risk factors is important.
- Patients should remain active physically and mentally. Physical exercise is among the best of all potential interventions against Alzheimer's disease.
- Multimodal lifestyle interventions, combining dietary changes as well as regular physical activity and cognitive engagement, have been shown to delay cognitive decline.
- When it comes to vitamins and minerals, if deficient, treat.
- There is no evidence that hormonal supplementation can decrease the incidence of dementia. If there is an indication for hormonal supplementation, the cognitive status should not be a factor in the decision-making process.
- Some agents that are touted as having cognitive protective effects should only be used under physician supervision. This is due to wide availability, lack of FDA oversight, cost, and possible contraindications/adverse effects.
- Patients with diagnosis of Alzheimer's dementia should be considered for FDA-approved medical therapy unless contraindicated.

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Driving Evaluation in Older Adults

15

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Introduction

Driving an automobile is crucial to maintaining autonomy and mobility and can become increasingly difficult with age. Approximately 200,000 of the 30 million drivers 65 years of age or older in the United States are injured in motor vehicle crashes each year [1], and there were over 4000 motor vehicle deaths for those aged 70 years or older in 2014 [2]. Even though many older persons self-restrict their driving to compensate for age-related changes and diseases [3], crash rates per mile traveled start increasing for drivers at age 70 and older and are highest after age 85 [1] Advanced age and the prevalence of age-related medical conditions (e.g., dementia) have been shown to negatively affect the cognitive, sensory, and motor abilities deemed necessary for safe driving. As a result, clinicians are increasingly called upon to comment on an older patient's ability to remain an active driver. The clinical recommendation to cease or limit driving can have negative ramifications on everyday activities (i.e., getting to work, opportunity to engage in social activities, access to medical appointments/needs) and sense of autonomy and has been associated with poor health and depression [4–6]. Clinicians are challenged to evaluate the safety of the older driver in society while balancing the patient's needs for mobility and quality of life.

The current chapter aims to provide the clinician with a practical understanding of the literature on research that has been conducted in older drivers. To accomplish this, we have sectioned the chapter into four main topics. The first section introduces some key concepts and challenges inherent in conducting driving research, and it is meant to provide a reference framework for the subsequent discussions. The second section provides a review of the literature on the effects of healthy aging on driving performance. By providing a description of common crash statistics and driving errors of older drivers free of neurological compromise, we aim to provide the clinician with an understanding of "typical" driving behaviors in older adults. This section also includes a summary of our current understanding of the relationship between cognition and driving in healthy aging. The third section focuses on the characterization of the older driver with

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neurological disease or compromise. Since the focus of this chapter is on clinical driving evaluations, we limit our review to Alzheimer's disease (AD), Parkinson's disease, and preclinical AD/mild cognitive impairment (MCI). The interested reader is urged to consult Schultheis et al. [7] for a review of additional age-related neurological disease or injury (e.g., stroke) that is known to effect driving performance. The final section includes a discussion of the clinical application of this research to clinical neuropsychology and aims to provide helpful guidelines for the clinician faced with evaluating driving capacity of an older adult.

Considerations in Driving Research

The relationship between driving performance and driving outcome can be conceptualized as an imaginary triangle or iceberg (see Fig. 15.1). Rizzo and colleagues [8] illustrate this point first raised by Heinrich et al. [9] and Maycock [10]. At the tip of the iceberg, above the "waterline," are driving errors that produce accidents. For example, running a red light is obviously dangerous and concerning to individual drivers and society at large, despite the fact that crashes are relatively rare events [11]. A greater portion of the iceberg is "below the waterline" and includes behaviors less obvious to individual drivers and society. This portion is comprised of driving errors that increase crash risk or result in near crashes. These more frequently occurring driving errors range in crash-risk severity. For example, errors such as "texting" while driving are more related to accidents than errors related to driving with one hand on the steering wheel. Two main areas of driving research have evolved in investigating driving errors. The first aims at elucidating the relationship between specific driving errors of varying severities and crash risk or crash involvement. A second aim is to understand driver characteristics that are related to a high likelihood of committing driving errors. From a clinical application perspective, understanding how driver characteristics such as age and cognition contribute to these driving errors may aid clinicians in detecting individuals who may be at greater risk for driving difficulties.

An important consideration in driving research is the variability in how driving outcome or driving performance is defined in a laboratory. There is a lack of consistency on how this very complex behavior is quantified. Most studies

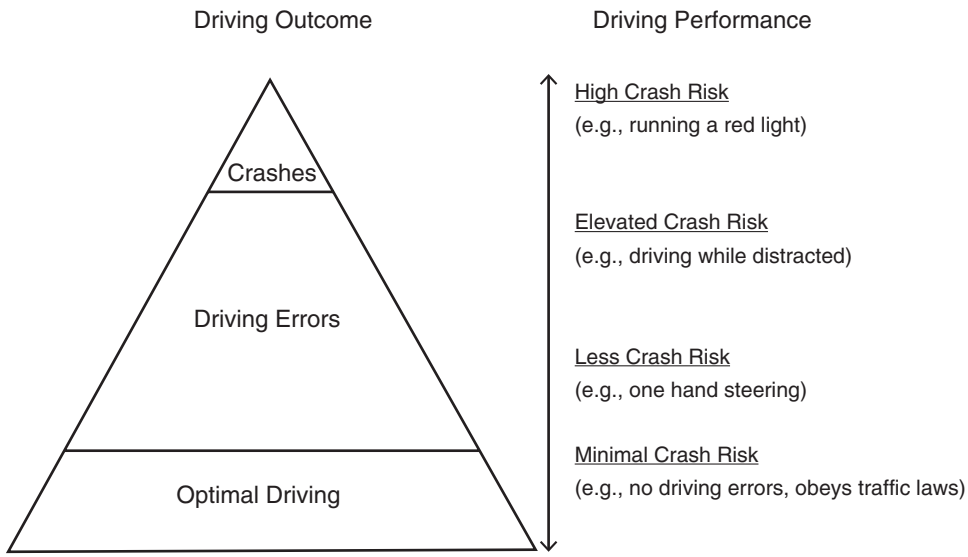

Fig. 15.1 Driving performance and driving outcome

have employed one of the following measures for defining driving performance: (a) behind-the-wheel examination (BTW), (b) performance on instrumented vehicles, (c) performance on driving simulators, (d) self-reported driving behaviors, (e) crash statistics, or (f) documented crash involvement (i.e., DMV reports). Despite the fact that all of these factors have been used to define "driving performance," there are significant differences across these methods (i.e., subjective vs. objective measures, real-world vs. simulated driving). A summary of the pros and cons to each of these approaches is summarized in Table 15.1. In this chapter, we have reviewed studies using any of these various methods to assess driving performance. In our own research, we have endorsed a multimethod approach, which commonly includes simultaneous measurement of more than one of these outcome measures.

It should be noted that the BTW driving evaluation is considered the most "clinically" useful method of evaluating driving performance in determining fitness to drive and is typically performed as part of comprehensive driving evaluations (CDEs). CDEs are commonly conducted by driving rehabilitation specialists (e.g., usually an occupational therapist specially certified in driving rehabilitation). The CDE consists of clinical assessments of vision, motor, and cognitive function in combination with a BTW assessment of actual on-road driving performance. Typically, BTW assessments are performed in a dual-controlled vehicle along a predetermined route. The route consists of a variety of traffic situations and maneuvers (including lane changes, unprotected turns, parking, and self-navigation challenges). The instructor provides the instructions systematically while observing how the driver interacts in traffic conditions. Usually, a part of the BTW assessment involves "self-navigation" where the driver needs to find a specific store or location utilizing signs or landmarks. During the assessment, the driving instructor's role is to provide instruction, maintain safety, and assess driving performance – not to "teach" driving skills.

While BTW assessments are considered the most widely accepted measure of driving competency, subjectivity and lack of standardized/reliable scoring of driving performance can impact generalizability of results. Typically, a qualitative global score (pass, marginal, fail) is provided along with a written narrative or rating scale (subjective) assessment of driving performance. More recently, more objective and quantitative scoring of number and type of specific driving errors that occurred on the BTW assessment is being implemented. The qualitative ratings (pass, marginal, fail) generally show good reliability between raters – but provide less detailed and more subjective information related to driving performance [12–15]. The quantitative scoring procedures are more standardized and objective but remain sparse in studies of inter-rater reliability [16, 17].

There are two existing literatures of driving research—studies conducted with a clinical/medical focus and studies conducted with a transportation research focus. Arguably, these two areas of research should inform each other; however, too often this is not the case. The majority of the studies examining driving performance of the older driver have been conducted by transportation researchers and are typically not published in journals that are commonly accessed by clinicians. This literature is substantial, contains important information for understanding aging and driving behaviors, and often utilizes crashes as an outcome measure. These studies, however, may lack the clinical data needed by clinicians to be useful in making medical determinations of fitness to drive. By contrast, the literature on driving in neurologically compromised older adults (i.e., drivers with dementia) is smaller and typically focuses on clinical contributions to driving performance (i.e., cognitive and physical changes) and the development of clinical measures for predicting driving performance using the BTW assessment as a main outcome measure.

Table 15.1 Methods of driving assessment

Measures	Description	Driving performance pro(s)	Driving performance con(s)
Behind-the-wheel exam (BTW) (Also known as performance-based road assessments)	On-road test conducted by a driving specialist who observes and directs the driving of the examinee	Direct measurement of driving on the road Face validity Qualitative and quantitative measurement Has been associated with at-fault crashes	Subjectivity with qualitative measurements Traffic conditions can change affecting standardization Safety concerns in a "real-world" setting Routes may not generalization to typical "at home" driving environment (city vs rural driving)
Instrumented vehicle	Instrumentation (e.g., cameras, sensors) is directly linked to vehicle inputs (e.g., steering, braking)	Direct measurement of driving on the road Quantifiable measurement Objective measurement Various types and levels of instrumentation available Instrumentation can be available to measure naturalistic driving in one's own vehicle	Unable to safely measure challenging driving scenarios Fully instrumented vehicles are expensive to implement Partially instrumented vehicles provide limited information Camera systems often do not portray a "realistic" view of the surrounding driving environment Instrumentation with naturalistic driving is difficult to compare between subjects due to lack of standardized driving routes
Virtual reality driving simulation	Mode of implementation varies from low-fidelity inexpensive computer-based to full immersion programs	Quantifiable measurement Objective measurement Allows safe presentation of challenging and potentially dangerous driving scenarios Provides assessment without patient "anxiety" related to a BTW driving assessment	Questionable if results from simulated driving can be translated to the real-world driving performance Risk of simulation sickness Simulators can be expensive to acquire Need adequate space for many simulators
Crash statistics	Data gathered from collisions and possible contributing factors	Very strong clinical relevance	Infrequent events Usually does not account for accidents that are not reported to the authorities Data collected after the fact At-fault information on crashes not easily accessible/available
Self-report questionnaires	Self-report of driving history (e.g., nonreported accidents, violations, driving behaviors)	Easily obtained information Family/significant other questionnaires can often provide valuable information	Limitations of self-report include over- and underestimation of events Self-report not beneficial if patient insight deficits exist

Characterization of the Healthy Older Driver

Crash Rates of the Healthy Older Driver

A common misconception surrounding older drivers is that they have a greater likelihood of being involved in automobile crashes compared to other age groups in the general population. Empirical evidence does not support this widespread claim [18, 19]. In fact, when the crash rates of 47,500 drivers of various ages were compared after adjusting for annual miles driven, the majority of older drivers had lower crash rates than all other age groups [18]. There are two important caveats to this finding. One is that crash risk increases as driving exposure (i.e., annual miles driven) decreases. Thus, older adults who drive less than 2000 miles annually, approximately 13% of all older drivers, have one of the largest crash rates [18]. Second, whereas older drivers are not at an *overall* increased crash risk, they are more likely to be involved in certain *types* of crashes compared to younger and middle-aged drivers. Evidence suggests that drivers aged 65 and above are significantly more likely to be involved in crashes at intersections and stop signs and while turning against oncoming traffic and changing lanes [11, 20–22]. These crashes that involve conflict with oncoming traffic or direct moving traffic flow can result in significant injuries and have been viewed as "high-risk" involvement. A closer evaluation of the specific errors provides insight into these commonly seen accidents in older adults.

Driving Errors in Healthy Older Adults

Consistent with evidence of an age-related increased probability of collisions at intersections and when turning/changing lanes [11, 20–22], BTW errors in cognitively normal older adults are commonly mild in severity and involve decreased visual scanning, trouble maintaining lane positioning or lane usage, lack of use of turn signals, limited knowledge of rules of the road, and difficulty with memory or following instructions [23]. Age-related declines in stopping behavior have also been described. Bao and Boyle [24] compared the driving performance of 60 younger, middle-aged, and older adults at rural expressway intersections controlled by a stop sign. Driving performance was measured with an on-road instrumented vehicle, enabling the precise calculation of stopping profiles based on time and distance from stop signs. Overall, high crash risk was noted in older (n = 20; age range 65–80) and younger drivers (n = 20; age range 18–21) who were significantly more likely to run stop signs compared to middle-aged (n = 20; age range 35–55) adults. The authors also analyzed stopping behavior and found that older drivers demonstrated a dangerous braking profile compared to middle-aged adults. Older adults braking was best characterized as sudden; they began breaking closer to the stop sign and progressed faster from the initial brake press to maximum breaking, resulting in a short stop. Described in further detail below, work using driving simulation has demonstrated that sudden stopping in older adults with Alzheimer's disease significantly increases crash risk at intersections [25].

Increased age is routinely found to be a predictor of worse or more impaired on-road driving performance [23, 26, 27] Moreover, evidence from BTW evaluations suggests global driving performance declines over time in cognitively healthy older adults [26, 28]. Ott and colleagues [26] examined the BTW performance of 44 cognitively normal older adults at baseline and then 18 months later (mean age = 73.5 ± 9.1; mean MMSE 29.1 ± 1.1; mean number of miles driven per week = 137.8 ± 121.5). Twenty-percent of the sample at baseline was rated as "marginal" drivers (meaning subjects passed the road test, but the driving examiner had specific concerns about their on-road behavior), whereas 38% of the 21 subjects who returned for follow-up received the same rating and 5% (one driver) was deemed unsafe. This decline in driving performance was observed despite the fact that no gross decline in cognitive performance was reported based on the

Clinical Dementia Rating Scale (CDR) [29]. Other investigators have observed a more modest decline in select driving safety errors in cognitively normal older adults. Aksan and colleagues [28] measured the BTW performance of 111 cognitively normal older drivers three times over 3 years (mean age = 69.9 ± 6.2; mean number of miles driven per week = 161.4 ± 193). Subtle statistically significant increases were observed in errors at stop signs and railroad crossings, but a composite score of non-serious errors (e.g., lane observance, speed control) remained unchanged over the 3 years, while serious errors (noted to be rare events) actually declined compared with baseline testing.

Cognition and Driving in Healthy Older Adults

Many researchers have attempted to examine the relationship between cognition and specific driving errors. Findings indicate that numerous specific cognitive abilities are significantly associated with various driving performance measures in healthy older adults free of cognitive impairment, including memory, attention, perceptual and visuospatial ability, information processing speed, and abilities falling under the broad domain of executive functioning (e.g., working memory, planning). In the following section, we provide a concise review of recent studies that investigate different aspects of driving performance in older adults free of neurological compromise. For a larger review of the literature on driving and cognition in older adults, consult Anstey et al. [30] and Mathias and Lucas [31].

Dawson et al. [27] administered a BTW exam to 111 healthy older adult drivers (age range = 65–89) and 80 middle-aged drivers (age range = 40–64). All participants were screened for neurological disorders and cognitive complaints. Rather than simply dichotomize performance on the BTW exam into "pass" or "fail," results of the exam were coded into 15 different categories of driving errors based upon the Iowa Department of Transportation's Drive Test Scoring Standards. Older adults had a propensity toward significantly more errors per drive on 7 out of the 15 categories including speed control, turning, lane changes, lane observance, parallel parking, railroad crossing, and starting the car and pulling away from the curb. The strongest predictor of driving in the older-aged cohort was a composite measure of eight cognitive tests, including tests of visual and verbal memory, constructional praxis, visual perception, working memory, and verbal fluency. Specifically, for every one standard deviation decrease in a cognitive function composite measure in healthy older drivers, there were 3.6 more driving errors observed after adjusting for age, sex, and education. Similar findings were observed between cognitive functioning and BTW driving errors 2 and 3 years later [28].

The Salisbury Eye Evaluation and Driving Study is a longitudinal study of vision, cognition, and driving of older adults on Maryland's Eastern Shore that investigated factors associated with a frequent antecedent to crashes: lane changes [32]. There are three major strengths of this work: (1) there is a large sample of cognitively intact licensed community-dwelling adults (n = 981; average Mini-Mental State Exam (MMSE) = 27.6 ± 2.2 [33]; average age 77.8 ± 5.2); (2) each participant was administered a comprehensive visual exam and five common neuropsychological tests of executive functioning, visuospatial abilities, and memory; and (3) driving performance was measured with the use of dual cameras and a driving monitoring system within each participant's vehicle for a period of 5 days. Results confirmed that older drivers often fail to check for traffic before changing lanes. Taking total lane changes into consideration, failure rates ranged from 16% to 24%, with drivers who most often changed lanes demonstrating the highest failure rate. Furthermore, findings revealed susceptibility to distraction, and higher-order visuospatial skills are important in lane-changing behavior. Worse performance on measures of visuoconstruction and auditory divided attention predicted a higher incidence of lane-changing errors after accounting for age and gender.

In an earlier body of work, Freund and colleagues used virtual reality driving simulation as an objective tool to provide older adults with clinical driving recommendations [34, 35]. Based upon driving errors measured during simulation, Freund and Colgrove [34] classified 108 older drivers (age range 61–96) as safe ($n = 35$), unsafe ($n = 47$), or restricted ($n = 26$). Safe drivers made no "hazardous errors" during simulated driving (e.g., crashes or running red lights), whereas restricted drivers committed at least one error and unsafe drivers at least two. Of several screening measures, Trail Making Test B was the only measure that significantly differed among the three groups, and a simple test of clock drawing correlated the strongest with total simulated driving errors ($r = 0.68$) and pedal confusion (i.e., confusing the gas for the brake) [35, 36]. The authors hypothesized that executive functioning may be especially relevant to driving in older adults "because executive functioning is a critical component of safe driving, and in the presence of executive dysfunction, the automatized and procedural skills learned over decades of daily living do not protect the older driver from errors" (p. 243) [36]. Although the sample consisted of community-dwelling older adults, participants had an average MMSE of 24.9 ± 4.3 and possibly met clinical criteria for MCI or dementia, limiting the generalizability of the findings to cognitively normal older adults.

Worse performances on tests of processing speed–executive functioning have recently been associated with BTW performance and self-reported driving restrictions in cognitively normal older adults. Rapoport et al. (2013) [37] found that worse performance on the Trail Making Test Parts A and B were associated with greater subjectively reported driving restrictions in a large sample ($n = 928$) of cognitively normal elders (average Montreal Cognitive Assessment or MoCA = 25.95 ± 2.49). Worse global cognitive functioning (measured with the MoCA) was not associated with subjective driving restrictions in the Rapoport et al. study. By contrast, self-imposed restrictions in driving were associated with global cognitive status when driving performance was measured objectively with cameras placed within subjects' own vehicles. Analysis of subjects' usual driving habits collected over a 2-week period revealed older drivers with cognitive impairment (mean MMSE = 25.6 ± 2.6) consistently drove in lighter traffic situations and more often in residential (as opposed to commercial) surroundings compared to older adults without cognitive impairment (mean MMSE = 29.5 ± 0.7). Importantly, older drivers with cognitive impairment also performed worse on a BTW examination compared to the drivers without cognitive impairment. These findings indicate worse cognitive functioning is correlated with self-imposed driving restrictions and worse on-road performance in older adults.

Summary: Driving in Healthy Older Adults

To summarize, subtle changes in the driving performance of cognitively healthy older adults occur with age. Older drivers who drive a low number of annual miles have one of the largest crash rates [18]. This is an important statistic, as our clinical experience suggests older drivers and their families commonly perceive low mileage driving as evidence of decreased crash risk (e.g., "Driving isn't really a concern as Dad only drives to the local grocery store."). But the point that someone only drives a certain number of miles per week or to select destinations might well be a warning sign of subtle or worse cognitive impairment and poor driving performance. Older drivers are more likely to commit driving errors that increase their crash risk at intersections and stop signs and while changing lanes or turning against oncoming traffic.

Driving in Older Adults with Neurological Disease

The Older Driver with Alzheimer's Disease: Crash Rates and Routine Driving Ability

Studies of older drivers demonstrate that a diagnosis of dementia, per se, does not universally impact the ability of individuals with Alzheimer's disease to pass a clinical driving evaluation [26, 38]. Time, or the severity of disease progression, is of the essence however, as the progressive nature of AD will lead to driving incapacity in all cases. That being said, longitudinal evidence suggests patients with very mild AD (i.e., CDR 0.5) can continue to drive safely for an extended period. Ott et al. [26] conducted a study of drivers with Alzheimer's disease spanning 3 years using the BTW assessment. Greater severity of dementia, increased age, and lower education were associated with higher rates of BTW failure at follow-up. However, only 22% of individuals with mild Alzheimer's disease (CDR = 1.0) failed the exam at 18-month follow-up and were judged as unsafe drivers. This failure rate was even less in the group of individuals considered to have questionable dementia or severe MCI (CDR = 0.5). However, an important caveat to these findings is that they reflect the performance of the best drivers who remained after others were previously terminated for safety reasons, and participants were not necessarily recruited due to concerns over driving performance. A larger proportion of poor driving in patients with mild AD was reported in a recently meta-analysis of 460 AD patients [39]. Hird et al. [39] reported that 56.5% of patients with very mild AD (CDR = 0.5) were judged to be safe drivers on a BTW test, whereas 13.6% were unsafe and 29.9% were rated marginal. BTW passes decreased and failures increased in patients with mild AD (CDR = 1.0); 41.7% of those patients safely completed the BTW, 33.3% were judged as unsafe, and 25.0% rated as marginal. Research recruitment sources likely contribute to differences in BTW failure rates across studies. For example, Carr et al. [13] found that out of 60 participants with dementia referred for a CDE, 16 (27%) were not allowed to continue the road test because of serious safety concerns, and 57% of participants with AD failed the BTW.

Older drivers with dementia who are deemed unsafe behind the wheel commonly struggle with turning in moderate to high traffic and maintaining accurate lane positioning [23]. For example, Davis and colleagues [40] found that 59 older adults with possible or probable AD (mean age = 76.0 ± 6.0; mean MMSE = 25.2 ± 2.8; average miles driven per week = 98.8 ± 90.5), when compared to cognitively normal older adults, were more likely to make errors during lane keeping, failed to use mirrors for changing lanes and checking blind spots, and were generally less aware of surrounding traffic. Elsewhere, Dawson et al. [41] administered a BTW exam to 40 licensed drivers with mild AD (mean MMSE = 26.5 ± 2.9) and 115 older adult drivers free of cognitive impairment. Errors from the BTW exam were coded into 15 categories including, among others, traffic signals, stop signs, turns, lane change, speed, and parking. Considering individual error types, older adults with AD made more driving errors compared to healthy older adults in only 1 out of 15 categories: lane changes. Yet, when total driving errors were tallied, adults with AD made significantly more errors (42.00 ± 12.84) than healthy older adults (33.18 ± 12.22), including significantly more high crash-risk errors.

The Older Driver with Alzheimer's Disease: Driving and Cognition

Virtual reality simulation proves a useful tool to investigate challenging driving scenarios. Rizzo et al. [25] studied 18 participants with mild to moderate AD (mean age 73) and 12 healthy older adults (mean age 70) using virtual reality driving simulation. Each participant drove an uneventful virtual route for 15 min before reaching a final intersection that triggered an illegal incursion by another vehicle. Optimal response in order to avert a crash required the driver to release the accelerator, apply the brake, and make a steering

correction. Findings revealed that participants committed a safety error while driving on uneventful segments of the virtual environment. However, 6 of the 18 subjects with AD crashed as a result of intersection incursion vehicle compared to 0 control participants. Overall, cognitive performance was associated with crashes, as were individual measures of visuoconstruction, working memory, and verbal fluency.

Following up their earlier work, Uc, Rizzo, Anderson, Shi, and Dawson [42] further demonstrated the benefits of virtual reality simulation in measuring driving performance in older adults with Alzheimer's disease. They studied 61 drivers with AD (average age 73.5 ± 8.5) and 115 healthy older adults (average age 69.4 ± 6.7). All participants underwent a crash simulation; specifically, after a segment of uneventful driving, each driver suddenly encountered a lead vehicle stopped at an intersection, creating the potential for a collision with the lead vehicle or another vehicle following closely behind the driver. Contrary to their earlier findings with incursion vehicles [25], crash rates did not differ between individuals with AD (5%) and healthy older adults (3%). However, individuals with AD were more likely to engage in sudden vehicle slowing, which significantly increased the risk of being struck from behind [42]. Furthermore, sudden slowing was associated with multiple cognitive abilities, but a brief measure of executive functioning (Trail Making Part B) was associated with the greatest increase in risk of unsafe behavior. These finding suggested that with each 30-s prolongation on Trail Making Part B, the risk of abrupt slowing increased by 31%.

Driving simulation can also be used in conjunction with cognitive assessments to predict on-road driving performance. Within a sample of 81 older adults with AD (mean age 72.3 ± 9.4; mean MMSE 23.2 ± 3.7), Piersma and colleagues [43] used a combination of structured clinical interviews (CDR), neuropsychological tests, and driving simulation to predict BTW performances. The sample included 35 (43.2%) patients who passed the on-road assessment and 46 (56.8%) patients who were rated either as marginal or unsafe drivers. Using the CDR, several cognitive measures of processing speed, executive functioning, visuospatial abilities, and general cognition, as well as driving simulation performance metrics, the authors correctly classified 87% of subjects as safe or unsafe to drive.

In an early meta-analysis, Reger et al. [44] categorized studies into three categories based on driving outcome: BTW, nonroad tests (e.g., virtual reality driving simulation), and caregiver report. Cognitive performance was grouped into six domains: mental status, attention, visuospatial abilities, memory, executive functions, and language. Results can be interpreted using Cohen's [45] classification of $r = 0.10$, 0.30, and 0.50, as small, moderate, and large effects. Overall, tests of visuospatial abilities demonstrated the strongest performance with driving outcome in adults with AD ($r = 0.29$ with BTW, $r = 0.31$ with nonroad tests, and $r = 0.19$ with caregiver report). No relationship was found between tests of executive functioning and the BTW performance ($r = -0.06$), whereas a mild–moderate relationship was found between executive functioning and nonroad tests ($r = 0.22$). By contrast, a recent meta-analysis by Hird et al. [39] found that three tests of processing speed–executive functioning, Trail Making Part A, Trail Making Part B, and Mazes, were the best predictors of worse driving performance in a large sample of older adults with AD and MCI. These three tasks strongly discriminated poor and adequate drivers (Cohen's $d = .61$–$.88$) on multiple driving outcome measures (i.e., BTW, driving simulation, caregiver report).

Summary: Driving in Alzheimer's Disease

Older drivers with AD as a group report more accidents in the years immediately preceding evaluation [26] and commit more high crash-risk driving errors than healthy older adults [41], yet many older drivers with very mild AD are able to safely maintain routine driving over several years when tested with the BTW [26]. Common measures of processing speed and executive functioning (e.g., Trail Making Test) are associated with

worse driving performance in older adults with AD. The BTW exam, the current clinical gold standard of driving evaluations, is sensitive to disease severity in AD, yet it does not allow for the administration of challenging and potentially dangerous driving scenarios [46]. Virtual reality driving simulation shows considerable promise in helping to predict on-road driving performance in elders with cognitive impairment.

The Older Driver with Parkinson's Disease: Driving Errors and Routine Driving Ability

Compared to healthy older adults, evidence suggests that older adults with Parkinson's disease (PD) are more likely to commit driving errors involving lane changes, failing to check blind spots, reduced usage of side- and rear-view mirrors, backing out of a space, and indecisiveness at intersections [14, 47]. Uc et al. [48] compared the BTW performance of 84 older adults with PD and 182 healthy older drivers. Similar to their work with other populations [27, 43], BTW performance was classified into 15 different error categories, and total safety errors were tallied as well as serious driving errors. Individuals with PD had an average illness duration of 5.9 ± 5.0 years, a mean Hoehn and Yahr stage of 2.2 ± 0.59, and did not significantly differ from the healthy group on age. Drivers with PD committed more errors than healthy adults while at stop signs, turning, and maintaining lanes. Furthermore, when total errors were tallied, the PD group committed significantly more safety errors (41.6 ± 14.6) than the cognitively healthy adults (32.9 ± 12.3). However, the PD group did not commit more high-crash-risk errors compared to healthy adults, consistent with earlier findings from Grace et al. [14].

The majority of older adults with PD are able to pass clinical driving evaluations. Singh and colleagues [49] analyzed data on 154 PD patients referred to a clinical driving assessment service over a 15-year period. Participants had a mean duration of illness of 5.9 years and a mean Hoehn and Yahr stage of 1.9, and the average age was 67.6 years (standard deviations were not reported). As part of the driving assessment, each individual received a BTW exam rated on 17 different parameters including physical control, response to other drivers, lane discipline, roundabout management, braking, and merging. Based on these parameters, a driving specialist rated participants as "safe" or "unsafe." Out of the 154 PD patients, 50 (32.5%) were judged as unsafe to drive because of concerns over road safety.

Overall, these results suggest that individuals with PD commit more driving errors compared to age-matched peers. Error types include difficulty maintaining lane positions, turning, failing to check blind spots, reduced usage of side- and rear-view mirrors, and difficulty navigating stop signs and intersections. However, when crash risk is compared in PD subjects and healthy older adults, there are no significant differences between groups on total high crash-risk errors. Analysis of driving frequency suggests PD patients do not limit their driving compared to age-matched peers. Older adults with PD average as many miles per week and make as many trips as do healthy older adults [14]. Furthermore, the majority of PD participants are able to maintain routine driving ability when tested with the BTW, at least in early in the course of their illness.

Recent studies have also identified some unique aspects of PD that can impact driving errors or behaviors. For example, in addition to the motor and cognitive symptoms that individuals with PD typically experience, psychiatric symptoms such as anxiety are also common. A recent descriptive phenomenological study, employing semi-structured interviews of 22 participants with PD and 12 family members, found that experiences of anxiety and worry had an impact on driving and driving cessation. The findings reveal that the experience of anxiety while driving, as well as anticipatory anxiety and/or worry related to driving cessation, affect the driving experiences and wellbeing of individuals with PD [50].

The Older Driver with Parkinson's Disease: Driving and Cognition

Neuropsychological measures of attention, visual–spatial ability, memory, and executive functioning are important in the assessment of driving performance in PD [8, 14]. Grace and colleagues [14] investigated the BTW driving performance of 21 PD subjects, 21 healthy older adults, and 20 AD subjects. PD participants had mild levels of impairment as evidenced by a mean MMSE of 28.1 ± 1.6, a mode Hoehn and Yahr stage of 2.0, and a mean Unified Parkinson's Disease Rating Scale motor section of 28.4 ± 7.7. Participants were classified as "safe," "marginally safe," or "unsafe" as a result of the BTW exam, and total driving errors were tallied. Results of global safety ratings are consistent with findings from Singh et al. [49] described above, where the majority of drivers with PD were characterized as "safe." In the study by Grace et al. [50], no PD driver was characterized as "unsafe," 67% (14/21) of PD participants were characterized as "safe," and 33% (7/21) were characterized as "marginally safe." However, driving performance differences between groups were statistically significant; 100% of the healthy older adult group was characterized as "safe," and PD drivers (7.6 ± 4.2) did commit more errors than the healthy adult group (3.7 ± 2.7). Cognitive performances were also statistically different between groups defined by driving safety ratings. When compared to the healthy control group, PD participants characterized as "marginally safe" drivers performed significantly worse on measures of verbal learning and memory, visuospatial ability, working memory, and finger tapping. The neuropsychological performance of drivers with PD labeled as "safe" did not significantly differ from the healthy adult group. Comparisons of "safe" and "marginally safe" PD drivers confirm the importance of visuospatial abilities and working memory in discriminating the two groups. Amick et al. [51] reported that performance on Trail Making Test, Rey Complex Figure Copy Test, and the Useful Field of View Divided Attention Subtest, a measure of visual attention [52], distinguished 14 safe PD and 11 marginally safe PD drivers tested BTW. More recently, Classen et al. (2015) examined the predictive validity of cognitive tests on the outcome of on-road driving evaluation (pass, pass with recommendations, or fail-remediable) for drivers with PD. The researchers found Trails B, Left Finger-to-Nose Test, and contrast sensitivity measures to be significant predictors for the pass and pass with recommendations subgroups [53].

Analysis of the neuropsychological performance of 84 PD participants revealed that visual processing speed and attention, motion perception, visuoconstruction, visual memory, and general cognition were significant predictors of total error counts on the BTW exam after adjusting for age and education [14]. Far visual acuity and contrast sensitivity (i.e., the ability to see objects that do not stand out from their background) were also significant predictors of total driving errors. Devos and colleagues [54] compared the clinical characteristics and cognitive performance of 29 adults with PD who "passed" a virtual reality driving simulation and 11 adults with PD who "failed" the simulation. Those adults with PD who failed the evaluation were older and had longer disease duration, worse contrast sensitivity, worse motor performance on the UPDRS, and worse performance on the Rey Complex Figure Copy Test. Disease severity did not significantly differ between groups when rated on the Hoehn and Yahr scale but was significantly different when rated with the CDR.

Application of driving simulation has continued to support the relevance of cognitive functioning for this population. For example, Verdaki et al. [55] studied drivers with PD (n = 10) aged between 50 and 70 years and a group of age- and sex-matched control drivers (n = 10) using a sign recall task while driving in a simulator. The results indicated that regardless of group membership, subjects' performance differed according to varying levels of task demand. Performance in the sign recall task was more likely to drop with increasing task demand (P = .03). This difference was significant when the variation in task demand was associated with a cognitive task, that is, when drivers were required to apply the instructions from working memory.

Review of the literature on PD and driving suggests the clinician should consider clinical and cognitive risk factors when evaluating fitness to drive in patients with PD. Important clinical factors include disease duration and severity, motor performance, visual acuity, and contrast sensitivity. Neuropsychological measures of attention, visual–spatial ability, memory, and executive functioning can inform driving recommendations and identify those in need of further evaluation [48].

Characterization of the Older Driver with Preclinical Alzheimer's Disease and Mild Cognitive Impairment

Driving changes are evident in the prodromal Alzheimer's disease process. Worse on-road driving performance has been found in cognitively normal older adults who have biomarkers suggestive of preclinical AD and in older adults with amnestic mild cognitive impairment. Roe and colleagues [56] investigated the on-road driving performance of 104 cognitively normal older adults (mean age 72.5 ± 4.6; mean MMSE 29.3 ± 1.0) who underwent AD-related biomarker measurements. Higher values of tau/amyloid in the cerebrospinal fluid, but not the presence of amyloid on a PET scan or an APOE e4 allele, predicted time to a rating of marginal or fail on the on-road test an average of 2 years later. Interestingly, miles driven, number of trips, and distances traveled were reported as similar throughout the study for the normal and abnormal biomarker groups, despite differences in road tests. Thus, objective driving measurements may capture early differences in driving performance, as a result of preclinical AD, before those changes are noticeable to patients and influence self-imposed driving restrictions.

Only two studies have investigated on-road driving in older adults with psychometrically defined MCI. Wadley et al. [57] investigated the BTW performance of 46 adults with MCI (mean age = 71.30 ± 7.79) and 59 cognitively healthy older adults (mean age = 67.07 ± 6.72) with MCI defined using Petersen criteria [58]. Forty-three of the MCI participants were characterized as amnesic MCI, and the majority of these participants were described as free of cognitive impairments in domains other than memory. Wadley and colleagues [57] recorded five BTW error types: turning, lane control, gap judgment, steering steadiness, and maintaining proper speed. Driving outcome was defined using two methods: (1) the total errors across the five error types and (2) the driving specialist's ratings of (A) "evaluator took control of the car," (B) "unsafe," (C) "unsatisfactory," (D) "not optimal," and (E) "optimal." Results revealed that overall mean errors did not differ between adults with MCI and cognitively healthy older adults. When groups were compared on the driving specialist's ratings, a higher proportion of adults with MCI were judged as demonstrating "not optimal" performance on left turns, lane control, and an overall global rating of driving performance. These authors discuss two major implications of their findings. First, driving abilities in individuals with MCI, while "less than optimal," were not impaired. No drivers received "unsafe" or "unsatisfactory" driver ratings, nor did the evaluator ever take control of the vehicle. The authors bring this point by summarizing, "It appears that individuals with MCI are less likely than cognitively normal peers to *seamlessly* perform certain routine driving maneuvers" (p. 92, italicized added) [57]. Second, Wadely and colleagues speculate that executive functions are important cognitive abilities affected in MCI that may underlie less than optimal driving performance, consistent with evidence that executive functioning abilities are significantly impaired even in adults who meet criteria for pure amnesic MCI [59].

Anstey et al. [60] recently expanded upon the work by Wadely et al. [57] by investigating the cognitive correlates of driving performance in older adults with MCI. The authors first contrasted the BTW performance of 57 adults with MCI (mean age = 75.43 ± 6.31; mean MMSE = 28.89 ± 1.25) and 245 cognitively healthy older adults (mean age = 75.68 ± 6.12; mean MMSE = 28.86 ± 1.37) where MCI was defined using the Winbald criteria. Consistent with Wadely et al. [57], whereas the MCI group

had a statistically significant lower BTW safety rating compared to cognitively healthy adults, this difference was less than one point, and the overall ratings for both groups suggested driving weaknesses that posed little threat to other drivers (i.e., mild errors secondary to poor habits). The authors next attempted to predict BTW performance using common neuropsychological tests and measures designed to address weaknesses specific to driving performance. Results indicated that common neuropsychological measures, including tests of executive functioning and processing speed (e.g., Trail Making Part B, Stroop Color Word) were not related to driving performance, whereas tests specifically developed to assess driving safety were (e.g., a composite measure of choice reaction time, motor inhibition, and postural sway).

Summary: Driving in Prodromal Alzheimer's Disease

Subtle changes in driving performance are associated with early manifestations of Alzheimer's disease defined using amyloid imaging and psychometric criteria (MCI). These changes have been measured with BTW performance. Future work is needed to understand whether driving simulation can add value to driving assessment of older adults with MCI or preclinical AD.

Application to Clinical Neuropsychology

Clinical neuropsychologists are often called upon to comment on the driving abilities of older adults. The recommendation to cease or continue driving entails significant responsibility, both to the patient and society. When specifically evaluating driving capacity, the clinical neuropsychological evaluation can serve as guide to inform whether further evaluation of driving ability is warranted. It is also important to recognize that what constitutes a sufficient clinical neuropsychological evaluation may not constitute adequate neuropsychological assessment of driving ability. Furthermore, despite the ample literature on the relationship between cognitive performance and driving, it remains challenging for clinicians to translate the statistically significant relationships between cognition and driving into clinically meaningful outcomes for older adults. Presently, there are no neuropsychological practice parameters or guidelines as to what constitutes a necessary and sufficient assessment battery for determining vehicle-driving fitness [61]. Fortunately, empirical evidence on the positive and negative predictive value of specific tests in determining driving performance in older adults has begun to emerge. The interested reader is encouraged to review several recent papers investigating the use of empirically defined threshold scores meant to raise concern over on-road driving performance in older adults. Carr and colleagues [13] also provide the interested reader with a regression-based excel formula to predict on-road driving performance in older adults with dementia for whom there is concern over driving performance severe enough to warrant a referral for a CDE. The authors found that three simple tests of cognition (i.e., Trail Making Part A, Clock Drawing [Freund scoring], and the informant reported AD8) explained .91 area under the curve in a ROC analysis. For example, were an older driver to score roughly 1 SD below the mean on Trails A and Clock Drawing and be rated as a 4/8 on the AD8, that person would have a 60% chance of being judged as unsafe on a BTW. These studies provide clinicians with objective data from which to recommend further evaluation.

Case Examples

Cases encountered in clinical practice are often far from "classic" and straightforward. Clinicians asked to comment on the functional performance of patients are often challenged by the relationship (or lack thereof) between objective cognitive performance and daily functioning. Furthermore, clinicians do not always have the luxury of lengthy evaluations.

Case 1

Mrs. Smith is a 78-year-old woman with 16 years of education who was referred for a driving evaluation due to several recent accidents in the last 2 years including running over curbs, hitting a pole, and scraping a wall in her garage. Her current driver's license was recently renewed by the state with the following restrictions: wear glasses when driving, stay on roads with speed limits under 45 mph, and daytime driving only.

History of Present Illness

- Mrs. Smith's medical history is positive for coronary artery bypass graft surgery 7 years prior to the evaluation, three falls 1 year prior to the evaluation (resulting in low back compression fractures), hypertension, and mild gait/balances deficits. No neuroimaging was available. Mrs. Smith acknowledged mild changes to her thinking and memory and depressive symptoms.
- Mrs. Smith currently lives alone. Her son has noticed some cognitive and functional decline in the last couple of years (AD8 = 6/8; CDR Total Score = 0.5). He reports she is not "motivated" to cook and can leave the phone of the hook due to "forgetfulness." He is helping with managing his mother's finances and grocery shopping. Mrs. Smith continues to do her laundry and dishes in the home.

Comprehensive Driving Evaluation Clinical Assessment

- Vision: Bilateral distance vision (corrected), bilateral near vision (corrected), and visual fields were within normal limits. Contrast sensitivity was at the low end of normal.
- Motor: Neck range of motion, strength in lower extremities, rapid pace walk, brake reaction speed, and fine motor speed (nine-hole pegboard) were all judged to be within normal limits. Mild loss of strength noted in her left non-dominant hand.
- Cognition (Table 15.2): Raw values are described as "questionable" or "adequate" based upon published data as it relates to driving performance [62–64].

Table 15.2 Cognitive test results for Case 1

Measure	Raw score	Description
Trail Making Part A	41 s	Questionable
Trail Making Part B	213 s	Questionable
Short Blessed Test (/28)	2 errors	Adequate
Freund Clock Drawing Test (/7)	6	Adequate
Visual Closure Assessment (Driving Health Inventory)	2 errors	Adequate
Useful field of view (Driving Health Inventory)	180.00 ms	Adequate

On-road assessment: Mrs. Smith was tested on a 60-min standardized driving route beginning in low traffic and progressing to moderate/high challenging traffic situations.

- Mrs. Smith was inconsistent in using her turn signals when turning and making lane changes
- Mrs. Smith ran a stop sign in a park at a pedestrian crosswalk (instructor brake was applied).
- Mrs. Smith did not maintain center in her lane and was unaware of when she "drifted" into the other lane (requiring verbal cueing to maintain lane position).
- Mrs. Smith drove 5–10 miles over the speed limit and had tendency to brake late when cars were stopped in front of her. Instructor cued her to allow more braking time, yet, Mrs. Smith was not able to follow thru with recommendation throughout remainder of evaluation.
- Mrs. Smith did not visually scan well while driving resulting in missing a designated location.
- Mrs. Smith became distracted and did not turn left as instructor (even when her turn signal was on). She attempted to drive straight from a left turn lane resulting in an instructor brake to avoid a collision.
- Mrs. Smith was driving fast in a parking lot, did not attend to a car in front of her backing into a parking spot, and required a brake intervention to not collide with the car.

Comprehensive Driving Evaluation Recommendation

It was recommended that it was time for driving cessation due to safety concerns observed on the

evaluation and recent history of accidents. Mrs. Smith was aware of the incidents that occurred on the on-road assessment and agreed to discontinue driving.

Case 2

Ms. Doe is 70 years old, with 18 years of education and referred for a comprehensive driving evaluation by her physician due to cognitive decline. She does not have any history of getting lost, accidents, or tickets. She currently self-restricts her driving to local, familiar areas close to her home.

History of Present Illness

- Ms. Doe's medical history is positive for obesity, hypertension, diabetes, coronary artery disease, and obstructive sleep apnea (lack of recent compliancy with CPAP).
- Ms. Doe's family reported that her cognitive performance has worsened over the last 2 years. She misplaces things often, has stopped playing games or using her computer, repeats herself often, gets upset over small things, is more "agitated," and is overly concerned about "the house getting broken into."
- Ms. Doe had a CDR of 1.0 (indicating mild dementia). The AD8 seven out of eight areas of function had been identified by her family as declining over the last several years. Ms. Doe struggled with autobiographical recall during clinical interview and scored a 22/30 on the MMSE. Ms. Doe is frustrated by her memory loss.

Comprehensive Driving Evaluation Clinical Assessment

- Vision: Bilateral distance vision (corrected), bilateral near vision (corrected), contrast sensitivity, and visual fields were within normal limits.
- Motor: Neck range of motion, strength in lower extremities, rapid pace walk, brake reaction speed, and fine motor speed (nine-hole pegboard) were all judged to be within normal limits.

Table 15.3 Cognitive test results for Case 2

Measure	Raw score	Description
Trail Making Part A	33 s	Adequate
Trail Making Part B	128 s	Questionable
Short Blessed Test (/28)	18 errors	Impairment
Freund Clock Drawing Test (/7)	6	Adequate
Visual Closure Assessment (Driving Health Inventory)	1 error	Adequate
Useful field of view (Driving Health Inventory)	167.00 ms	Adequate

- Cognition (Table 15.3): Raw values are described as "questionable" or "adequate" based upon published data as it relates to driving performance [62–64].

On-road assessment: Ms. Doe was tested on a 60-minute standardized driving route beginning in low traffic and progressing to moderate/high challenging traffic situations.

- Ms. Doe showed good driving skills throughout the on-road assessment: safe lane changes, good visual scanning, and decision-making in traffic situations.
- Ms. Doe did require frequent repetitions of instructions. In the vast majority of situations, Ms. Doe was able to recognize when she did not remember information and requested the repetition.
- Ms. Doe drove slightly right of center in the lane but was always independent in her ability to recognize and safely reposition.
- On one occasion, Ms. Doe did not get into the correct lane to turn into as she forgot the instructions. She was able to make the independent decision to not turn from the wrong lane and improvised appropriately and safely.
- Ms. Doe drove safely throughout the on-road assessment.

Comprehensive Driving Evaluation Recommendation

Ms. Doe showed good insight throughout the evaluation of the existence of her memory deficits.

She was provided the following recommendations and restrictions related to continued driving:

- Restricted to driving in familiar areas – within 10 miles radius from her home
- Recommendation: GPS cell phone technology for Mr. Doe and family to track her driving and location to verify adherence to restriction, limit nighttime driving, re-eval as condition changes, and begin discussions of alternative transportation resources for when driving cessation occurs

Additional Risk Factors

There are additional risk factors for driving errors besides age and cognition. Other medical conditions, often comorbid in older adults, can impact driving. Age-related changes and diseases affecting vision (e.g., reduced contrast sensitivity, cataracts, glaucoma), respiratory diseases (e.g., sleep apnea), and musculoskeletal conditions (e.g., arthritis) are but a few. The clinician should also carefully consider the potential impact of medications on driving performance [65, 66]. LeRoy and Morse [67], in conjunction with the National Highway Traffic Safety Administration, analyzed the medication use of 33,519 individuals involved in a traffic accident and 100,000 controls who had not crashed. Results suggested the side effects of individual medications and combinations can impair cognitive functioning and lead to unsafe driving. Common medications prescribed in older adults include medication classes associated with increased likelihood of accidents:

- Clopidogrel (antiplatelet; 69% increased likelihood of accidents)
- Escitalopram (SSRI; 59% increased likelihood of accidents)
- Ranitidine (H2 blocker; 55% increased likelihood of accidents)
- Levothyroxine (thyroid hormone; 29% increased likelihood of accidents)
- Lisinopril (angiotensin-converting enzyme inhibitor; 23% increased likelihood of accidents)

The reader is referred to Looco and Staplin [68] for a comprehensive review on the impact of polypharmacy on the older driver.

Interventions and Recommendations

Potential driving cessation should be discussed as early as possible with the older patient. This is especially true for adults with a neurodegenerative illness who will eventually cease driving. In the case of progressive disorders (i.e., dementia), it is beneficial to have an ongoing dialogue about driving ability and to consider that multiple driving evaluations may be required during the course of the disease. Clinicians, especially neuropsychologists, have a responsibility to counsel and educate the patient and his or her family on the impact of relinquishing a driver's license. Inclusion of family members in this counseling process can serve to alleviate common communication strains between patients and family members about this sensitive topic. It is important to recall that one robust finding in the literature is the relationship between driving cessation and depression and loss of autonomy. Practical considerations include finding alternate transportation to doctors' appointments, work, and other activities outside the home. A useful review of interventions for older adults who have ceased driving is included in Windsor and Anstey [69]. It is important to remember for those who require driving cessation due to cognitive impairment, the same cognitive impairments that limit their ability to drive safely will also likely limit their ability to plan and follow through independently with alternative transportation resources. Planning and scheduling a transportation resource can be very difficult for an older adult with cognitive challenges and clinicians should provide guidance to significant others to provide the assistance that is needed [70].

Clinicians should also be familiar with interventions for older drivers who do not need to relinquish their driving privileges but require modification of their driving habits. These interventions include driving education (i.e., refresher course). There is moderate evidence that driving education improves behavior and awareness in older drivers. Increasing evidence also suggests computerized cognitive training programs are beneficial in prolonging driving cessation in older adults with sensory and motor difficulties [71]. The combination of driving education, cognitive stimulation, and physical exercise [72] may allow older drivers to successfully maintain safe driving for extended periods of time.

Neuropsychologists should be familiar with the work of driving specialists in their area who conduct clinical driving evaluations (see additional resources below for help finding a driver specialist in your area). Knowledge of the driving specialist's clinical examination will enable a frank discussion with patients as what they can expect from further evaluations. Finally, the clinician should be familiar on state laws on mandatory reporting, which vary considerably. For example, in Pennsylvania, state law requires all health-care personnel authorized to diagnose or treat disorders to report within 10 days the full name and address of any patient who has been diagnosed as having a condition that could impair his or her ability to safely operate a motor vehicle. However, not all states require mandatory medical reporting and instead temper their recommendations (e.g., Arkansas' guidelines include "We do encourage unsafe drivers to be reported to our office"). An excellent resource that includes a review of state guidelines and descriptions of driving assessment methods is the "Clinician's Guide to Assessing and Counseling Older Drivers" sponsored by the American Geriatrics Society and National Highway Traffic Safety Administration and available from the AGS website.

Driving is a complex behavior. To date, there remains much controversy about which clinical tools or methods are the best predictors of driving capacity. One important contribution that a clinical neuropsychologist can contribute to this process is to support the evaluation of driving capacity at multiple levels. The literature provides support that using a combination of measures can provide the best data for making recommendations. As clinical neuropsychologist, the most commonly requested contribution is the identification of the cognitive impairments that may impede driving performance. As clinicians specializing in brain–behavior relationship, we should recognize the complexity of this behavior and promote the evaluation of other domains affecting driving (i.e., vision, motor, psychological, and driving history). The integration of data from these various areas is a unique contribution that neuropsychologist can provide to patients and their families.

Clinical Pearls

- *Know the law*. State laws vary in their requirements for reporting and assessing drivers. Clinicians are strongly encouraged to be familiar with their individual state requirements (additional resources listed below).
- *Ask about driving*. Clinicians should be aware that driving cessation is often a topic of conflict. Too often, older adults do not raise the issue for fear of complete loss of driving privileges. Family members are also conflicted and in many cases are unsure about how to handle/raise the discussion. Clinicians can help minimize this conflict by including questions about driving performance in their regular checkups or appointments.
- *Know what cognitive domains are most relevant*. Although there is not a specific pattern or defined group of tests that 100% predict driving performance, general domains of cognition relevant to driving are identified in the literature. Neuropsychological test selection should be based upon empirical evidence with multiple abilities assessed under the domains of attention, information processing speed, working memory, executive functions, visual–spatial abilities, visual–spatial learning, and memory.
- *Be familiar with the complex role cognition contributes to driving performance*. The ability

to respond to a complexity of driving demands in a quick, safe manner in a rapidly changing traffic environment is one of the more complex activities common to most older adults. Essentially, all areas of cognitive domains are utilized throughout the driving process. Consider the following:

- *Changing lanes*: Involves the ability to alter and divide attention from looking to the front, to the side mirror, to behind to plan and safely decide if and when there is time and space to change lanes. This may simultaneously involve monitoring weather conditions or a conversation in the car.
- *Making a left turn*: Involves the ability to plan in a timely manner to get into the correct lane for the turn. This not only involves the necessary executive function but also the knowledge that it is necessary to turn from a designated turn lane. It involves the knowledge of what various signal lights mean (flashing yellow arrow, solid green light, green arrow, red light, or red arrow), simultaneously monitor any pedestrians, and being able to initiate the turn at the correct time – judging and perceiving distance of other cars approaching accurately.
- *Looking for a specific store while driving*: Involves having to maintain the car at an appropriate speed and in center of the lane while simultaneously visually scanning for a the appropriate landmark. If the landmark is missed, it might be necessary to efficiently and safely problem solve a turn around and the working memory to retrace the way back to the original destination.
- *Car maintenance:* Involves having the prospective memory to put gas in the vehicle and to maintain the car properly.
- *Be familiar with the clinical driving evaluation process*. This includes identifying referral procedures and locations offering BTW evaluations with certified driving rehabilitation specialist (CDRS) accreditation. The neuropsychological evaluation should serve as guide to inform further evaluation of driving ability and should not serve as a substitute for a comprehensive driving evaluation.
- *Be familiar with age-related medical conditions* (i.e., dementia, stroke, seizures) that affect driving. Communication with the treating physician (i.e., neurologist, cardiologist) can help educate colleagues of the need to consider driving capacity.
- *Be on the lookout for medication effects*. Given the high number of medications commonly used by older adults, clinicians should consider the effect (individual or combined) of medications on driving behavior. Medications altering cognition, alertness, increasing fatigue, drowsiness, or altering sleep patterns may warrant consideration.
- *Potential driving cessation should be discussed as early as possible*. It is often beneficial to include significant others or additional family members in this dialogue as they may provide additional insight into driving performance.
- *Familiarize yourself with transportation options*. Clinicians have a responsibility to counsel and educate the patient and his or her family on the impact of relinquishing a driver's license. Being prepared with appropriate referrals (i.e., medical transportation services) or community information (i.e., transit schedules) can help adults begin to explore/plan alternate methods of transportation. The same cognitive difficulties that limit driving safely will also likely limit the older adult's ability to schedule and arranging transportation alternatives independently.
- *Consider interventions*. Interventions can benefit individuals who do not need to relinquish their driving privileges but require modification of their driving habits. These interventions can range from structured approaches (i.e., improving field of view) to more practical recommendations, such as restricting or limiting driving.

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Additional Resources

National Highway Traffic Safety Administration: Guidelines and strategies for working with older drivers; statistics on older driver's traffic safety (http://www.nhtsa.gov/Senior-Drivers)

Association for Driver Rehabilitation Specialists: Includes a directory for locating a driver specialist in your area (http://www.aded.net)

The Handbook for the Assessment of Driving Capacity (2009). Schultheis, M.T.; Deluca, J.; and Chute, D.L. Elsevier Publishers.

CanDrive: Website for driving research with older adults; includes publications and other resources (http://www.candrive.ca/)

16 Capacity Evaluations in Older Adults: Neuropsychological Perspectives

Joel E. Morgan, Bernice A. Marcopulos, and Emily F. Matusz

Few would disagree that older adults are among the most vulnerable members of society. Scientific research and technological advances over the last half century have led to improvements in medicine and health-care delivery, resulting in greater numbers of the older adults living to advanced years. For many, late life typically brings age-related changes in health that often affect physical status, cognitive functions, or emotional and social adjustment. Consequently, changes in cognition and mental status often have significant bearing on an individual's capacity to make informed decisions about important aspects of their life, including their health care, living status, finances, beneficiaries, and other personal matters [1]. While some older individuals are fortunate enough to remain cognitively intact well into their 80s or 90s, many are not, and they may therefore be vulnerable to exploitation by others or unknowingly victimized by their own poor judgment and delimited cognitive capacity.

Neuropsychological consultation in forensic (legal) contexts is growing at exponential rates [2] where neuropsychologists lend their expertise to a wide range of services to the trier of facts [3]. Among the various roles pursued by neuropsychologists in forensic contexts is the assessment of an individual's competencies [4]. In this chapter, we discuss the issues regarding the assessment of competency in older adults, that is, that aspect of mental ability recognized in law as sufficient for the making of decisions [5], such as for giving informed consent to one's health care, the making of a will (i.e., "testamentary capacity"), and the management of one's finances [6], among others. We will discuss the general principles of law as they pertain to such issues of these capacities, the common disorders affecting older adults that may impede cognition and decisional capacity, and suggest appropriate assessment methodologies and assessment instruments in a variety of such competency evaluations. Case examples from the authors' practices are utilized to illustrate these issues and methods.

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The Legal Perspective

Capacity refers to *mental capacity*, or mental ability, that is, competency. The concept may be expressed by the question, "Does this person have the requisite mental abilities to perform this specific task?" From the legal vantage point, the presence of a mental disorder or disability does not necessarily equate with or imply an inability to perform a given task, that is, incompetency. Although necessary, the presence of a disorder or disease affecting cognition is insufficient by itself to form a judgment of incompetency. One must demonstrate specific functional impairment on tasks necessary to meet minimal standards for that particular capacity as a consequence of the disorder. Civil competency, similar to competency in criminal contexts, refers to a person's functional ability to make a particular kind of decision or to perform a particular kind of task [7]. The context of the decision at issue is critical to the determination of competency, not merely the examinee's mental status.

In matters involving criminal competency, questions arise concerning a defendant's capacity or ability to proceed to trial (e.g., does he have the presence of mind to know the principal players in the court setting, that he is in a court of law, the ability to assist his attorney, etc.), to waive rights, make a plea, be sentenced, be executed, and the like [4]. Civil competency is similar conceptually, most generally expressed by the question: Does the person have the competency, the mental capacity, to make a certain decision (i.e., to consent to health-care treatment, to care for oneself and one's property, to control their own finances, to make a will, etc.)? Both criminal and civil competency questions entail the mental status of the individual, that is, does one have the ability and the capacity? Is one *competent*?

Ingrained within the American psyche and reflected throughout the American jurisprudence system is the concept that people have the right to self-determination. Self-determination extends to individuals with mental disorders as well, except when significant harm to others results from their actions or if they are considered incompetent to make the *particular* decision in question. Thus, the right to self-determination "is not absolute" [7]. The precise meaning of competence may differ depending on the specific question and the context; there is no single legal criterion that applies to all questions of civil competency [8]. Jurisdictional differences or subtleties in statutes must also be considered, and the reader is cautioned to be familiar with individual state laws.

Neuropsychological assessment should take into account not only the cognitive status of the examinee but the nature of the capacity issue or question with which the examinee is expected to comprehend and act on in a reasonable, rational, and informed manner. As the reader will see in later sections of this chapter, the mere presence of cognitive impairment, psychiatric disorder, or mental status abnormality by itself is insufficient to declare someone incompetent. In a similar vein, an individual may be considered competent for a particular task or decision but not for another. Therefore, the legal standard of competency may be said to vary as a function of the issue or question at hand, and the neuropsychological assessment of competence must consider general cognitive functions as well as case-specific abilities. Because of their expertise in general clinical skills, knowledge of the effects of aging and disease on cognition and behavior, and their diagnostic acumen, neuropsychologists are well suited for such evaluations [9]. Formal psychometric assessment is just one of two prongs of necessary assessment methodology; the other prong of assessment requires detailed questioning of the examinee relative to his understanding of the issues and decisions involved, their ramifications, potential effects on self and pertinent others, reasoning behind one's choice, and in all, a comprehensive assessment of the examinee's judgment. Thus, even though a neuropsychologist might find deficits in those cognitive abilities that are most salient for a particular capacity evaluation, this does not mean the respondent lacks capacity. The specific tasks must be directly assessed.

The neuropsychologist may be consulted to evaluate persons in a number of different types of civil competencies. The ABA–APA Working Group on the Assessment of Capacity in Older Adults prepared a handbook to guide psychologists evaluating civil capacities of older adults which covers six civil capacities: medical

consent capacity, sexual consent capacity, financial capacity, testamentary capacity, capacity to drive, and capacity to live independently. The most common of these include the need for guardianship in making health-care decisions and the management of one's finances and testamentary capacity, that is, the competency to make a will, among others. Grisso [8], as well as the American Bar Association [10] and Moye and Braun [11], has proposed conceptual models for the assessment of capacity. The current chapter discusses some of these methodologies, but the interested reader is referred to these sources for greater details concerning those models.

Guardianship is a legal determination where the state delegates authority over a person's estate (property) or decisional capacity (for instance financial management or health care) to another individual. Decisions regarding guardianship typically emanate from family after concern arises about the elder person's decisional abilities, often after an "incident" occurs that raises such concerns. Depending on the jurisdiction, guardianship may be specific to a particular issue, such as in the management of one's finances or in making decisions regarding one's health care. Conversely, some jurisdictions provide for more general as opposed to specific guardianship.

In matters concerning the management of one's finances, the neuropsychologist examiner will need to probe into the examinee's financial background, monetary expenditures, and other related matters that are typically thought of as quite personal. As the subject of such legal determinations, the elder will of course be required to disclose such information, traditional privacy concerns notwithstanding. Assessment of financial capacity necessarily entails addressing abilities and judgments beyond those ordinarily assessed in a neuropsychological evaluation, such as knowledge of one's assets and liabilities, income, expenses, savings, math skills involving money, and knowledge of reasonable costs of goods and services. There are numerous specialized instruments for assessing financial capacity in older adults, but none are without shortcomings [12], though age and education corrected norms have recently been developed for one instrument, the short form of the Financial Capacity Instrument [13]. Older adults are particularly prone to exploitation by unscrupulous individuals regarding monetary matters [14].

Assessment of one's judgment regarding health-care decisions is multidimensional, as is true of all of the capacity decisions in this chapter. Judgment has been described as "…the capacity to make sound decisions after careful consideration of the available information, possible solutions, likely outcomes and contextual factors" [15]. Beyond traditional psychometric assessment, the examiner will need to probe the examinee's understanding of the health-care issue(s) in question. Does the elder understand the pros and cons of the decision? Does the elder know what to expect with agreement or disagreement of the medical issue? Does the examinee have sufficient reasoning capacity to weigh the decision, and its consequences, to a reasonable extent? Is the elder emotionally prepared to make such a decision, or will he/she be prepared with treatment? These and other pertinent health-care decisions must be comprehensively addressed in an assessment. MacDougall and Mansbach have shown that the Judgment Test of the NAB (Neuropsychological Assessment Battery) may be useful in such clinical evaluations [16].

Testamentary capacity is an issue that most typically arises after the will has been prepared. That is, questions concerning an individual's judgment at the time the will was executed commonly arise after the will's execution and often after the death of the testator (the person preparing the will) [7]. In the latter instance, postmortem analyses of the testator's capacity and judgment are required of the neuropsychologist, a process involving a good deal of research, review of documentation, and collateral interviews [6, 17]. Executive functions are particularly important for testamentary competence [1]. Questions concerning the vulnerability of the testator to undue influence necessarily arise in many of these assessments, as well [18], what with the growth of blended families and transfer of enormous intergenerational wealth [19].

Cognitive and Behavior Change in Older Adults

Cognitive change is generally thought to be an inevitable part of aging, most commonly affecting speed of cognitive processing that typically affects memory and executive functions [20]. These changes are referred to as "cognitive aging" and are thought to be normal and expected [21]. Researchers characterize the age-related changes in cognition as either "benign" or "malignant" [22]. Benign cognitive change, or cognitive aging, is sometimes also referred to as "age-related cognitive decline" (ARCD) and is thought to be the hallmark of generally healthy aging. Contemporary practice indicates that ARCD is typically used interchangeably with normal aging [22, 23]. Normative studies have determined performance/ability levels for older adults on many neuropsychological instruments [24–26]. Neuropsychologists retained in this type of referral context should be familiar with norms for older adults and expectations of both normal and pathological cognitive change.

Contrasted with ARCD, or normal aging, is abnormal or malignant cognitive aging, where greater cognitive impairment is present (i.e., dementia). An "in-between" state has also been identified, mild cognitive impairment (MCI; [22, 27]), characterized by the presence of a memory complaint, poor performance in at least one measure of cognition, normal activities of daily living (ADL), normal global cognitive functions, and abnormal memory functions when compared to age and education norms [28, 29]. A diagnosis of MCI includes, but expands beyond, the changes in executive functioning and memory expected in ARCD. Most typically, MCI is typified by additional changes in attention, language, and visuospatial skills [29]. Clinically, MCI patients manifest memory impairment to a similar extent as patients with mild Alzheimer's disease (AD) type, and both MCI and AD patients commonly experience difficulties completing instrumental ADLs [29]. The point of differentiation between the two diagnoses lay in the patient's ability to complete basic ADLs. Instrumental ADLs remain intact in individuals with MCI, whereas individuals with AD experience difficulties completing these tasks [29]. Additional cognitive functions in MCI patients remain relatively unimpaired, whereas cognitive impairment in AD patients expands to areas beyond the cognitive domains most commonly associated with MCI [21, 22, 28]. The concept of MCI, however, is not without some controversy. This controversy concerns the accuracy and utility of the concept of MCI and essentially whether or not MCI, the putative "in-between" state, represents an independent, largely nonprogressive entity or simply represents the earliest stages of AD and progressive decline [30, 31]. Conceptual and diagnostic issues aside, the major concern relative to the present chapter has to do with the examinee's cognitive abilities in the real world, particularly as they relate to concerns about ability to make informed decisions, that is, capacity/competency.

There are numerous neuropathological processes of a neurodegenerative nature that occur in older adults. Research suggests that nearly 70% of the dementias seen in older adults are accounted for by Alzheimer's disease (AD), Parkinson's disease dementias (PD-D), Lewy body dementia (LBD), and frontotemporal dementia (FTD) [32]. Vascular dementia (VaD) and other forms of dementia make up the rest, with VaD thought to be the second most prevalent dementia after, or in combination with, AD [33, 34]. Each of these dementias may present somewhat differently and have a different course over time, but with progression, all usually result in severe global impairment [35]. These disorders typically impair many aspects of cognitive functioning, eventually rendering patients incapable of managing their affairs and providing for normal ADLs. Approximately half of dementia patients receive assistance completing ADLs, and approximately one third receive assistance with financial management [36]. Depending on the severity of their symptoms, these patients may be unable to form reasonable judgments or make informed decisions. They therefore may be vulnerable to undue influence by others and be in need of guardianship to protect their interests.

Changes in personality, behavior, and/or social comportment are not uncommon in older adults. These may be the essential features of an emerging FTD, exacerbation of chronic psychiatric disorder, behavioral sequelae of cerebral neoplasm (e.g., glioma), vascular process (e.g., subcortical vascular dementia), delirium, or paraneoplastic syndrome, among others. Some alterations in behavior or cognition may be reversible with treatment or static in nature, while others are inexorably progressive. The examining neuropsychologist will need a complete medical history and recognition as to the nature of the disorder, its typical course, and prognosis.

Some disorders affecting older adults may result in changes of cognition or behavior, but as previously noted, these changes may not rise to a level for a determination of definite incompetency. In the case of decreased cognition, mild attention, memory, executive functioning, verbal comprehension, conceptualization, and processing speed, decrements may not have a deleterious effect on one's capacity to render appropriately reasoned decisions regarding finances, health care, and so forth [37–41].

Case Example: Refusing Medical Care

Although such mild cognitive loss may not demonstrably affect decisional capacity, changes in mood, behavior, or personality may render decision-making quite impaired. Take, for example, the case of a hospitalized elderly female who refused treatment/surgery of her gangrenous foot. Surgeons said that unless amputated, her foot would eventually lead to widespread infection throughout her body and her death. The physicians making the referral for competency to refuse medical treatment believed she had dementia, likely Alzheimer's. She was uncooperative, spoke little, remained in bed, ate very little, and had no living family. She was brought to the hospital by her landlord, from whom she rented a small apartment, paid for with her social security and small teacher's pension. The landlord became concerned when neighbors reported they had not seen her come or go in weeks. Upon entering her apartment, the landlord found her in bed, unkempt with poor hygiene, in an apartment that obviously had not been cleaned in some time. Concerned about her condition, he brought her to the hospital.

On examination, the patient was only marginally cooperative at first, refusing to be interviewed. After meeting with her briefly several times, she became more cooperative and testing was completed. It was clear that her generally normal psychometric test results were not consistent with deficiencies of cognition; she was certainly not demented. But her mood, behavior, lack of hygiene, and collateral contact with neighbors were consistent with severe depressive illness. A psychiatric consult was requested, and the patient agreed to a trial of antidepressant medication. With eventual improvements in her depression, she did agree to the surgery. Interestingly, on interview, she noted, "…looking back it really didn't matter to me about my foot or my life… I thought I didn't have much life left anyway… so why bother?" It is worth noting, however, that in some instances where a mentally ill patient refuses lifesaving treatment, the examining psychiatrist or hospital administrator may be appointed as a temporary guardian. This is most common in cases originating in hospitals or nursing homes when patients refuse to have treatment that physicians recommend, especially lifesaving treatment. Refusal of lifesaving treatment by patients is almost always questioned by their physicians, raising the specter of diminished mental capacity [42].

This case is illustrative of two important considerations: (1) factors other than cognitive impairment due to neurologic disease (e.g., dementia) may affect decision-making capacity, depression in this case, and (2) some conditions that adversely affect judgment are reversible with treatment (but many are not).

Case Example: Financial Guardian

Do persons with mental retardation necessarily lack the capacity to manage their financial affairs? Most readers would probably agree that the answer is "not necessarily." Although the right to self-determination for persons with intellectual disability has come under the scrutiny of the law for some time, the central issue and related questions are far from resolved [43]. The following case presentation highlights some of these concerns.

At the time of the referral, Ms. M.W. was a 73-year-old, single never-married female living semi-independently in a home willed to her by her parents. She had a male boarder who assisted with chores and related matters and a bookkeeper who came every 2 weeks to pay bills and handle such record keeping. She had a long history of documented intellectual impairment, having attended a private school for the disabled where a Stanford–Binet test administered at age 14 indicated her Full Scale IQ to be 63. M.W. completed high school and afterward "helped" in her father's office but had never had gainful employment. She lived at home with her parents and after their deaths, remained in the house. Her father had arranged for several trust funds for her that paid a monthly annuity on which she lived. She had an older brother who was the executor of his parents' estate. He lived out of state but was nonetheless in good contact with M.W. and provided appropriate support.

M.W. used a credit card for purchases of clothes, groceries, and other items and provided purchases to the bookkeeper. But M.W. could also write checks, and although she did this very infrequently, concern arose after a number of very large expenditures were noted by the bookkeeper. It seemed that M.W. had been exploited by a number of unscrupulous individuals and had paid for a new roof, appliances, and other high-ticket items when she was approached by a phone call or "knock on the door." It is common for older adults and the disabled to be exploited in this manner.

When her brother found out about these unnecessary expenditures, totaling many thousands of dollars, he sought financial guardianship, claiming that his sister's judgment in financial matters was seriously deficient. M.W. had not consulted with him, the bookkeeper, her boarder, or *anyone* about the necessity of replacing the roof and purchasing these expensive items but had made the decision to do so on her own. She had apparently not remembered that the roof had been replaced 3 years previously at a cost of $12,000.00 and would be good for at least another 25 years!

The examination methodology included a review of many records, collateral interviews with M.W.'s brother and bookkeeper, and neuropsychological evaluation. Neuropsychological assessment was supplemented with many questions concerning money, arithmetic, and related concerns. It hardly needs to be noted, but the reader will know that ethically, it matters little what side in a forensic context retains your services, simply call it like it is.

Interestingly, M.W.'s IQ (Wechsler) was now 58, yet she drove her car around town and maintained social activities in her church and bingo club. In fact, she seemed to function quite well within her very predictable and structured lifestyle, that is, with the exception of her judgment and awareness of monetary matters. M.W. had little knowledge of her annuity, monies spent, bills, and other obligations, and even worse, she had extremely impaired basic arithmetic skills. In fact, she was observed leaving a ten-dollar bill as a tip in a restaurant for a lunch that was less than $6.00!

Ultimately, M.W. was judged to be "financially incompetent," and her brother was awarded financial guardianship. The assessment report was very clear, however, that in the opinion of the neuropsychologist, none of M.W.'s other independent activities needed monitoring.

This case illustrates the fact that sometimes guardianship is appropriate, particularly in a well-documented, circumscribed, and specific domain. The reader will note the importance of amending standard neuropsychological assessment methodology with appropriate, detailed questions, observations, and interviews. Professional tests and psychometric considerations are obviously important, but so are in vivo assessment techniques.

Case Example: Dementing Illness and the Will

In a case in which one of the authors was involved, a wealthy, prominent gentleman was sued by his son-in-law for changing his will and cutting out his now deceased daughter and her heirs. The man had progressive supranuclear palsy (PSP) and was quite physically and cognitively impaired. He had hypophonia, limited visual gaze, impaired swallowing, other physical limitations, and was thought to be demented, thus providing a rationale for the suit. Had the man's ne'er-do-well son talked his father out of leaving part of his fortune to his sister's child after her death? The reader may think this scenario is right out of a bad B movie of the 1940s, but it is not fictional.

In this case, the testator's condition made assessment almost impossible since he was physically limited and speech was barely intelligible. Assessment methodology had to utilize as much multiple choice questioning as possible, limiting the assessment considerably. In addition to neuropsychologists, both sides of the legal challenge called neurologist experts as well. Because of the gentleman's condition, greater retrospective analysis needed to be utilized, as well as interviews with many family members. The essential question was: Did the gentleman's condition cause cognitive impairment to a sufficient extent that he was vulnerable to the purported undue influence of his son?

Experts for the testator opined that despite his medical condition, he was competent to have changed his will, that he was aware of the pertinent facts and issues, and that the new will was made free of any outside influence. However, ultimately, the man's condition made it impossible for plaintiff expert (representing the daughter's estate, the granddaughter) to obtain enough reliable and valid information from him to adequately and competently assess his status at the time the will was changed. In such instances, the court usually responds in a conservative fashion, siding with the testator in that plaintiff failed to document beyond a reasonable doubt that the gentleman was so impaired at the time the new will was executed that he did not know what he was doing. In this case, the examinee's condition had no doubt worsened since the execution of the will, given the progressive nature of PSP.

The reader will note that it is not uncommon that competency evaluations present difficult clinical and methodological issues. Sometimes, providing a scientifically informed, competent examination and forensic opinion is extremely challenging. The reader will want to use best neuropsychological practices [44], appropriate norms, and collateral interviews, all supplemented with comprehensive and specific questioning concerning the examinee's understanding of the issues involved. It is important to remember that the presence of cognitive impairment is insufficient by itself to warrant a determination of incapacity and that ultimately it is one's clinical judgment that must take precedence.

Clinical Pearls

- Just because someone has a diagnosis of dementia does not mean that they lack capacity, although this greatly increases the likelihood. Capacity must be assessed by directly examining the skills needed to meet the particular legal standard.
- Lacking capacity in one area (such as testamentary) does not automatically render a person incompetent in others (such as medical treatment).
- Lacking capacity at one point in time does not mean that the person will lack capacity in the future, unless the cause for incapacity is due to a known progressive illness such as Alzheimer's disease. Capacity may need to be reassessed in the future.
- Capacity involves both execution of tasks and decision-making about the issue.
- Impairment on neuropsychologist tests does not equate to lack of capacity. The clinical neuropsychologist needs to augment neuropsychological test results with specific task information to make a recommendation about capacity.

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Fitness for Duty Examinations

17

Michael Chafetz

Background

Employers occasionally have a concern about an employee's ability to perform usual work duties. If the employee has shown psychological or emotional instability, anger in the workplace, psychosis, or drug or alcohol problems, the employer may request a psychological fitness-for-duty (FFD) examination. If the employee has experienced a seizure, stroke, traumatic brain injury, or developed other forms of neuropathology, the employer may request a neuropsychological FFD examination.

In a psychological FFD examination, the employer wants to understand the impact and risks of the psychological or emotional instability. In particular, will this instability pose any risk of harm in the workplace, either to the employee or to other coworkers? The employer also wants to know whether the disturbance has an impact on the employee's abilities to perform the essential duties of their job. The questions become especially important in safety-sensitive positions in which risk factors are multiplied by the potential loss to human life and the particular vulnerabilities of the workplace itself. The employer will also want to know if the employee can return to work, whether treatment will facilitate the return and whether there are any signs that the employee might need more support or assistance once they return to work.

In a neuropsychological FFD examination, the employer's questions center on the impact of the employee's neuropathology in the workplace. The questions about risk in a safety-sensitive position are essentially the same, but the issues typically concern the cognitive abilities of the employee and whether these can be ameliorated so that the particular job can be performed without limitations or restrictions.

Nature of the Referral

The referral for a psychological or neuropsychological FFD examination may come directly from the employer, or it may occur through a company especially dedicated to handling medicolegal referrals. The referral through an independent company may be preferable from the points of view of the employer, the employee, and the examiner. If the referral is handled correctly, the independent company can help educate the employer about the legal nuances of the FFD examination, informing the company about what to expect and how to ask the right kinds of questions. It can be more difficult if the referral is done directly from the employer to the examiner, as the examiner will have to understand the

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limitations and nuances of the referral in order to help educate the employer appropriately. Moreover, the independent company provides a buffer between the employer and the examiner. This buffer is useful from the employee's point of view, as it can be communicated that the examiner's opinion is independent of the employer's particular point of view, being derived from standardized psychological and neuropsychological methods that include standardized testing, direct and collateral interviews, and a review of relevant records.

Whether the evaluation is done directly through the employer or through an independent company, it must be made clear to the employee at the outset that there will not be the typical doctor-patient relationship and that federal privacy laws under HIPAA may be limited. It must also be clear to the employee that the information gathered in the evaluation will be shared with the employer and that the findings may have an impact on employment.

Nature of the Examination

Under Equal Employment Opportunity Commission (EEOC) rules, the medical records sought by the employer for review by the examiner must be particularly related to the psychological or neuropsychological issue that is causing the workplace problem. Moreover, neither the employer nor the examiner can ask for information that violates the Genetic Information Nondiscrimination Act (GINA). This means that neither the employer nor the examiner can ask the examinee whether relatives have had similar symptoms or problems. If genetic testing has been performed, that information cannot be sought or disclosed. Essentially, the entire examination and all the inquiries must be job-related and borne out of business necessity [1]. The reader will note that these restrictions are the opposite of what is typically necessary in a clinical referral or disability independent examination in which such information may become probative in determining the nature and extent of relevant psychological or neuropsychological problems.

Informed Consent

Whether the FFD examination is being performed through an independent company or not, this writer finds it helpful to include his own informed consent (IC) notice. The employee must initial each paragraph of the consent form and paraphrase its content so that the examiner is clear that the employee's consent is truly informed. The employee must also sign and date the IC notice.

The IC notice ethically discloses the purposes, intended uses, and possible outcomes of the FFD examination [2]. It is helpful in the beginning to disclose that the employer's company has requested this evaluation. If an intermediary (e.g., independent company) is being used by the employer for the examination arrangement, that fact is also stated. The employee is notified that the employer is paying the fee for the evaluation and that the employer is regarded as the examiner's client. The employee must also be informed that the examiner will produce a report that answers the employer's questions about the employee's fitness for duty for the employee's particular job position.

The nature of the evaluation and its purpose must be fully explained. The employee must know that the goal is to determine if the employee can perform essential job tasks. The potential benefits and risks of a FFD examination should also be explained. Potentially, the examination could help or hurt the employee's chances to return to work, and discussion of the employee's problems may also be upsetting.

Thus, the employee must be informed that the usual rules about confidentiality do not apply, as the employer will get to see the report, which answers the employer's questions. However, the employee must also be informed of the typical limits of confidentiality based on applicable state laws about abuse or harm to vulnerable persons or about a duty to warn if another person's life is specifically threatened.

Concerning the provision of information, particularly if an independent company is involved, the employee must be informed that the examiner will be exchanging information with this

intermediary company and vice versa, which may include medical records, job position duties, and the employer's concerns, not to mention the final report.

The employee must also be informed that while participation and the authorization of records exchange are voluntary and that revocation can be achieved by writing a revocation letter to the examiner or to the IME company, the act of revocation can only be achieved if the examiner and the independent company have not already relied upon the authorization to submit a report or exchange records. This writer finds it useful to use the metaphor, "You can't unring a bell." The employee should also be informed that they do not have to answer questions that are too distressing, though the examiner may ask why the employee is distressed and record the reasons in the report.

It is also important to inform the employee that no recordings of the examination are permitted, though some states require that employees be allowed to do this if they want to. This policy exists to protect the integrity of the examination, particularly about test security [3] and third-party observer issues [4].

The examiner should make it clear that the employee is not the patient of the examiner and that treatment or advice cannot be proffered. This writer finds it helpful to state within the IC notice that the examiner will offer respect for the employee's dignity and person, but if treatment or advice is needed, it must be obtained from the employee's own doctor(s).

Short and Long Reports

The typical long report is just like any psychological or neuropsychological disability IME report, providing all the background, records review, interview, collateral interviews, findings of testing, analyses, diagnoses, summary, and the answering of questions.

For a FFD examination, however, a short report is frequently done in an ethical manner that discloses that full testing, records review, interviewing, collateral interviews, and test findings were all done using standard procedures, but only the answering of questions is being tendered. The short report thus achieves the minimum necessary communication to answer the referral questions about the employee's work-related issues, whether further time off or treatment is necessary to achieve work stability; whether there is a risk to employee, coworker, or work if environment safety exists; and whether management can identify any red flags concerning future problems the employee might have.

By issuing a short report, the examiner protects the client (i.e., the employer) against disclosure that may be seen as discriminatory against the employee. Moreover and more to the point, the short report is seen as being entirely work-related, as it simply states that a psychological or neuropsychological evaluation was done and then merely answers the work-related questions about the employee.

However, even though purely work-related, no report is entirely free of incidental disclosures about the employee's condition, as the employer's work-related concerns will naturally involve the psychological or neuropsychological reasons the employer has asked the employee to take a leave from work and the reasons the employer has asked the examiner for evaluation.

When using a short report, all of the testing, background, and results are archived (by the examiner and potentially by the independent company psychologist, if they have one) against a possible future legal action that may render it necessary for this information to come to light.

Disclaimer in Report

Disclaimers are usually based upon prevailing psychological wisdom. The evaluator is certainly not going to promise perfect predictability, but it must be kept in mind that the employer is seeking psychological opinion and some confidence in the advice about the work-related issues regarding the psychological or neuropsychological problem(s) the employee has.

First, it is helpful to state the obvious to the employer: *The evaluation is based only on information available to the examiner at the time*

of the evaluation. The disclaimer should make it clear that additional information might yield different opinions or conclusions. It is helpful to state the other obvious fact that other records or resources that were not available to the examiner might actually exist. The message conveyed is clear, namely, that the evaluator is limited by the information given to them at any one time.

Of course, the entire psychological enterprise of assessment is based upon probabilities that are inherent in classification accuracy and in error terms concerning cognitive status and impairment levels. While the employer is typically not interested in the scientific background regarding the psychologist's methods, the examiner must still convey that absolute statements and conclusions cannot be rendered and that any opinion will be given within a *reasonable degree of psychological probability*.

This phrase about psychological probability is somewhat ritualistic and fairly diluted, and it is analogous to the *reasonable degree of medical certainty* often uttered by medical experts in the courtroom. The more diluted *probability* terminology is in my opinion preferable, as it more directly relates to how psychologists interact with their data. While these FFD cases rarely, if ever, go to court, the psychologist should be prepared to articulate the factors that participated in the opinions offered and the reasoning that led to the ruling out of alternative hypotheses. This preparation is especially important in the writing of a short report, which does not usually include the examiner's reasoning or other probability statements. Parenthetically, this is the reason that a short report may not take that much less time than a long report, and thus the pricing of the short report should take these factors into consideration.

It is also helpful to include a warning that it is not possible to predict dangerous behavior in individual cases with any degree of confidence. Concerning the risks of dangerous and violent behavior, the evaluator may wish to consult the *Handbook of Violence Risk Assessment* [5], with the caveat that most of the techniques and statistics discussed are about criminal offenders, which renders the predictions somewhat out of context for FFD examinations.

Nevertheless, knowledge of approaches to risk assessment is important. From the introductory chapter on risk assessment tools [6], it is helpful to note the three main approaches to risk assessment: (1) structured professional judgment, (2) actuarial, and (3) a behavioral approach, termed *anamnestic*; all rely on the gathering of prior information concerning the behavior of the individual. The structured approach focuses on known risk factors; the actuarial approach is considered a formal method that relies on predictors and the weights assigned to them; and the anamnestic approach is more of a process of gathering detailed information about the individual's history, especially the history of violence. The goal is to identify risk factors that are recurring in this individual's violence history, thereby identifying the "red flags" that are helpful for discussing this individual's history of violence.

The reader will note that these methods are likely to be far more detailed in the context of criminal violence and recidivism and are less likely to be as productive in the context of a single outburst that necessitated a FFD examination. Therefore, it is wise to advise management in the context of a disclaimer that a psychological evaluation is complementary to (but does not replace) a more detailed investigation of the employee as might be done in a private investigation. Moreover, the psychologist will not be making the ultimate managerial decision in the FFD examination, which is the sole responsibility of the employer.

Nevertheless, the disclaimer notwithstanding, the rubric that understanding the detail of previous behavior is helpful in predicting future behavior should be kept in mind. Thus, the detailed questioning that identifies the context and history of the employee's violence or emotional outburst goes a long way to explain results on psychological testing.

Validity of the Examination

In a FFD examination, the employee typically desires to return to work. The presentation for someone with this motivation usually involves an

attempt to look as good as possible to the examiner in all kinds of ways, especially emotionally and psychologically. Thus, the presentation often involves a denial of emotional and psychological pathology and frequently an attempt to appear almost virtuous and as having exceptional psychological adjustment.

This presentation is opposite that in examinations for disability, civil litigation, and criminal adjudication in which the motivation may be for "secondary gain," which includes monetary benefits or awards, or freedom from punishment. In these cases, many individuals attempt to appear worse than they are in terms of having neurocognitive, emotional, or psychological pathology. This kind of negative impression management for the purpose of receiving "secondary gain" is termed *malingering*.

Chafetz, Prentkowski, and Rao [7] published a work motivation study that compared social security disability (SSD) claimants, who were asserting an inability to work due to cognitive or psychological problems, with state vocational rehabilitation (SVR) claimants, who were ostensibly attempting to work or to be educated in order to work. The third group for comparison was child protection (CP) claimants, who were required to undergo examination during the process of attempting to get their children back from state custody.

In this study, 45.5% of the SSD claimants met established criteria for malingering, while only 6.7% of the SVR claimants did so. When the individuals in the SVR group who met criteria for malingering were further investigated, it was discovered that all of these individuals were either simultaneously seeking disability or had been sent from the disability office for concerns about residual functional capacity. Thus, it was indeed possible that these individuals had a hidden agenda concerning disability that was different from their ostensible reason for seeking help through the SVR office. Moreover, none (0.0%) of the CP claimants met criteria for malingering. In all three groups, IQ (for non-malingering individuals) was between 68 and 72, thus indicating that it was the goals of the claimants, rather than intellectual impairment, which affected validity test failure.

In a FFD examination, the psychologist typically has access to several scales that are helpful in assessing the validity of the examination when someone is attempting to look as good as possible and in doing so may be hiding pathology. For example, the Personality Assessment Inventory (PAI) [8] has a positive impression management (PIM) scale with item content that involves a very favorable impression or the denial of relatively minor faults. These items had low endorsement frequencies in the normative groups. Moderate elevations of the PIM scale indicated that the examinee attempted to present as relatively free of shortcomings that are commonplace and usually freely admitted. This presentation likely involves underreporting of pathology. When PIM scores are significantly elevated (>67 T), it is an indication the examinee attempted to present as exceptionally free of common shortcomings, indicating a significant level of underreporting that leaves interpretation of the clinical scales suspect. The examiner needs to be clear that this is not a case involving lack of pathology but merely a presentation as if the examinee has no pathology.

On the Minnesota Multiphasic Personality Inventory-2-Restructured Form (MMPI-2-RF) [9], the uncommon virtues (*L*) scale assesses whether the examinee presented in a favorable light by denying common shortcomings that are usually easily admitted. While this scale was previously termed the *lie scale*, the new name reflects a more objective behavioral description rather than an attempt to draw an inference about motives. As with the PIM scale on the PAI, the *L* scale assesses underreporting from the point of view of denial of common faults and thus ultimately denial of pathology. When *L* <65 T, there is no evidence of underreporting, and the profile is considered interpretable. The next two successive levels occur in the *L* ranges of 65 T–69 T and 70 T–79 T. In an otherwise consistent profile without significant evidence of positive (yea-saying) or negative (nay-saying) response bias, these ranges indicate successively higher levels of underreporting versus having traditional upbringing (that usually includes religious virtues). When *L* >79 T, the MMPI-2-RF findings

are probably invalid due to underreporting, though occasionally some scales may be elevated in spite of the underreporting. However, absence of clinical scale elevations is uninterpretable.

Curiously, the issue of traditional religious or faith-based upbringing as the counterpart to attempted underreporting in the modestly elevated ranges of *L* does not have much empirical support. Rosen, Baldwin, and Smith [10] performed meta-analyses of 11 published MMPI studies and 12 MMPI-2 studies with religious or faith-based samples. Only one of the MMPI religious samples had an elevated mean *L* scale score. The MMPI-2 samples had considerable heterogeneity, with overall moderate *L*-scale elevations in religious samples of only about 5 T points.

The MMPI-2-RF also employs the Adjustment Validity scale (*K*). Elevations on *K* indicate that the examinee presented as well-adjusted. With higher *K* scores, the presentation is that of more and more adjustment, with the consequent view that the examinee is underreporting. This interpretation is especially apparent in a FFD examination in which the examinee might have a drinking/drug problem, a divorce, or some other emotional upheaval. The contrast between life upheaval and exceptional psychological adjustment is often quite telling. When $K < 60$, no underreporting is evident. As *K* moves up into the 60 T–65 T and 66 T–69 T ranges, there is increasing evidence of underreporting versus the examinee having better and better psychological adjustment. In these ranges, the examiner must contrast the adjustment hypothesis with the life circumstances. However, when $K > 69$ T, the exceptional adjustment becomes more unlikely, and the interpretation is that of underreporting.

The Paulhus Deception Scale (PDS) [11] is also useful in the FFD context, as it measures two kinds of socially desirable responding: impression management (IM) and self-deception (SD). The PDS is a freestanding self-report questionnaire that takes about 5–7 min to complete, and it requires only a fifth-grade reading level. The IM scale is relatively uncorrelated with the SD scale. The scoring on the PDS assigns points only for extreme responses (1 or 5) on a 5-point scale (though sometimes 2 or 4 are extreme enough to derive a point).

Consistent with the *L* scale on the MMPI-2-RF and the PIM scale on the PAI, the IM scale of the PDS measures the degree to which examinees say they typically perform desirable, yet uncommon, behaviors (e.g., in the manual: "I always obey laws even if I'm unlikely to get caught"). If several of these kinds of items are rated in the extreme, with high claims on unlikely desirable behaviors, it appears that the examinee is attempting to impress the examiner. In "high-demand" situations such as the FFD examination, the interpretation tends more toward deliberate distortion [11].

The SD scale indicates a form of self-enhancement described as rigid overconfidence [11]. According to Paulhus [11], high scorers on this scale tend to claim to "know it all," even when they are questioned about things they could not possibly know. Thus, this scale is measuring a kind of self-deception that involves a lack of insight [11]. This can be useful in the FFD examination, especially for understanding why an employee might not be getting along well with coworkers.

Case Examples

The following cases have been heavily masked so that employers and employees cannot be identified. The first two cases are younger adults but provide context and address issues that could just as readily occur in older adults.

Neuropsychological FFD Examination of a Government Agent with Traumatic Brain Hemorrhage

A 38-year-old female had experienced a fall, striking her head and suffering a subsequent bleed into the brain that affected the use of her right, dominant hand and altered her speech patterns. CT and MRI of the brain were both positive for the disturbance. The agency was concerned about her ability to handle a firearm. She was attempting to recertify for her firearms qualification after returning from medical leave, but she was struggling to do so. The agency asked for specific neuropsychological opinion about

her abilities related to motor and executive functioning and generally about her neurocognitive strengths and weaknesses. Her instructors agreed she was not proficient, as she was not taking instructions well and not loading and using her weapon with proficiency. Although she had improved in her abilities since the medical incident, the neuropsychological findings showed bilateral fine motor difficulties that were more pronounced on the right than the left, slowed processing speed, and word-finding difficulties with dysfluency. The examiner concluded that she would have difficulties in motor skills, judgment, and communication, particularly under stressful or fast-moving conditions and that her safety and the safety of her coworkers would be affected under these conditions.

Bank Employee with Progressive Cognitive Impairment

Employer was concerned about a 71-year-old female bank manager showing apparent memory problems. Neuropsychological evaluation showed evidence of short-term memory and executive functioning problems that would impair her performance at work. While she remembered crystallized occupational information related to technical financial information and she remembered her long-term customers, she had difficulty with fluid problem solving and memory functioning that included remembering what she had done for a customer, remembering new computer operations, and remembering what coworkers have told her. The examiner recommended a neurologic workup and potentially medications for memory decline, along with physician-approved exercise. Management already provided her with a memory book and a buddy system/partner to help in her work. One suggestion to extend her employment was to consider letting her bring in clients while someone else handles the computer work. Other suggestions included a daily checklist of tasks to perform and someone to log customer requests for her. Other than to have a full neurologic workup, medical leave (time off) was not recommended. However, it was made clear that it was not possible for this employee to perform all her work duties due to neuropsychological impairment.

Other Types of FFD Examinations

Federal Aviation Authority (FAA) – Pilot Examinations

The examination of pilots who have experienced psychological or neuropsychological pathology represents a specialized type of FFD examination. First, the examinations must adhere to FAA specifications that not only require specialized testing (e.g., Cogscreen; see http://www.cogscreen.com) but also rely on experience and knowledge concerning proper normative groups and the issues involved in subtle impairments that affect pilot performance. According to the Cogscreen website overview (http://www.cogscreen.com), Cogscreen is not a test of aviation knowledge or flying skills but a battery of neuropsychological tasks that measure the underlying visuomotor, perceptual, and information processing abilities associated with the operation of aircraft. Parenthetically, drone operation is now under the rubric of FAA medical specifications, and drone operators who have experienced psychological or neuropsychological pathology are required to undergo the same evaluations.

At the 4th Annual Aerospace Psychology Seminar in Denver, CO, Kay and Atkins [12] spoke on the specialized use of norms in FAA examinations, providing the hypothetical case of an 80-year-old pilot with 13 years of formal education. The hypothetical pilot responds correctly to 12 out of 20 math problems known to have a 10th grade level of math equivalence. This performance places this hypothetical older pilot at the 32nd percentile according to norms corrected for age and education but only at the 5th percentile compared to non-corrected norms. The authors go on to discuss pilot norms for typical neuropsychological tests and that Cogscreen has norms that relate specifically to pilot performance. The warning given, which has become lore in pilot examinations, is “there are no age-normed runways.” Indeed, we want our pilots

to be able to operate aircraft as competently as pilots who do not have any pathology. A comprehensive look at pilot psychological examinations can be found in *Aeromedical Psychology*, by Kennedy and Kay [13].

Licensing Board Examinations

The mission of all licensing boards is essentially the same: to protect the public from the misdeeds or incompetence of its licensees. This writer has conducted psychological and neuropsychological examinations for several different licensing boards, including medical, nursing, chiropractor, counselor, social work, and psychology boards. The FFD issues are similar for licensing board examinations (as well as pilot examinations), including positive impression management and normative issues. Indeed, one might extend the lore of pilot examinations to the highly skilled aspects of being a surgeon: "There are no age-normed scalpels." Thus, age norms that place the 85-year-old surgeon in the high average range for his age for tasks that involve fine visuomotor control (e.g., Grooved Pegboard) may actually be at a much lower level if the older surgeon were compared to their much younger counterparts.

Otherwise, the issues for licensing board examinations revolve around the same competency issues brought about by drug/alcohol abuse, psychological or emotional instability, medication use, and neurocognitive compromise (e.g., from stroke, seizure disorder, traumatic brain injury, etc.). The examiner will be providing the licensing board with specific opinion about psychological or neuropsychological impairment. While the psychologist must be careful not to provide opinion outside the scope of their own field, it is not uncommon to provide opinion about psychological or emotional stability with coworkers or patients or about the underlying neurocognitive components of fine motor skills such as might be required in surgical operations. As with any other FFD examination, these are medicolegal examinations in which clean boundaries between the examiner and examinee must always be apparent.

Clinical Pearls

- Fitness-for-duty examinations are a type of medicolegal evaluation in which the psychologist's client is the employer or an agency (FAA, licensing board).
- Clear boundaries are essential, and it must be clear that no typical doctor-patient relationship exists, though respect for the employee's dignity and person is offered.
- The purposes and nature of the evaluation must be specified to the examinee at the outset, and the fact that the findings may have adverse consequences for the employee must also be conveyed.
- In the process of informed consent, the nature of the evaluation is fully explained; in particular, the goal is to answer the employer's questions about the employee's psychological or neuropsychological functioning as to whether it has an impact on the workplace.
- Validity issues mostly have to do with positive impression management and consequent underreporting in which the absence of evidence of pathology does not constitute evidence of absence of pathology.

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18 Clinical Assessment of Postoperative Cognitive Decline

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Introduction

Since the introduction of cardiac surgery with cardiopulmonary bypass in the 1950s, severe neurological injuries due to cerebral ischemia have been recognized as a major complication [1]. Shortly thereafter, it was also observed that patients dying shortly after cardiac surgery from cardiovascular causes without apparent concomitant neurological deficits often had cerebral ischemic lesions on autopsy [2]. This observation suggested that cardiac surgery may induce mild cerebral ischemic injury without producing evident neurological deficits. After decades of clinical outcome reports in the literature, it is well understood that cardiac surgery is associated with a spectrum of neurological complications, from severe injuries resulting in major focal neurological deficits, stupor, and coma, to the relatively milder syndromes of delirium and postoperative cognitive decline (POCD) [3].

In the 1980s, researchers began using neuropsychological testing to assess milder forms of neurological deficit following cardiac surgery [4, 5]. Early studies found a very high incidence of declining test scores from pre- to postoperative cognitive assessments exceeding one standard deviation in magnitude, with 79% at 7 days postoperatively and 57% at 6 months postoperatively [6, 7]. Since recognition of the problem, numerous cognitive outcome studies have been performed in cardiac surgical patients, and the findings have played a significant role in driving the evolution of cardiopulmonary bypass technology, surgical technique, neuroprotective strategies, and the use of monitoring devices.

In recent years, interest has expanded to the study of cognitive outcomes following non-cardiac, non-neurological surgical procedures, especially in geriatric patients. In 1998, initial results of the landmark International Study of Postoperative Cognitive Dysfunction (ISPOCD1) were published [8]. This prospective study examined 1,218 patients aged ≥ 60 years who underwent a variety of non-cardiac, non-neurosurgical procedures, excluding those with conditions that would confound the cognitive test data (e.g., MMSE score ≤ 24), as well as a control group comprised of 321 age-matched, healthy volunteers. Cognitive testing was performed before surgery, 1 week after surgery, and approximately 3 months after surgery. At 3 months postoperatively, the incidence of cognitive decline was 9.9% in the surgical group versus 2.8% in the control group.

In the subgroup of surgical patients who were ≥ 70 years of age, however, the incidence was 14%, compared to 7% in the 60–69 years of age

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group [8]. Further studies have confirmed that the elderly are particularly affected by POCD [9–11]. Structural and functional changes associated with normal aging may render the elderly more vulnerable to POCD [12]. These changes include decreases in the number of neurons, the size of neurons, the dendritic tree complexity, and the number of synapses, as well as changes in transmitter systems [13, 14].

Within the POCD research literature, patients are identified as having POCD on the basis of a pre- to postoperative decline in cognitive test performance that meets the specific study criteria. Thus, the oft-used terms "postoperative cognitive dysfunction" and "postoperative cognitive deficit" are misleading, because the postoperative test scores do not necessarily reach the deficit range relative to normative data. We prefer the term "postoperative cognitive decline," as it more accurately describes the entity reported by most studies.

Studies of incidence, etiology, prevention, and treatment of POCD, however, have not yielded strong consensus or consistent findings. Consequently the topic has stimulated controversy, as some view POCD as a hidden epidemic, while others question its societal and economic relevance and even its existence [15–17]. There *is* consensus in the literature that widely varying neurocognitive assessment methods contribute to the inconsistencies [18]. Weak and flawed assessment methods and test data interpretation have also contributed [19].

While there is a large body of research literature pertaining to the topic of POCD, there is a paucity of literature related to the *clinical* neuropsychological assessment of POCD following non-neurological surgery. Yet neuropsychologists are called upon to perform clinical neuropsychological evaluations in patients with a history of cognitive decline following non-neurological surgery. Given the lack of practice-related resources, such assessments may not be as useful as they could be. This chapter aims to address this need by (1) presenting an overview of mechanisms of intraoperative cerebral injury and (2) setting forth a set of recommendations to aid clinical neuropsychologists in the clinical assessment of POCD.

Mechanisms of Intraoperative Cerebral Injury

Just as an understanding of the basic mechanisms and localization of neuropathology is necessary for planning any neuropsychological assessment, a similar understanding of perioperative cerebral injury is essential for planning the clinical neuropsychological assessment of POCD. Since there are multiple mechanisms of intraoperative cerebral injury, the planning depends on the surgical context. Among non-neurological surgical procedures, cardiac, thoracic aortic, and carotid artery surgical procedures carry the highest risk of adverse neurological outcomes, including POCD, and are addressed in this chapter. The influence of anesthetic agents and techniques is also described.

Cardiac Surgery

Coronary artery bypass graft (CABG) surgery and heart valve surgery performed with cardiopulmonary bypass (CPB) carry a risk for cerebral ischemia due to macroembolization, microembolization, and/or hypoperfusion. These mechanisms are considered to be the major causes of neural injury in this patient population; however, neuroinflammation and blood-brain barrier disruption may also play a role [20–23].

Macroembolization and Microembolization

Extracorporeal circulation exposes patients to gaseous and particulate embolization, as evidenced by histological examination of brain microvasculature in autopsy specimens and other techniques [24–26]. Due to the presumption that embolic load is an important cause of morbidity related to CPB, including POCD, much of the evolution in cardiopulmonary bypass technology and surgical technique has focused on reducing embolization. Concern regarding the neurocognitive effects of CPB was one of the major factors leading to the development of off-pump CABG techniques [27].

The applicable research has not demonstrated a clear and consistent association between microembolic load, as detected by transcranial Doppler (TCD) and cognitive outcome. A systematic literature review of studies examining the relationship between intraoperative embolic load and cognitive outcome reported that of 18 studies, 9 reported an association and 9 did not [28]. Meta-analyses of randomized controlled trials comparing neurocognitive outcomes of on- and off-pump CABG surgery have generally concluded that there is no difference [29–31]. Randomized control trials comparing on-pump vs. off-pump CABG surgery found that while off-pump CABG was associated with fewer intraoperative cerebral microemboli detected by TCD, it was not associated with better neurocognitive outcome [32, 33].

More recently, cardiac surgery-related cerebral ischemic injury has been studied using diffusion-weighted magnetic resonance imaging (DW-MRI) [34]. Acute ischemic lesions become visible within 24 h of onset and disappear within 14 days of onset. After resolution on DW-MRI, the chronic ischemic lesions become apparent on T2-weighted MRI images, indicating persistent structural damage. DW-MRI studies have found new ischemic lesions in a high percentage (30–50%) of patients who underwent CABG and/or cardiac valve surgery with CPB [35–45]. In the majority of patients, the lesions were not associated with overt neurological signs (i.e., they were "clinically silent"). Most of the lesions were small, and in most cases, they were multiple and bilateral. Risk factors for new ischemic lesions included age, pre-existing cerebral vascular lesions (assessed by T2-weighted MRI), and mild-moderate atheromatous disease of the thoracic aorta. Studies examining the relationship between new ischemic lesions on DW-MRI and cognitive outcome, however, have yielded inconsistent results. A systematic literature review found that of 18 studies reporting MRI change, 6 reported an association with POCD and 12 did not [46].

Thus, the series of TCD and DW-MRI studies neither confirms nor rules out a causal link between emboli from CPB and POCD [47]. The lack of association with POCD is unsurprising in light of the fact that the clinical manifestations of embolic cerebral ischemic lesions depend on a variety of factors, including lesion size, lesion location, and total lesion volume. Many of these lesions are "clinically silent" and do not result in measurable deficits.

Transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation (TAVI), is a minimally invasive procedure that allows for aortic valve replacement in patients with severe aortic valvular stenosis who are considered to be high- or moderate-risk for surgical aortic valve replacement. TAVR carries a higher risk for cerebral embolic shower, perioperative stroke, and embolic lesions (detected by DW-MRI), compared with surgical aortic valve replacement. Filter devices designed to capture and retrieve embolic material are increasingly employed for cerebral protection during TAVR, which significantly reduce the number and volume of new cerebral lesions and associated neurological complications [48]. Neurocognitive outcome studies have shown that about 10% of TAVR patients showed a decline in cognitive function that persisted at 1 year [49].

Cerebral Hypoperfusion and Hypoxia

Hemodynamic deviations occur commonly during cardiac surgery; however, autoregulation provides steady blood flow to the brain despite variations in mean arterial blood pressure (MAP) and cerebral perfusion pressure. During CPB, MAP is typically maintained between 50 and 100 mmHg, based on the assumption that cerebral blood flow autoregulation is maintained within this range. The range of intact autoregulation, however, varies between individuals and shifts to higher thresholds in elderly and hypertensive patients [50]. Impaired cerebral blood flow autoregulation thereby predisposes patients to intraoperative hypoperfusion. Brain regions supplied by the distal branches of the major cerebral arteries are most vulnerable to hypoperfusion ischemic injury; a large proportion of strokes related to cardiac surgery are infarcts in the watershed territories [51]. Episodes of cerebral hypoperfusion and hypoxia also appear to be particularly important in off-pump CABG surgery, due to low cardiac output and hypotension related

to transient displacement of the heart to facilitate surgical exposure [52]. Studies examining the relationship between intraoperative noninvasively determined cerebral oximetry and neurocognitive outcomes in cardiac surgical patients have reported inconsistent findings, with some studies reporting an association and others reporting none [53–60]. Factors that may contribute to these heterogeneous findings include inter-study variations with respect to near-infrared spectroscopy (NIRS) technologies, definitions of cerebral desaturation, cognitive assessment methodologies, and definitions of POCD.

Neuroinflammation and Blood-Brain Barrier Disruption

CPB elicits a systemic inflammatory response. The prevailing hypothesis is that exposure of blood to the foreign surfaces of the cardiopulmonary bypass circuit initiates inflammatory cascades that may impair blood-brain barrier (BBB) integrity. A pilot study that employed dynamic contrast enhancement MRI to assess BBB disruption in CABG surgery patients found evidence of postoperative BBB disruption in five of seven (71%) of the patients 1 day postoperatively, which resolved by postoperative day 5 [61]. The BBB disruption was most prominent in the frontal lobes. The location and intensity of the BBB disruption correlated significantly with postoperative decline in attention and executive functions.

Thoracic Aortic Surgery

Surgical repair of the thoracic aorta for aneurysms and dissection puts the brain at even greater risk for ischemic injury than standard open cardiac surgical procedures. When the brachiocephalic vessels that branch off of the aortic arch are being surgically attached to the aortic graft, the normal path of circulation to the brain is temporarily interrupted. Protecting the brain from ischemic injury, therefore, is one of the most critical challenges posed during thoracic aortic surgery, and the adequacy of cerebral protection is an important determinant of clinical outcome. Various neuroprotective strategies are employed to reduce the potential for cerebral ischemic injury during periods of discontinuity between the aorta and the cerebral circulation. These include hypothermic circulatory arrest (HCA), retrograde cerebral perfusion (RCP), and anterograde selective cerebral perfusion (ASCP) [62].

Cerebral hypothermia is the principal means of protecting the brain from ischemic injury during periods of reduced perfusion and circulatory arrest. In the context of cardiac and thoracic aortic surgery, hypothermia is induced using cardiopulmonary bypass; the blood (perfusate) is cooled as it passes through a heat exchanger and circulated through the body via the cardiopulmonary bypass circuit. This is known as core cooling. In order to facilitate brain cooling and prevent an upward drift of brain temperature during the period of circulatory arrest, the head may be packed in ice. This is known as surface cooling.

It is well established that cerebral ischemic insults sustained under hypothermic conditions result in less histopathology and better functional outcomes. The traditional rationale underlying the use of hypothermia is that drastically reducing the cerebral metabolic rate for oxygen and glucose preserves adenosine triphosphate levels, thereby enabling the brain to endure longer periods of ischemia, minimizing cell death and gross neurological injury. Metabolic suppression, however, is not the only mechanism underlying hypothermic neuroprotection. Temperature-sensitive secondary injury processes include excitotoxicity, free radical generation, programmed cell death, and neuroinflammation [63, 64].

The safe duration of HCA is not unlimited. In order to facilitate complex aortic repairs that would exceed the “safe” duration of HCA, two techniques have been employed for selectively perfusing the brain. In RCP blood is delivered to the brain during systemic circulatory arrest via the superior vena cava at moderate pressures (15–40 mm Hg) and drains via the carotid and vertebral arteries. Mechanisms by which RCP is proposed to reduce perioperative cerebral injury include (1) tissue perfusion that delivers oxygen

and nutrients sufficient to meet cerebral metabolic demands, (2) flushing out embolic debris, and (3) maintaining cerebral hypothermia [65]. ASCP provides blood flow at systemic pressures (50–80 mm Hg) to some or all of the brachiocephalic vessels, intermittently or continuously. During the past 15 years, more profound HCA and RCP have been employed less commonly as brain protection strategies; ASCP has emerged as the technique of choice at many surgical centers.

Most of the literature regarding neurological complications and efficacy of neuroprotection strategies in this patient population focuses on stroke outcomes, but there are a few small neurocognitive outcome studies. Longer durations of circulatory arrest (≥ 25 minutes) have been associated with worse neurocognitive outcomes [66, 67]. RCP has been found to have no beneficial effect and in fact was associated with worse cognitive outcome than HCA alone, even when controlling separately for age and cerebral ischemia time [68]. A study comparing patients undergoing CABG vs. thoracic aortic procedures with RCP < 60 min or ≥ 60 min showed that thoracic aortic procedures with long duration RCP were associated with worse neurocognitive outcome [69]. Complex thoracic aortic repairs requiring prolonged ASCP also have been associated with worse neurocognitive outcome compared to HCA [70]. It is unclear from these studies, however, whether the complexity of the repairs necessitating prolonged ASCP or RCP or the perfusion techniques themselves contributed to worse cognitive outcomes.

A study that compared patients undergoing aortic arch surgery with ASCP versus CABG surgery on brain PET, DW-MRI, proton magnetic resonance spectroscopy, and neuropsychometrics performed preoperatively, and at 1 week and 6 months postoperatively, found that ASCP was associated with significant vasogenic cerebral edema and glucose hypometabolism in the occipital lobes postoperatively [71]. At the 6-month assessment, edema resolved, but there was still evidence of hypometabolism in some patients, which was attributed to the lack of left subclavian artery perfusion during ASCP. There was, however, no evidence of ischemic brain injury or cognitive decline after ASCP.

Carotid Endarterectomy and Stenting

Carotid revascularization procedures carry a risk of perioperative ischemic stroke. They also carry a risk of cognitive decline, which is believed to reflect perioperative neurological injury of a lesser degree than stroke-inducing injuries [72–74].

The mechanisms of ischemic stroke following carotid endarterectomy (CEA) are embolism, thrombosis, or hypoperfusion. Obstructive stroke may occur if clamp placement on the diseased carotid artery dislodges plaque or if a thrombus forms in the region of the surgical repair. Hypoperfusion can occur due to temporary vessel occlusion (i.e., cross-clamping) when there is insufficient collateral circulation. Impairment of collateral circulation is likely in patients who undergo CEA, due to the prevalence of diffuse vascular disease that affects the cerebral circulation [75]. A neuroprotection strategy that is variably employed during CEA is shunting, with catheter tips placed proximal to the common carotid artery clamp and distal to the internal carotid artery clamp, preserving blood flow to the ipsilateral hemisphere. In carotid artery stenting (CAS), embolic stroke occurs when plaque material is dislodged during stenting [76]. Cerebral protection devices designed to trap the embolic material are increasingly employed to prevent distal embolization of plaque debris and thrombus formation associated with manipulation of wires and stent deployment.

Both CEA and CAS may introduce microemboli into the cerebral circulation, as detected by TCD monitoring, and produce new cerebral ischemic lesions, as revealed by DW-MRI [77–79]. CEA and CAS are also associated with cognitive decline in 10–15% of patients, with no measurable difference between the two procedures [80, 81]. Increasing age raises the risk of cognitive decline [82]. CEA patients with early cognitive dysfunction have elevated biomarkers of neuronal injury and asymmetric cerebral blood flow on

magnetic resonance perfusion brain scans [83, 84]. Neurocognitive outcome, however, has not been found to be associated with TCD-detected microembolic counts or the number or volume of new ischemic lesions on DW-MRI [80, 85, 86]. There is, however, some evidence that postoperative hypoperfusion following carotid revascularization is associated with cognitive decline [87–90].

Carotid revascularization also may result in improved hemodynamics, and in patients with impaired blood flow in the middle cerebral artery (MCA) prior to intervention, carotid revascularization is associated with improved cognitive function following the procedure [91].

Other Surgical Procedures

Perioperative stroke is rare in patients undergoing non-cardiac and non-cerebrovascular surgical procedures, with an incidence of approximately 0.1% [92]. A prospective MRI study of patients undergoing non-cardiac, non-carotid artery surgery, however, found that 10% of patients had a "covert" stroke (i.e., an imaging finding without neurological sequelae) [93]. Orthopedic surgical procedures, such as hip fracture repairs, total hip arthroplasty, and total knee arthroplasty, carry a risk of intraoperative cerebral microembolism and embolism. The most frequent etiology is embolization of fat and bone marrow during operative manipulation of bone and thromboembolism after tourniquet release.

Surgical procedures performed in the sitting or beach chair position, such as arthroscopic shoulder surgery or sinus surgery, especially when combined with induced hypotension, carry a risk of cerebral hypoperfusion when the perfusion pressure falls below a critical value, near the lower limit of cerebral blood flow autoregulation [94, 95]. A common clinical error is measuring blood pressure at the level of the thigh and failing to correct for hydrostatic pressure differences between the lower body and the brain. One study comparing patients who underwent shoulder surgery in the beach chair position versus the lateral decubitus position, however, found no differences in cognitive outcome [96].

Anesthesia

Anesthetic medications and techniques are intuitively compelling candidate causes of POCD, due to their potent effects upon neurons. This is a very active area of research, and there is a large literature summarizing the preclinical and clinical evidence regarding the capacity for anesthesia and surgery to induce or accelerate neurodegeneration [23, 97–108].

In vitro and in vivo laboratory studies have shown that general anesthetics may be neurotoxic, especially to young and older brains [109–114]. Specifically, there is evidence that some inhaled anesthetics (i.e., isoflurane and sevoflurane) precipitate or exacerbate ß-amyloid plaques, neurofibrillary tangles, and neuroinflammation, which are neuropathogical changes that occur in Alzheimer's disease. It has been hypothesized that surgery and anesthesia could either accelerate the onset of or even cause dementia, and the consensus statement from the First International Workshop on Anesthetics and Alzheimer's Disease in 2009 indicated the need for human studies to evaluate this risk [115].

The gap between the basic and clinical neuroscience evidence, however, remains large. The majority of epidemiological studies have found no relationship between history of exposure to surgery and anesthesia to the later development of Alzheimer's disease, or between a history of POCD and later development of dementia [116–125]. A large study of middle-aged and elderly twin pairs, in whom one had a history of major surgery and the other did not, found no association between exposure to surgery and level of cognitive functioning [126]. Large randomized controlled trials and a meta-analysis of 26 randomized controlled trials comparing general vs. regional anesthesia have found no difference in POCD incidence among anesthetic techniques [127–129].

Clinical Assessment of POCD

It is important for the clinician who is conducting a clinical assessment of POCD to recognize that the prospective POCD research literature is based on studies of patients who were scheduled to undergo surgery, recruited into studies, and underwent pre- and postoperative cognitive testing. Most patients identified as having POCD in research studies are asymptomatic; thus, the phenomenon of POCD as defined in the research literature is quite distinct from the population of patients who experience cognitive symptoms and present for clinical evaluation.

POCD is undoubtedly a clinical phenomenon that is anecdotally and widely reported by physicians who have noticed that some patients are "just not the same since surgery." This point was made by Bedford in the first report on adverse cerebral effects of anesthesia in the elderly in 1955, and it was the driving force for many of the early studies of POCD [130]. It is common for clinical neuropsychologists to be called upon to perform neuropsychological assessments in patients with a history of cognitive decline following surgery.

Definition of Postoperative Cognitive Decline

Postoperative cognitive decline is not an established diagnostic entity, and there are no standard diagnostic criteria. We offer here the following working definition for clinical purposes. POCD is a pre- to postoperative decline in cognitive function that is (1) temporally related to surgery, (2) syndromally distinct from postoperative delirium, and (3) not attributable to another condition.

The combination of a clinical history of abrupt decline that is temporally related to surgery *and* a pre- to postoperative cognitive test score decline would strongly support a diagnosis of POCD. Since it is uncommon to have both clinical history and objective test data for individual patients who present for evaluation, the diagnosis must often be made with less information. Research studies usually do not incorporate clinical history data. Based on cognitive test data alone, they have some "false-positive" risk of identifying *any* pre- to postoperative decline that meets the study criteria as POCD [131].

Clinical assessments, conversely, rarely have preoperative cognitive test data available as a point of baseline comparison. When cognitive test scores show evidence of a deficit relative to normative data or an estimated level of premorbid function, the clinical history may help determine whether the cognitive deficit meets the practical definition of POCD. A detailed history that includes information about the onset and course of the cognitive decline, perioperative complications (including delirium), and other neurological or systemic conditions that may be associated with cognitive decline is likely to provide qualitative information regarding the preoperative condition.

We consider below each of the criteria of our working definition of POCD and other factors that clinicians should consider when performing clinical assessments in patients who present with a history of cognitive decline following surgery.

Decline in Cognitive Function Temporally Related to Surgery

A temporal relationship between surgery and cognitive decline is most firmly established when patients undergo pre- and postoperative cognitive testing, as they do in a POCD research study. Since patients presenting or referred for clinical neuropsychological assessments following surgery typically have not undergone preoperative cognitive testing, postoperative test scores have to be interpreted relative to normative data and/or relative to estimated premorbid function for the patient. Clinical assessments of POCD also rely on a detailed history of the onset and course of cognitive symptoms in order to determine whether the cognitive decline was sudden and temporally related to the surgery.

An abrupt decline in cognitive function that is apparent soon after surgery (following the resolution of effects of analgesics and sedatives) obviously raises a suspicion of POCD. When clinical evaluations reveal both objective evidence of

cognitive deficit on postoperative testing and a history of abrupt postoperative decline, further diagnostic investigation with neuroimaging is indicated. Many surgical procedures carry a risk of cerebral ischemic injury that may justify the medical necessity of the imaging study.

Decline in Cognitive Function Distinct from Postoperative Delirium

Identification of POCD requires ruling out postoperative delirium as the cause of the current cognitive symptoms [132]. Delirium is characterized by (1) a core disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment), (2) an abrupt onset (over several hours to a few days) and fluctuating severity over the course of a day, and (3) additional disturbances in cognition (e.g., memory, language, visuospatial ability, or perception) [133].

Ruling out postoperative delirium is especially important since it occurs commonly, especially in cardiac and geriatric surgical populations. It is transient by definition but can last for days to weeks after surgery. Some cases may go undetected. This is particularly true of hypoactive delirium in which there is a normal level of psychomotor activity accompanying the disturbance in attention and awareness (i.e., mixed level of activity), and subsyndromal delirium in which some, but not all, of the core diagnostic symptoms are present.

Precipitating factors for delirium in the perioperative period include pharmacological agents (e.g., anesthetics, analgesics, sedatives), pain, infection, surgical trauma, acute metabolic disturbances (e.g., electrolyte abnormalities, anemia), organ failure (e.g., congestive heart failure, renal insufficiency), and hypoxemia [134, 135]. Risk for postoperative delirium increases with procedure complexity and duration and patient factors, such as age greater than 70 years and pre-existing cognitive impairment [134, 135].

Thus clinical neuropsychological assessments performed in patients shortly following surgery should always assess for postoperative delirium. Among the various delirium assessment scales, the confusion assessment method (CAM) is considered to be the most useful diagnostic instrument because of its accuracy, brevity, and ease of use [136, 137]. A modification of this scale for use in intensive care unit patients is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [138].

Decline in Cognitive Function Not Attributable to Another Condition

When cognitive test scores show evidence of a deficit relative to normative data or decline relative to an estimated level of premorbid function, the neuropsychologist needs to determine whether the deficit or decline is attributable to POCD or some other condition. This determination relies on a clinical history that inquires as to the onset and course of cognitive symptoms. Information should also be obtained as to whether the patient had previously experienced delirium postoperatively, as this could be a marker for occult brain disease. We now examine these in greater detail.

Onset and Course of Cognitive Symptoms

The presence of cognitive symptoms predating the surgery raises the possibility that the pre- to postoperative decline in cognitive function is related to a condition that was present presurgically, rather than as a consequence of the surgery. Preoperative cognitive symptoms are common in surgical, especially geriatric and cardiac, patients. Mild cognitive impairment (MCI) has a prevalence of 14 to 18% in non-demented, community-living elders aged 70 years and older [139]. In geriatric surgical patients, Alzheimer's disease and cerebrovascular disease are the most likely causes of preoperative cognitive deficit, but alcohol-induced neurocognitive disorders also are common. Cardiac surgical patients often have mild preoperative cognitive deficits relative to healthy age-matched peers and published normative test data [140, 141]. In this patient group, preoperative cognitive deficits are associated with cerebral

ischemic lesions, reduced cerebral blood flow, and vascular health status/risk factors [142–145].

The presence of cognitive symptoms predating the surgery, however, does not exclude the possibility of POCD, and it may increase vulnerability to surgically related declines. Pre-existing brain pathology, such as medial temporal lobe atrophy, white matter lesions, cerebral infarction, and cerebral hypoperfusion, are all associated with increased risk for POCD [146–151]. Surgical patients with CSF $A\beta_{[1–42]}$ levels below the cut point for Alzheimer's disease have a higher incidence of POCD 3 months postoperatively, compared to patients with normal levels [152]. Conditions that may be considered markers for probable brain pathology, such as alcohol abuse and cognitive impairment, are also associated with increased risk for POCD [153–155].

In cases with a history of cognitive symptoms prior to the surgery, progression of pre-existing cerebral pathology can be mistaken for a postoperative cognitive decline. Knowledge of the cognitive trajectory following surgery, as determined by the clinical history and/or longitudinal postoperative cognitive testing, can aid in determining whether the cognitive decline may be attributable to surgery. A static or gradually improving course is consistent with POCD, whereas a gradually progressive course of cognitive decline following surgery is a distinct progressive condition. Information about the *preoperative* cognitive trajectory also can be informative, because patients who have declining trajectories before surgery are more likely to have declining trajectories after surgery [156].

Many studies of POCD have examined cognitive function at multiple times postoperatively. These studies usually report the incidence at each time point, without examining the course of POCD within individual patients. A long-term follow-up study in a subgroup of ISPOCD study patients found that 10.4% met the operational definition of "POCD" 1–2 years following surgery, but only 0.9% did so consistently at all three postoperative time points (1 week, 3 months, and 1–2 years) [157]. This is a robust finding that is highly unlikely (1 in 64,000 chances) to have been a random finding. Thus, in some patients, POCD does not resolve.

There is neither good evidence nor reason to believe that surgery or anesthesia causes *progressive* neurocognitive decline. While long-term neurocognitive outcome studies in cardiac surgical patients have observed progressive declines in cognitive test scores over the course of years following surgery [158], these declines can be fully accounted for by progressive cerebrovascular disease. Studies comparing cardiac surgery patients to nonsurgical control groups such as patients with coronary artery disease (CAD) treated with medication or coronary angioplasty have demonstrated comparable long-term progressive cognitive declines that exceed those of healthy control subjects without CAD [159–164]. Similarly, studies in non-cardiac surgical patients have shown that long-term cognitive decline is not attributable to surgery [157, 165]. Thus, with increasing time after surgery, cognitive test data may be increasingly confounded by the effects of aging, age-related brain disease, and new medical problems.

History of Postoperative Delirium

Postoperative delirium is a risk factor for the development of dementia [166]. In cognitively intact elderly orthopedic surgery patients, those who developed postoperative delirium had a much higher incidence of dementia 5 years after surgery, compared to those who did not develop postoperative delirium (69% versus 20%) [167]. Some have interpreted this association as evidence that delirium triggers a dementing process, but the alternate interpretation that postoperative delirium is a flag for a subclinical dementing process seems much more likely.

Cognitive impairment and brain pathology predispose patients to developing delirium precipitated by any cause. The precipitating causes of delirium are the same for patients with and without cerebral compromise, but the former group has a lower threshold of tolerance and a higher vulnerability for delirium.

Studies of postoperative delirium have also found that preoperative cognitive impairment and brain pathology increase risk. In older adults who underwent elective orthopedic surgery, greater late-life cognitive reserve (i.e., engagement in intellectually challenging activities) was associ-

ated with lower delirium incidence [168]. In patients who underwent total hip/knee replacement under spinal anesthesia, those with biomarkers for Alzheimer's disease (low CSF ß-amyloid/tau ratios) had the highest incidence of delirium [169]. Surgical patients with preoperative diffusion tensor imaging abnormalities of several brain structures have a higher incidence and greater severity of postoperative delirium, compared to patients without such abnormalities [170].

Since postoperative delirium may be a marker for preclinical or unrecognized brain pathology and neurocognitive impairment that was present preoperatively, we recommend that all patients who develop postoperative delirium should be referred for neuropsychological assessment after the delirium clears. This assessment should be performed after hospital discharge and recovery from surgery.

Test Selection

The neuropsychological test battery employed for assessment of POCD should contain sensitive indicators of cerebral dysfunction consistent with neurocognitive processing models, have documented reliability and diagnostic validity, and be suitable for repeated administration. Test battery design and test selection should be driven by hypotheses regarding the underlying pathological processes and/or cerebral localization of the putative injury.

The POCD test battery should minimally include tests of episodic memory, working memory, and cognitive processing speed. Tests of episodic memory are essential, since the hippocampus is highly vulnerable to transient cerebral ischemia. Memory is particularly vulnerable to decline in older surgical patients, even when test performance in other cognitive domains is preserved [171]. Tests of working memory and processing speed are also essential, as these cognitive processes are most prominently affected by injury to the deep cerebral white matter.

The test battery must also test hypotheses regarding cognitive impairment that was present *prior* to surgery. Due to shared risk factors, patients who underwent cardiac, thoracic aortic, or carotid artery procedures could have vascular cognitive impairment due to occult subcortical small vessel ischemic disease [172]. Similarly, in geriatric surgical patients with a history of preoperative cognitive symptoms, symptoms present postoperatively could be due to Alzheimer's disease, the most common cause of age-related cognitive impairment.

Occasionally, perioperative stroke may result in a circumscribed neurocognitive deficit. In these cases, the history of signs and symptoms will guide test selection. The functional localization and affected vascular territory should be consistent with the putative etiology. For example, embolic injury due to carotid artery revascularization would be expected to affect the MCA or a branch of the MCA, since the MCA is a direct extension of the internal carotid artery and it carries the majority of anterior circulation blood flow. Cases of circumscribed cognitive deficits with acute onset that are temporally related to surgery should also be investigated by neuroimaging.

Additional Considerations

A temporal relationship between a surgical episode and cognitive decline does not prove a causal relationship. Some patients referred for neuropsychological assessment of POCD may have cognitive decline that is factitious or an erroneous self-diagnosis.

In the case of factitious cognitive decline, patients or their representatives may be considering medical malpractice litigation or applying for disability benefits. The examining neuropsychologist must be aware that, given the potential for secondary gain, some subset of these patients may be motivated to exaggerate or feign symptoms of cognitive impairment. Therefore, neuropsychological examinations for POCD should include assessment of symptom and performance validity.

Surgery is a major health event, and the general public is aware of the potential dangers of anesthesia, as well as surgery. Patients who present for neuropsychological assessment because of complaints of cognitive impairment following surgery

often explicitly voice concerns that anesthetic agents and techniques have harmed their brains. Their concerns and expectations may be fueled by unsubstantiated claims, often published on the Internet, of causal associations between general anesthesia and memory loss or Alzheimer's disease. This has been documented in a study of patients who expressed such concerns in preoperative anesthesia consultation [173]. These concerns are not unique to the Internet age, however. Bedford in 1955 noted that "Patients and family members may misattribute cognitive symptoms to surgery rather than covert disease processes that began prior to surgery." [130]

Subjective complaints of cognitive decline following surgery must be substantiated by objective and quantitative neurocognitive test data. Many patients who present with such subjective complaints are found to have normal cognitive function upon neuropsychological examination [174]. A frequent occurrence is that patients who have clinical depression subjectively experience what they perceive as cognitive impairment. In patients 40–60 years of age, subjective complaints of cognitive impairment persisting 3 months postoperatively that occur in the absence of objective psychometric evidence of POCD have been positively associated with depression [175].

Conclusion

The research literature substantiates that POCD occurs commonly during the early weeks and months following non-neurological surgery. It usually resolves, and it is not progressive. The etiology is multifactorial. Older surgical patients are at greatest risk. We recommend performing neuropsychological assessments in all patients with a history of cognitive decline following non-neurological surgery.

Clinical Pearls

- Patients presenting to their physicians with concerns of cognitive decline following surgery should be referred for formal neuropsychological examination.
- Subjective complaints must be carefully investigated and substantiated by objective, quantitative neurocognitive test data.
- A firm diagnosis of POCD requires that postoperative delirium has been ruled out or has resolved.
- Neuropsychological assessment for POCD should be performed well after surgery in order to limit potential confounding factors, such as pain, current use of analgesics and sedatives, and sleep disturbances.
- The clinical history must probe (1) the onset and course of the cognitive decline; (2) perioperative complications, including delirium; and (3) other neurological or systemic conditions that may be associated with cognitive decline.
- The test battery should address the established and putative underlying mechanism(s) of cerebral insult and should employ tests that are suitable for repeated administration.
- A history of abrupt decline in cognitive function immediately following surgery should be investigated by neuroimaging studies.
- Abrupt onset followed by a static or resolving postoperative course is consistent with POCD, but a progressive course is not. Longitudinal postoperative cognitive testing may be used to objectively determine the course.
- In many cases, additional assessment of depression and/or symptom and performance validity may be warranted.

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Substance Related Cognitive Dysfunction in Aging

19

Dora Kanellopoulos and Pablo Sanchez-Barranco

Background

The population of older adults is expected to rise considerably as baby boomers age [1]. Although historically, older adults tend to have equal or lower rates of substance use disorders than younger adults [2, 3], among aging baby boomers, the prevalence of substance use disorders is high [2]. Furthermore, the overall number of older adults with substance use disorders is expected to more than triple from 2009 to 2020 [4, 5, 163]. Despite this dramatic projection, stereotypes and aging-related stigma often contribute to under-identification or misdiagnosis [2, 3] of substance use disorders in this population.

Older adults are particularly sensitive to the effects of psychoactive substances due to neurocognitive, metabolic, and physical changes during this stage of life [6]. As a result, substance use in the elderly can give rise to transient cognitive dysfunction (e.g., delirium), worsening of existing neuropsychiatric disorders, or new neurocognitive impairments [6]. However, clinicians frequently attribute substance-related symptoms to dementia, depression, anxiety, or other common aging-related medical problems [2]. Misidentifying problematic substance use could lead to a delay in appropriate treatment.

Neuropsychologists are uniquely positioned to identify and characterize the influence of substance use on cognitive function. Accurate assessment has the potential to distinguish and address reversible causes of cognitive impairment, enhance the probability of successful participation in cognitive rehabilitation programs, and dramatically improve patients' recovery and functional outcomes [7–9].

The initial approach to neuropsychological examination should include a cognitive screening instrument to briefly assess overall cognitive functioning. Instruments with established reliability and validity in this population include the Montreal Cognitive Assessment (MoCA) [10, 11], the screening module of the Neuropsychological Assessment Battery (NAB) [10, 12], and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [13]. These screening instruments are particularly useful when patients are acutely intoxicated or are still experiencing the effects of withdrawal at the time of assessment. Screening for cognitive dysfunction at the onset of treatment could alert clinicians to foreseable substance treatment adherence barriers [14] and help to tailor interventions for the patient's level of cognitive functioning and type of cognitive difficulties. More extensive neuropsychological evaluations are likely to be useful when a period of

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abstinence has been established (see Table 19.1 for recommended battery).

Once the use of substances is established, although tempting to attribute cognitive impairments to substance use, it is also important to consider medical conditions (which in many cases are secondary to substance misuse). For example, alcohol use could result in cirrhosis of the liver and subsequently to hepatic encephalopathy; brain injury (i.e., subdural hematomas, axonal injuries) could result from falls or car accidents related to intoxication; chronic seizures resulting from withdrawal could adversely impact cognition; communicative diseases due to shared substance use (e.g., HIV, hepatitis C) could have neurocognitive implications. Finally, psychiatric conditions (e.g., bipolar disorder, depression) are highly comorbid with substance use disorders and should be screened for in a neuropsychological assessment.

Among older adults, the most frequently misused substances include alcohol and prescription medications (e.g., benzodiazepines and non-benzodiazepine hypnotics) [17]. Due to the metabolic effects of these substances, the potential for addiction, and drug interaction effects, alcohol and prescription medications frequently contribute to neurocognitive impairments that precipitate a neuropsychological consultation. This chapter therefore focuses on the neurocognitive assessment of alcohol, benzodiazepine, and opioid use in older adults and includes characterization of the neurocognitive dysfunction that follows varying lengths of use and states of abstinence.

Part I. Neuropsychological Assessment of Older Adults with Alcohol Use Disorders

In order to ascertain the impact of substance use disorders on cognition, it is important to obtain a detailed history of current and previous alcohol use, as well as prescribed and non-prescribed medications. Pertinent information includes total daily dose, pattern of use, duration of exposure, the presence of periods of abstinence or discontinuation of use, and specifics regarding last and most recent use. Verifying use with collateral sources of information is recommended whenever possible, as cognitive impairment may influence patient tracking of use [2].

Screening for the Presence of Alcohol Use Disorder in the Elderly

Prevalence and Risk Factors

Alcohol use disorder may develop at any point in the lifespan. Although many patients present with lifelong chronic alcohol use disorder, some patients report first onset of problematic drinking in late life in the context of major psychosocial stressors [18]. Among community-dwelling elderly adults, 15.4% have symptoms of alcohol use disorder [7] and 6% report heavy drinking (> 2 drinks per day). Up to 30% of all older medically hospitalized patients and 50% of psychiatrically hospitalized elders have comorbid alcohol use disorder [19].

Risk factors associated with alcohol use disorder in older adults specifically, include being Caucasian, an older male [7–9], or divorced or widowed [20], as well as experiencing chronic pain, physical disabilities, poor overall health, social isolation, bereavement, affluence, and unexpected/forced retirement [21]. Among older women, financial strain is a risk factor for heavy drinking [22]. Notably, women who first begin to increase their alcohol use after the age of 50, intensify intake considerably within a short period of time [23]. Furthermore, older adults post-bariatric surgery are at increased risk for developing alcohol use disorders [24]. These important demographic and psychosocial variables should be assessed through clinical interviews with the patient and collateral sources whenever available.

Identification and Diagnosis of Alcohol Use Disorder

Symptoms of alcohol use disorder in older adults can be mistaken for depression or dementia. Since older adults have lowered tolerance for alcohol, they are also more likely to experience delirium during withdrawal or intoxication periods [25]. Furthermore, symptoms of alcohol use

Table 19.1 Recommended neuropsychological battery for late-life substance use disorders

Stand-alone screening instruments
Montreal Cognitive Assessment (MoCA)
Screening Module Neuropsychological Assessment Battery (NAB)
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Pre-morbid functioning
ACS Test of Premorbid Functioning (TOPF)
Wechsler Test of Adult Reading (WTAR)
General cognitive functioning
Dementia Rating Scale- 2 (DRS-2)
Wechsler Abbreviated Scale of Intelligence – II (WASI-II)
Attention/Working memory
Wechsler Adult Intelligence Scale – IV (WAIS-IV) Digit Span Subtest
Symbol Digit Making Test
Processing speed/Executive function
Clock Drawing Test
DKEFS Verbal Fluency/Controlled Oral Word Association Test
DKEFS Trails/Trails A & B
DKEFS Tower Test/Tower of London Test
Wisconsin Card Sort Test
WAIS-IV Similarities/WASI-II Similarities
Visuospatial function
Clock Copy
Rey-Osterrieth Complex Figure Copy
Judgment of Line Orientation
WAIS-IV Block Design/WASI-II Block Design
Brief Visuospatial Memory Test Revised (BVMT-R)- Copy Condition
Learning and memory
California Verbal Learning Test-II (CVLT –II)
Brief Visuospatial Memory Test-Revised
WMS-IV Logical Memory (Older Adult Version)
Three Words Three Shapes (for suspected amnestic disorders)
Rey-Osterrieth Complex Figure Test
Language
NAB Language Module
BDAE Boston Naming Test
BDAE Commands
BDAE Sentence Repetition
WAIS-IV Vocabulary/WASI-II Vocabulary
Motor function
Purdue Pegboard
Luria Sequences
Apraxia Exam
Emotional function
Beck Depression Inventory-II (BDI-II)
Beck Anxiety Inventory (BAI)
Substance use assessment
Short Michigan Alcoholism Screening Instrument-Geriatric Version (SMAST-G) [15]
CAGE- Adapted to Include Drugs (CAGE-AID) [16]

disorder may mimic medical comorbidities associated with aging (e.g., gastrointestinal problems, falls) [26]. Due to the frequency of multiple comorbidities, clinicians should screen for alcohol use disorder in patients with psychiatric (e.g., depression, sleep disturbance, anxiety) and cognitive (e.g., confusion, memory) complaints that present along with medical illness (e.g., heart, liver, kidney, and gastrointestinal diseases or nutritional deficiencies) [26, 27].

Screening for alcohol use disorder can begin by asking a single question which has been found to identify alcohol abuse or dependence with high sensitivity and adequate specificity: "On any single occasion in the past 3 months have you had more than 5 drinks containing alcohol?" [28] Formal questionnaires that can be used to further identify the presence of a syndrome and characterize severity of use include the CAGE (acronym of four questions) and Alcohol Use Disorders Identification Test (AUDIT-C) questionnaires or the Short Michigan Alcoholism Screening Instrument – Geriatric Version (SMAST-G) [15, 29, 30].

While problematic drinking is defined as alcohol use resulting in adverse medical, psychological, or social consequences, alcohol use disorder is generally defined as chronic problematic and compulsive use of alcohol, loss of control over alcohol intake, and a negative emotional state when not using alcohol. Formal diagnosis of alcohol use disorder includes meeting two of eleven criteria outlined in the DSM-5 (Tables 19.2 and 19.3), and diagnostic modifiers of mild, moderate, or severe are given based on the number of criteria met [31].

Table 19.2 DSM-5 criteria for alcohol use disorder: if the answer is "yes" for two or more of the below questions, then patients meet criteria for alcohol use disorder

In the past year have you:	
Had times when you ended up drinking more or longer than you intended?	Y/N
More than once wanted to cut down or stop drinking, or tried to, but couldn't?	Y/N
Spent a lot of time drinking? Or being sick or getting over after effects?	Y/N
Wanted a drink so badly you couldn't think of anything else?	Y/N
Found that drinking – or being sick from drinking – often interfered with taking care of your home or family? Or caused job trouble?	Y/N
Continued to drink even though it was causing trouble with your family or friends?	Y/N
Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?	Y/N
More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?	Y/N
Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?	Y/N
Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?	Y/N
Found that when the effects of alcohol were wearing off you had withdrawal symptoms such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	Y/N

Alcohol Use Disorder and Neurocognitive Impairment

Characteristics related to alcohol use, such as chronicity and patterns of use, contribute to variations in cognitive function. Chronic moderate to severe alcohol users have increased risk of alcohol-induced neurocognitive impairments [32], and this risk is potentiated in older adults [33]. Whereas moderate drinking has been found by some to confer neuroprotection [34, 35], binge drinking as well as the amount of recent rather than lifetime alcohol use may contribute to greater cognitive deficits [36, 37]. Neuropsychological profiles and neurological symptoms are therefore varied according to use patterns and chronicity [33, 38, 39].

Patients with neurocognitive impairments related to alcohol use are, on average, 10 years younger than patients with other dementia syndromes and exhibit milder and more stable cognitive impairments [40]. The impact of alcohol use on neurocognitive functioning may be greater in older versus younger adults [41].

Table 19.3 Neuropsychological impairments in alcohol use

	Neurocognitive impairments		
	Chronic use		Abstinence
	Amnestic profile	Dysexecutive profile	
Alcohol	Confusion Global cognitive impairment Severe anterograde amnesia Retrograde amnesia that is temporally graded Visuospatial impairments Visual working memory Executive dysfunction Higher-order organization Planning and cognitive flexibility	Executive dysfunction Working memory Mental flexibility Divided attention Decision making Problem solving Prepotent response inhibition Verbal abstract reasoning Episodic Memory* Encoding and retrieval impairment Intact storage (in non-amnestic patients) Visuospatial function Visuospatial processing Visuospatial learning and memory Visuoconstruction Visual organization	Slow recovery of visuospatial, working memory, and motor functions

* Secondary to the effects of executive dysfunction or related to hippocampal/ mammillary body atrophy

Therefore, later initial onset of alcohol use disorder [42] may result in greater than expected neurocognitive impairments, even in the absence of chronicity of use.

Challenges exist in identifying and diagnosing alcohol-related neurocognitive decline in older adults. Specifically, clinical symptom overlap with other syndromes, variability in the relationship between cognitive and behavioral symptoms, and lack of uniform postmortem histopathology [43, 44] can confound accurate diagnoses. Alcohol-related neurocognitive impairments may be distinguished from other late-life cognitive syndromes (e.g., those of Alzheimer's and vascular etiologies) [38] by the course of symptom progression, as the tendency of alcohol-related neurocognitive impairments is to stabilize or improve with abstinence.

Neuroimaging of chronic alcohol users often reveals alterations in frontal lobe structure and function [45–48]. Older adults are particularly vulnerable to these effects, as aging differentially influences the frontal lobes [49, 50]. Although the frontal lobes are particularly susceptible [51], neurons in other areas of the brain including the corpus callosum, hypothalamus, and cerebellum are often compromised as well [52, 53]. With abstinence, partial structural recovery (i.e., white matter) may occur, possibly through restoration of myelination [36], and can be observed via clinical improvement in cognitive and motor function [36, 54].

The neurotoxic effects of alcohol may be related to thiamine deficiency, neurovascular or neuroimmune injury, or metabolic dysfunction [55]. Severity of cognitive impairment has also been linked to neuronal damage sustained through multiple episodes of withdrawal from alcohol, with greater degree of cognitive impairment in those that have more than one detoxification [56]. Similarly, repeated binge drinking and withdrawal promote neuronal injury [57, 58].

Neuropsychological Profiles

The new classification system of the DSM-5 now defines alcohol-related cognitive impairment as neurocognitive impairment with an etiological subtype qualifier of substance and/or medication use-related impairment [39]. Qualifiers are given for mild (1–2 standard deviation (SD) decline

from prior functioning) or major (>2 SD decline from prior functioning).

Heuristically, alcohol-related cognitive profiles can be defined as consisting of (1) primary amnestic impairments with additional deficits across multiple domains secondary to chronic use of alcohol and (2) executive deficits with no impairment of memory and without global cognitive dysfunction, or a dysexecutive syndrome with memory impairments in the context of no global cognitive decline [59–65].

Amnestic Profiles

Twelve to 14% of individuals who misuse alcohol will be diagnosed with Wernicke encephalopathy [66] an acute condition secondary to combined effects of alcohol-related thiamine deficiency and neurotoxicity. Diagnosis typically involves observation of the "classic triad" of neurological symptoms: ophthalmoplegia (i.e., weakness of muscles that control eye movement), gait ataxia, and marked confusion. However, patients often present with only one or two neurological symptoms [27], and older adults presenting with confusion may be misdiagnosed with delirium. Wernicke's encephalopathy is therefore often under-identified, prolonging thiamine deficiency and resulting in persistent confusion [27, 67].

Among patients with untreated Wernicke encephalopathy, approximately 80–90% will develop Korsakoff's syndrome, a mostly irreversible dementia characterized by severe progressive retrograde and anterograde memory impairment [68, 69]. In Korsakoff's syndrome, retrograde amnesia is temporally graded [70]. Visuospatial deficits [71], poor visual working memory [72], and executive dysfunction are also commonly observed [73, 66, 69, 74]. Among executive functions, higher-order organization, planning, and cognitive flexibility (i.e., verbal fluency, divided attention) are most commonly impacted [66, 75, 76]. Implicit memory is relatively spared in comparison.

Dysexecutive Profiles

Frontal lobe dysfunction is common among chronic or severe alcohol users [77]. The resulting impact on executive function is variable depending on the severity, and the pattern of additional cognitive deficits may also vary. These patients often present with different degrees of attention [63, 78, 79], visuospatial (i.e., clock drawing, design copy) working memory, mental flexibility, divided attention, decision making, problem solving, and response inhibition impairments relative to controls [80, 81]. Deficits in fine motor dexterity and speed [80], as well as verbal abstract reasoning [81], and on letter fluency tasks have been documented [80]. Consistent with executive dysfunction, memory deficits are characterized by encoding and retrieval difficulties but intact storage [80, 81]. Behaviorally, patients typically exhibit elevated perseverative errors and reduced initiation abilities [80]. Notably, general intelligence, vocabulary, general knowledge, and implicit memory appear to be intact in contrast to controls.

In evaluating differential diagnoses, when compared with to neurocognitive syndromes other etiologies (e.g., those of Alzheimer's or vascular etiologies), alcohol-related neurocognitive impairment differs in severity and pattern of performance on neuropsychological measures [38]. Relative sparing of language functions occurs [43, 55], particularly in semantic tasks (e.g., confrontation naming, category fluency, general knowledge) [57]. Recognition memory is typically impaired in patients with Alzheimer's disease, whereas patients with alcohol-related neurocognitive impairment perform similar to controls on these tasks despite verbal learning and delayed recall patterns that are similar to patients with Alzheimer's disease [80].

Abstinence and Recovery of Cognitive Function

Abstinence from alcohol use may result in time-related improvements; the longer the length of abstinence, the greater the cognitive improvements regardless of lifetime use patterns [32]. Abstaining from alcohol for at least 1 week results in resolution of many of the acute cognitive impairments observed in heavy alcohol use. With further abstinence, cognitive improvements may occur over the course of several years. The rate of recovery of cognitive functions may differ according to domain of functioning. For instance, dysfunction of work-

ing memory, executive, visuospatial, and motor functions may recover at a slower rate than verbal deficits [32, 51].

The pattern of abstinence-related cognitive recovery is slowed in older adults [32]. One way to distinguish alcohol-related neurocognitive impairments from common neurodegenerative processes in late life is to examine cognitive functioning after long-term abstinence (i.e., greater than 6 months, to years). While alcohol-related neurocognitive impairments will stabilize or improve with abstinence, patients with Alzheimer's or vascular dementia will continue to experience cognitive decline [38, 82, 83].

Implications for Alcohol Rehabilitation Treatment

Alcohol-related cognitive impairments can interfere with engagement in addiction recovery programs [32]. Older adults with alcohol use disorder are more likely to experience alcohol-related changes in cognition [84, 85]. Abstinence-focused treatment may confer cognitive improvements; however, the presence of cognitive impairment reduces the ability of patients to benefit from traditional alcohol treatment programs [86]. Inpatient abstinence-based programs can support older adult abstinence and thereby contribute to improvements in cognitive function while addressing common medical comorbidities.

Neuropsychological examination should lead to recommendations for ongoing monitoring of nutritional deficiencies and restricting availability of alcohol in order to reduce the possibility of acute states of confusion and/or delirium. Psychiatric treatment may also be needed to address behavioral or psychological symptoms secondary to alcohol-related neurocognitive impairments, and higher levels of supervision should be recommended for severe cases [18].

Conclusion

Differentiating alcohol-related neurocognitive impairment from other neurodegenerative illnesses of late life is challenging. A thorough clinical interview should focus on identifying problematic use in older adults while being mindful of clinician biases to refrain from asking older adults questions related to alcohol misuse. During the formal assessment, the presence of chronic and heavy misuse history, along with greater visuospatial, motor, and executive impairments with relatively spared language functions, is suggestive of alcohol-related cognitive dysfunction. A pattern of relatively intact remote memory versus impairments in short-term learning and memory may be indicative of cognitive deficits consistent with Wernicke-Korsakoff syndrome. Abstinence from alcohol often results in improvement of alcohol-induced neurocognitive dysfunction and may help differentiate alcohol-related cognitive impairments from other neurodegenerative disorders in late life. While abstinence from alcohol may reverse many, but not all, cognitive impairments in younger adults, in older adults, impairments may be not be as easily reversible, further complicating differential diagnosis and treatment in older patients with alcohol use disorders.

Clinical Pearls

- Older adults with alcohol use disorder are at risk of greater and more stable cognitive impairments than younger adults.
- Alcohol use disorder may first present in late life, and an absence of a lifetime history does not eliminate the possibility of a current use disorder.
- Patients with established drinking histories and confusion, ophthalmoplegia, or gait ataxia should be evaluated for Wernicke's encephalopathy and immediate treatment with B vitamins.
- Neuropsychological dysfunction secondary to alcohol use disorder (i.e., likely Wernicke-Korsakoff syndrome) includes a prominent amnestic and dysexecutive profile.
- Alternate and more commonly occurring patterns of neurocognitive dysfunction include prominent executive function deficits of varying degree, in the context of intact global cognitive function. Neuropsychological profiles

of these patients can include some combination of visuospatial deficits and encoding and retrieval difficulties, in the context of intact language and recognition abilities.
- In contrast to other late-life neurocognitive disorders, which tend to be progressive, alcohol-related cognitive impairments are relatively stable when use is discontinued and may even improve with abstinence from alcohol.
- Alcohol-related cognitive impairments may hinder addiction recovery efforts and worsen medical comorbidities, resulting in poor outcomes for older adults.

Part II. Neuropsychological Assessment of Older Adults with Prescription Medication Use Disorders

Benzodiazepine Use

Despite the potential for addiction, prescription benzodiazepines are the most common therapeutic intervention for insomnia and anxiety in the elderly [87]. Prescription of benzodiazepines persists despite consensus that behavioral rather than pharmacological modalities should be the first line of treatment for these disorders [88, 89]. Identification of benzodiazepine misuse in older adults is paramount, as it may lead to additional adverse consequences including repeated falls, motor vehicle accidents, cognitive decline, and higher mortality [90–94]. Notably, the rates of benzodiazepine use in older adults may be impacted by overprescription, misdiagnosis, or polypharmacy rather than volitional misuse or abuse [95].

Prevalence and Risk Factors

Annual prevalence of benzodiazepine use in adults over 65 years old is estimated to be 8.7% [96], although some have reported rates as high as 41% [97]. Non-psychiatrists issue the vast majority of prescriptions [96] and, in one-third of the cases, for longer periods than recommended [98]. Older age, female gender, a declining state of health, acute bereavement, and institutionalization all increase the probability of receiving a prescription [96].

Age-related pharmacokinetic and pharmacodynamic changes [99, 100] increase susceptibility to benzodiazepine-induced cognitive deficits, which clinicians often misattribute to other neuropsychiatric conditions [5]. Furthermore, older adults rarely endorse substance use problems [5] and tend to overestimate the therapeutic benefits associated with benzodiazepine use [101]. Consequently, diagnosing benzodiazepine use disorders among the elderly is difficult but crucial, especially among adults presenting with neuropsychiatric symptoms [102].

Among risk factors for benzodiazepine use, female gender, use of more than one agent, prescription misuse, involvement of multiple prescription providers, history of premature requests for refills, exaggerated fear of impairment with missed dose, history of substance use disorder, multiple falls, or motor vehicle accidents should alert clinicians to the possibility of benzodiazepine misuse [101, 103, 104]. Behaviorally, indicators for potential problematic use of benzodiazepines may include disinhibited or aggressive behavior as well as accidents and interpersonal difficulties. Verification of the patient's history through collateral informants is critical, as poor insight and cognitive impairments may compromise the value of self-reports [3].

Identification and Diagnosis of Benzodiazepine Use Disorder

Problematic use of benzodiazepines among older adults may require imminent intervention due to the unique medical risk these substances pose to older relative to younger adults [5]. Even short-term use at prescribed doses may be associated with increased risk of falls or deficits in cognitive function, as benzodiazepine metabolism decreases with age. Notably, benzodiazepine-induced dysfunction is not always apparent to the patient and therefore seldom self-reported [105] [106] [107]. This lack of awareness often contributes to multiple falls and accidents before the patient is evaluated.

DSM-5 diagnostic criteria for sedative, hypnotic, or anxiolytic use disorder can be found in Table 19.3; however, older adults may not formally meet DSM-5 criteria due to reduced social and work responsibilities owing to retirement. As such, others have suggested that in regard to characterizing substance use in older adults, a system of identifying level of risk in use should be used instead (Tables 19.4 and 19.5) in order to adequately capture problematic use in older adults that do not formally meet DSM-5 criteria.

Table 19.4 DSM-5 criteria for sedative, hypnotic, or anxiolytic use disorder: if the answer is "yes" for two or more of the below questions, then patients meet criteria for sedative, hypnotic, or anxiolytic use disorder

In the past year have you:	
Taken benzodiazepines in larger amounts or over a longer period than was intended?	Y/N
More than once wanted to cut down or stop taking benzodiazepines, or tried to, but couldn't?	Y/N
Spent a lot of time in activities needed to obtain benzodiazepines? Or being sick or getting over after effects?	Y/N
Wanted to take a benzodiazepine so badly you couldn't think of anything else?	Y/N
Found that taking benzodiazepines – or being sick from taking them – often interfered with taking care of your home or family? Or caused job trouble?	Y/N
Continued to take benzodiazepines even though it was causing trouble with your family or friends?	Y/N
Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to take benzodiazepines?	Y/N
More than once gotten into situations while or after taking a benzodiazepine that increased your chances of getting hurt (such as driving, swimming, using machinery)?	Y/N
Continued to take benzodiazepines even though it was making you feel depressed or anxious or adding to another health problem?	Y/N
Had to take much more benzodiazepine than you once did to get the effect you want? Or found that your usual dose of benzodiazepines had much less effect than before?	Y/N
Found that when the effects of benzodiazepines were wearing off you had withdrawal symptoms such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	Y/N

Table 19.5 Categorizing substance use in older adults who may or may not meet DSM-5 criteria for substance use disorder [5]

Level of use	Characteristics
Abstinence	No use of benzodiazepines
Low-risk use	Only appropriate/prescribed use of prescription medications
High-risk/ hazardous use	Intentional or unintentional off-label use of prescription or over-the-counter medications; taking medication, even intermittently that is not prescribed for that person
Problematic use	Substance use resulting in social/ medical/psychological consequences regardless of quantity/frequency of use

Table 19.6 Classification of benzodiazepines by half-life [109]

Half-life	Benzodiazepine name
Short-acting (<10 h)	Alprazolam Triazolam Temazepam
Intermediate-acting (10–15 h)	Lorazepam
Long-acting (>15 h)	Diazepam Clorazepate Clonazepam Chlordiazepoxide

Neuropsychological Profile

Acute Use

Acute benzodiazepine use results in neurocognitive effects that may influence neuropsychological performance. Identification of the specific agent and time of last dose are important factors in determining impact of these medications on test performance [108].

Benzodiazepines are classified according to their half-life into short-, intermediate-, or long-acting compounds (Table 19.6) [109]. Sedation and psychomotor delay are the most common manifestations of acute benzodiazepine use [110], reflecting a dose-dependent GABAergic effect on the central and peripheral nervous system [111, 112]. The enhancement of GABA neurotransmission may also cause behavioral disinhibition [113] or motor symptoms including slurred speech or poor coordination [31]. As such, if slowed psychomotor functioning or disinhibited/impulsive behavior is noted on exam,

patients should be asked to withhold benzodiazepine dosing, if possible, prior to subsequent test sessions to help determine medication influence on test performance.

Depending on the type of agent, acute benzodiazepine exposure can result in impairments of new learning, processing speed, attention, language comprehension, and executive function [108, 110, 114]. Benzodiazepines can also disrupt memory consolidation, thereby resulting in anterograde amnesia [115], which is most prominent with short-acting, high-potency agents such as alprazolam, and with parenteral use [116–119]. Benzodiazepines, however, do not cause retrograde amnesia [120–123] and may in some cases actually facilitate retrograde retrieval by ameliorating anxiety [123, 124].

Selective and sustained attention is vulnerable to the effects of acute short- and intermediate-acting benzodiazepine (e.g., alprazolam, clonazepam) use [110, 117]. Divided attention is also affected by short-acting [125], but not long-acting, benzodiazepines [126].

Prolonged/Long-Term Use

Long-term use of benzodiazepines may lead to cognitive dysfunction. Although methodological differences and the paucity of research in this area limit definite conclusions, studies to date suggest that extended benzodiazepine use impairs function across several cognitive domains [127]. Specifically, chronic use detrimentally affects information processing speed, psychomotor speed [128–130], motor coordination [131, 132], encoding, attention, arousal, and nonverbal memory [112, 107, 118, 133, 134]. However, some have noted that vigilance and attention deficits may be secondary to impairments in integration of sensory and fine motor functions [132].

One of the most consistent cognitive findings is that long-term benzodiazepine use is related to deficits in visuospatial functions. Significantly impaired visuomotor and visuospatial abilities, relative to controls, were reported in multiple trials of patients with a history of long-term benzodiazepine use [135–137]. Even past long-term use of benzodiazepines has been linked to impaired visuospatial ability [135]. This is a finding that is unique to chronic and not short-term users, suggesting long-term exposure may permanently affect visuospatial functions.

Long-Term Use and the Risk of Dementia

In older adults, increased cognitive decline has been reported with long-term benzodiazepine use. Specifically, the association between long-term benzodiazepine use and dementia has been extensively investigated [138]. Results of these studies suggest a relationship between prolonged benzodiazepine exposure and subsequent development of irreversible cognitive impairment [104, 139–144] [145–147] [148–150]. Although the neuropathology underlying this relationship is still a topic of investigation, some suggest that reverse causation may be responsible for the risk of dementia brought on by benzodiazepines (i.e., prodromal symptomatology of dementia such as insomnia or anxiety may lead to benzodiazepine prescription) [138].

Abstinence and Recovery of Cognitive Function

After 4 or 6 months of benzodiazepine use, abrupt discontinuation will cause a withdrawal syndrome in 60–80% of cases [151]. Typically, physiological withdrawal starts after 24–48 h following last use and may last several days [152]. Initial manifestations (prior to 24 h) that include anxiety or insomnia may reflect a rebound of underlying psychiatric symptoms, an anticipatory fear of physical discomfort (pseudo-withdrawal), or early stages of withdrawal [109].

Older adults experiencing benzodiazepine withdrawal may appear disoriented, often have visual and tactile perceptual disturbances, and perseverate about somatic complaints [153]. Further symptoms may include tremor, tachycardia, paranoia, delusions, and delirium. Common neuropsychological findings during withdrawal include poor executive function, psychomotor excitability (e.g., clonus, tremor), compromised

attention, sensory hypersensitivity, an erratic pattern of responses, and mild or moderate retrieval difficulties [104].

Sustained abstinence for at least 6 months may yield modest improvements in visuospatial functions, concentration, sustained attention, and nonverbal memory [154, 155]. Attention and psychomotor performance do not improve [156]. Long-term benzodiazepine users continue to underperform cognitively after prolonged abstinence as a result of long-lasting, perhaps irreversible, drug-related neurocognitive changes [155, 156].

Case Study: **Benzodiazepine withdrawal presenting as motor dysfunction and cognitive impairment on an inpatient psychiatric unit.**

Ms. X was a 78-year-old widowed female with a history significant for multiple cerebrovascular risk factors who presented to an inpatient psychiatric unit for treatment of generalized anxiety disorder. As an outpatient, Ms. X was treated for 2 years with Klonopin for her symptoms; her dose prior to admission was up to 9 milligrams. When examined, she was on 6 milligrams of Klonopin due to a rapid taper that had been conducted prior to admission due to several falls that the patient had experienced while at home. The patient was observed to have bimanual tremor and tremulous voice on exam. Mental status exam indicated that she was only partly oriented to time but was oriented to place and person. Neuropsychological exam revealed impairments (>2 standard deviations) on tasks of psychomotor processing speed and visuospatial/visuoconstruction skills. Deficits (1.5-1 standard deviation below the normative comparison) in executive function were found (e.g., set-shifting, response inhibition, motor inhibition) as well, in the context of intact global cognitive function. The patient was determined to be experiencing acute withdrawal from benzodiazepines; during the course of her hospitalization, her medications were stabilized. Repeat examination with alternate forms after 3 weeks was significant for cessation of motor tremors and improvement in visuospatial functions but persistence of executive dysfunction.

Opioid Use

Opioids are a collection of naturally occurring, synthetic, or semisynthetic compounds with central and peripheral analgesic effects [157]. Opioids are considered safe pharmacological agents in the management of pain in the elderly [84] as the side effect profile remains relatively constant across the life span [158]. However, older adults on pain management regimens should be closely monitored by their physicians, for side effects [159].

Screening for the Presence of Opiate Use Disorder in the Elderly

Prevalence and Risk Factors

Older adults are more likely that individuals in other age groups to experience chronic health conditions that require treatment with prescription medication. Increased rate of physical disability in late life, and the aging process itself decreases the threshold for low intensity pain [160] thereby increasing the need for analgesic agents. The prevalence of chronic pain among older adults is over 40% [161, 162].

Statistically, younger adults report higher use of opioid medications, relative to older adults, even though older adults are prescribed more medications overall [164, 165]. A subset of older adults who are prescribed opiates may develop opiate use disorder, and the potential risk of death by overdose is much higher for this group of patients. There is some indication though that older adults may underreport prescription opiate misuse [103, 166]. Furthermore, while the estimated prevalence of prescription opioid use disorders among adults over 50 years old in the community is low (0.13%), a recent study reported that 1.4% of adults aged 50 years and older used prescription opioids nonmedically in the last year, a higher rate than the use of sedatives, tranquilizers, and stimulants (<1% each) [167, 168]. Risk factors for misuse of opiates include high prescribed dose, frequent dose increases, and long duration of treatment.

Identification and Diagnosis of Opiate Use Disorder

Older adults are receptive to supportive, nonconfrontational, nonjudgmental evaluation approaches [169], but late-life opioid use disorders are difficult to identify with questionnaires based on formal diagnostic criteria (Table 19.7) [5].

Opioid Use Disorder and Neurocognitive Impairment

Cognitive dysfunction is a problem with opioid use across the age span [170], but in the context of aging, opioid misuse presents unique challenges as it can potentiate the neurocognitive effects of aging. Further, under-identified chronic opioid use, along with the effects of pain disorders on cognition, likely interfere with neuropsychological performance [171]. Contrary to the assumption that modulation of pain improves cognitive function, opioid use has a synergistic impairing effect [172] in these patients.

Table 19.7 DSM-5 criteria for opioid use disorder: if the answer is "yes" for two or more of the below questions, then patients meet criteria for opioid use disorder [31]

In the past year have you:	
Taken opioids in larger amounts or over a longer period than was intended?	Y/N
More than once wanted to cut down or stop taking opiates, or tried to, but couldn't?	Y/N
Spent a lot of time in activities needed to obtain opiates? Or being sick or getting over after effects?	Y/N
Wanted to take opiates so badly you couldn't think of anything else?	Y/N
Found that taking opiates – or being sick from taking them – often interfered with taking care of your home or family? Or caused job trouble?	Y/N
Continued to take opiates even though it was causing trouble with your family or friends?	Y/N
Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to take opiates?	Y/N
More than once gotten into situations while or after taking opiates that increased your chances of getting hurt (such as driving, swimming, using machinery)?	Y/N
Continued to take opiates even though it was making you feel depressed or anxious or adding to another health problem?	Y/N
Had to take much more opiates than you once did to get the effect you want? Or found that your usual dose of opiates had much less effect than before?	Y/N
Found that when the effects of opiates were wearing off you had withdrawal symptoms such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?	Y/N

Acute Effects

The severity of opioid-related cognitive dysfunction correlates with type of agent, dose amount, and route of administration (parenteral > oral > transdermal) [102, 173]. Acute effects include poor sustained attention, delayed reaction time, decreased psychomotor speed, and impaired encoding and recall of information [174–178].

Toxic encephalopathy is common in elderly patients, and opioid use promotes its development [179, 180]. The likelihood of delirium differs among different agents [181], and those with anticholinergic properties such as meperidine or tramadol have been associated with an increased risk [179, 182].

Chronic Effects

Extensive research on nonaddicted and addicted populations has characterized the neurocognitive impact of prolonged opioid use [173], [183–185]. Although some view opioids as non-neurotoxic [186], opioids induce structural changes in the brain [187]. Neuroimaging studies reveal: bilateral volumetric losses in frontotemporal regions including the amygdala; white- matter tract abnormalities in the internal, external capsules, and amygdala pathways; and significant disruption of networks connecting the anterior insula, amygdala, and nucleus accumbens [187, 188].

Chronic opioid use results in a distinctive pattern of neuropsychological impairments best characterized by executive dysfunction. Specifically, deficits in verbal working memory, impulsivity (risk taking), cognitive flexibility (verbal fluency), and inhibitory control [183, 189, 173] have been reported. Others have reported disruptions in attention, learning and memory, visuospatial functions [190–192], and

processing speed [193]. Chronic opioid use, unlike use of alcohol or benzodiazepines, has not been linked to dementia [194, 184].

Abstinence and Recovery of Cognitive Function

Repeated exposure to opioids induces neuroadaptive changes that result in tolerance of greater amounts. When opioids are discontinued, an acute withdrawal syndrome occurs [195]. During withdrawal, neuropsychological performance worsens with effects on complex working memory, executive function/cognitive flexibility [196], and fluid intelligence [197, 198]. Following 3 months of abstinence, improvements in these domains correlate with neuroimaging findings showing reversibility of structural changes [188, 187, 197, 199, 200]. However, others have noted that cognitive deficits similar to those observed in chronic opioid users persist in recovered nonusers [201]. Further, deficits in learning and memory persist despite cessation of opioid use [201].

Conclusion

Prescription psychoactive drug misuse may be more common than previously thought in older adults, and its presence intensifies age-related functional and cognitive changes. However, further research in this area is necessary, as existing studies focus mainly on younger adult populations and are limited by methodological differences, the heterogeneity of samples, the effect of

Table 19.8 Neurocognitive effects associated with the use and discontinuation of prescribed opioids and benzodiazepines

	Neurocognitive effects		
	Acute	Chronic	Post-discontinuation
Benzodiazepines	Impaired new learning Anterograde, but not retrograde, amnesia Slow processing speed Attention and executive dysfunction Disruption of memory consolidation Retrograde facilitation by enhancing retrieval processes Impairment in selective and sustained attention Delirium	Impaired sensory processing Decreased psychomotor speed Impaired visuospatial processing Attention deficits Memory deficits, associated with encoding MCI Dementia	Acute withdrawal: Poor executive function Compromised attention Sensory hypersensitivities Retrieval difficulties Prolonged abstinence: Visuospatial deficits Attention/ concentration General intelligence Psychomotor speed Nonverbal memory
Opioids	Psychomotor slowing Poor sustained attention Delayed reaction time Decreased psychomotor speed Impaired recall delirium	Verbal working memory Cognitive impulsivity (risk taking) Cognitive flexibility (verbal fluency) Strategic planning Episodic foresight Attention Long-term memory Visuospatial functions Bilateral volumetric losses in frontotemporal regions and the amygdala White-matter tract abnormalities in the internal, external capsules, and amygdala pathways Significant functional deficits in networks connecting anterior insula, amygdala, and nucleus accumbens	Acute withdrawal: Working memory Executive function Fluid intelligence Prolonged abstinence: Restoration of the majority of deficits

polypharmacy, and the impact of medical and neuropsychiatric comorbidities on cognition.

Identifying late-life prescription use disorders is challenging. Neuropsychological assessment of older adults with prescription drug misuse or use disorder is most likely to be effective when clinicians use a nonjudgmental approach that relies less on traditional diagnostic criteria and considers the unique psychosocial and biological characteristics of the patient. Older adults exposed to benzodiazepine and opioid derivatives may experience a broad range of neurocognitive changes that may be mistaken for neuropsychiatric disorders. The type of prescribed drug, the length of exposure, and the duration of abstinence will impact the results of neuropsychological assessments. Repeated evaluations following prolonged periods of abstinence are warranted to ascertain the reversibility and magnitude of medication-related cognitive impairments.

Clinical Pearls

- Older adults are often prescribed benzodiazepine or an opioid agents.
- Late-life prescription use disorders are on the rise but remain underdiagnosed due to stigma, provider bias, and a tendency for older adults to underreport misuse.
- Late-life prescription use disorder assessment is complex and benefits from a nonjudgmental evaluation that does not rely exclusively on DSM-5 criteria.
- Benzodiazepine-induced psychomotor and cognitive dysfunction is not always apparent to the patient and are seldom self-reported.
- Long-term benzodiazepine, but not opioid use, is a risk factor for dementia.
- Diagnostic interpretation of neuropsychological findings should take into account the influence of psychotropic medications during acute, chronic use, and abstinence periods.
- After a prolonged abstinence period some, but not all, cognitive deficits may improve. Repeated neuropsychological assessment is therefore recommended.

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Pain in Dementia

20

Rachel K. Bieu and Joseph F. Kulas

Pain

Pain is endemic to the human experience and advantageous when understood as manifesting a signal indicating harm. Conceptualized in this way, pain is transitory, the expected result of an acute injury, illness, or surgery and resolving with removal of the source of pain and healing [1, 2]. Conversely, the experience of chronic or persistent pain is not consistent with this conceptualization. Understandably so, chronic pain can be devastating to individual well-being (physical, social, emotional, financial) as this pain serves little or no purpose in persisting beyond the expected window of healing or the understood resolution of the source of pain [1–3]. Persisting pain is increasingly becoming a global health problem with estimates suggesting that 20% of adults suffer from pain, with 10% newly diagnosed with chronic pain each year [4]. The average length of suffering for those experiencing chronic pain is 7 years [4].

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Pain in the Elderly

The population over 65 in 2008 was estimated at 506 million and anticipated to rise to 1.3 billion by 2040 [5, 6]. Pain is not a part of normal aging; nonetheless, a disproportionate number of this fastest growing population experience pain [5–7]. Demographically speaking pain is not equally distributed, such that the risk for experiencing chronic pain increases as one ages, with high rates in the elderly and the highest rates of chronic pain experienced by the oldest of the old [8–10]. Epidemiological studies estimate that between 25% and 65% of the elderly living in the community and up to 80% living in an institutionalized setting experience chronic pain [11]. Older adults are frequently medically complex, contending with multiple chronic health conditions, and so persisting pain in this population represents a particular challenge [12]. Commonly occurring pain in the elderly is nociceptive pain associated with osteoporosis or arthritis versus neuropathic pain resulting from diabetes as an example [13]. In the aging population, pain can restrict an individual's ability to carry out activities of daily living, result in change in gait increasing fall risk, poor sleep or poor nutrition, polypharmacy, cognitive changes, and increase susceptibility to other chronic disabling conditions, psychiatric or otherwise [5–7, 12]. Further, pain coping is often complicated by stressful events unique to aging including losses,

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bereavement, and a change in socializing and available supports [11, 14–16].

Despite an increase in prevalence as persons age, pain is consistently undertreated in the elderly [11]. This has been attributed to multiple factors including reporting habits of older persons, acceptance of these reports by caregivers, ability of caregivers to identify pain, and assessment variables. Additional contributors include reluctance to provide pharmacological agents given increased risk (e.g., polypharmacy, adverse side effects, and intoxication), insufficient training in pain management, and misconception with regard to non-pharmacological pain interventions [11].

Pain in Dementia

In addition to chronic pain, age is also the principal risk factor for dementia. Presently, 5% of persons over the age of 65 carry a dementia diagnosis, rising to in excess of 50% in those aged over 90 years [8, 17]. Studies have reported prevalence of pain in people with dementia at approximately 50% [13].

For those who are cognitively impaired, behaviors such as vocalizations (e.g., sighing, moaning, calling out, verbal abuse, repetitive vocalizations, noisy breathing), facial expressions (e.g., grimacing or frowning), restless or strained body expressions (e.g., fidgeting, increased pacing or rocking), or agitation and resistance to care may represent the most prominent or the only indicator of pain. Unfortunately, it is often the case that such signs are disregarded or interpreted as characteristic of dementia rather than recognized as a sign of pain [16].

Further, individuals with dementia report pain less often, less spontaneously, and at a lower intensity than their cognitively intact counterparts, with the ability to verbally communicate pain or discomfort generally decreasing as the severity of dementia increases [16, 18, 19]. In considering possible pathophysiological mechanisms, it has been posed that older adults are less sensitive to pain [12, 20]. However, research would suggest that this population does not experience pain differently. Rather, in mild to moderate dementia, response to noxious stimuli with more enhanced facial responses might suggest heightened pain processing [21].

There is a growing body of research into chronic pain management for older adults and a growing awareness that individual management is a viable strategy for this population no matter the level of cognitive ability [22]. However, assessment of pain in the elderly and demented individual demands a comprehensive multidisciplinary approach for the description, diagnosis, and management of chronic pain including physicians and mental health, physical, and occupational therapists [6].

Pain Assessment

The assessment of painful conditions in the elderly can be complicated, even in the absence of cognitive impairments. To address the complexities associated with the assessment of painful conditions in the elderly, consensus documents have been created to provide frameworks for the assessment of this complex issue. Drawing from these consensus guidelines and using the communications framework of pain, Hadjistavropoulos [23] described a practical method to the assessment of painful conditions. Briefly, Hadjistavropoulos argued that pain is encoded into two main pathways of expressive behavior, verbal expression and nonverbal communication. Verbal expression, which requires higher-level cognitive processes, provides a higher level of precision. Nonverbal pain responses which are more reflexive in their elicitation require less cognitive control but are more ambiguous and open to misinterpretation by observers. Hadjistavropoulos [23] argues that although all aspects of pain assessment are relevant, the importance of verbal report compared to nonverbal observations shifts as the cognitive functioning of a patient deteriorates. With that said, Hadjistavropoulos [23] argues that the evaluation of the patient with or without dementia does not differ with the exception that the evaluation of the patient with dementia may require additional support.

Pain and Neuropsychological Testing

A host of cognitive deficits, most paramount changes in attention, processing and psychomotor speed, have been associated with pain arguing further for routine assessment, although the exact mechanism of action of pain on cognitive functioning remains unknown [24–26]. As a result, teasing apart pain's role in cognitive test results from other etiological sources can be difficult [24–26]. In interpreting results, providers need to consider pain in the context of larger neurological disease while also being mindful of variables associated with pain that might come to bear on results including treatments for pain, poor sleep and fatigue, mood, and somatic symptoms and effort [24–26]. Evaluators are encouraged to make attempts to alter the testing environment as needed for comfort, which is particularly important if pain is not being directly treated [24]. This can be as simple as providing a pillow or may include breaking a neuropsychological evaluation into multiple parts or delaying testing.

Pain Assessment in Dementia

Assessment of pain, as in most areas of psychological and medical assessment, should include a comprehensive assessment of historical and background information. This will provide important aspects to understanding the biopsychosocial elements of pain. In the earlier stages of dementia when cognitive decline is not pronounced (i.e., mild to moderate cognitive deficits), self-report should be attempted. Most pain assessments begin with a single question to identify the presence and intensity of pain (What is your average level of pain over the past 24 h on a scale of 0 (no pain) to 10 (worst pain imaginable)). Although the most commonly used brief self-report measures are understandably limited in that they are unidimensional, pulling for pain intensity without quality, location, or impact on function, they are still considered the gold standard in the assessment of pain [27]. Further, they are generally reliable and valid in those who are able to report verbally. Research suggests that individuals with mild to moderate dementia can interpret self-report measures correctly. Common self-report measures used to assess pain intensity in older populations include visual analogue scales (VAS), numerical rating scales (NRS), and the verbal descriptor scales (VDS). The VAS is comprised of a 10 cm line with extremes of "0" or no pain to "10" worst pain. The VAS, although one of the most frequently used measures with younger adults, is not recommended for use with older adults due to higher error rate [6, 27]. Numerical rating scales are often used by placing the patient's rating scale along a numeric continuum, often from 0 to 10 with 0 representing no pain and 10 representing their worst pain. NRS have been found to be reliable and valid for use with older adults. However, some difficulty is reported with older adults completing these measures, particularly when administered verbally [6]. Further, completion rate is high in those without cognitive impairment but decreases substantially when cognitive limitations are at play [19]. Verbal descriptor scales place rating of pain along a continuum but use verbal indicators rather than numeric ones (i.e., no pain, mild, moderate, severe, etc.). Studies suggest that older adults prefer the VDS to other forms of measurement; however, its use can be problematic in the presence of declining language abilities. With that said, up to 90% of people with moderate dementia are able to use this measure. It should be noted that individuals with severe dementia are able to use these language dependent scales, with modification at times being necessary. Finally, an instrument using combination approaches such as Iowa Pain Thermometer (IPT) [28, 29] or the Faces Pain Scale (FPS) [29] may be considered as an alternative to these single approaches.

When self-report is compromised, behavioral-observational pain assessment instruments can assess for nonverbal expressions of pain. These assessment approaches utilize direct observation of nonverbal behaviors. Table 20.1 contains a list of common pain behaviors used in validated observational pain assessment measures. Owing to limitations in the use of these measures, includ-

Table 20.1 Common pain behaviors in cognitively impaired elderly used in validated observational pain scales

1. Facial expressions	Grimacing, tighter face, wrinkled nose
	Brow lowering, closed or tightened eyes, upper lip or cheek raising
	Squinting or narrowing eyes
	Mouth opening
2. Vocalizations	Moaning, groaning, grunting, crying
	Specific sounds or words e.g., "ow", "ouch"
	Gasping or noisy breath
3. Body movements	Flinching or pulling away
	Thrashing, rocking
	Refusing to move, moving slow
	Bracing, avoidance of certain body positions
	Rubbing, holding, and/or guarding sore area
	Limping
	Clenched fist
	Going into fetal position, knees pulled up
	Stiff or rigid
	Shaking or trembling
4. Changes in interpersonal interactions	Not wanted to be touched, not allowing people near
	Decreased social interactions and communication
	Difficult to console or reassure
5. Changes in activity patterns or routine	Sleep changes
	Sudden halting of common routines, decreased activity
6. Mental status changes	Crying or tears
	Increased confusion
	Irritability or distress

From Achterberg et al. [8] & Hadjistavropoulos et al. [27] according to the AGS panel on persisting pain in older adults.

ing the lack of distinction between chronic and acute pain and the need for the management of observational biases [8, 27], Hadjistavropoulos [23] recommends that a number of factors be taken into account with their use: (1) cutoff scores not be used in older adults with dementia owing to concerns over the impact of patient and observer factors which may impact the assessment of pain, (2) use of an individualized approach to allow for the observation in changes in pain levels over time when possible, (3) conduct the assessments under consistent circumstances to allow for reliability of the pain scores, (4) recognition that assessment of pain will more likely be expressed during movement, and (5) recognition that pain behaviors observed may be manifestations of symptoms of other conditions. Finally, Hadjistavropoulos [23] also recommends the gathering of information from collaterals and the importance of assessing the other psychological states that could emerge secondary to the presence of pain, including delirium and depression. Although these recommendations complicate the choice of measures, a number of observational assessments exist and can be used effectively. The more positively rated of these measures include the Abbey Pain Scale (Abbey) [30], the DOLOPLUS-2 [31], the Pain Assessment in Advanced Dementia (PAINAD) [32], and the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) [33].

The Abbey is a scale comprised of six items including facial expression, change in body language, vocalization, behavioral change, physiological change, and physical change. The Abbey differentiates non-painful from painful situations, has satisfactory internal consistency, and has established concurrent validity [27]. The DOLOPLUS-2 is comprised of two psychomotor, five somatic, and three psychological items. It has satisfactory internal consistency. Scores on this measure differ between groups of patients believed to have pain and who have been judged to be pain free [27]. The PAINAD includes five items including breathing, negative vocalizations, facial expression, body language, and consolability. It has moderate internal consistency and concurrent validity. Scores on this measure decrease following pain management (i.e., analgesics) and vary dependent on activity [34]. Finally, the PACSLAC is comprised of 60 items rating symptoms as present or not. It is the only instrument that incorporates all observational domains deemed appropriate and important by the American Geriatrics Society guideline [35] (see Table 20.1). It is also recognized as one of

the most psychometrically strong instruments having good internal consistency and inter-rater and retest reliability. The PACSLAC-II was created as a short form (31 items) of the original measure, removing items that could be mistaken for signs of delirium while at the same time maintaining psychometric integrity [8].

Treatment of Pain in Dementia

In a demented population, regularly scheduled non-opioid analgesic medication (acetaminophen) has been found to have a positive effect on activity and socialization with no effect seen for agitation, emotional well-being, or the need for psychotropic medication [36]. It has also been suggested that first-line pharmacological treatment for chronic pain in the aged is most effective when combined with non-pharmacological intervention [11, 37]. Thus, the combination of a medically appropriate analgesic (acetaminophen, ibuprofen; preferably non-opioid given numerous risks including intoxication and falls) with a first-line psychological intervention may be a useful treatment approach in populations unable to verbalize the source of their distress effectively. A thorough review of the medication treatments for pain in dementia is beyond the scope of this chapter, but a comprehensive review can be found in the guidelines provided by the *American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons* [38]. However, when pain is thought to be a potential precipitant, it is thought that first-line analgesics which have a prompter response combined with non-pharmacological intervention already proven, efficacious in treating a greater number of symptoms common to individuals with dementia, will have a greater positive impact.

Psychological approaches to pain management have largely centered on three main approaches: cognitive-behavioral, mindfulness, and self-regulatory. A brief review can be found in Bieu, Kulas, and Kerns [39], with a more comprehensive review to be found in Turk, Wilson, and Cahana [40]. Table 20.2 provides a listing of studies that have investigated psychological approaches to pain management in elderly

Table 20.2 Psychological interventions in the treatment of pain in the aged and demented

Study	Mean age	N	Treatment
Cook (1998) [44]	77.0	22	Cognitive behavioral pain management
Reid, Otis, Barry, Kerns (2003) [45]	77.4	14	Cognitive behavioral therapy
Andersson, Johansson, Nordlander, and Asmundson (2012) [9]	72.0	21	Cognitive behavioral group intervention
Morone, Greco, and Weiner (2008) [46]	74.9	37	Mindfulness meditation/MBSR
Arena, Hightower, and Chong (1998) [47]	69.0	10	Progressive muscle relaxation therapy
Arena, Hannah, Bruno, and Meador (1991) [48]	65.0	8	Electromyographic biofeedback training
McBee, Westreich, Likourezos (2004) [49]	85.0	14	Psychoeducational relaxational group
Nicholson and Blanchard (1993) [50]	66.7	14	Combined relaxation training, cognitive therapy, and biofeedback
Kabela, Blanchard, Appelbaum, and Nicholson (1989) [51]	Range 66–77	16	Various combinations of relaxation (e.g., PMR, breathing), cognitive stress coping, and biofeedback
Cipher, Clifford, and Roper (2007) [35][a]	82.0	44	Multimodal CBT

[a]Single study speaking to pain treatment in a demented population

patients and the limited research that has been conducted in populations with dementia. The available research suggests that a modified CBT protocol can be effective in reducing symptoms of pain and associated behaviors [34, 35, 41–43], with the degree of cognitive impairment determining how overtly behavioral and directive the therapy will need to be. Intervention will necessitate continued assessment and flexibility such that if one strategy is not working, the technique should be adjusted. In most cases, the use of this approach should be done in an individual or small group format with the involvement of caregivers strongly encouraged. This will be important to increase the likelihood of and facilitating practice outside of sessions. Intervention length may vary, from 5 to 10 weeks depending on resources and patient needs, with patients attending weekly. Sessions should be shortened (30–45 min) to accommodate for fatigue, and skills should be introduced one at a time, with two skills at a maximum recommended per session. The number of skills introduced may be less than in cognitively intact individuals. Staff should promote repeated exposure with regular summation of material, the patient's active involvement in the establishment of cues or prompts serving retrieval, and extra time spent practicing new skills. Patients should be provided with simplified written instructions during each session and a short concrete homework plan to be completed outside of session. In the presence of severe cognitive deterioration, much of the treatment will focus on the training of caregivers to recognize pain behaviors and to utilize appropriate behavioral approaches in dealing with those symptoms. Support provided to the caregivers, particularly as it relates to treatment fidelity and understanding the limits imposed by the patient's cognitive status, will be important to assure that the caregiver has confidence in the treatment (Table 20.3).

Table 20.3 Instruments for use in the assessment of pain in older adults with dementia

Abbey Pain Scale
Check-list of Non-Verbal Pain Indicators (CNPI)
Certified Nursing Assistant Pain Assessment Tool (CPAT)
DOLOPLUS-2
Discomfort Scale in Dementia of the Alzheimer's Type (DS-DAT/DS-DAT modified)
EPCA-2
Mahoney Pain Scale
Mobilization-Observation-Behavior-Intensity-Dementia (MOBID and MOBID-2) Pain Scale
Non-Communicative Patient's Pain Assessment Instrument (NOPPAIN)
Pain Assessment in the Communicatively Impaired (PACI)
Pain Assessment Checklist for Seniors with Limited DisAbility to Communicate (PACLSAC and PACSLAC-II)
Pain Assessment for the Dementing Elderly (PADE)
Pain Assessment in Advanced Dementia (PAINAD)
Pain Assessment in Noncommunicative Elderly Persons (PAINE)
The Rotterdam Elderly Pain Observation Scale (REPOS)

From Hadjistavropoulos et al. [27]

The Role of Neuropsychology

Given base rates for chronic pain in the aging population, the assumption that the patient is in pain should be the rule rather than the exception [11]. As such, a standardized portion of neuropsychological assessment should include the assessment of pain. Given that neuropsychological assessment is uniquely able to ascertain the cognitive status of the patient, it is particularly useful in guiding the pain assessment process. Furthermore, the incorporation of the information gathered from a neuropsychological evaluation is invaluable in shaping recommendations to more effectively meet the needs of the patient and more fully ascertain the impact on a patient's well-being. The impact pain can have on a patient's functioning and the continuing issue with knowledge by providers and how infrequently pain is assessed heighten our responsibility to assess this area appropriately so that treatment recommendations will provide appropriate, comprehensive care for the patient with dementia. Simply stating that the difficulties associated with the assessment of pain in this population are not a good fit with the nature of your practice does not absolve one of the responsibility to provide appropriate care. Our unique role and training can help to bridge gaps in

care that patients who receive our services may be experiencing.

In examining the literature cited, most neuropsychological evaluations would not need to be modified substantially to be consistent with the requirements for the assessment of pain in a population with (or without) dementia even in outpatient settings (see Fig. 20.1). The primary starting point is the clinical interview that most neuropsychologists routinely use as a part of their evaluation. Inclusion of a more comprehensive discussion with the patient and caregivers about

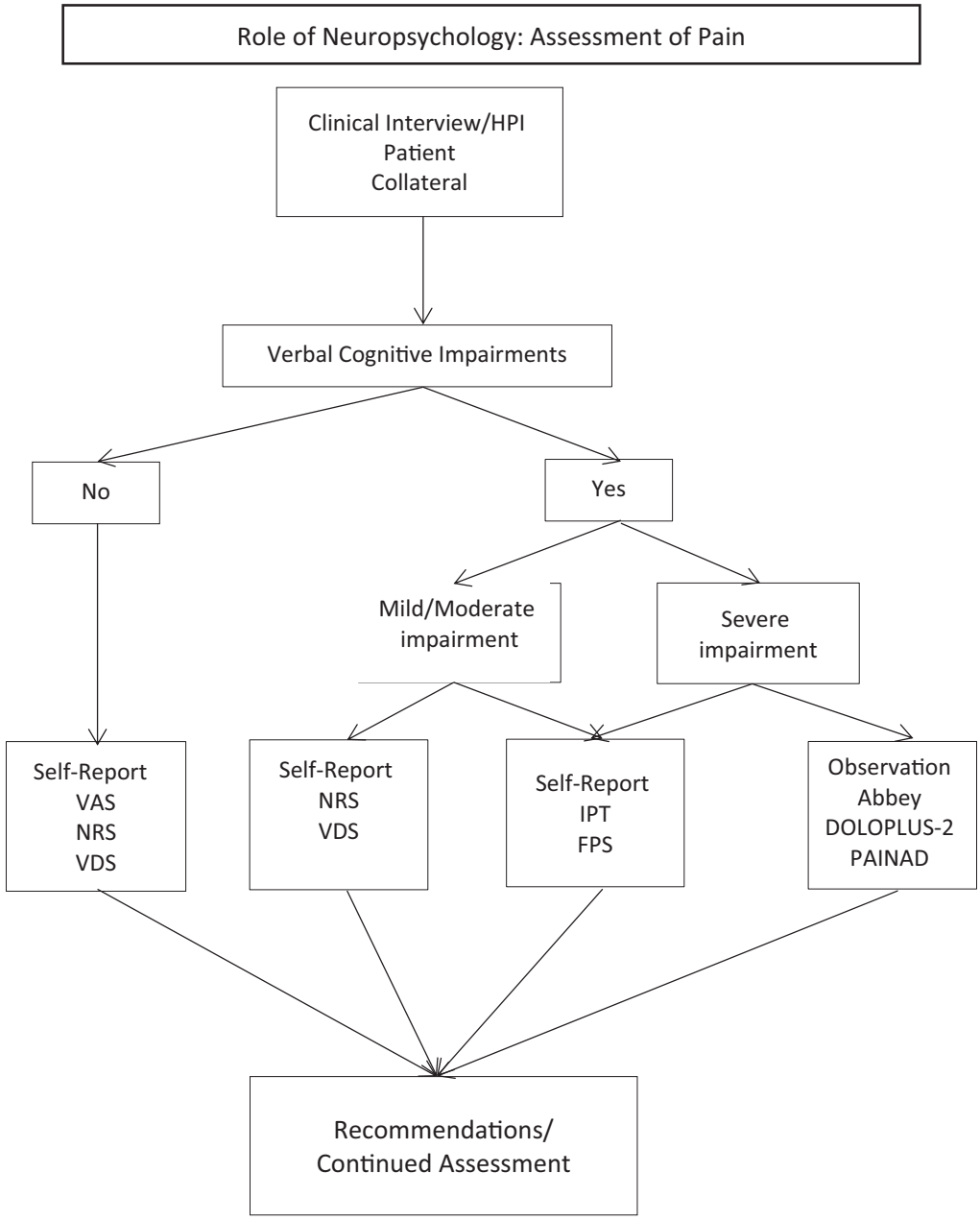

Fig. 20.1 Assessment of pain in practice

their experience of pain would help to characterize the issue broadly. The utilization of simple self-report measurement of pain can be easily incorporated into an evaluation process and should be routinely asked regardless of patient population given the impact that acute pain can have on test validity. For patients with less severe cognitive limitations, this inclusion will likely be sufficient to adequately assess pain and provide sufficient information for the neuropsychologist to make appropriate treatment recommendations to treat the patient's symptoms and associated conditions. It will also likely provide understanding of the impact that the patient's experience of pain has on their emotional and physical symptoms and how their physical and emotional symptoms can impact their experience of pain. In more significant cases of dementia, the neuropsychologist may need to use the nonverbal measures that were discussed to determine if the patient is currently in pain. Further, following on the recommendations of Hadjistavropoulos [23] it may be necessary for the neuropsychologist to assess the patient over time, or conversely, assist other practitioners in using these measures to assess the patient's pain over time. At times, a consultative approach may be most appropriate to obtain the needed information. Follow-up evaluations can be useful to gauge the impact that these recommendations have had on the patient's experience of pain and associated symptoms.

However, dementia in the elderly is rarely a static entity, and as such, understanding of progression of the patient's cognitive abilities will be paramount to appropriate intervention. This argues for a system of continuous assessment that will determine how treatment is disseminated to the patient on an ongoing basis and guide how it will need to be modified with potential disease progression. This further argues for the ongoing participation of the neuropsychologist in the care of the patient with dementia to provide expert guidance on the impact that the patient's cognitive functioning is having on their symptom presentation and report. Ongoing assessment of cognitive status can be operationalized via the use of brief repeatable cognitive assessments or batteries which will allow for accurate longitudinal comparisons that can provide information concerning the effectiveness of the treatment at the time of the assessment. The cognitive information that would be derived from these evaluations can help guide treatment by other providers in providing treatment as well, particularly in very late stages of cognitive deterioration. At that time, assessment will likely focus more on an individual's functional ability and ability to communicate their needs and understand questions posed to them, rather than their absolute cognitive level in comparison to peers. The assessment provided by a neuropsychological evaluation can be extremely useful to help frontline caregivers understand the issues that the patient is experiencing, particularly if a neuropsychologist is able to leverage their broad knowledge across medical, psychological, and behavioral domains.

Conclusion

In conclusion, the presence of underreported or undertreated pain continues to be an ongoing problem that often leads to ineffective patient care and unneeded suffering. Given the size and scope of the issue, the development and application of a successful comprehensive pain assessment and management intervention for individuals with cognitive impairment is a pressing need, as the number of individuals with dementia is expected to climb dramatically. The unique skill set of neuropsychologists provides them with the tools to effectively assess pain and associated conditions within the context of dementia, and these skills make them particularly suited to the development of treatment plans which will help reduce the experience of pain in this vulnerable population. Failure to consider the "fifth vital sign" in the context of an evaluation and care of an individual with dementia will lead to an incomplete evaluation that will not comprehensively treat the issues that are most important to that patient.

Clinical Pearls

- Despite increasing prevalence with age, chronic pain is consistently under-evaluated and undertreated in the elderly and even more so in cognitively impaired populations.
- In populations with dementia, behaviors that are indicative of pain are too frequently attributed to sequelae of dementia and thus go untreated or may be treated with ineffective and/or potentially sedating medications.
- For patients with cognitive impairment, behaviors such as vocalizations, facial expressions, restless or strained body expressions or agitation, and resistance to care may represent the most prominent and/or only feature of pain.
- The evaluation of patients with or without dementia does not differ with the exception that evaluation of a patient with dementia may require additional support.
- Given base rates, pain should be assumed to be the rule as opposed to the exception and routinely assessed via expressive behavior, verbal expression, and nonverbal behavior.
- Neuropsychologists, having an understanding of cognitive and emotional factors manifesting in behavior, are uniquely qualified to evaluate pain within the confines of the neuropsychological evaluation and to assist in developing an appropriate treatment plan that incorporates these factors.
- In addition to a thorough clinical interview, self-report scales are the gold standard. Observational pain assessment measures are used when self-report is compromised.
- As neither dementia nor pain is static, continuous assessment and adjustment of recommendations accordingly is advised.
- Available research suggests that a modified CBT protocol, combined with a medically appropriate analgesic, can be effective in reducing symptoms of pain and associated behaviors, with the degree of cognitive impairment determining how overtly behavioral and directive the therapy needs to be.

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Neuropsychological Assessment and Management of Older Adults with Multiple Somatic Symptoms

Greg J. Lamberty and Kimberly K. Bares

Introduction

Traditional Views of Somatoform Symptoms

Older adults routinely present with worrisome somatic symptoms to a greater extent than most any clinical population. Because of this, somatic concerns need to be evaluated with a clear understanding of their history and context. For many clinicians, there is a temptation to regard such symptoms as normal consequences of the aging process. The ubiquity of symptoms such as pain, fatigue, sleep difficulty, and motor slowing can be attested to by most anyone surviving four or five decades. Further, such symptoms are often associated with other important risk factors for cognitive decline like decreased levels of activity, weight gain, and increased neuropsychiatric symptoms. It is always important to rule out treatable medical conditions that might be associated with common physical complaints, but distinguishing these from pain complaints and gastrointestinal, pseudoneurological, and sexual symptoms used to describe somatoform disorders can be especially challenging [1]. While the diagnostic validity of the *Diagnostic and Statistical Manual* (DSM) criteria have been widely criticized [2], the clinical reality is that "normalcy" in older adults may well involve more complaints of pain and discomfort than that seen in younger adult samples [3, 4].

Historically, there has been great variability in the prevalence of the various DSM somatoform disorders, particularly somatization disorder, which prompted researchers to modify criteria for diagnosis in a way that more accurately reflected the common and troubling presentations seen in many clinical settings. The reported prevalence of somatization disorder as described in the DSM-IV is very low (0.2–2%) [1], but rates of clinically significant somatoform symptomatology have been reported to be as high as 20–30% of all patients seen in some medical clinic settings [5–8]. Early epidemiologic studies on the DSM-based somatoform diagnoses did not typically examine differences in these presentations across the lifespan. Several reviews have failed to indicate greater prevalence of somatoform disorders with increasing age, though the association between somatoform symptoms and neuropsychiatric disorders (especially depression) is particularly high in older patients [9–11]. In other words, the presentation of multiple medically unexplained symptoms as a clinically relevant syndrome is not observed to be more common in older individuals, despite a general tendency to experience physical symptoms more commonly.

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Distinguishing between symptoms that relate directly to physical disorders or disease processes and those that are related to what have become known in popular parlance as "mind–body" disorders continue to be a vexing clinical challenge [12]. With older patients' greater tendency to report physical complaints, this can be particularly challenging. Finally, the importance of understanding these dynamics is essential for working effectively with patients in the assessment context and subsequently making effective treatment recommendations [2].

This chapter will provide an overview of how somatic symptoms have been conceptualized in older adults and will provide guidance in making the important distinctions between "normal" presentations and those suggesting a somatic symptom disorder (the new term used in DSM-5). We will also discuss a range of treatment options for effectively managing patients with a high level of somatoform symptomatology, particularly considering the increased likelihood of cognitive dysfunction seen in aging populations in general.

Somatoform Disorders in DSM-5

Somatoform disorders were first introduced as an official diagnostic category in 1980 with the publication of the DSM-III [13]. Hysteria was the "neurotic" disorder that somatization replaced from the second DSM [14] and was based on the presumption that multiple physical symptoms were the product of underlying psychic conflicts. Rather than relying on underlying psychodynamic origins, the DSM-III focused on specific criteria that were thought to be descriptive of a distinct syndrome, as originally described in Briquet's famous monograph from the mid-nineteenth century [15]. This afforded many advantages for researchers of some disorders (e.g., schizophrenia, depression), while the lack of a proposed biological mechanism for somatization disorder relegated it to an apparently less compelling status where researchers were concerned. As noted above, it was clear that somatization disorder, as defined in DSM-III, was rare. Nevertheless, it was also the case that patients in many settings were presenting with medically unexplained symptoms that were problematic and resistant to treatment. As a result, more clinically relevant conceptualizations such as *abridged somatization* or *multisomatoform disorder* [16, 17] evolved to account for the observation that patients with large numbers of medically unexplained symptoms comprised a substantial percentage of primary care and specialty clinic (e.g., neurology) visits. Over time, problems with the DSM-IV classification scheme for somatoform disorders were also identified, and calls for change issued forth [18–21]. The reasons for these calls were numerous and included concerns about the "…dualistic nature of the diagnoses, problems with patients' acceptance of the diagnoses, lack of ability to exclude physical causes of some symptoms, restrictiveness of the diagnostic criteria, and general problems with reliability and validity…" ([2]; p. 14).

With the publication update of DSM-5 [22], the category of somatoform disorders was reconceived as somatic symptom and related disorders (SSRD). The latest classification system seeks to improve the reliability and validity of somatically based diagnoses and minimize the mind–body dualism inherent in previous conceptualizations of somatoform disorders. As such, the current diagnostic criteria focus on the presence of positive symptoms (distressing or disruptive somatic symptoms and excessive thoughts, feelings, and behaviors in response to them) while acknowledging that somatic conditions can be present with or without known medical factors. The SSRD category now includes somatic symptom disorder, illness anxiety disorder, conversion disorder, factitious disorder, psychological factors affecting other medical conditions, other specified SSRD, and unspecified SSRD.

Somatic symptom disorder requires one or more somatic symptoms that cause significant disruption or distress (Criterion A), as well as excessive thoughts, feelings, and behaviors that relate to the symptoms (Criterion B). Additionally, the condition must be chronic (>6 months; Criterion C). These criteria are less exclusive than those for somatization disorder,

but the essential nature of a chronic and disabling condition related to an individual's concerns or preoccupation with physical symptoms seems to capture the essence of the presentations seen with high frequency clinically. DSM-5 indicates that about 75% of individuals previously diagnosed with hypochondriasis are now subsumed by the somatic symptom disorder diagnosis. The other 25% of individuals with hypochondriasis characterized by high health anxiety (i.e., preoccupation with having a serious illness) but without prominent somatic symptoms are now captured by the diagnosis of illness anxiety disorder (IAD).

Medically unexplained symptoms remain central to a conversion disorder diagnosis, which has at its core altered neurological function (e.g., motor or sensory changes such as paralysis, slurred speech, swallowing problems, glove anesthesia) not compatible with known neurological conditions. Conversion differs from somatic symptom disorder in that individuals often don't have excessive thoughts, feelings, and behaviors seen in SSD conditions. There is no longer a required judgment about whether the symptoms are intentionally produced, as is the case with factitious disorder. This latter condition retains as a central feature the purposeful falsification (feigning) or induction of illness symptoms for some manner of secondary gain (e.g., to assume a sick role). Malingering is retained as a V code characterized by intentional production of symptoms to obtain an external incentive (e.g., money, drugs) or to avoid responsibilities such as work, military service, or legal consequences.

Generally speaking, the DSM-5 conceptualization of somatic symptom disorders represents an effort to make the category and diagnoses more relevant and clinically useful. The changes reflect a more pragmatic approach to mind–body problems. Rather than forcing dualistic distinctions, the SSD category represents a clinical reality in which patients often struggle to deal with pain, neuropsychiatric symptoms, and behavior patterns that interfere with more optimal functioning. How this applies to work with older patients is considered below.

Difficulties in Characterizing the Physical Complaints of Older Patients

Neuropsychologists who are less familiar with issues confronting older adults may be inclined to over- or underestimate the role of somatic symptoms in a given patient's health status. There are a number of ways to assure that information about a patient is objective, though care must be taken in all phases to make proper determinations.

In instances where records are available for review, neuropsychologists should be able to obtain a reasonably objective sense of difficulties confronting the patient. This often presupposes that the referral source has expertise with older patients, which may or may not be the case. The number of physicians specializing in geriatrics is very small, and the offset between the number of specialists and the number of patients over the age of 65 is likely to increase in dramatic fashion over the next several decades [23]. This means that older patients will likely be referred by an expanding and diverse base of practitioners, many of whom may have an incomplete sense of issues confronting the elderly. The appropriateness of dementia referrals can vary widely because of this variability in practitioner's expertise. Practically speaking, this means that record review, no matter how extensive, cannot replace the clinical interview and observation for an appreciation of an individual's appearance and behavior and how this squares with his self-report.

A thorough clinical interview is an essential part of the assessment process as well as an important source of information about somatic concerns. Many popular neuropsychology texts discuss the importance of behavioral observations within the interview process and how they ultimately inform the conclusions and recommendations made in neuropsychological reports [24–26]. Careful observation of the older patient will afford insights into factors such as gait, mobility, pain behaviors, affect, orientation, and speed of processing. It is important to note differences between the patient's self-report of

symptoms and whether such things are apparent in his behavioral presentation. Lamberty [2] noted two general patterns of behavior in somatizing patients—stoic and expressive. The outward appearance in these examples is strikingly different, even though the overall level of self-reported symptomatology and corresponding functional disruption in both kinds of presentations can be similar.

Many older adults employ a normalizing strategy wherein they present themselves as "no worse off" than any of their colleagues or others their age. There is a certain charm and sensibility to this approach, though obviously the neuropsychologist should not be lulled into assumptions of normalcy simply because a patient takes a stoic approach to reporting her symptoms. Older patients who affect a more stoic presentation are often characterized by a different dynamic than the younger somatizing patient. With the older patient, medical history and general psychological adjustment are important to assess to look beyond stereotypes of "not wanting to be a burden." Some of these claims are fairly transparent, and within a brief period of time, it becomes clear that either (1) the patient has multiple medical issues that account for his symptoms or (2) emotional or psychological distress is exerting some influence on the patient's experience and reporting of symptoms. It is also important to get a sense of the natural history of current symptoms, as well as a general history of health and medical problems over the years. The likelihood of a complex somatic symptom disorder is much higher in an individual with a long history of engagement with the medical field.

Interviews with collateral sources are valuable, particularly in cases where cognitive difficulties might interfere with a patient's ability to provide a thorough and descriptive history. When patients minimize their symptoms, family members can provide a clearer sense of what kinds of problems are apparent to them. The same can be true in instances when the older patient is focused on physical complaints. Of course, the neuropsychologist must be mindful of the various roles played by friends and family members and how that might impact their reporting of what they observe in the patient or know about their history. As always, the forensic implications of an evaluation need to be considered in cases where guardianship or estate matters loom.

The cautions offered regarding the report of somatic symptoms are basically the same for complaints about cognitive difficulties. Recent work has drawn comparisons between somatoform syndromes and similar presentations that focus primarily on reports of cognitive dysfunction. Cognitively oriented analogs of somatic symptom disorders have been suggested and have evocative names like "cogniform disorder" [27] and "neurocognitive hypochondriasis" [28], though these presentations are basically two sides of the same coin. Neuropsychologists encounter many patients that present with such a focus. Just as with physical concerns, it is important to appreciate age-related cognitive difficulties in older patients. Accounting for age-related cognitive complaints is a regular part of the assessment process for neuropsychologists, so the risk of misattributing cognitive difficulties should be lower than it is when attempting to determine the nature of physical complaints. In other words, neuropsychologists are better equipped to empirically assess cognitive difficulties than they are to somatic concerns.

Understanding the Role of Physical Discomfort in the Examination Process

Older patients often find the neuropsychological evaluation process overwhelming and intimidating. The prospect of having one's cognitive functioning assessed can awaken fears about whether or not there are major deficits, degenerative changes in the brain, or impending major changes in the ability to live independently. In this context, aches and pains that complicate everyday life can become magnified and serve as significant obstacles to the successful completion of a neuropsychological examination. Older patients frequently present with limited mobility, arthritic pain, fatigue, and visual and hearing limitations secondary to a range of age-related changes. Most neuropsychologists are prepared for these basic obstacles and can alter the examination processes accordingly. Common

adaptations include tables that accommodate wheelchairs, enlarged type protocols, magnifiers, sound amplifiers, allowing for extra time and breaks, and generally shortened testing protocols. Beyond these basic physical adaptations, neuropsychologists and psychometrists need to be prepared to work with the anxiety, reticence, and outright refusal to cooperate. As an exam wears on and failure experiences mount, there is increased likelihood that performance will decline and become less representative of actual abilities. The spectrum of how this presents is broad and includes decreased attentional focus and carelessness on one end, all the way to rejection of tasks and refusal to continue on the other. The parallels with pediatric assessment in this regard are substantial and can sometimes be navigated by a skilled evaluator. Regardless, it is difficult to know with certainty the impact that waning attention or investment in performance may have on the patient's overall performance. As with the clinical interview, careful observation of behaviors during testing is also important in interpreting performances that may be atypical for reasons that do not involve cognitive difficulties alone. Behaviors such as frequent sighing, moaning, pain behaviors, crying, and agitation are obviously notable and possibly suggestive of challenges to the validity of an assessment, no matter what they are motivated by.

The ability to thoroughly assess personality and psychopathology in a typical neuropsychological evaluation for the older adult is often perceived to be limited. Asking patients to complete lengthy personality inventories such as the MMPI-2 [29] after 2–3 h of testing is typically thought to place an unrealistic burden on a patient who might be experiencing difficulties with motor control, fatigue, and emotional exhaustion. Instead, more focused symptom measures such as the Beck Depression Inventory-II [30] or the Geriatric Depression Scale [31] are often employed to get a sense of whether there is notable neuropsychiatric symptomatology or, even more basically, distress. Scales specifically developed for use with older adults have typically limited the amount of somatic symptomatology assessed, presumably to avoid overdiagnosing disorders such as depression that have a significant somatic component [31]. Nevertheless, to the extent that good measures of somatoform symptomatology are thought to be important in the diagnostic differential, consideration should be given to lengthier measures, such as the MMPI-2. Lamberty [2] noted that few instruments allow the extensive assessment of somatoform features that the MMPI-2 and its various subscales do. Specifically, elevations on scales 1 and 3 are prototypical indicators of a high level of somatoform symptomatology, as is an elevation on scale RC1 (somatic complaints) from the MMPI-2-RF [32]. In addition, the commonly used FBS validity scale [33] is often significantly elevated in individuals whose primary issues involve reporting of physical discomfort or concerns about cognitive difficulties. The use of more extensively validated measures allows clinicians a greater level of certainty with regard to the effects of such symptoms on general cognitive performance as a function of the literature examining these relationships.

Finally, many neuropsychologists struggle with the prospects of providing feedback to patients in cases where the results will be, frankly, difficult to hear. In some ways, talking about somatoform symptoms with older patients is facilitated by the reality that many are legitimately fearful of the prospects of having a dementing disorder. This sets up one of a few reasonable "good news/bad news" scenarios confronted by neuropsychologists. In the event that an older patient's difficulties upon testing are thought to be due to variable effort, or that they are actually performing within normative expectations, there should be some solace in knowing that their cognitive functioning is actually reasonably sound and not a great cause for concern. This also provides a good basis for a discussion about the issue of mind–body problems. Most patients are receptive to respectful feedback about how anxiety, stress, and depression symptoms can impact cognitive efficiency. Intellectually, most anyone can understand that "unseen" factors can influence cognitive or

mental functioning and that there are many different ways that these problems might be treated. Again, older patients are often receptive to approaches that do not involve additional medications or surgical procedures. The remainder of this chapter focuses on a range of treatment options that are thought to represent some of the better options for working with older adults struggling with mind–body symptoms and issues.

Treatment Approaches with Older Adults

As theoretical conceptualizations and diagnostic criteria for somatoform disorders have evolved over time, so too have clinical treatment approaches expanded to better address the complex psychiatric and medical needs of patients with these conditions. Historically, treatment interventions consisted of intensive psychotherapy aimed at developing insight into psychic trauma thought to underlie the expression of psychological pain as physical symptoms. In such discovery, it was believed that patients would find relief from and resolution of their somatic ailments due to increased self-awareness and willingness to confront psychological issues more directly. These strategies were met with limited success, leading to a broadly held belief that individuals with somatoform conditions are, nearly by definition, incapable of insight and unlikely to benefit from psychological interventions. Somatizing patients became viewed as inconvenient and bothersome at best, or exasperating and draining of time and costly services at worst [34]. More recently, approaches in the field of health psychology have begun to bridge the mind/body gap between medical illness and psychological functioning. Additionally, much focus has been directed at reducing national health-care costs and finding empirically supported, cost-effective treatments for consumers of medical care. These factors have resulted in renewed interest in providing appropriate treatment interventions for individuals with somatoform conditions who are often heavy consumers of health-care services. Goals of treatment have appropriately shifted from symptom elimination and insight to symptom management, improving quality of life and daily functioning and decreasing service utilization.

In this section, we will highlight important treatment considerations in providing care to older adults with somatoform disorders. Empirically supported treatment approaches will be reviewed, and suggestions will be made for other psychotherapeutic strategies that may hold promise in working with these patients more effectively. Challenges specific to treating older somatizing patients are presented, with an eye toward how those obstacles might be overcome. Finally, practical recommendations are made regarding the important consultative role neuropsychologists can play in helping medical colleagues work more effectively with these patients.

Treatment Considerations

It is helpful to acknowledge the challenges involved in engaging somatizing patients in nonmedical treatments. Ironically, the first stumbling block may be a medical provider's hesitation to make a referral or a mental health clinician's hesitation to accept one. As noted above, there is a broad skepticism about the capacity of somatizing patients to benefit from therapy. This may stem from clinical training that stresses the importance of capacity for insight and a willingness to consider one's role in the development and maintenance of problems. Because the presence of somatoform conditions typically presumes a lack of conscious awareness of symptom production, with little or no insight into the condition, providers may conclude that there is little use in pursuing psychological treatment for these individuals. It is helpful to keep in mind that there are many other patient groups where insight is neither a prerequisite nor a goal of therapy. For example, patients with traumatic brain injuries with clearly decreased insight may still benefit from psychosocial intervention strategies. Likewise, individuals with deeply entrenched delusional belief systems are sometimes able to benefit from therapeutic strategies to decrease and manage distress more effectively and increase quality of life.

Patients with medically unexplained symptoms can be particularly challenging for healthcare providers. Countertransference reactions such as dislike, anger, and exasperation may cause medical providers to limit/discontinue contact with these patients and can interfere with thoughtful consideration of mental health referrals. Therapists may be unwilling to accept patient referrals and may discontinue interventions prematurely when patients are not cooperative or are otherwise aversive in session. Thus, providers (both referral sources and mental health clinicians) will benefit from acknowledging and attending to countertransference reactions. These reactions often mirror a patient's emotional state and can inform clinicians of the frustration, anger, and hostility that the patients feel in not getting the medical attention and relief they are seeking. Additionally, case consultation with peers and treatment teams can be used to get support and generate ideas about how to proceed in helpful ways.

Even when providers are open to referring for mental health services, many patients will vehemently protest such a referral, as they tend to be symptom-driven and seeking medical solutions. By this logic, they assume that mental health providers who do not prescribe medications or order medical tests could not possibly help with their medical problems. If patients do follow through with a mental health referral, they may present with a clear goal of convincing clinicians of the legitimacy of their physical symptoms, with much focus on the failures of the medical system to properly diagnose and treat them. They may be keenly attuned to any language that implies that their symptoms are "all in their head."

Considering the complexity and difficulty that SSDs can present, how do medical and mental health providers bridge this gap? Drawn from the field of addictions, motivational interviewing (MI) holds promise for facilitating readiness for therapeutic intervention and meaningful lifestyle change. First described in 1983, MI is a simple yet elegant counseling stance that meets patients where they are in their understanding of problems and readiness to explore options for improving their lives. The approach involves clinician-guided collaborative conversations during which the patient's personal goals, values, and reasons for wanting things to be different are elicited. MI is increasingly used by primary care providers and has been shown to be effective in preparing patients to commit to behavior change, not only in alcohol and drug abuse but also in individuals with chronic illnesses such as heart disease, obesity, and psychosis [35].

With a somatizing patient, a provider using MI would inquire about how somatic conditions impact an individual's life and how things would be different if physical concerns were less prominent. Frequent validation and reflection of concerns convey understanding and acceptance. Clinicians listen actively and probe for "change talk," (e.g., comments from patients suggesting a wish to resume former activities). Patients are encouraged to explicitly state what they would like to be different in their lives and what that suggests about their personal values and future goals. Ambivalence is common and validated genuinely. Inquiries from patients about *how* change is possible are used as opportunities to discuss treatment options. Typically, over the course of 2–3 guided conversations in which clinicians actively listen, elicit personal values, explore ambivalence, and highlight change talk, patients may begin to feel more empowered to improve their quality of life, even if pain or other somatic concerns persist.

When providers and patients are committed to explore treatments for somatic conditions, there are a number of empirically supported and potentially promising treatment interventions that may be of benefit. We describe several below.

Cognitive–Behavioral Therapies

Cognitive–behavioral therapy (CBT) is perhaps the most studied psychotherapeutic intervention with demonstrated effectiveness for somatoform conditions. These approaches are based on the notion that irrational thoughts and perceptions strongly influence mood states and behavior, resulting in the development and maintenance of depression, anxiety, and other psychosocial problems [36]. As such, CBT interventions help patients to examine and change unhelpful

cognitions, thereby influencing mood and behavior in a positive manner. In a review of randomized controlled treatments for patients with various somatic conditions (e.g., somatization disorder, medically unexplained symptoms, and others), 34 published studies involving 3922 patients were examined [37] with CBT (group or individual therapy) as the primary intervention in 13 of those studies. Positive outcomes were noted in 85% of the studies (11 of 13), as defined by treatment groups faring better on at least one outcome measure relative to controls. Similar conclusions were drawn by Sumathipala [38] who examined six previous review articles spanning hundreds of patients treated with CBT for somatoform disorders. In general, significant beneficial effects were noted both for individual and group CBT in reducing physical complaints and mood disturbances while improving quality of life. CBT was also noted to be more efficacious than antidepressant treatments. Caution was raised, however, about the lack of data on long-term outcome in the majority of studies reviewed. Unfortunately, neither of these comprehensive reviews included meta-analytic procedures or specifically examined age cohort differences in response to CBT, illustrating the need for future studies in this regard. Finally, a recent Cochrane review of nonpharmacologic treatments for somatoform symptoms also indicated that only CBT has been studied extensively enough to allow conclusions to be drawn [39]. According to this review, "CBT reduced somatic symptoms, with a small effect and substantial differences in effects between CBT studies. The effects were durable within and after one year of follow-up" [39].

Clinically, we have observed that older patients require some modifications to CBT due to age-related changes in their capacity to process and remember written material and to think flexibly when challenged to reframe their cognitions. This can usually be minimized by meeting with patients more frequently, slowing the pace of sessions, explaining concepts in more basic terms, and repeating/reviewing new information. One must also exercise caution to not invalidate patient's beliefs as "irrational," which quickly undermines trust and triggers defensive reactions. This can usually be addressed by resuming an empathic, reflective stance, and perhaps shifting the focus from changing cognitions to changing behaviors that stand in the way of their preferred lifestyles.

Physical and Complementary Integrated Interventions

Patients with somatoform symptoms are generally disinclined to seek assistance in mental health settings [2]. Rather, they are more likely to seek relief from physical symptoms, suggesting greater receptiveness to physically oriented rather than psychologically oriented interventions. The use of complementary and alternative or integrative health interventions such as mindfulness, yoga, and other physical exercise has proliferated in the past two decades, but there has been a relative paucity of empirically based studies examining their efficacy and effectiveness. Fortunately, considerable efforts are being made by the National Center for Complementary and Integrated Health (NCCIH), a division of the National Institutes of Health (NIH), to address this need. This division, established in 1999 as the National Center for Complementary and Alternative Medicine (NCCAM), was renamed NCCIH in 2014 to acknowledge that contemporary medicine and the lay public now often routinely integrate historically nontraditional, non-Western medicine practices into health care. The mission of NCCIH is to "define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care." NCCIH funds basic and applied scientific research with the goals of improving care for hard-to-manage symptoms and fostering health promotion and disease prevention. The interested reader is referred to the NCCIH website (nccih.nih.gov) which is a helpful resource highlighting currently funded studies and published results. Clinicians should always be mindful that somatizing patients may invest considerable time, energy, and expense into finding

relief from their symptoms. We can serve an important role in educating and cautioning patients about the likelihood of benefit from these approaches, based on knowledge derived from sound empirical studies.

An increasing body of literature supports the benefits of mindfulness-based approaches in managing a wide variety of medical ailments including chronic pain, cancer, fibromyalgia, migraine headache, and morbid obesity [40–43]. Success with these patient groups suggests the promise of similar benefit for a variety of patients with troubling somatic symptoms. Contemporary mindfulness-based interventions developed out of traditional Far Eastern medicine practices that have acknowledged for centuries that the mind and body are intimately related. Mindfulness-based strategies involve focused attention to bring body and mind perceptions into greater awareness while assuming a nonjudgmental, observer stance. In doing so, individuals may be able to move toward greater acceptance of negative feelings (both physical and emotional) that detract from contentment and appreciation of the present moment. Strategies of mindfulness may include mindful breathing, body scan, mindful sitting, standing, and walking, and mindful listening to sounds and thoughts [40]. These techniques are particularly adaptable for older patients who may have decreased mobility and pain tolerance that interferes with more active physical interventions such as physical therapy and exercise.

Yoga comprises a number of mind/body practices including physical postures, controlled breathing, meditation, and relaxation. With regular practice, yoga is thought to improve the functional balance of various organ systems and to relieve muscular and nervous tension, leading to improved general health and sense of well-being [44]. In a review article on yoga and mindfulness, Salmon et al. [45] pointed out positive outcomes (reduced symptoms, improved quality of life, or emotional well-being) in randomized trials of yoga with several patient groups including diabetes, chronic back pain, irritable bowel syndrome, fibromyalgia, chronic pancreatitis, lymphoma, and in healthy older adults. Because several of the yoga postures, or *asanas*, involve kneeling, stretching, and twisting, older patients may require modifications to accommodate their physical capabilities and pain tolerance. Fortunately, yoga is easily adapted and, in fact, encourages a stance of "start where you are," allowing participants to accept their current mind/body state and to work patiently within their present limitations.

While clinicians and patients may have reason to be optimistic and eager to try alternative/integrated approaches, the value of empirical data cannot be overstated in guiding clinicians' treatment recommendations or cautions given to patients. As an example, a double-blind, placebo-controlled NCCIH-funded study examined the utility of two forms of Reiki "healing energy" in treating patients with fibromyalgia [46]. Results showed no impact on pain reduction, physical and mental functioning, medication use, or health-care visits from direct touch or distant Reiki therapy relative to placebo interventions. The authors stressed the need for rigorous study of energy medicine therapies such as Reiki before recommending them to patients with chronic pain. In contrast, a study partially funded by NCCIH evaluated the benefit from Tai Chi in managing fibromyalgia symptoms. Participants were randomly assigned to either a Tai Chi group or an attention control group that received wellness education and practiced stretching exercises. Results showed that the Tai Chi group had greater reduction in Fibromyalgia Impact Questionnaire scores, as well as significantly greater improvements in mood, sleep, and quality of life relative to the attention controls [47].

Older adults may also find benefit in regular physical exercise or perhaps the social support afforded by attending exercise classes. Peters et al. [48] conducted a randomized controlled study of aerobic exercise in a large sample (n = 228) of patients ranging from 9 to 73 years with persistent medically unexplained symptoms. All participants were scheduled to attend 20 1-h sessions of either aerobic exercise or stretching, the control condition. Measures of

health-care use and symptoms, emotional state, and perceived disability were completed before, during, and 6 months after training. Results showed that primary care consultations and prescriptions were significantly reduced in the 6 months following training for both groups, with no particular benefit of aerobic training over the stretching control group. The extent of reduction in medical care was dependent on the number of sessions attended. The authors suggested that these positive outcomes may have been resulted from group support from fellow sufferers and counseling by physiotherapists, resulting in reduced reliance on general practitioners and medications for symptom management.

Psychotropic Medications

Systematic reviews and meta-analytic studies provide good support for beneficial effects of antidepressant medications in the treatment of somatoform disorders. While no meta-analysis has examined treatment benefits specifically for older patients, many samples in the available meta-analytic literature include older adults with medically unexplained illnesses and chronic pain. In 1 meta-analysis of 94 placebo-controlled studies, patients taking antidepressants showed more than 3 times greater improvement in medically unexplained symptoms compared to placebo controls [49]. Benefits were seen both for tricyclic antidepressants (76% of studies with positive outcomes) and selective serotonin reuptake inhibitors (SSRIs; 47% of studies with positive outcomes), though there were an insufficient number of studies with SSRIs in this meta-analysis to conclude that tricyclics were of greater benefit than SSRIs. In a smaller meta-analysis of 11 randomized controlled studies using antidepressants to treat somatoform pain disorder and psychogenic pain, patients treated with antidepressants showed significantly decreased pain intensity with a moderate effect size relative to patients treated with placebo [50]. Onghena and Van Houdenhove [51] also noted moderate to large effect sizes for treatment of chronic pain patients with antidepressants in a meta-analysis of 39 studies. It also has been shown that antidepressants that act on both serotonergic and noradrenergic receptors (tricyclics and SNRIs) may have more analgesic effects than other antidepressants [52].

While the impact of medication treatment with older patients with somatic symptom disorders has not been extensively studied, psychiatric consultation with a geriatric psychiatrist is recommended, especially when patients have multiple health conditions and medications that can complicate medication management. Typically, a "start low and go slow" dosing approach is taken, as older patients may experience (or anticipate) side effects which prompt them to quickly discontinue psychotropic medications before any benefit can be appreciated. Again, many older somatizing patients will resist a referral to psychiatry, both because of a preference for medical solutions and their greater generational perceived stigma of being seen by a mental health provider. This may be lessened by assurances that they are not being abandoned by their medical providers and will continue to be seen for follow-up care and renewals of psychotropics. A similar approach was found efficacious by Hoedeman et al. [53] who showed improved health outcomes in somatizing patients whose psychiatrists sent a consultation letter to the patient's primary care providers about diagnosis and treatment options to be incorporated into their medical treatment plans. In an older study, Smith et al. [54] used a crossover randomized controlled design to evaluate the efficacy of psychiatric consultation in reducing medical costs of somatizing patients. After psychiatrists consulted with the patients' primary care providers, quarterly health-care charges declined by 53% in the treatment group and were significantly lower than controls. After the control group crossed over, their quarterly medical charges declined by 49%. They concluded good benefit from psychiatric consultation to physicians in reducing costs, without affecting health status or patient satisfaction with health care.

Family Psychoeducation and Therapy

Clinicians often hear from exasperated spouses and family members of older somatizing patients, imploring clinicians to "do something" to relieve the patients' suffering or worries and, in turn, lessen caregiver burden. To date, no studies are available that speak of the efficacy of family interventions in working with patients with somatoform conditions. However, our clinical experience has suggested that couple/family interventions are sometimes just as or more effective in reducing somatic complaints and improving quality of life than individual interventions. Family counseling offers the opportunity for concerns to be aired and validated, reassurances to be provided, and coping strategies to be explored. Behavioral approaches such as pleasant-event scheduling (e.g., weekly brunch) can reduce loneliness and boredom and increase opportunities for physical activity while distracting patients from physical discomfort and worries. Family members can be encouraged to reinforce positive healthy behaviors while reducing inadvertent reinforcement of somatic complaints. Narrative therapy approaches such as those developed by White and Epston [55] invite participants to develop a richer narrative, or story, about an individual's life and capabilities while naming and externalizing the problem (e.g., "the fibromyalgia") as separate from the person. Narrative therapy stresses that "the person is not the problem; the problem is the problem." Patients and family members are interviewed to focus on "exceptions" to the problem (e.g., "When did you not allow the fibromyalgia to get in your way this week?"). They are also encouraged to team up against the problem rather than each other and to develop ways to limit the problem's influence in their lives. By developing these broader narratives, patients often begin to view themselves as more than a sick person, with greater self-efficacy and hope to be able to live more contentedly. Family members, by extension, may also experience decreased caregiving stress and have renewed energy to continue to support their loved ones in helpful ways.

Primary Care Interventions

Neuropsychologists are uniquely suited to objectively assess brain dysfunction as well as psychological conditions that may influence cognitive performance and daily functioning. In providing feedback to referral sources, we also have the opportunity to serve an important consultative role regarding how to work more effectively with an older somatically focused patient. Some practical recommendations include the following:

- Determine a single "go-to" provider (e.g., PCP, nurse practitioner) with whom the patient can establish a collaborative alliance. This helps to reduce overlapping providers and opportunities for "splitting" or pitting of one provider against another regarding treatment approaches.
- Plan regularly scheduled appointments to reduce emergency calls or visits.
- Explicitly state that the goal of medical contacts is functional restoration and maintenance of health and well-being, not to find a cure for conditions or to eliminate all somatic worries.
- Proactively ask about new symptoms and current life stressors at each visit, making a point to acknowledge and validate distress while providing reassurance that grave conditions have been ruled out.
- Limit medical testing and referrals to specialists that patients may seek for reassurance but are not medically indicated.
- Avoid opiates, anticholinergic medications, and polypharmacy whenever possible, to reduce potential clouding of cognition.
- Initiate brief conversations about the mind–body connection and how chronic physical conditions often take a toll on mood, sleep, and quality of life.
- Monitor for depression, anxiety, and substance abuse issues and seek psychiatric consultation/referral when indicated.
- Characterize referrals for mental health services as one of the many available tools in

medicine to address their complex needs. Reassure patients that they will continue to be followed for regular medical care.

Conclusion

Many clinical challenges exist for neuropsychologists and others providing services to older patients with somatic symptom disorders. In this chapter, we have highlighted traditional and emerging schemes for describing somatic symptom disorders, as well as the difficulties inherent in identifying these problems in patients whose baseline often involves physical symptomatology related to normal aging. Physical concerns can impact the assessment process, and it is important to have strategies for dealing with behaviors and complaints that can limit the ability to conduct a complete assessment. In an era that emphasizes empirically supported treatments, it is important to consider treatments that have been proven effective, even if the evidence base with more specific groups of patients have not yet been extensively studied. Promising treatments that involve mindfulness-based approaches appear particularly well suited for somatizing patients given their emphasis on acceptance and increased awareness. Further, many complementary and alternative approaches appeal to somatizing patients because of a seeming lack of focus on psychological and emotional and are increasingly integrated into standard medical care. Neuropsychologists are in a unique position to evaluate, consult with, and recommend effective interventions for their older patients. Careful attention to the patient's needs and a collaborative approach can improve outcomes in these challenging patients, and this should be the goal of all neuropsychologists working with older adults.

Clinical Pearls

- Always attempt to obtain thorough clinical records regarding the patient's health concerns. Be mindful of whether or not the records come from experienced geriatric clinicians.
- Carefully observe patient behaviors that suggest difficulties with pain, mobility, affect, and general cognition. Attend to the context in which these behaviors are emitted.
- Consider information from family members and other collateral sources judiciously, but be aware of the relationship with the informant and the clinical context and how that might impact the nature of the report.
- Understand that over- and underestimating the impact of somatic symptoms result from not adhering to the first three suggestions.
- Be prepared for older patients to struggle with completing the neuropsychological evaluation process secondary to a range of physical, perceptual, and emotional challenges.
- Do not underestimate the importance of standardized assessment of somatic and emotional symptoms, even if older patients have limited stamina.
- Take advantage of the opportunity to reinforce an understanding of the complexity of mind–body relationships while sharing encouraging news about a lack of cognitive findings in a positive way.
- Familiarize yourself with empirically supported treatments like MI and CBT, but understand that they can sometimes be impacted by cognitive limitations in older patients.
- Be aware of and open to complementary and alternative/integrated approaches like mindfulness meditation, yoga, and Tai Chi that may be preferable to psychologically oriented therapies for somatizing patients.
- Use resources such as NIH's National Center for Complementary and Integrated Health (NCCIH) to stay abreast of current research findings and help guide treatment recommendations for patients.
- Work closely with family members to reinforce a better understanding of the interrelatedness of stressors, somatic symptoms, and the range of treatments that can be used to lessen the impact of these symptoms.
- Work collaboratively with older patients' primary care providers to maximize the benefit of your consultation, minimize the overuse of

medications, improve therapeutic recommendations, and improve patients' and families' overall adjustment and quality of life.

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22 After the Diagnosis of Dementia: Considerations in Disease Management

Steven Hoover and Mary Sano

Introduction

When an individual begins to notice a decline in his/her memory and cognitive functioning, the instinctual reaction is often one of denial and fear. People often rationalize these changes as simply being a part of normal aging, feeling as if the concerns of friends and family are excessive and unnecessary. The additional stigma of being formally diagnosed with dementia creates a challenge to coping strategies for both patients and their families. For decades, both the general public as well as the medical community held the misconception that individuals with cognitive deficits or dementia, even in the initial stages of the disease, lacked insight into their disease and were unable to grasp the implications and future repercussions of their diagnoses. However, recent research provides increasing evidence that even those with dementia, including Alzheimer's disease, retain a level of awareness into their own health and prognosis [1]. In addition, the progression of dementia can be quite variable [2]. Particularly during the early stages of the disease, those with dementia are often acutely aware of not only the relative impact of the disease on their own functioning but also of the responses and reactions of others to their diagnosis. This reaction is exacerbated by the misconceptions about the disorder promulgated by popular culture, such as comparisons of those with dementia to the "walking dead" [3]. These factors create a very vulnerable population with unique needs and special considerations.

When dealing with a patient who has been recently diagnosed with dementia, it is crucial to acknowledge that this is a disease and there are approved treatments and recommendations for medical management. It is also important to facilitate an understanding of what it means to be diagnosed with dementia, its course, and prognosis. This chapter will describe some of the hurdles that lie ahead for patients and families and provide information to help manage these hurdles. It is important not only to educate those coping with a diagnosis of dementia but also to instill perspective and ensure quality of life for both patients and their families. This chapter aims to discuss frequently encountered questions, special considerations, and resources available to this population. It also discusses the importance of identifying and treating comorbid

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behavioral conditions and nonpharmacological approaches to treatment of both the patient and their family/caregivers. The identification and use of community resources and social services by patients and their families will also be discussed. The opportunities available to patients to participate in dementia research and clinical trials are described and the crucial role these studies play in ensuring continued advancement in understanding both the disease and its treatment.

Treating Dementia

Although there are approved treatments for the cognitive symptoms of dementia, the effectiveness is modest (see Table 22.1), with cholinesterase inhibition being the most established approach to treatment. This approach blocks the action of the enzyme acetylcholinesterase (AChe), an enzyme that breaks down the neurotransmitter acetylcholine in the synapse. The inhibitors permit the transmitter to sustain activation of the postsynaptic neuron, allowing the synapse to remain active longer. This class of agents has been used for the treatment of Alzheimer's disease since 1993, when tacrine was first approved. Tacrine, the first drug in this class, is not commonly used today as it is short acting, requiring treatment four times a day and routine assessment of liver enzymes. The second agent to be approved in this class, donepezil, has proven easier to use with once-a-day dosing. Donepezil is indicated for the treatment of Alzheimer's disease and has been demonstrated to be effective in patients with mild, moderate, and severe disease. Donepezil is approved for mild to moderate (5 or 10 mg) as well as severe disease (10 and 23 mg). Other drugs in this class include galantamine, which is available in a sustained release at a dose of 16–24 mg per day and in a generic form. Rivastigmine, another agent in the

Table 22.1 Pharmacological treatments of dementia

Drug	Drug class	Indication	Target dose	Most common side effects
Tacrine[a]	Reversible acetylcholinesterase inhibitor	Mild to moderate dementia	40–160 mg/day (10–40 mg, four times daily)	Transaminase elevations requiring LFT monitoring
				Nausea and/or vomiting, diarrhea, dyspepsia, and anorexia (dose dependent)
			4-week titration	Myalgia, anorexia, and ataxia
Donepezil	Reversible acetylcholinesterase inhibitor	Mild to moderate AD	5 and 10 mg daily	Nausea, diarrhea, vomiting, insomnia, muscle cramp, fatigue, anorexia
			1-week titration	
		Severe AD	10 mg	Nausea, diarrhea, vomiting, anorexia
			23 mg	
Galantamine	Reversible acetylcholinesterase inhibitor	Mild to moderate AD	16–24 mg/day (8–12 mg twice daily)	Nausea, vomiting, diarrhea, weight decrease, anorexia, dizziness, headache, depression
			OR	
			16–24 ER daily	
			4–8-week titration	
Rivastigmine	Reversible acetylcholinesterase inhibitor	Mild to moderate AD	6–12 mg/day (3–6 mg twice daily)	Nausea, vomiting, anorexia, diarrhea, dyspepsia, dizziness, headache
		Dementia of Parkinson's disease	2–6-week titration[b]	
Memantine	NMDA antagonist	Moderate to severe AD	20 mg (10 mg twice daily)	Dizziness, headache, constipation, confusion
			3-week titration	

AD Alzheimer's disease, *ER* extended release formulation

[a]Tacrine, the first drug to be approved for the treatment of AD, is rarely used because of the burden of QID administration and the need for routine assessment for liver enzyme elevations

[b]Available as liquid and patch

same class, is available both as an oral agent and as a transdermal preparation and has been approved for the treatment of mild to moderate dementia, including Parkinson's dementia, at a dose of 6–12 mg per day, given as twice-a-day dosing. The side effect profile of these agents includes nausea and vomiting in 10–30% of the cases, which may be reduced with exposure. Although cholinesterase inhibitors have been studied in many types of dementia, approval is limited to Alzheimer's disease and Parkinson's disease. There is anecdotal evidence that cholinesterase inhibitors may be ineffective or cause clinical worsening in frontotemporal dementia [4]. Although not approved for treatment of mild cognitive impairment (MCI), several trials have demonstrated the benefit of cholinesterase inhibitors on cognitive, functional, and global clinical outcomes.

Memantine is another agent approved for the treatment of moderate to severe AD. It is an orally active NMDA receptor antagonist. The recommended starting dose is 5 mg once daily, and the recommended target dose is 20 mg per day. Despite several trials, to date there is no evidence that this drug has an effect in mild disease. There is evidence that the combination of memantine and donepezil is more effective than donepezil alone in the moderate to severe dementia population [5], which has been the basis of usage of memantine in combination with cholinesterase inhibitors. While the benefits from this agent have been labeled as minimal, it is robust with most trials demonstrating statistically significant benefits on measures of cognition and of clinical global change in subjects with AD [6].

Vitamins, Supplements, and Medical Foods

Many vitamin and neutraceutical regimens have been examined in studies to determine benefit in subjects with AD. For example, a multicenter randomized trial of vitamin E in moderately severe AD subjects demonstrated an effect in clinical outcomes, including delayed time until nursing home placement [7]. However, no benefit was identified in studies in milder individuals with MCI in either cognition or clinical outcomes [8]. Lowering of homocysteine through regimens of folate, vitamin B6, and B12 has also been studied with no evidence of benefit in patients with mild to moderate AD [9]. Further, there was some indication of increased depressive symptomatology in those receiving the vitamin regimen [9]. Omega-3 fatty acids have also been proposed as treatments for cognitive loss and dementia. A trial of DHA demonstrated no benefit in clinical or cognitive outcomes in AD, even among those who had relatively low levels of omega-3 in their diet [10]. Effects in malnourished elderly populations have not been studied, but these are infrequently seen in US aging cohorts.

Medical foods, a relatively new category regulated by the FDA as part of the Orphan Drug Act in 1988, are defined as products intended for the specific dietary management of a disease or condition that has distinctive nutritional requirements, established by medical evaluation. In contrast to FDA-approved drugs, no premarket review process exists for medical foods. Instead, they are regulated after they have become available to consumers. Axona, an example of a medical food that became available in 2009, claims to target the nutritional needs of people with AD. Specifically, it has been proposed that AD hinders the brain's ability to break down glucose and Axona provides an alternative source of glucose that the brain can use for energy. Axona has been shown to improve cognition in AD [11], and a review of available data indicates relative safety [12]. Another medical food, Souvenaid, which is not currently marketed, is now in clinical trials. A single trial reported in 2010 describes small positive effects on memory testing but not on other traditional measures of cognition, function, and quality of life [13]. In general, there is little evidence of benefit to recommend medical foods for the treatment of AD; however, there appears to be little identified risk with their use.

Nonpharmacological Interventions for Cognitive Symptoms

Nonpharmacological interventions have been proposed for the range of symptoms in AD and other dementias. In a recent review that included both randomized and nonrandomized studies, Hulme et al. [14] identified 33 studies of nonpharmacological interventions, 10 of which addressed cognitive symptoms (described in Table 22.2). Of these, eight also examined functional and behavioral outcomes. The single most common nonpharmacologic approach described in the literature is cognitive stimulation/cognitive training. While individual studies report moderate effects on a number of different cognitive domains, no single domain was consistently improved. There is great diversity in the type of training proposed in these studies, making it difficult to prescribe any single approach. Counseling was found to have no beneficial effect on cognition or any other symptom. Two research groups studied transcutaneous electrical nerve stimulation (TENS) and found some cognitive benefit of very brief duration but no lasting benefit.

In general, the critical elements of nonpharmacological interventions are not well described, study designs are weakened by poor or absent control groups, and effects are poorly characterized. Most importantly, there is little information on how these interventions might be translated for broad use, including limited discussion on required training of individuals who deliver the intervention, and no information on the cost or required resources needed to disseminate the intervention in the community.

Importance of a Comprehensive Physical and Psychological Exam

When a patient receives a diagnosis of dementia, it is crucial to continue to address the presence of comorbid medical and psychiatric disorders. The presence of comorbid disorders may exacerbate a patient's symptoms and create additional burden that can challenge the patient's quality of life. In addition, the presence of these symptoms can have a significant influence on family members as well. These comorbid disorders can also increase the use of health-care resources and, ultimately, the outcomes of care [15, 16]. Many medical and psychiatric comorbidities can be treated with either pharmacological or nonpharmacological interventions. Identification of these conditions is the first step, and appropriate management and follow-up care are essential.

Depression

Depression is common in the aging population and is highly associated with cognitive loss and dementia. Prevalence estimates suggest that approximately 20–25% of those with AD also experience clinical depression, with some estimates as high as 50% [17]. Depressive symptoms in dementia may be due to the perceived loss of independence and the patient's awareness of their own cognitive decline, particularly in the early stages of the disorder [16]. Depression has also been associated with increased aggression and agitation in those with dementia [18]. Caregivers report that a patient's depression is the single most distressing symptom, and high rates of depression are also observed in caregivers themselves [19].

Depression and dementia have several overlapping symptoms, and the differential diagnosis can be difficult. Special diagnostic criteria have been proposed by the National Institutes of Mental Health (NIMH) in order to differentiate depressive symptoms associated with the patient's primary cognitive decline or dementia and those due to a secondary diagnosis of depression [20]. The guidelines indicate that when diagnosing depression, symptoms that can better be explained by the patient's primary dementia diagnosis should be excluded (e.g., increased apathy). For the diagnosis of depression in the presence of dementia, it is recommended to rely more on objective evaluation of symptoms (i.e., observed tearfulness or more easily discouraged, presence of irritability, or social isolation) rather than exclusively on self-report of depressive

Table 22.2 Nonpharmacological treatments for the cognitive symptoms of dementia

	Description	Effectiveness	Weaknesses
Cognitive stimulation therapy/cognitive training	Focus on information processing rather than rehearsal of factual knowledge	May work for improving memory, cognitive functioning, neuropsychiatric symptoms, behavior, depression, quality of life, learning, and activities of daily living	Less effective in more advance stages of dementia
Light therapy	Improving the patient's exposure and timing to natural and artificial light sources	May work when used to improve behavioral and psychological symptoms (sleep, behavior, mood, agitation) and cognition	–
Music therapy	Exposing patients to music	Effective in reducing behavioral and psychological symptoms, including agitation, aggression, wandering, restlessness, irritability, social and emotional difficulties, and improving nutritional intake	Effect of therapy did not persist over time
Physical activity	Promoting physical activity such as dance, support, drama, etc.	Effective for behavioral and psychological symptoms and functional ability. Moderate intensive exercise may reduce wandering and improve the quality of sleep	–
Reality orientation	Reality orientation aims to decrease confusion and dysfunctional behavior patterns in people with dementia by orientating patients to time, place, and person	May work to improve cognitive ability, depression, and apathy	Inflexible and may be confrontational in its administration
Reminiscence therapy	Involves discussion of past experiences. Photographs, familiar objects, or sensory items are used to prompt recall	May work to improve cognition, mood, and general behavior	–
Snoezelen/ multisensory stimulation	Consists of visual, auditory, tactile, and olfactory stimulation offered to people in a specially designed room or environment. Used to increase the opportunity for communication and improved quality of experience	May improve disruptive behavior, mood, depression, aggression, apathy, cognition, social/emotional behaviors, wandering, and neuropsychiatric symptoms. May reduce apathy in the latter stages of dementia	Many improvements reported were not statistically significant. Overall beneficial effects were not sustained
Transcutaneous electrical nerve stimulation (TENS)	The application of an electric current through electrodes attached to the skin	May produce short-term benefits (directly after treatment) in recall, face recognition, and motivation	–
Validation therapy	Focuses on the emotional content of what someone is saying rather than the factual content. The patient is validated by acknowledging the emotions being expressed	May improve affect and behavioral disturbance	–

Adapted from Ref. [14]

symptoms. Depressive symptoms include changes in mood; decreased positive affect; changes in sleep or appetite; psychomotor changes; fatigue; feelings of guilt, worthlessness, or hopelessness; increased discouragement or tearfulness; or possible suicidal ideation, and treatment should focus on these specific symptoms. It is helpful for patients and their families to understand which symptoms are likely to improve as a result of treatment and which are not. For example, antidepressants are unlikely to have a noticeable impact on a patient's memory or level of cognitive functioning. However, treatment of depression can have an impact on a patient's mood and their ability to function on a daily basis.

The pharmacology of depression in the presence of dementia has some special considerations. Tricyclic antidepressants are contraindicated in dementia patients due to their anticholinergic activity, which can adversely affect cognition [21]. Selective serotonin reuptake inhibitors (SSRIs) are often used in this population; however, these medications have been associated with an increased risk of falls and to a lesser degree with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [22].

Both cognitive and behavioral therapies have shown to produce improvement in depressive symptoms in a dementia population [23]. Cognitive strategies are more successful in the earlier stages of the disorder when a patient's cognitive abilities are still conducive to this style of therapy [23]. Cognitive therapy has been successful in challenging the patient's negative thought patterns and reducing cognitive distortions [24].

When depression is reactive, focusing on increasing pleasant events and interactions and minimizing aversive events that maintain the depression can be helpful [25] and can reduce disruptive behaviors [26]. Behavioral therapies can be used at all stages of dementia severity to focus attention on simple and familiar single-step tasks that will likely lead to success and avoid demanding activities with a high probability of failure [27].

Anxiety

Anxiety may be common in the early stages of cognitive loss when a patient's insight into his/her cognitive decline is high. At any stage of dementia, anxiety has been associated with an increased irritability, aggression, and pathological crying [28], as well as repetitive or stereotypical behaviors such as pacing, chanting, or focused motor movements [29]. Anxiety can impair the patient's ability to function, including refusal to allow necessary care. These symptoms continue to increase as an individual's cognitive decline and confusion become more severe [25]. Anxiety is present in more than 20% of patients with cognitive decline or dementia [30]. Anxiety often manifests as irritability, fear, paranoia, aggression, or depression [16]. Patients can have difficulty with articulating their emotional and psychiatric symptoms, particularly in the later stages of the disorder. It is often preferable to treat a patient's symptoms without medications because the most commonly used pharmacological agents have well-established side effects. For example, benzodiazepines, which may be useful as antianxiety agents in younger individuals, can exacerbate cognitive deficits and be associated with increased falls [31], and both the typical and atypical antipsychotics can be associated with significant risks in older adults, including increased mortality [32]. Behavioral management focuses on simplifying the environment, providing a structured routine, reducing choices, and avoiding new learning. It is also useful to minimize anticipation of either positive or negative events, keeping a patient focused on the present day [27]. Anxiety may manifest as repetitive questioning to family members or caregivers, despite efforts to continually providing newer or better answers. For these patients, the answer to the question is not as important as maintaining contact with the caregiver. It is typically the patient's need for reassurance and comforting that leads to additional questioning [27], thus providing a supportive and calming environment can be effective.

Treatment with antidepressants (e.g., SSRI) has been reported with some success [22]. Cholinesterase inhibitors have been shown to reduce symptoms of anxiety in those with minimal symptoms [33], but there is little evidence that they can successfully treat more severe anxiety. In general, treatment with benzodiazepines should be avoided as they have been shown to increase the risk of falls and delirium [16, 34]. If benzodiazepines are employed, it is generally preferable to use nonoxidated, short-acting benzodiazepines (e.g., lorazepam) because they are less likely to accumulate and lead to eventual toxicity [35].

Other Behavioral Disturbances

Delusions and hallucinations also occur in dementia, tend to increase as a patient's disease progresses, and have been correlated to increased agitation and aggression [36]. For some, these delusions may be an attempt to organize information in the face of poor memory. For example, commonly reported delusions such as the belief that people are stealing things (occurring in 18–43% of dementia patients), that the patient is being abandoned (3–18% of dementia patients), and that the patient's spouse is being unfaithful (1–9% of dementia patients) [37] may be a result of forgetting the antecedent observations (e.g., losing things, not recalling the details of a planned absence of a spouse). Delusional or paranoid beliefs are associated with changes in a patient's daily routine or the presence of strangers [27]. The onset of delusional beliefs may be an indication that the patient's current level of activity is too stressful. Proper treatment of anxiety can also assist in alleviating suspicion and the formation of delusions. These environmental circumstances can often be avoided if a caregiver is made aware of them.

Hallucinations occur in 12–15% of patients with AD and can be auditory or visual [38]. However, in some cases, these experiences may actually represent an independently treatable disorder. For example, the presence of both tactile and visual hallucinations may actually indicate a reversible drug-induced delirium (described below), and auditory hallucinations instructing the patients to harm themselves may be a symptom of clinical depression [27]. Hallucinations may also be a manifestation of a patient's specific wishes and fears, particularly the fear of abandonment [27]. This fear is often improved by keeping caregivers visible and providing a controlled environment, adequate distractions, and continued reassurance. Pharmacological treatment of these symptoms can be quite difficult. Studies have shown modest improvement of hallucinations, delusions, and the accompanying agitation in dementia patients when being treated with antipsychotic medications such as olanzapine and risperidone [16, 39]. In addition, these medications have significant side effects including sedation and extrapyramidal symptoms. In one study, quetiapine was associated with worsening of cognition and no improvement in psychiatric symptomatology [16]. Both conventional and atypical antipsychotics have also been linked to increased mortality and risk of cerebrovascular events in elderly patients [40].

Aggression

Aggression in patients with dementia is the most common reason that caregivers contact their clinicians requesting assistance [41] and is a common reason for placement a residential facility [42]. Physically aggressive behaviors are estimated to be present in 25–50% of community-based dementia patients and even more frequently within a nursing home setting [43]. Some patients will experience increased agitation that is isolated to later in the day (sundowning), which is particularly common in moderate to severe dementia. This may be related to fatigue or the loss of visual cues in the environment. An early awareness of these behavioral problems may help in planning for future care but must be weighed against anticipation anxiety in family members.

Treatment of aggressive behaviors requires identifying the underlying reason for the agitation. Some behavioral interventions for

aggressive behaviors have shown promise. When aggression occurs as a consequence of a patient's anxiety or delusional beliefs, then the contributing symptoms should be addressed as described above. Reassuring patients and providing them with a controlled environment can alleviate their fears and suspicions. Marginal success has been noted in studies involving physical exercise, distraction-based interventions, and increased caregiver training [44]; however, additional research is necessary in order to determine their broad efficacy.

Delirium

Delirium is a sudden change in mental status characterized by severe confusion that is attributed to a discrete physical or mental illness that is usually temporary and reversible [45]. Within an elderly population, the most common causes of delirium are electrolyte disturbance (often from dehydration), infection, and postsurgical recovery. The presence of a dementia diagnosis increases a patient's susceptibility to developing a delirium [46], and this risk continues to increase as the dementia becomes more severe [47]. Prevalence estimates of delirium within a dementia population range from 22% to 89% in community and hospital studies [16], increasing the risk of developing delirium roughly twofold over elderly individuals without dementia [48]. Benzodiazepines increase the duration of a delirium and as a result should primarily be used when the delirium is related to withdrawal from alcohol, a benzodiazepine, or another cross-tolerant sedative hypnotic [34]. After a delirium is successfully treated, the underlying cognitive and emotional symptoms of primary MCI or dementia will remain.

Considerations for Specific Non-Alzheimer Dementias

Vascular dementia is the most common dementia after AD. Memory impairment may be secondary, while executive and attention deficits are typically more prominent, particularly early in the disease course. Vascular dementia is associated with increased depression and anxiety [49] and disrupted sleep–wake cycles [50]. It is important to consider that vascular dementia and AD may co-occur, and the expectation would be a combined symptom constellation.

Another relatively common neurodegenerative disorder is Lewy body dementia (LBD), which is estimated to affect 1.3 million people in the United States. It is characterized by cognitive impairment, parkinsonian motor symptoms, fluctuating mental status, and visual hallucinations [51]. Rapid eye movement (REM) sleep disorders [52] and an increased sensitivity to neuroleptics [53] have also been associated with LBD.

Frontotemporal dementia (FTD) represents 10–20% of all dementias and is characterized by changes in behavior, personality, and language or motor skills, but memory may be relatively intact. The most disturbing symptoms in FTD are inappropriate and disinhibited behaviors in social and work settings, including impulsivity, compulsivity, and verbal outbursts. Patients may have difficulty organizing activities, and self-care may be impaired resulting in increasing dependence. The average age of onset is 60, although earlier and later onset have been observed. Treatments with cholinesterase inhibitors are not effective and may actually have deleterious effects [54, 55].

Utilizing Support Groups, Social Services, and Planning for the Future

Patients and their families may benefit from education and psychosocial services to provide support and assistance with coping as they confront a dementia diagnosis [56]. Services are most useful when tailored to consider the patient's specific level of functioning, support structure, and cultural background. Education and services can also address legal issues and financial planning. Early attention to these issues can take advantage of a patient's ability to participate in their own decision-making and treatment planning [57].

While the availability of resources and services may vary in different locations, the current chapter attempts to discuss the types of options available and where to begin looking for appropriate groups and services.

Patient Support Groups

An effective approach for providing support and coping strategies for patients, particularly in the initial stages of the disease, is to connect with others experiencing the same emotions. The group setting can provide evidence that one is not alone and provide comfort in shared experiences. In response to this need, the Alzheimer's Association (www.alz.org) has instituted programs to help bring these patients together and provide both education and support. These groups allow patients to share their experiences and concerns, learn more about the disease, reduce feelings of isolation, and assist with coping and long-term planning [58]. These groups are often flexible in structure to accommodate an individual patient's availability, level of function, specific concerns, and inclusion of caregivers.

Patients may be resistant to the idea of attending support groups due to reluctance to accept their diagnosis or fear of having their stereotypes of the disease confirmed; however, several studies have explored the efficacy of these early-stage support groups and have consistently shown them to be beneficial. Patients enrolled in these programs report an increased sense of camaraderie, affirmation, improved confidence, education, and a decrease in their perceived helplessness and frustration [58–61]. Caregivers also reported increased awareness and acceptance and stated that they helped to initiate difficult discussions about planning for the future (e.g., future medical, legal, and financial planning) and improved caregiver education regarding available community resources [58, 61]. Those with the greatest level of distress at enrollment demonstrate the most significant improvement in quality of life by attending these groups [58].

Support Groups for Caregivers

Caregiving by family and friends can prove both satisfying and challenging. For informal caregivers, challenges include a shift in a relationship confronted by the patient's loss of independence and the caregiver's new responsibility, which requires time and energy, and can take a psychological toll. This toll can result from the loss of companionship of the patient, the weight of the responsibility, and the uncertainty regarding the course of the illness. High rates of depression and increased medical problems are observed in caregivers [19]. Caregiver support groups provide an opportunity to exchange information and benefit from the experience and knowledge of those in a similar situation [62]. Within these groups, caregivers are offered the opportunity to discuss their stressors and problems and receive emotional support [63]. Support groups have been shown to provide a positive effect on a caregiver's knowledge, increase a caregiver's well-being, and reduce the sense of burden [64]. Mittelman et al. [65] demonstrated that structured caregiver support groups had direct effects on patients including delay in nursing home placement by nearly 1 year. National organizations such as the National Association of Area Agencies on Aging (www.n4a.org) can provide information on resources for programs, training, and support.

Support groups are underutilized, and estimates of participation range from 5% to 14% of caregivers [62]. It is important to make caregivers aware of the options that are available to help them cope with these stressors and to help them understand that attending caregiver support groups is not an indication of "failure" by the caregiver.

Social Services and Patient Care

Service needs in aging and dementia may include care for patients as well as support for caregivers; these needs will change over time and require reassessment during the course of the disease. At each stage of the disease, service goals include

maximizing independence in a safe environment for the patient and supporting the social, psychological, and physical needs of the caregiver. A case manager can be useful in assisting with identifying these services. Typically trained in social work, their tasks are to assess needs, including the needs of the caregiver, and establish care planning and implementation. This may include an assessment of current resources and financial constraints, evaluation of coexisting medical needs of the patient, and establishing the capacity of the informal caregiving provided by family and friends. The assessment may identify a need for patients and family members to acknowledge their limitations and accept help. Case management can be particularly helpful for families who oversee care from a distance and when the process begins as early as possible so that continuity of care can be achieved.

Online resources are also available for managing care needs. For example, the Alzheimer's Association provides a CareFinder service at www.alz.org/carefinder. While web-based resources can be helpful and easy to access, it is important to understand their sponsorship, purpose, and mission. Those sponsored by patient advocacy groups such as Alzheimer's Association or by governmental entities such as the National Institute on Aging usually vet information through credible sources and disclose financial conflict. While providing easy-to-use information, commercial sites are likely to have product sales as a goal, and caution should be used.

During the initial stages of dementia, the need to modify the environment may be minimal, and the patient may remain very active in the decision-making process. If informal caregiving is available, insuring that the caregiver is supported and stable may be all that is required. Supplemental services at this early stage may include identifying support groups, community day programs, or respite care. Additional support in the home may include help with housekeeping and companion services. Assistance from a home health aide may also be useful if medical problems interfere with independence. Home health aides can also provide assistance managing medications and appointments and facilitate travel. As the dementia progresses, patients will require more assistance including additional medical help such as a visiting nurse or other professional, constant supervision, or even hospice for comfort care at end stages of the disease. For the majority of patients, at-home services such as visiting nurses and home health aides are sufficient throughout the progression of the disease. In addition, insurance providers and Medicare typically supply coverage for respite services designed to lighten the burden of the caregiver such as homemaking, housekeeping, and companionship services.

For some, circumstances necessitate consideration of residential placement. Patients may not have family members who are available or in adequate health to assist with patient care, or the patient's cognitive decline or behavioral symptoms may require greater resources than are available in a home setting. Residential facilities can provide different levels of care in these circumstances, and one should consider the level of care that is most appropriate for each individual patient at each stage of their illness. Assisted living facilities may provide a transition between living independently and residing in a nursing home. These facilities typically provide a combination of housing and meals, as well as supportive and health-care services. Skilled nursing facilities provide continued medical supervision and have services designed specifically to address advanced care issues such as patient nutrition and medical care.

Medical–Legal Considerations

When cognitive loss and dementia are present, making plans to assist in future care decisions is advisable. It is useful to review existing advanced care directives or health-care proxy, and if they do not exist, it is advisable to put them in place. It is important to note that as long as a patient maintains his/her ability to competently make decisions on his/her own behalf, these opinions will take precedence over family or caregiver wishes, even if a health-care proxy or power of

attorney has been appointed. Below we review important options and considerations for advance care initiatives.

Health-Care Proxy, Advance Care Directives, and Legal Planning

One of the key decisions to be made is who will be responsible for making health-care decisions if the patient loses the ability to make his/her own decisions. The diagnosis of dementia is not synonymous with incompetence, but as the dementia progresses, the likelihood of losing the ability to make decisions is high. It is therefore advisable for a patient to appoint a health-care proxy while they are still able. By appointing a health-care proxy, patients are assigning a person (typically a family member) to act on their behalf with regard to medical and end-of-life decisions. A patient may choose to document specific wishes regarding future medical care and decisions, either by advance care directives or a living will. These decisions can record a patient's wishes regarding issues such as the use of artificial life support, feeding tube placement, and comfort measures. By providing families and caregivers with specific instructions regarding what actions should be taken in different health-care scenarios, the patient ensures that their wishes will be followed. In the absence of these advance directives, a patient's health-care proxy will make decisions regarding their care. When assigning a proxy, patients also have the option of providing the person with varying degrees of authority. A proxy can be granted total control of medical decisions or can be given authority over only certain ones. When a patient decides to grant a proxy with only limited authority, consideration should be given to other types of scenarios in order to ensure that appropriate accommodations are made.

If a proxy has not been appointed or if a proxy's authority does not address the issue at hand, then health-care decisions are made by either the patient's family or the doctors involved in their care. Using substituted judgment, doctors and family members try to make the decision that the patient would have made if they were able to make decisions. Given the difficulty of these decisions, as well as the moral considerations involved, it is generally preferable to rely on advance care directives and appointed health-care proxies whenever possible.

A power of attorney assigns a person with the ability to speak (and sign documents) on a patient's behalf with regard to legal and financial matters. However, the power of attorney does not provide an individual with the authority to override a patient's wishes. Patients maintain the power to also make their own legal decisions, as long as they maintain the capacity to do so. In addition, unless a power of attorney is irrevocable, patients have the authority to change and withdraw the appointment as they see fit (again, assuming the patient is still deemed to have the capacity to make this decision). Powers of attorney may also be "durable," which allows this appointment to be maintained even after a patient is no longer able to make decisions for himself/herself. The power of attorney will also make decisions regarding a patient's finances and assets.

Legal Capacity and Guardianship

In order to appoint representatives (i.e., health-care proxy or power of attorney) or make legal decisions, a patient must maintain the capacity to do so. Legal capacity is generally defined as an individual's ability to understand and appreciate the consequences of one's actions and to make rational and informed decisions. The diagnosis of cognitive loss or dementia is not synonymous with lack of capacity, and judgments of capacity may actually differ for each type of decision. When patients maintain capacity to participate in their own legal planning, the wishes of others are subordinate. However, as a dementia progresses, a patient can become increasingly impaired and confused and may even demonstrate paranoia directed toward those trying to assist them.

In order to determine an individual's capacity to sign legal documents during the initial stages of a dementia, family members are often able to

simply speak to the patient to ensure that they adequately understand and can rearticulate the implications of the documents they are signing. In other cases in which uncertainty regarding a patient's capacity persists, additional assistance can often be obtained by speaking to a lawyer or by referring the patient to a psychologist to assess his/her mental status and cognitive limitations. For cases in which a patient is deemed to lack capacity to make decisions on his/her own behalf, the court may appoint a guardian (typically a family member) to speak for the patient. A court-appointed guardian (also referred to as a conservator) can be responsible for making financial and health-care decisions for the patient.

Finding a Lawyer

While health-care proxy, advanced care directives, responsibility, and power of attorney can all be executed without an attorney, it may be preferable to seek legal advice to avoid undesired consequences of these actions. Elder law focuses on estate planning and administration, disability, long-term care issues, and issues of guardianship including fiduciary. Elder law attorneys in a specific area can be obtained from the local chapter of the Alzheimer's Association (www.alz.org). Free legal advice is also available in some areas. Available resources can be found at the local Eldercare Locator (www.eldercare.gov).

Dementia Research: Current State, Future Trends, and Opportunities to Participate

There are many stakeholders in the efforts to find a treatment for AD, and themes of research include both better diagnostics to provide early detection and distinctions among types of dementias as well as initiatives to understand the underlying pathological mechanisms of the disease in order to identify new treatments. Neuritic plaques composed of amyloid and neurofibrillary tangles composed of the protein tau, the hallmark pathology of the disease, have been the primary target for drug discovery with the hope that modifying the aggregation of these proteins into pathological structures will modify the course of the disease. The breadth of research initiatives is wide, and there are three broad areas that have received significant attention and support from the National Institute on Aging (NIA): diagnostics, interventions, and genetics.

Research on Diagnostics

Early detection of AD may provide the ability to intervene more effectively. To this end, many studies of the transition from health to cognitive impairment and dementia are under way. One of the most prominent findings is that memory deficits predict the progression to AD, and from this work the criteria for recognition of MCI were developed. Work continues, defining other cognitive and biological markers that predict the disease. A large effort in this area is the Alzheimer's Disease Neuroimaging Initiative (ADNI) [66]. This public–private partnership has been working to identify biomarkers that predict disease in the mildly symptomatic and nonsymptomatic individual. Specific biomarkers that are being studied are quantitative MRI, PET images, and cerebrospinal fluid (CSF) and blood biomarkers. The imaging techniques measure the size of specific brain structures (MRI) and the energy used by specific brain areas (PET). Additional imaging studies use ligands that label proteins in the brain to identify the presence of amyloid and tau. Other studies are measuring amyloid and tau in the CSF to find early evidence of AD-like changes. These studies have been enrolling research participants with and without dementia to determine which biomarkers differentiate the groups and to track change over time. Today, these studies continue with the hope of recruiting very mildly impaired individuals, who may only demonstrate biomarker evidence of disease without accompanying impairment [67]. The hope is that finding a marker to detect those at risk will help to target a population most likely to benefit from early intervention.

More information is available about ADNI at their website (www.adni-info.org).

Studies have suggested that these biomarkers are as important as the clinical presentation of the patient, and recent guidelines for the diagnosis of Alzheimer's disease have been reevaluated to focus on cognitive change, regardless of type, and the presence of an amyloid biomarker. Additionally, research guidelines have been proposed which include the concept of "prodromal" Alzheimer's disease, a research diagnosis that requires a positive biomarker with no evidence of clinical impairment [68].

Research on Interventions

Current treatments for Alzheimer's disease are referred to as "symptomatic" in that they produce a benefit on the cognitive, functional, and behavioral symptoms associated with the disease. Today, experimental therapeutics focus on treatments that modify the disease course. This may include slowing or stopping the disease progression or preventing the onset of the clinical symptoms of the disease. Some approaches to therapy focus on modifying biomarkers of the disease in the hope that it will change its clinical course, and many clinical trials have examined agents that would reduce amyloid in the brain. Areas that remain active today are gamma secretase inhibition and immunization (both active and passive). Blocking the gamma secretase enzyme appears to reduce the accumulation of amyloid into plaques. However, to date, this mechanism has not proven effective in modifying clinical outcomes in AD. Immunization therapeutics, both active and passive, are also being developed. Animal data support the notion that antibodies against amyloid beta (Aβ) can lead to clearance of cerebral Aβ deposits, and human trials have further demonstrated this clearance [69]. However, clinical improvement has not always accompanied the clearance, leading researchers to believe that effectiveness requires administration at much earlier stages of the disease, such as the "prodromal" stage proposed in new diagnostic criteria. Another mechanism under study is neural regeneration, and the NIA along with Ceregene pharmaceuticals has sponsored one such trial of nerve growth factor, which is stereotaxically implanted in the brain. Other regenerative agents are also in development. Drug development in Alzheimer's disease is very active with more than 96 studies actively recruiting, as reported on the clinicaltrials.gov website.

Genetics

Three genes associated with the development of rare early-onset forms of familial AD have been known for many years: mutations in the amyloid precursor protein (APP) gene found on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1. The most common form of the disease, late-onset (typically defined as over the age of 60) AD, is a complex disorder, and it is likely that many genes may play a role in disease development. Until recently, however, only one gene variant, apolipoprotein E-ε4 (APOE-ε4), has been confirmed as a significant risk factor gene for late-onset Alzheimer's disease. In the past several years, however, researchers have confirmed additional gene variants of complement receptor 1 (CR1), clusterin (CLU), and the phosphatidylinositol-binding clathrin assembly protein (PICALM) as possible risk factors for late-onset Alzheimer's. The newest genome-wide association scan (GWAS) confirms that a fifth gene variant, Myc box-dependent-interacting protein 1 (BIN 1), also affects the development of late-onset AD. Several other genetic variants were identified at EPHA 1, MS4A, CD2AP, and CD33; these genes may implicate pathways involved in inflammation, movement of proteins within cells, and lipid transport as being important in the disease process. These studies utilized DNA samples from more than 56,000 study participants and are made possible through the Alzheimer's Disease Genetics Consortium (ADGC), a collaborative body established and funded by the NIA [70].

Identification of new genes may provide major clues as to the cause of AD. Genetic variants may influence risk of disease, the age of onset of symptoms, rate of progression, the amount of amyloid plaques or neurofibrillary tangles, concentrations of amyloid beta and tau in CSF, and responses to environmental factors such as medications. In addition, genetic studies can also provide new insights critical for drug discovery. The identification of new genes associated with AD is a very important preliminary step toward identifying biological pathways leading to disease. These pathways help to identify new targets for therapeutic strategies to treat and prevent the disease.

Participation in Research

There are many reasons why an individual may be motivated to participate in research. First, many individuals appreciate the opportunity for additional standardized follow-up. Often, experimental instruments and techniques are used to assess novel aspects of disease or health, and tracking that performance can provide support and insight for research participants. Research participation can also provide early access to new techniques and treatments. While there is no guarantee of a positive outcome, the requirement for safety in research demands close observation to ensure that untoward results are identified early and modifications to procedures, treatments, and study designs are made quickly. This attention can add confidence to participating in studies that might expose an individual to unnecessary or ineffective procedures. In the case of positive results, participants get the earliest exposure. In many studies, even those initially assigned to the placebo group are given the opportunity to receive the active intervention, even before the agent is fully available for marketing or before a diagnostic is fully approved.

The nature of participation in research in dementia and cognitive impairment often requires participation of a study partner, usually a friend or family member. Because they play an important role, support for family and friends is often provided in research. This can take the form of activities to maximize retention such as support groups or informational material that is often provided by study staff who are experts in the particular aspect of dementia care and management. It can also occur informally through exposure to others participating in research who offer peer support and shared experiences.

The most common and sustaining reason for research participation is altruism. The ability to make contributions that benefit others with the disease remains the highest motivator. This is an important factor in research recruitment. Long-standing characteristics of generosity in an individual are often unchanged in the presence of illness, and in the face of mortality, they may even be enhanced. Offering research participation is acknowledging the patient as an important contributor to knowledge of his/her disease and to the welfare of others.

Critical Information About Research Participation

While many practitioners acknowledge the benefit of research participation for their patients, it is not always clear how to go about identifying and evaluating studies or preparing patients for the rejection they may feel if not eligible for a given study. Additionally, many commercial entities can solicit participation with little oversight. However, there are several resources that are well established that can be helpful to patients, families, and friends. For example, because of both regulatory and publication guidance, most clinical trials as well as many other clinical studies are posted on www.Clinicaltrials.gov. Clinicaltrials.gov offers up-to-date information for locating federally and privately supported research studies that use human volunteers to answer specific health questions. The website was developed by the US National Institutes of Health (NIH), through its National Library of Medicine (NLM), and in collaboration with the Food and Drug Administration (FDA), as a result of the FDA Modernization Act (Public Law Number 105–1

15, 1997). The registry describes studies conducted in all 50 states and in 174 countries. The website receives over 50 million page views per month and 65,000 visitors daily. This registry has an easy-to-use search engine and, as of this writing, is posting over 900 studies in AD with more than 200 currently recruiting. The study postings describe basic entry criteria for given studies along with location and contact information. The website requires annual updating of information and posting of study results. Another opportunity for those with AD is the Alzheimer's Association TrialMatch™, a clearing house designed to help people with AD, caregivers, families, and clinicians locate clinical trials based on specific criteria such as diagnosis, stage of disease, and location. More than 100 research studies pertaining to AD and related dementias are underway and recruiting volunteers through this service, and Alzheimer's Association TrialMatch lets you search these trials quickly and easily. It also narrows results to those trials where there is a reasonable chance to be accepted for enrollment. Individuals may register by providing information about a potential participant, and with the registrant's permission, an Alzheimer's Association Contact Center specialist will provide unbiased trial result options and trial site contact information. Specialists will not recommend any particular trial but will identify trials that match specific eligibility criteria.

Finally, the National Center for Research Resources, part of the NIH, sponsors ResearchMatch through the Clinical and Translational Science Awards (CTSA) program. ResearchMatch has a simple goal—to bring together two groups of people who are looking for one another: (1) people who are trying to find research studies and (2) researchers who are looking for people to participate in their studies. It is a secure registry that has been developed by major academic institutions across the country in order to develop a nationwide effort to enrich participation in research. This effort is not disease specific and offers opportunities to both patients and healthy individuals.

Research participation may not be for all individuals, and both the investigator and the participant have opportunities to evaluate the specific match of the potential subject and the project. From the investigator perspective, a study must be designed to answer a specific question. Selection criteria therefore focus on identifying subjects who can help answer specific questions. Inclusion criteria might define the severity of the disease or the age of a participant or exposure to other treatments. Other criteria may be used to ensure safety, requiring exclusion of some individuals based on the presence of comorbid conditions or concurrent medications that could increase risks if exposed to a new treatment or test. Some criteria may be based on ensuring that the effectiveness can be measured. For example, studies involving cognitive evaluation may exclude subjects with significant hearing or visual loss that might potentially interfere with testing.

From a participant's point of view, it is critical to work with a trusted group. The research group may be identified by a physician or vetted through one of the websites described in this chapter. It is also important to evaluate how much participation is right for the participant. A study may require frequent visits. Some procedures may be particularly noxious. The participant needs to weigh these against the benefit of making a contribution. An important aspect for participants to keep in mind is that participation is voluntary and one can always change his/her mind if circumstances change. In the end, it is the faithful participation in clinical research that will identify the treatments of tomorrow.

Clinical Pearls

- Pharmacological treatments available for Alzheimer's disease require careful titration to find the best dose; modest effects have been observed at all stages of the disease.

- Nonpharmacological interventions can be particularly helpful for behavioral problems associated with dementia. Environmental modifications can improve safety and extend functional independence.
- Behavioral and psychiatric symptoms are common and should be treated using both pharmacological and nonpharmacological means.
- Acute medical problems can potentially exacerbate cognitive and behavioral symptoms; routine health maintenance should be an integrated part of dementia care.
- Identifying the etiology of the dementing disorder is critical for planning and management, as subtypes have differential presenting symptoms and rates of disease progression.
- Support groups and resources are available and can improve the quality of life of both patients and their caregivers.
- Care needs in dementia will change with the progression of the disease. Matching the level of care with the patient's disease severity will contribute to maximizing independence. Case management can be helpful in identifying and accessing care needs.
- The cognitive decline associated with dementia has both legal and financial implications, and patients and their families should explore of assigning health-care proxy, power of attorney, and making advance care directives.
- There are many opportunities for those with dementia and cognitive loss to participate in clinical research and clinical trials. Clinicians can introduce the possibility of research participation for the hope it offers to their patients and to the generations to come.

Resources

The websites listed in Table 22.3 are excellent resources for information, programs, support groups, and other resources (Table 22.3).

Table 22.3 Additional internet resources

Information available	Website
For information, resources, and support groups specifically pertaining to Alzheimer's disease	www.alz.org
For recent news and events specifically pertaining to Alzheimer's disease	www.nia.nih.gov/Alzheimers
For information, resources, and support groups specifically pertaining to Lewy body dementia	www.lbda.org
For information, resources, and support groups specifically pertaining to frontotemporal dementia	www.theaftd.org
For a directory of local programs and resources	www.eldercare.gov
For additional programs, training, and support	www.n4a.org
For information regarding legal and financial advice	www.caringinfo.org
For a list of clinical trials currently enrolling	www.clinicaltrials.gov

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23 Management of Behavioral and Psychological Symptoms in Dementia

Michelle Braun

Management of behavioral and psychological symptoms of dementia (BPSD) is among the most difficult aspects of dementia care and a frequent focus in neuropsychological evaluations. Given that the rate of Alzheimer's disease (AD) is projected to increase exponentially to 7.1 million by 2025, and nearly triple to 13.4 million by 2050 [1], determining effective strategies for the management of BPSD is imperative.

Ineffective management of BPSD has significant negative emotional and functional consequences for the person with dementia (PWD) and his or her caregivers, and is the leading cause of nursing home placement [2]. BPSD often present with a sense of urgency due to distress experienced by the PWD and/or his or her caregivers, and sometimes due to related safety concerns. BPSD are frequently challenging to manage because they often require (a) customization of treatment recommendations, based on a detailed understanding of the problem behavior(s); (b) an iterative, context-dependent approach in determining effective treatment; (c) implementation of some interventions by caregivers; and (d) ongoing follow-up to adjust treatment as behaviors change in the context of increasing cognitive impairment.

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This chapter provides a seven-step model for tailoring treatment of BPSD, based on empirically supported strategies from systematic reviews and meta-analyses, and clinical considerations. Pharmacological management strategies are summarized when applicable. Given that AD and AD-related mixed dementias account for 60–80% of all cases of dementia [1], BPSD in AD is a major focus of this chapter. Information on BPSD in other subtypes of dementia is also summarized when applicable.

BPSD Are Common and Persistent

Approximately 60–90% of patients with AD develop behavioral and psychological symptoms including hallucinations, delusions, agitation, dysphoria/depression, anxiety, irritability, disinhibition, apathy, sleep disturbances, and eating changes (3). Multiple studies have shown variable relative frequencies of different types of BPSD. Although mixed research findings make it difficult to determine the most common BPSD, there is great overlap in subtypes of BPSD across studies (see Table 23.1). For example, a recent systematic review and meta-analysis of 48 studies over 50 years showed that the most common BPSD in AD were apathy (49%), depression (42%), aggression (40%), anxiety (39%), sleep disorder (39%), irritability (36%), appetite disorder (34%), aberrant motor behavior (32%),

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Table 23.1 Common BPSD

Apathy
Depression
Agitation/aggression
Anxiety
Wandering
Sleep disorder
Irritability
Appetite disorder
Aberrant motor behavior
Delusions
Disinhibition
Hallucinations

Table 23.2 Tailoring treatment in BPSD: A seven-step model

1: Determine subtype and severity of dementia
2: Specify BPSD symptoms and potential contributing variables
3: Assess and strengthen caregiver engagement
4: Consider increasing daily engagement for the PWD
5: Add customized management strategies based on BPSD subtype, with a focus on behavior therapy
6: Recommend medical consultation
7: Recommend treatment tracking and follow-up

BPSD Behavioral and psychological symptoms of dementia, *PWD* persons with dementia

delusions (31%), disinhibition (17%), and hallucinations (16%) [4]. Another systemic review of 23 studies demonstrated that the most common BPSD are delusions, wandering, agitation, aberrant motor behavior, and apathy [5], while other research showed that apathy, sleep problems, depression, irritability, and wandering were most common [6].

A study examining the relationship between BPSD and mortality over 10 years showed that most BPSD were persistent [6]. However, some BPSD may increase over time, while others may remain relatively stable. For example, a 3-year longitudinal study showed that delusions, hallucinations, agitation, anxiety, apathy, disinhibition, irritability, and aberrant motor behavior increased over time, whereas depression, euphoria, nighttime behavior, and appetite did not [7].

Predictors of BPSD in Different Subtypes of Dementia

Risk factors for increased BPSD in mild AD include younger age, male sex, and greater functional impairment. Increased severity of dementia and frontotemporal dementia (FTD) have also been associated with more BPSD at baseline [7]. Lewy body dementia has been associated with more hallucinations and fewer appetite disturbances as compared to FTD or AD, and AD has been associated with lower levels of BPSD than other dementias at baseline [7]. In AD, lower education has been shown to be associated with greater distress/tension, and Caucasians exhibited a higher prevalence of affective disorders than other groups [8].

The overall prevalence of BPSD in AD and vascular dementia (VaD) was comparable, and the relationship between higher rates of BPSD and impairment in activities of daily living in AD and VaD was similar, though the types of BPSD differed between groups. For example, patients with AD exhibited more agitation/aggression and irritability/lability than patients with VaD, and AD caregivers reported significantly higher levels of distress. Both groups showed significant associations between impairments in daily functioning and depression, apathy, irritability, and disordered sleep and eating [9].

Tailoring Treatment for BPSD: A Seven–Step Model

A multi-step approach to tailoring BPSD treatment (see Table 23.2), designed for integration into neuropsychology practice, helps ensure consideration of variables that have been shown to impact BPSD treatment success.

Step 1: Determine Subtype and Severity of Dementia

As previously noted, given that different subtypes of dementia are associated with different relative frequencies of BPSD, and given that

BPSD incidence increases with dementia severity, determining the subtype and severity of dementia will help guide the focus on BPSD in the context of the neuropsychological evaluation.

Step 2: Specify BPSD Symptoms and Potential Contributing Variables

Several studies have shown that the success of nonpharmacological interventions in minimizing BPSD is dependent on tailoring the intervention to patient characteristics [10–12]. However, this is often challenging because BPSD may have multifactorial causes that directly impact the expression of symptoms, including neurobiological disease-related factors, unmet needs, caregiver variables, and environmental triggers [13].

As detailed elsewhere [14], a useful framework for specifying BSPD and clarifying potential contributing variables involves two primary steps:

(a) Topographical assessment of BPSD, including
  (a) Identification of target behavior(s) (see Table 23.1)
  (b) Describing the intensity and frequency of target behaviors
(b) Functional assessment of BPSD, including
  (a) Identification of factors that contribute to the etiology of BPSD through examination of the context in which BPSD occurs, with a focus on:
    (i) Factors that precede BPSD ("Antecedents") (e.g. specific situations such as bathing, the presence of others, etc.)
    (ii) Factors that occur after the BPSD ("Consequences"), including adding favorable stimuli (positive reinforcement) or removing aversive stimuli such as task demands (negative reinforcement)
    (iii) "Setting events" that impact antecedents and consequences through contextual factors (e.g. pain, time of day, emotional state, etc.)

Data on these issues can be gathered in the context of the neurobehavioral interview. If there is a desire to obtain more detailed information, several inventories are available to measure these constructs [14].

Step 3: Assess and Strengthen Caregiver Engagement

Caregivers are fundamental partners in supporting effective behavior management and treatment compliance for the PWD. As dementia progresses, the PWD often becomes increasingly dependent on caregiver assistance with daily tasks and oversight of safety. This dependence often shifts the nature of the relationship between the caregiver and the PWD, and may contribute to caregiver stress.

During the neuropsychological assessment, it is often helpful to interview the primary caregiver in person (or via telephone if necessary) to determine the caregiver's insight into the potential need for assistance, their level of engagement in caregiving activities, readiness to implement recommended treatment strategies, and need for support. Caregiver support can be helpful at many time points, but is ideally provided proactively to minimize chronic caregiving stress.

The Alzheimer's Association provides a 24-h Helpline, support groups, and educational information that many caregivers find invaluable on the caregiving journey [15]. Many states also have local Aging and Disability Resource Centers that connect caregivers and PWD with local agencies to assist with management of medications, finances, housework, travel, meals, day programming, and respite services. Connecting caregivers to these and other support services early in the diagnostic process may help enhance caregiver readiness to implement treatment strategies. This may benefit the caregiver and the PWD, given that increased caregiver readiness is associated with a decrease in distressing behavioral symptoms in the PWD and greater caregiver confidence [16].

Beyond connecting caregivers to supportive resources, specific caregiver interventions have been identified as helpful in supporting community-dwelling PWD, including (a) providing opportunities for engagement of both the PWD and the caregiver; (b) encouraging caregiver participation in educational interventions; (c) offering individualized programs rather than group sessions; (d) providing information in an ongoing fashion; and (e) focusing on reducing specific concerning behaviors [17]. Individual behavioral interventions and multicomponent interventions are also helpful in improving the psychological health of caregivers, with the latter intervention also decreasing the rate of institutionalization for the PWD [18].

Step 4: Consider Increasing Daily Engagement for the PWD

Regardless of whether BPSD exist, regular exercise under the direction of a healthcare provider, a routine schedule, and increased engagement in personally enjoyable activities may help improve quality of life for the PWD and, by extension, the caregiver. Recommendations for increasing daily engagement are helpful to make early, at the point of dementia diagnosis (or even when a suspected progressive mild cognitive impairment is diagnosed), to potentially minimize the likelihood and/or severity of current or future BPSD.

Several factors have been shown to increase engagement for PWD. For example, stimuli that are personalized to the interests of the PWD [19, 20] or presented through one-on-one socialization [10] have been shown to be maximally engaging. Engagement in the visual arts has also been shown to be therapeutic for PWD [21], making museum and art programs for PWD and caregivers an increasingly popular activity [22]. In the nursing home setting, dog-related stimuli – including live dogs, puppy videos, and a dog-coloring activity – were associated with increased engagement [20]. In addition, live stimuli (including people) and social (vs. nonsocial) stimuli have been related to increased engagement [23]. However, the impact of simulated presence therapy [24] and massage/touch in promoting engagement in PWD has been inconclusive [25].

Aerobic exercise is another form of engagement that may assist in decreasing current and future BPSD. In individuals with AD, aerobic exercise has been shown to improve quality of life, psychological well-being, and systemic inflammation [26]. In early AD, aerobic exercise is associated with modest gains in functional ability, cardiorespiratory fitness, and reduced hippocampal atrophy [27], all of which – in addition to the increased fatigue and positive distraction that accompanies aerobic exercise – may help decrease BPSD intensity. Attempting to proactively offset the impact of variables that decrease exercise engagement may also help minimize future BPSD severity. Variables associated with decreased exercise engagement include female sex, older age, and increased medication use, while those associated with increased exercise include higher functional and cognitive status [28].

New directions for increasing engagement in persons with early-stage dementia include the use of positive psychological measures, including constructs of gratitude, life satisfaction, meaning in life, optimism, and resilience, with the goal of developing strength-based psychosocial interventions [29].

Step 5: Add Customized Management Strategies Based on BPSD Symptoms, with a Focus on Behavior Therapy

Individualized behavior therapy has been shown to be helpful in reducing all BPSD summarized below and as such is recommended as a first-line nonpharmacological treatment consideration for agitation/irritability/aggression, depression and anxiety, apathy, sleep disturbance, and wandering. Music therapy also has robust effects in reducing agitation/irritability/aggression, as well as depression and anxiety. Details on these findings and other specialized interventions are summarized below.

Agitation, Irritability, and Aggression

Agitation occurs especially in the middle and late stages of AD [30]. Common behavioral expressions of agitation include excessive psychomotor activity, aggressive behaviors, irritability, and repetitive behaviors. Three psychosocial models have been postulated to explain possible contributors to agitated or aggressive behavior, and suggest that behavior may represent (a) an expression of "unmet needs"; (b) a response to environmental stimuli; and/or (c) a reduced threshold for stress [31]. Examining these potential factors can help refine treatment recommendations.

Nonpharmacological Interventions

Nonpharmacological interventions are recommended as a first-line treatment, unless BPSD symptoms are severe, persistent, or recurrent [5]. Adding pharmacological agents may lead to side effects and increase overall medication burden. In cases of moderate to severe agitation, a combination of pharmacological and nonpharmacological interventions should be considered. Tailoring interventions by examining agitated behaviors from the standpoint of how the PWD may be expressing "unmet needs" has been shown to help decrease aggression [32]. Some research has shown that agitation is the most responsive BPSD to nonpharmacological interventions, as compared to other BPSD including depression, apathy, repetitive questioning, psychosis, aggression, sleep problems, and wandering [33].

Across multiple studies, music has been shown to be a powerful tool in reducing aggressive behaviors. For example, a recent meta-analysis of 12 studies demonstrated that music had clinically and statistically robust effects on agitation (as defined by repetitive acts, restlessness, wandering, and aggressive behaviors; [34]). Similar findings were noted in a recent review of eight randomized controlled trials that showed individualized and interactive music therapy was optimal for management of agitation in institutionalized patients with moderate to severe AD [30]. A recent systemic review of 34 studies provided similar support for individualized music [35].

Music therapy and behavioral techniques were shown to be superior in reducing aggression, agitation, and anxiety, as compared to other therapies including sensory stimulation, cognitive/emotion-oriented interventions (e.g., music/dance therapy, reminiscence therapy, and simulated presence therapy), exercise, and animal-assisted therapy [36]. Another study demonstrated similar positive effects of behavioral therapies in reducing aggression [37]. The relationship between aromatherapy and agitation has also been studied, though findings have been mixed. One study found no significant benefit of aromatherapy in managing agitation [30], though another study showed aromatherapy helped to reduce agitation but not other behaviors such as restlessness/wandering, anger, and anxiety [38].

Engaging with animals, dolls, and robotic animals has also been found to reduce agitation. In a review of 12 studies, doll therapy – a person-centered therapy involving holding, talking to, feeding, cuddling, or dressing an anthropomorphic doll – was found to effectively reduce agitation and aggression [39]. Engagement with animals [40] and a robotic cat was also shown to decrease agitation [41].

Pharmacological and Other Medical Interventions

Although antipsychotic medication is sometimes used to manage agitation in dementia, it has been linked to increased mortality [42], and the use of antipsychotics has declined in light of the black box warning from the Food and Drug Administration [43]. However, the need for effective treatment of agitation has contributed to the study of several other pharmacological agents.

Cholinesterase inhibitors have been shown to be effective in reducing and delaying agitation [3, 44] as well as reducing the need for other medications to manage agitation [3]. Dosage of cholinesterase inhibitors may be an important factor in managing BPSD, based on findings that increasing the dosage of donepezil (from 5 to 10 mg day) improved behavioral symptoms in individuals with Lewy body dementia [45]. Memantine for BPSD in AD has also been

shown to reduce the dose of other medications that are used in managing agitation, including diazepam [46].

Multiple studies have indicated the benefit of citalopram in treating agitation in AD [47, 48], though side effects have also been noted. For example, one study showed that citalopram decreased delusions, anxiety, and irritability after 9 weeks, but increased the severity of sleep behavior disorders after week 9 [49]. Another study found that 30 mg daily of citalopram helped to significantly decrease agitation in AD. However, cognitive worsening was also noted, and it was thus recommended that citalopram 20 mg daily be considered as a first-line treatment in addition to psychosocial interventions [50]. A review of clinical trials evaluating pharmacologic interventions for agitation in AD noted that a range of medications hold promise in treating agitation, including dextromethorphan/quinidine, scyllo-inositol, brexpiprazole, prazosin, cannabinoids, citalopram, escitalopram, and pimavanserin [51].

Electroconvulsive therapy (ECT) is another potential treatment for agitation, based on a study demonstrating that 72% of individuals with acute aggression, agitation, and disorganized behavior secondary to dementia showed a clinically meaningful response to ECT. Maintenance treatment was effective in sustaining the treatment response in 87% of cases, though two cases of significant cognitive adverse effects were noted [52].

Depression and Anxiety

Increased involvement in positive events and enhanced caregiver problem solving have been shown to decrease depression in PWD [53]. Music has also been found to be helpful in treating depression [35, 54, 55] and anxiety [35, 54]. However, the therapeutic benefit of music may depend on dementia severity. For example, in elderly patients with severe dementia, multisensory stimulation environments were shown to reduce anxiety and agitation more than individualized music sessions [56]. Reminiscence interventions were also linked to improved mood, decreased caregiver burden, decreased dysfunctional behaviors, and reduced institutionalization in AD [37].

In regard to pharmacological management, Citalopram has been shown to be helpful in treating anxiety [49]. However, a 2017 analysis of double-blind randomized controlled trials comparing antidepressants versus placebo for depression in AD found no statistically significant difference between antidepressants (including sertraline, mirtazapine, imipramine, fluoxetine, and clomipramine) and placebo, and concluded that higher-quality randomized controlled trials are needed [57].

Apathy

Apathy is associated with poorer disease outcome, reduced daily functioning, and increased caregiver distress [58]. Apathy is also the most stable and persistent BPSD over 10-year follow-up, and is associated with a threefold increase in mortality compared to other BPSD [6]. Given that disruption of frontal-subcortical networks is likely linked to apathy in AD [59], assessing for the presence of apathy in individuals with frontal subcortical neurocognitive deficits can be informative. Nonpharmacological interventions such as individualized therapeutic activities [60] have demonstrated promise in treating apathy. In addition, short-term occupational therapy was shown to be more effective in reducing apathy than engaging in an activity of choice [61]. Pharmacological agents including acetylcholinesterase inhibitors, gingko biloba, and methylphenidate have been found to help reduce apathy in patients with AD [58].

Sleep Disturbance

Light therapy, increased physical and social activity, and multicomponent cognitive behavioral interventions have been shown to help treat sleep disturbance in dementia [62]. Unfortunately, a recent review on pharmacological management for sleep disturbances in dementia found a lack of evidence to guide drug treatment, including no randomized controlled trials of the many drugs that are widely pre-

scribed for sleep problems and dementia, such as benzodiazepine and non-benzodiazepine hypnotics. There was no evidence that melatonin (up to 10 mg) helped sleep problems in individuals with moderate to severe AD. There was some evidence that low-dose trazodone (50 mg) was helpful, though a larger trial was recommended. There was no evidence of any effect of ramelteon on sleep problems in moderate to severe AD [63].

Wandering

The risk of wandering and getting lost increases as dementia and cognitive impairment worsen. Wandering also frequently creates anxiety, distress, and decreased interactions in PWD [64]. Proactively connecting caregivers to the Alzheimer's Association to learn about the Safe Return registration program [15] can provides support and education about wandering, and more rapid identification of the PWD if wandering occurs. Analyzing patterns related to wandering (e.g., time of day, presence/absence of others, boredom, hunger) can assist in assessing potential "unmet needs" and other variables related to wandering, and provide tailored solutions. Environmental modifications are also often helpful, including disguising locks on doors or doorknobs and using door alarms. Some studies have examined the potential of using global positioning system (GPS) devices to promote safe walking and provide early alerts about potential wandering, though legal issues related to privacy and autonomy are noted [65].

Wandering often increases in residential environments where hallways and/or rooms are undifferentiated. The use of visual cues to assist in wayfinding is beneficial, including the use of colorful, easily identifiable, personally meaningful cues at key environmental decision points such as resident rooms [64]. Other strategies in long-term care settings include environmental modifications (e.g., a secure place to wander, a wall mural, and other visual strategies to disguise exits), music, exercise, structured activities to decrease wandering, and caregiver education [66]. Environmental modifications are discussed in greater detail in other chapters.

Step 6: Consider Medical Consultation

Medical consultation is often helpful in creating the most effective BPSD treatment plan and helps determine whether BPSD are related to metabolic or other medical issues, and whether adjunctive pharmacological therapy or other medical treatments are warranted. Ongoing communication with medical colleagues about the efficacy of treatment interventions helps ensure that treatments are complimentary and coordinated.

Step 7: Recommend Treatment Tracking and Follow-Up

As previously discussed, caregiver engagement is crucial to treatment success. It is often helpful to recommend that caregivers keep a journal regarding the effectiveness of recommended interventions and are encouraged to share that information with healthcare providers. Caregivers also benefit from having a point of contact for questions that arise between appointments. Caregivers often report feeling more engaged and empowered when they perceive they are part of a team of healthcare professionals and community experts that are dedicated to providing care for their loved one.

Clinical Pearls

- At the point of initial diagnosis of dementia or when a suspected progressive mild cognitive impairment is diagnosed, consider recommending strategies to increase engagement and quality of life for the PWD – including exercise, maintaining a schedule, and engagement in personally enjoyable activities – in

order to minimize the likelihood of current and future BPSD.
- Medical issues should always be ruled out as a contributing factor to BPSD, even if BPSD are chronic.
- An iterative approach to behavioral management is often required before behavior consistently improves, and often necessitates that the caregiver have an ongoing point of contact for treatment input.
- Neuropsychologists are uniquely trained to customize BPSD treatment plans by integrating information from cognitive, psychiatric, and behavioral variables, and would benefit from highlighting this skill to referral sources if this is a desired area of practice.
- When in doubt about what to recommend for BPSD treatment, consider suggesting a behavioral intervention, given that behavioral interventions have the strongest and widest range of support across different subtypes of BPSD.

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24 Cognitive Training and Rehabilitation in Aging and Dementia

H. Allison Bender and Jessica Spat-Lemus

Cognitive Training Versus Rehabilitation

The terms "cognitive training" and "cognitive rehabilitation" are often used interchangeably; however, these terms have different connotations and implications for service delivery [1]. Specifically, cognitive training paradigms typically require a carefully guided, frequently repeated, and highly standardized sequence of exercises to address specific deficits or domain impairments. This approach is frequently manualized and not unique to each patient's unique neuropsychological profile of strengths and weaknesses. Rather, cognitive training assumes that repeated exposure and practice have the potential to improve performance in a discrete area of cognition and the effects of this practice will generalize beyond the immediate training context [2]. The ability of cognitive training to generalize to non-targeted domains will be reviewed throughout this chapter, as several investigations have failed to support the generalizability of such training in this population [3]; potential limitations that can impact study results will also be discussed.

In contrast, a cognitive rehabilitation approach to treatment in patients with dementia acknowledges the progressive nature of neurodegenerative disorders at a biological, psychological, and psychosocial level and endeavors to maximize the patient's engagement in activity (as described by Clare and Woods [1]). To this end, cognitive rehabilitation prioritizes the maintenance of cognitive abilities and compensatory strategies over direct improvements on single cognitive skills [4]. Also, this type of approach is a more collaborative process between the patient, his or her caregiver, and an interdisciplinary care team [4], including the treating neuropsychologist. Together, deficits in adaptive functioning are identified, and multimodal exercises are individually planned for the patients' everyday life. Moreover, cognitive rehabilitation most often takes place in "real-world" environments, as there is no assumption to generalizability from task to task [2].

A Brief History of Cognitive Training and Rehabilitation

One of the earliest iterations of cognitive training and rehabilitation was a "school for soldiers" to serve the needs of returning German veterans following World War I [5]. Although attempts at

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formalized programs aimed at improving cognition may have existed before then, there is little documentation of their treatments and outcomes. Alexander Luria (1963, 1973, and 1979, as cited in www.proedinc.com/Downloads/12625Ch01.pdf) [6, 7, 8] described similar efforts in regard to neurorehabilitation taking place with wounded veterans in a neurosurgical unit of the Ural Mountains and at the Burdenko Institute of Neurosurgery in Moscow. The post-World War II era brought similar efforts to Great Britain, where the continuing debate regarding the efficacy and generalizability of compensatory strategies vs. neuroplasticity first began (i.e., Zangwill, 1945 & 1947, as cited in www.proedinc.com/Downloads/12625Ch01.pdf) [9, 10]; this debate will be reviewed later in the chapter.

Moreover, as the field of neuropsychology and rehabilitation psychology began to develop increasingly sophisticated metrics to identify areas of deficit in patients with stroke and traumatic brain injury (TBI), cognitive training and rehabilitation have also grown as an increasingly valuable resource to the patient populations served by neuropsychologists. This, too, furthered the development of cognitive remediation in the United States post-World War II. Much of the evolving field of neurorehabilitation was derived from the initial, seminal works of Luria and other pioneers in the field, including Ben-Yishay, Diller, Gianutsos and Gianutsos, Sohlberg, and Mateer. Interestingly, the multidisciplinary model of cognitive training and rehabilitation pioneered at that time has a striking resemblance to a more modern-day approach to brain injury treatment [11].

Training and Rehabilitation in Different Settings

The application of cognitive training and rehabilitation techniques also varies from setting to setting, each with differing levels of structure and support. Below includes an overview of such techniques, the application of which is predicated by the severity of the patient's impairment and the level of engagement in treatment and functional needs, including degree of community engagement.

Neurocritical Care Unit

Individuals with dementia often experience comorbid or co-occurring neurological diseases, such as stroke or TBI. For critically ill patients, neurocritical care units are a patient's first exposure to a coordinated, multidisciplinary team aimed at improving long- and short-term outcomes in patients with potentially profound consequences to their physical and cognitive health.

In most settings where patients have limited consciousness, basic neurorehabilitation may begin shortly after vital signs and acute neurological sequelae have been stabilized. In such contexts, a patient's therapy program may include cognitive activities in their most rudimentary form, such as repeated presentation of simple stimuli via multiple sensory channels. Facilitating a sensory-rich environment for patients with limited consciousness can stimulate neural plasticity [12] via promoting arousal and behavioral responsiveness. Although a thorough review of this literature is beyond the scope of this chapter, briefly, empirical support exists for interventions which are multimodal (i.e., tactile, visual, and auditory), possess emotional salience to the patient, preferably have autobiographical content, include output processing (i.e., covert responses), and take place in a naturalistic, dynamic environment [13].

Group Settings

Interventions performed in group settings, also described as "cognitive stimulation," have clear applications in patients with dementia. According to a review of the literature completed by Woods and colleagues [14], such interventions have consistently shown that both general cognitive stimulation and reality orientation have improved cognition and health-related quality of life in

patients with mild to moderate dementia. For example, in a study conducted by Bernhardt and colleagues [15], the authors investigated the effects of a group memory training program on older adults diagnosed with either mild cognitive impairments or dementia living in a retirement facility. The program was developed so that it captured participants' varying level of neurocognitive abilities and focused on short- and long-term memory training, as well as activities of daily living in a group format. The results indicated that participants in the training program demonstrated some improvement in memory when compared to controls, when incorporating tasks of daily living and when taking into account an individual's level of neurocognitive abilities [15].

Day Treatment Programs

In the early 1980s, Yehuda Ben-Yishay and colleagues at New York University Medical Center began a joint venture between the Rusk Institute of Rehabilitation Medicine and the Israeli Defense Ministry. From this collaboration was borne the first post-acute brain injury day treatment program. This therapeutic milieu day treatment program was the first of its kind to serve "trainees" (the terms "patient" and "client" are not used in this type of setting) who have sustained: traumatic brain injury, stroke, surgical or post-radiation sequelae, and/or encephalopathies and have been discharged from other inpatient and/or outpatient programs, but have not yet made the requisite functional and cognitive improvements needed to return to their desired baseline. Although the foundations of this type of program have been described in detail elsewhere [16], briefly, it integrates three mutually reinforcing features [17], including: (1) prioritized, sequenced, and coordinated multidisciplinary interventions; (2) a therapeutic community which provides the trainee with a supportive network of peers and opportunities to practice evolving interpersonal and cognitive skills; and (3) a therapeutic milieu setting which helps facilitate the transition of skills to a patient's home environment, including exploration of returning to work.

Cognitive Training and Rehabilitation in Dementia Patients in Clinical Practice

As the population of older adults living in the United States grows exponentially, the rates of cognitive decline and neurodegenerative disease increase and, along with it, staggering health-related costs and caregiver burden [18]. While pharmacological agents are thought to be the primary source for symptom improvement in patients with neurodegenerative processes, drug development and government approval are time-consuming and costly [19]. Therefore, the use of safe, inexpensive, and efficacious non-pharmacological interventions aimed at improving and/or maintaining cognitive functioning in older adults is essential. While not a substitute for treatment with appropriate medications or clinical trials, adjunctive non-pharmacological interventions, such as cognitive training and rehabilitation, are often valuable additions to a patient's care plan and may actually enhance the therapeutic effects of standard-of-care treatments, such as cholinesterase inhibitors [20].

The current state of cognitive training and rehabilitation therapies appropriate for patients with dementia has largely been guided by the following overarching goals: (1) optimizing encoding and retrieval; (2) promoting the acquisition of new information in amnestic patients; and (3) coping with memory problems through compensatory strategies [21]. Per these authors, the selection of technique is guided by the specific characteristics of the patient's memory impairment and spared abilities (poor encoding vs. retrieval vs. recognition), the degree of impairment, and the patient's strategies at baseline (i.e., notetaking, etc.).

Optimizing Encoding and Retrieval

The optimization of encoding requires effortful processing on behalf of the patient which most often is achieved through mnemonic devices, including mental imagery, and other strategies

aimed at "active" information processing (i.e., chunking information together into categories or into smaller groups, as suggested by [22]). In a study by Kaschel et al. [23], a patient group with mild memory impairment demonstrated improved immediate and delayed story recall on testing, as well as better recall of appointments after receiving instruction in mental imagery techniques. Although these data suggest promise for the clinical utility of this technique in patients with memory disorders of different etiologies (i.e., dementia), its use for more severely impaired patients is questionable; the studied sample was only mildly impaired and highly motivated to improve [23].

Acquisition of New Information

Memory theory implicates errorless learning as a potential avenue to support the encoding of new material [24] that addresses implicit memory abilities. In brief, the goal of errorless learning is to drastically reduce the frequency of errors made during the learning process. Individuals with dementia, such as Alzheimer's disease, may not be aware of their deficiencies in explicit memory, and, therefore, errors may not be corrected, but rather consolidated into their long-term memory storage [24].

Spaced retrieval has been an effective technique in increasing the recall and retention of newly learned information for progressively longer intervals (e.g., 1 min, 2 min, and 5 min). The delay is increased following each correct (errorless) response [25]. This technique echoes the belief that spaced practice is more effective than distributed practice (Ebbinghaus, 1885/1992; as cited in Ptak et al. [21, 26]). In their review of 17 studies assessing the utility of techniques with efficacy in improving memory in patients with dementia, Grandmaison and Simard [27] indicated that both errorless learning and spaced retrieval were the most promising training techniques for populations with primary neurodegenerative disorders, such as Alzheimer's disease. Errorless learning and spaced retrieval are often most effective when paired together. Beyond errorless learning and spaced retrieval, Bier, Desrosiers, and Gagnon [28] also identified vanishing cues as another effective technique for use in the cognitive training of patient's with primary neurodegenerative disorders. Vanishing cues aims to use prompts to recall information that is gradually withdrawn until recall is successfully achieved [29]. Although this technique was initially believed to facilitate memory in amnestic patients [29, 30], Baddeley and Wilson [24] posited that vanishing cues is theoretically flawed, as this technique promotes error production. In their small case series ($N = 2$), Thivierge, Simard, Jean, and Grandmaison [31] developed interventions that combined errorless learning and spaced retrieval techniques to relearn forgotten activities of daily living (ADLs using voicemail and managing telephone messages on their answering machine). On direct measures of this training, both participants improved significantly and reached near-perfect (96.9%) or perfect performances (100%). Similar to the study conducted by Loewenstein et al. [20], cognitive training on functional tasks did not improve the patients' scores on measures of general cognitive functioning, everyday memory, and quality of life in this investigation [31].

Coping Through Compensatory Strategies

Outpatient Settings

While different in their specific approaches, the overarching goal of outpatient cognitive rehabilitation programs servicing individuals with dementia is to facilitate a patient's greatest possible level of functional independence. Rees, Marshall, Hartridge, Mackie, Weiser, and Erabi Group [32] indicated strong evidence for the use of external memory aids to compensate for memory failures in day-to-day life, without necessarily improving a patient's underlying memory-related abilities. One such approach aimed at achieving both goals is the use of a

memory notebook to both reinforce previous events and to facilitate prospective memory abilities. During outpatient cognitive rehabilitation sessions, patients and their caregivers can be trained on how to use a notebook as an external aid to compensate for everyday memory failures. When used in individuals with TBI, pioneers in the field [33] describe highly positive outcomes utilizing a three-phase learning method for the individualized teaching of notebook use in patients with profound memory impairments. These authors reported that with this technique, three amnestic patients were able to resume independent living. As is the case with much of the cognitive training and rehabilitation literature, these improvements were not readily observed on formal measures of delayed recall, making improvements difficult to quantify. A similar, well-designed study evaluating the effectiveness of a 9-week memory notebook treatment for individuals who sustained closed head injuries also demonstrated fewer everyday memory failures (as noted on both retrospective questionnaires and observed reports) [34]. This training incorporated both in-session work and homework assignments, with clear goals and activities designed to help participants learn to use their notebooks. Notebook sections were dedicated to: a daily log, calendar (critical to fostering prospective memory), names of new people, current work procedures/assignments, and personal notes, such as autobiographical information or personal goals. Again, though patients were noted to have fewer memory-related deficits in day-to-day life than their peers receiving only supportive group psychotherapy, no improvements were noted on formal memory testing. In addition to helping a patient with dementia remember to complete a future activity or task and to recall a previous day's events, others have shown a less direct impact, such as a reduction of repeated questions after notebook training [35, 36].

Despite their obvious applications as useful tools, technology-based external memory aids are often challenging to the patients who need them most due to an inability to independently program or consistently manage them. Moreover, for patients with more significant memory impairments, the external aid may only be useful when the individual remembers to use/wear them, ensuring that they are adequately powered (batteries/charged), and are near enough to the patient to be heard.

Neuropage

The need for stand-alone external memory aids has slowly decreased in the years since the advent of smartphones and other related technology. That said, for less technology-savvy patients, external memory aids, such as a portable paging system, like NeuroPage [37], remain a relatively straightforward means of improving medication compliance by sending reminders to its users at a specific date and time (i.e., "take medication"). Developed by the father of a young brain injury survivor (Treadgold) and his son's neuropsychologist (Hersch), NeuroPage is a relatively simple alphanumeric radio pager, which provides the patient with reminders of things to do and when to do them. The patient and/or caregiver provides a list of reminders to a central computer, which automatically sends reminders to the pager, which, in turn, beeps or vibrates when a message is received on the screen. In most versions of NeuroPage, only one button is needed to receive the message and to clear it, making it more user-friendly and easier to provide training for even the most basic mobile phones with similar applications. That said, for patients who regularly use mobile telephones, NeuroPage messages are also accessible via cell phone. Early studies using NeuroPage [38, 39] suggest that users retain their ability to appropriately respond to reminders after using the service for several weeks, therefore underscoring its value as a potential application for supporting individuals with memory disorders.

Wearable Cameras

Wearable cameras are another technological advancement, which may develop into a clinically effective intervention used to treat autobiographical memory deficits in patients with dementia. Similar to a memory notebook, as

described elsewhere in this chapter, wearable cameras, such as the Sense Cam ® (a 5 cm by 6 cm camera worn around the neck by a lanyard), document a memory disordered patient's experiences for their later review. However, unlike conventional diary techniques, wearable cameras continually record visual information from a first-person point of view, which removes burden on a patient's memory, both to prospectively remember to write in the diary and to accurately recall the day's events as they actually unfolded. Removing such barriers has also been shown to improve the patient's confidence and ability to better cope with their functional impairments [40].

Woodberry and colleagues [41] reported the first case series of patients with Alzheimer's disease using Sense Cam ® technology versus a more conventional diary approach. Findings suggested that Sense Cam ® outperformed the diary method for five out of the six patients who were studied; overall, the amount of information recalled after 3-month follow-up was more than three times higher for those using Sense Cam ® than the diary condition.

In a more recent review of the relevant literature, Alle, Manning, Potheegadoo, Coutelle, Danion, and Berna [42] not only highlighted the potential utility of wearable cameras but also the limitations and ethical issues that arise in using such techniques for research and remediation. Taken together, researchers that have used such devices have begun to elucidate the specific neural processes involved in autobiographical memory and demonstrated their potential to better understand memory systems [42]. Patients with various kinds of memory disorders, such as major neurocognitive impairments, have benefited from utilizing this technology as part of remediation. That said, studies supporting their clinical uses have also presented with smaller sample sizes and shorter than 12-month follow-up data that limit their ecological validity and generalizability. Moreover, while wearing a camera is less effortful than writing a daily diary, it can be stigmatizing for individuals who may already be at risk for lower self-esteem. Finally, privacy and confidentiality may be areas of concern for patients and individuals that the patient interacts with, as personal information and images are taken through the Sense Cam ®.

In-Home Visits

Another aspect of cognitive rehabilitation may include visits to the patient's home or immediate community. Such visits focus on improving the patient's day-to-day activities through environmental adaptation. During home visits, clinicians can work with the patient and their caregivers to cultivate more structured, organized day-to-day surroundings. To illustrate, repeated misplacement of household keys may be reduced in patients with dementia if a habit or routine, such as always placing them a designated key holder near the door of the home, is established. This type of training may require a treatment plan including practical applications of multiple underlying tenets of cognitive training and rehabilitation, including, but not limited to, mnemonics, spaced retrieval, errorless learning, and vanishing cues.

Compensation Versus Neuroplasticity

The literature on aging populations is replete with studies suggesting a benefit from engaging in cognitively stimulating activities, whether serving as a protective factor against cognitive decline or preventing further degeneration in individuals already experiencing mild impairment. This information is especially important as the research supports that the aging brain is considered plastic, with the capacity to adjust or compensate secondary to changes in its environment [43]. The brain's potential to adapt or maintain neurocognitive abilities in response to a neurological injury is thought to be related, in part, to individual differences in cognitive reserve. According to Stern [44], cognitive reserve (e.g., "pre-existing experiences and/or neurocognitive processes") may limit a person's vulnerability to a neurodegenerative pro-

cess or the impact of "age-related cognitive decline."

A patient's level of cognitive reserve may directly impact their ability to benefit from cognitive interventions. Generally, the primary goals of both cognitive training and rehabilitation are to reduce the impact of cognitive difficulties and improve a person's overall functioning in several aspects of his or her life. To accomplish these goals, interventions may be developed on the basis of two primary approaches: a restorative or compensatory approach. Specifically, the restorative approach seeks to conduct repetitive drills that target cognitive deficits, with the hope of recuperating and/or restoring the impaired function [45]. In contrast, the compensatory approach supports patients in learning several strategies that may be used in place of the cognitive tactics that are currently impaired and nonfunctional [45, 46]. The mechanisms inherent to neuroplasticity and cognitive reserve provide evidence for the possibility of developing neurocognitive interventions that may eventually reduce the risk of acquiring a neurodegenerative disorder. Additionally, positive changes in connectivity due to neuroplasticity (i.e., increased synaptic strength and synaptogenesis) have been demonstrated in individuals receiving cognitive training [47]. As this body of literature continues to emerge, neuroplasticity-based treatments may become an increasingly important part of best treatment practices in the future [48].

Normal Aging

There has been a growing emphasis for older individuals to improve the "whole body," by maintaining appropriate nutritional habits and sleep hygiene, participating in physical activities, seeking and sustaining social interactions and, more importantly, engaging in cognitively stimulating activities. An expanding body of literature has emerged citing the reported efficacy and ongoing benefits of neurocognitive interventions for older adults post-training, with the goal of stopping or limiting cognitive decline and/or acquiring a neurodegenerative disease.

The benefits of cognitive training have been documented in several randomized-controlled clinical trials and longitudinal studies [45]. For example, one of the most readily cited randomized-controlled trials of neurocognitive training for cognitively intact older adults is the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study. The ACTIVE study was conducted to investigate the effects of neurocognitive training on everyday functioning, whereby healthy, community-dwelling older adult participants were randomized to one of three cognitive intervention groups in the areas of memory, reasoning, and processing speed and compared to a non-trained control group [18, 49]. Findings from this study demonstrated that positive effects on memory were maintained up to 5-year post-intervention and with regard to reasoning and information processing speed, up to 10 years [18, 49–51]. Further, individuals from each of the three training groups described more positive long-term effects and fewer problems with iADLs when compared to controls [49] [51]. Similarly, findings from the Seattle Longitudinal Study suggest that after a brief training program, a majority of older adults that had cognitive difficulties demonstrated significant improvement in these abilities, with evidence that these were maintained post-training [45, 52, 53].

Research studies on cognitive therapies have focused on the memory domain and training participants in this area; this is likely due to the fact that memory is the most common cognitive complaint among aging adults. A randomized control study investigating the effects of an experimental training program found that there were significant improvements in the exercises directly related to the training tasks, and these improvements generalized to unrelated standardized neurocognitive measures of memory [54]. Memory benefits were reportedly maintained even after a 3-month period of no training [54]. The authors described that the results from this study are

promising, in that they suggest that when older individuals are provided with rigorous, cognitively-stimulating intervention, neurocognitive abilities may be improved [54].

While most studies have focused on the positive effects of cognition resulting from cognitive remediation and rehabilitation, fewer have sought to evaluate the effects on physical outcomes, such as gait. Mobility has been found to decrease as individuals age, contributing to a decrease in quality of life due to slowed gait and increased risk of falls [55]. While specific cognitive domains, such as attention and executive functioning, are thought to be associated with mobility, studies that sought to improve these domains with the purpose of improving gait were scarce [55]. In a study conducted by Verghese et al. [55], the authors found that overall, older adults who were randomly assigned to an 8-week computerized remediation program improved gait velocity, both during normal walking and walking while talking tasks, when compared to that of controls. Similarly, a randomized control trial (RCT) assessing whether a computerized cognitive remediation program improved cognition and balance in older adults was found to be effective (Lee, Jang, Bak & Yoon [56] in Sharma et al. [45]).

Mild Neurocognitive Disorders, Patients Previously Known as Having "MCI"

Identifying individuals prior to the development of a neurodegenerative disorder and intervening with non-pharmacological approaches to prevent further cognitive decline has been an increasing goal in aging research. Given that mild neurocognitive impairments are typically thought to be the precursor to Alzheimer's disease, interventions aimed at prolonging maintenance of this milder stage have been of particular interest; however, relatively few research studies have been conducted in this area. The authors from a Cochrane Review of RCTs ([57]; Cochrane Dementia and Cognitive Improvement Group) described that available data conducted with individuals with MCI was severely limited given that the criteria used to define MCI varied. While there were some differences, the review did not demonstrate a substantial benefit of cognitive training when compared to controls. In a review conducted by Rodakowski and colleagues [58], the authors reviewed 32 randomized controlled trials designed for older adults with mild cognitive impairment or early-stage dementia that either used cognitive training, which included remediation or compensation approaches, physical exercise, or psychotherapeutic interventions [58]. The authors concluded that there were mixed results regarding whether or not neurocognitive training using remediation and physical exercise could positively affect cognitive abilities. It was suggested that training that utilized compensation and psychotherapy may assist with the influence of neurocognitive changes in the lives of these older adults [58].

There have been some positive improvements in trials of multi-domain cognitive therapies with individuals with MCI. For example, in a randomized, longitudinal study conducted by Rozzini and colleagues [59], the authors found that individuals who were treated with both neurocognitive training and a cholinesterase inhibitor demonstrated a significant improvement in various neurocognitive domains and reduction of depression-related symptomatology.

Research studies that have evaluated memory improvement in individuals with MCI have noted a possible benefit from cognitive training for the domain of memory, particularly when the intervention is multifaceted [60]. However, the extent to which these results can be generalized to establish consistent and effective interventional techniques is variable, due in part, to methodological flaws in established studies. To this end, Hampstead, Gillis, and Stringer [61] have suggested a hierarchical model to address the difficulties inherent in this research, such as accurate and consistent diagnostic criteria for MCI, variability in the cognitive remediation techniques, standard amount of trials/session (dose), outcome measures, and generalizability to practical real-world settings (please see Hampstead et al. [61]).

Alzheimer's and Vascular Dementia

Although cholinesterase inhibitors are considered standard of care for patients with early-stage Alzheimer's disease, a subset of patients do not derive benefit or need to discontinue treatment due to intolerable side effects. In such cases, as well as in patients where the therapeutic benefits of such medications have ceased, cognitive training and rehabilitation are often useful tools in optimizing a patient's adaptive functioning.

The utilization of cognitive remediation in individuals with Alzheimer's disease has received mixed reviews in the literature, with several meta-analytic studies of RCTs suggesting that there are no significant positive benefits from cognitive training in this population [1, 2, 62]. However, in a meta-analysis investigating the effect of cognitive training in AD, the authors concluded a benefit in neurocognitive functioning in several domains trained, particularly when restorative approaches were used [63] though the generalizability of these skills for use in real-world settings remains questionable. It is important to note, however, that one RCT using cognitive rehabilitation indicated some preliminary positive findings [1, 2, 62]. Similarly, a study using cognitive rehabilitation in individuals with early-stage AD demonstrated a benefit when compared to controls [64]. Several other studies have also demonstrated that cognitive rehabilitation of memory can have positive effects in individuals with dementia [65–67].

Overall, the effects of cognitive rehabilitation and/or cognitive remediation remain inconclusive with regard to benefitting individuals with dementia due to AD and/or cerebrovascular disease likely secondary to methodological limitations, which will be discussed in greater detail below.

Posterior Cortical Atrophy

Patients diagnosed with posterior cortical atrophy (PCA), or the "visual variant of Alzheimer's disease," typically experience an array of visuospatial and visuoperceptual deficits pathognomonic to the disorder, which may include apraxia, optic ataxia, spatial neglect, visual scanning deficits, visual agnosia, and alexia, as well as difficulties with depth perception, simultagnosia, and topographical disorientation (as described by Metzler-Baddeley, Baddeley, Lovell, Laffan & Jones [68], Caine [69], Goenthals, & Santens [70]). Several case studies/case series describe the efficacy of treatment interventions aimed at improving visuoperception in patients with this disorder [71, 72].

Roca and colleagues [71] describe a cognitive rehabilitation program undertaken with a 64-year-old gentleman with a constellation of deficits including object localization, difficulties in reading, and sporadic disorientation. Neuropsychological testing reportedly revealed severe impairments on a measure of visual attention, in the context of preserved auditory attention. Visuoperceptual deficits were appreciated on the complex geometric figure, as well as on a measure of nonverbal recall. Following a session of psychoeducation and collaborative goal setting with the patient and his wife, ten weekly 45-min sessions of cognitive training and rehabilitation were conducted, with supplemental at-home exercises, which included activities that were being practiced at the time. Post-treatment, the patient improved on measures of visual attention and complex visuo-reproduction; both the patient and his wife endorsed improvement on subjective questionnaires. Of note, after the initial improvement described by these authors, additional treatment with cognitive therapy (for another 12 months) failed to yield objective improvements on cognitive metrics; however, the patient and his wife continued to endorse subtle improvements in other aspects of his functioning.

Another case study evaluating the clinical impact of cognitive training and rehabilitation in a 60-year-old female with PCA employed a more multidisciplinary approach; the patient's program included elements of speech therapy, occupational therapy, and physical therapy for a period of 6 months [73]. The patient received various therapies (speech, occupational, and physical) and training (handwritten letter formation and use of a

line guide). Serial neuropsychological testing suggested that the patient's functioning remained stable over the course of the 6-month treatment period, despite likely disease progression.

Most recently, Alves et al. [72] described an intervention with a 57-year-old, highly-educated, bilingual patient diagnosed with PCA. Neuropsychological assessment reportedly revealed pronounced deficits in the areas of perception, visuoconstruction, learning, memory, and temporal orientation. Interventions included exercises aimed at improving the patient's written reproduction of auditory and visually presented numbers, word writing, phrase writing, temporal and spatial orientations (e.g., asking the patient to recall past, present, or future days), and addition exercises to improve the patient's level of independence while functioning within the community. Psychoeducational and compensatory strategies encouraging good sleep hygiene and use of daily clues, such as meals, to facilitate orientation to time were also employed. Upon completion of the intervention, repeat neuropsychological testing revealed modest evidence of improvement on measures of temporal and spatial orientation, attention, psychomotor abilities, and verbal learning [72]. These authors further reported that while still far below age-based expectations, the patient's performances on both Trail Making Test parts A and B were improved from baseline.

Primary Progressive Aphasia

Primary progressive aphasia (PPA) has a younger mean age at disease onset, with the median age being 62 years [74]. By affecting younger populations than other dementias, PPA often has early, devastating effects on the patient's functional status. Frequent neuropsychological complaints include severe anomia, comprehension difficulties, impaired confrontation naming/object recognition, speech apraxia/speech sound production errors and conduction aphasia (see Mesulam [75, 76] and Gorno-Tempini et al. [77]).

In 2013, Carthery-Goulart et al. [78] completed a comprehensive review of the range of non-pharmacological interventions for treatment of the cognitive impairments in patients with PPA and known variants. These authors comprehensively evaluated both impairment-driven (i.e., slowing the progression of naming deficits, agrammatism, speech apraxia, and dysgraphia) and functional interventions (i.e., compensatory strategies, increasing levels of participation in communication activities, and/or environmental modification). Despite using inclusive criteria in their review, the authors described that many of the studies related to PPA were based on single-case descriptions, limiting the generalizability of the findings. These data were particularly scarce for nonfluent/agrammatic (NFPPA) and logopenic (LPPA) variants. Although future large-scale studies with improved experimental designs are highly warranted, findings from the extant literature suggested promise for impairment-directed therapies aimed at lexical retrieval and naming in patients with semantic PPA (SPPA).

Given the early and profound impact on spelling in patients with PPA (i.e., Mesulam [75]), several interventions have focused on remediating this specific skill with positive effects [79]. More recently, early evidence of combined neuromodulation and behavioral language treatment has shown exciting preliminary results [80]. Tsapkini and colleagues targeted the left inferior frontal gyrus (IFG), an area of the brain shown to be involved in the phoneme-to-grapheme conversion (PGC) necessary to spell unfamiliar words in prior investigations [81], via transcranial direct-current stimulation (tDCS). These authors evaluated the degree and duration of improvement following combined therapies in a cohort of six native English speakers with PPA via a within-subjects crossover trial design. Results revealed that the combination of frequent, intensive spelling interventions (N = 15) and neuromodulation therapies was more effective than language-based therapy alone for both improving the PGC for untrained items, and these improvements were sustained in both 2-week and 2-month follow-ups. Although conducting similar interventions are likely beyond the scope of practice for most neuropsychologists, clinicians serving populations

with dementia are encouraged to remain abreast of this promising avenue of PPA treatment as it continues to emerge.

Neuropsychological Evaluation and How It Guides Cognitive Training and Rehabilitation

Together with a thorough background history obtained through clinical interview with the patient and a collateral informant, a neuropsychological evaluation provides the clinician conducting cognitive training and/or rehabilitation with information regarding the patient's neurocognitive strengths and weaknesses and produces hypotheses about possible successful remediation methods. More specifically, the pattern of performance on cognitive metrics is used to obtain a more accurate depiction of the patient's premorbid and present levels of functioning in all areas. In addition, results provide further information regarding a patient's spared abilities, capacity for developing compensatory strengths, and ability to participate in cognitive remediation and actively learn and benefit from this intervention [82].

Some of the foundational goals established for the patient in cognitive therapies and adapted from the rehabilitation literature includes two general paradigms, known as traditional and contextualized [46]. A traditional approach seeks to ameliorate neurocognitive deficits and restore functioning. It relies largely on repetitive, retraining exercises that target specific neurocognitive areas [2]. The inability to restore an individual's cognitive functioning through these drills would generally indicate the need to help patients develop compensatory strategies or obtain assistive devices [46].

In contrast, a contextualized paradigm aids a patient to compensate for those neurocognitive skills that are negatively impacting their daily lives. The neuropsychological assessment results are used to develop specific hypotheses that are most likely to lead to positive results during training [46]. Standardized cognitive metrics are coupled with observations and assessment of the individual's ability to conduct functional tasks. An emphasis on collaboration with both an individual's social support network and care team is essential.

For example, after the clinical interview and neurocognitive testing, a patient was found to be experiencing significant difficulties with attention and concentration, which were negatively affecting the patient's interpersonal, social, and occupational functioning. After discussion with the patient, repeated and graded interventions that targeted this area of cognition were thought to be most helpful. Therefore, cognitive remediation with an emphasis on attention processing training (APT; [83]) was initiated. The patient was also provided with at-home activities that required similar levels of attention and could generalize to real-world settings. After several weeks of training in the home and office, the patient reported improvement in his attention through everyday examples, and this improvement was evident on repeat neurocognitive testing.

Goal Setting

In a cognitive rehabilitation manual created in collaboration by Trinity College of Dublin and the Alzheimer Society of Ireland [22], the authors provide a useful mnemonic for goal setting. Interventions should be SMART: Specific, Measurable, Achievable, Realistic, and Time limited. These easily understood principles should be explicitly discussed with patients and caregivers and goals modified accordingly. Structured goal-setting approaches may also be of value in operationalizing desired outcomes in a more formal way, such as through the use of the Bangor Goal Setting Interview (BGSI; [84]) or the Canadian Occupational Performance Measure (CPM; [85]). The BGSI can also be used as an outcome measure to ascertain the patient's performance and satisfaction with each identified goal from the patient, caregiver, and clinician perspective.

Critical Evaluation of Cognitive Training and Rehabilitation Research Practices

Limitations of Research

Several research studies have sought to understand the role of cognitive training in healthy older adults and clinical populations in both maintaining current neurocognitive abilities, as well as preventing further decline and/or the emergence of a neurodegenerative disorder. However, difficulties in determining the efficacy of these interventions lie in the methodological approach used in these studies including, but not limited to: differences in cognitive training procedures, methods of providing such training, and neurocognitive abilities targeted, among other factors. In a systematic review of the literature, Martin and colleagues [57] analyzed RCTs that evaluated the effectiveness of cognitive training for healthy older adults and those with mild cognitive impairment, which found variable to little evidence for the benefits of memory interventions in these populations. A review article evaluating the benefits of cognitive intervention programs targeting healthy older adults found some improvement, though it noted difficulties in concluding an overall efficacious effect given the varying methodological applications of each [86]. Specifically, the authors discussed the fact that there were significant differences across training programs and interventions, the size of the sample, and the amount of neurocognitive domains assessed [86].

Evidence-based practice is particularly relevant and germane to the practice of cognitive rehabilitation owing to the increasingly shortened length of inpatient stay and outpatient therapies offered to patients following a brain insult or injury (e.g., [87]). Unfortunately, the relatively poor quality of the research methodology employed in many studies within this field significantly limits the stakeholder's ability to evaluate the evidence base. By extension, the discipline of cognitive therapy continually needs to prove its efficacy to insurance carriers to be a covered expense for patients with dementia. Therefore, an effort to establish clinical practice parameters, which are derived from evidence provided by the extant literature is needed.

However, much of the extant cognitive therapy and rehabilitation literature is comprised of case studies, case series, and investigations with small sample sizes; by extension, they may also lack statistical power to detect treatment effects [2].

Small Sample Sizes

In addition to highlighting the many benefits of cognitive training and rehabilitation in patients with dementia, meta-analytic studies are also useful in highlighting the limitations which are pervasive throughout this body of extant literature. Data yielded by single case reports or studies with small sample sizes, regardless of how promising or novel, are insufficient to justify the use of specific techniques in clinical settings. Rather, large-scale investigations are needed in order to replicate and extend preliminary findings.

Practice Effects

The use of conventional, repeated neuropsychological test measures presents multiple potential confounds when used in cognitive training and rehabilitation studies. This is a particular concern for the short intervals often required in pre−/post-testing for efficacy studies. For example, practice effects [88] can limit the reliability and validity of treatment effects unless adequately controlled for in analyses (i.e., Reliable Change Indices), which are not widely addressed throughout the literature (e.g., [73]).

Questionable Ecological Validity of Conventional Neuropsychological Tests Often Used in Dementia Patients

Alternatively, conventional neuropsychological test measures may not adequately assess treatment outcome for cognitive training and rehabilitation

studies, as rehabilitation efforts often focus on trained, circumscribed tasks, rather than a broader cognitive domain (i.e., [32, 89]). To this end, cognitive metrics evaluate the transfer of benefits from training to untrained tasks, rather than capturing the effect of the training on a trained skill [2]. For example, Loewenstein et al. [20] demonstrated significant benefits of cognitive rehabilitation on multiple tasks, including those instrumental for community living (i.e., making correct change with a purchase or balancing a checkbook) using specific evaluations designed to directly assess these skills (i.e., the Modified Making-Change-For-A-Purchase Task (based on the Direct Assessment of Functional Status [DAFS]) and the Balancing-A-Checkbook Task (also based on the DAFS [90])). Moreover, even well-designed interventions which fail to improve a patient's neurocognition or performance on activities of daily living are often helpful in more indirect ways, such as improving a patient's health-related quality of life (Brueggen et al. [91]).

Other Limitations

Other limitations adversely impacting efficacy studies of cognitive remediation include: variability in client characteristics and treatment settings, lack of standardization of frequency and intensity of treatment, and a lack of appropriate control conditions. Assessment of improvement can also be confounded by placebo effects (on behalf of the patient, caregiver, and/or family).

Limited Generalizability

The generalizability of cognitive training and rehabilitation (including both cognitive training and cognitive rehabilitation) from a therapeutic setting to a patient's day-to-day life has also been equivocal, particularly in dementia populations (e.g., [91]). Beyond the aforementioned difficulty of operationalizing and accurately measuring improvement on both neuropsychological testing and in real-world contexts, it is possible that the severity of the patient's dementia is yet another limiting factor. To illustrate, despite a well-designed, well-conceptualized group cognitive rehabilitation intervention for patients with mild to mild-moderate AD, Brueggen and colleagues [91] failed to show any significant effect on ADLs. These authors posit that the lack of positive transferability may be secondary to the diminished memory and abstraction abilities of the studied cohort to apply the newly learned skills in novel settings. In such cases, transfer should be increasingly supported in a domestic setting by the patient's caregivers and therapist.

Improvements in Experimental Design of Future Studies

More rigorous experimental designs are needed in order to provide more robust, evidence-based information regarding treatment efficacy. Neuropsychologists should critically evaluate the existing cognitive literature examining both the treatment efficacy and clinical effectiveness of the proposed technique/paradigm [92]. Per these authors, treatment efficacy studies typically evaluate time-limited interventions of selected homogenous samples in a highly constrained way. In contrast, studies establishing clinical effectiveness evaluate posttreatment effects in clinical settings; evaluations of value and utility may include clinical judgment and strategic modification of the intervention. Although RCTs comparing the intervention to a no-treatment control intervention are optimal, such investigations are not always feasible in most clinical settings [92]. Rather, Cicerone et al. [92] proposed that controlled studies of treatment effectiveness may examine the unique benefits of a specific intervention, as compared to an alternate therapeutic intervention (the "best available" treatment with known effectiveness). In such cases, the "best available" treatments may include both individualized treatments informed by clinical experience and the application of standardized treatment protocols [92].

Technology, Training, and Rehabilitation

Overall, while the literature on the benefits of technological applications of cognitive training and rehabilitation is relatively limited, the use of computerized cognitive training remains an area for safe, noninvasive, inexpensive, and effective alternatives to pharmacological interventions in older adults. Further research is needed to determine whether this potential avenue can improve cognition, slow down age-related decline, and/or provide a transfer of cognitive benefits to real-world settings.

While the extant literature supports a neurocognitive benefit from engaging in stimulating mental activities, the research concerning the positive benefits from using computerized programs are limited. Lampit, Hallock, and Valenzuela [93] conducted a meta-analytic study of RCTs assessing the efficacy of computer cognitive training programs on several neurocognitive domains in healthy older adults. General findings revealed that there was a moderate effect size with regard to improvement in cognitive performance in healthy older adults, with variable benefits depending on the domains assessed. Further, computer cognitive training completed in the home and without supervision did not demonstrate effectiveness and neither did training more than three times per week [93].

Mainstream media has been replete with controversial reports regarding the pros and cons of "brain training" or "brain fitness" programs. Yet, individuals in the United States have collectively spent large sums of money on cognitive training computer software that claims to enhance cognitive capacity [93, 94]. While the list of available neurocognitive, web-based applications has grown exponentially, the empirical evidence supporting their efficacy is variable.

Lumosity [95] is a computer-based training program with exercises across multiple neurocognitive domains. Research studies conducted using Lumosity [95] have demonstrated mixed results. Some have indicated variable generalization of skills [96], and others demonstrated a transfer of neurocognitive abilities to measures unrelated to the training [97]. Per research authors, Lumosity [95] has been thought to have the potential to identify individuals at risk for age-related decline in cognition [98].

In a study conducted by Miller and colleagues [99], researchers randomized two groups of community-dwelling healthy older adults to either a computer program (Brain Fitness, Dakim®, Inc) [100] or to a wait-list control group, with neurocognitive testing completed at three time points for each participant. The authors concluded that the use of this computerized program appeared to have improved delayed memory scores after 2 and 6 months. However, despite whether or not participants were in the control or intervention groups, they improved in all cognitive abilities assessed, also suggesting a general benefit of cognitive training for more than 6 months [99].

Cogmed working memory training (http://www.cogmed.com/) [101] is another computerized program designed to focus on working memory training. The literature on the use of Cogmed [101] or tasks similar to it has suggested that there are notable improvements on trained tasks, as well as some evidence of generalizations to other tasks. However, studies using Cogmed [101] with older adults have been limited. A recent study conducted by Hyer and colleagues [102] evaluated a sample of community-dwelling older adults with reported memory impairment and MCI. Participants in the study were randomized to either a Cogmed [101] or a sham computer training program, and pre-, post-, and follow-up neurocognitive metrics and questionnaires were administered [102]. Results from the study indicated that although those in the Cogmed group demonstrated greater benefits overall compared to the sham group, both evidenced improvement [102]. Researchers have also demonstrated a transfer of training on tasks of executive functions with older adults using a real-time strategy videogame [103].

Dyadic Interventions

Beyond technological advances, dyadic interventions, which support both caregivers and patients (caregiver recipients), have also increased in recent years. Modalities of care have included

dual supportive seminar groups (i.e., [104, 105]), one-on-one and dyadic counseling (i.e., [106]) and group memory notebook interventions (i.e., [107]). In their critical review of 12 studies published between 2000 and 2011, Moon and Adams [108] report that these types of dyadic interventions applied in early-stage dementia patients were both feasible and well tolerated, indicating improved cognition for the patient and social relations for the caregiver. These authors further report that in most studies, partners experienced improved dyadic relationships or increased quality of life, as well as improved knowledge of dementia and how to cope with this diagnosis. For neuropsychologists who do not provide training or rehabilitation as part of their practices, providing patients with information of local chapters and national organizations that provide such interventions is highly recommended (i.e., Alzheimer's Association (http://www.alz.org) [109] and the Alzheimer's Disease Education and Referral Center (ADEAR) (http://www.nia.nih.gov/Alzheimers/) [110]).

Additional Resources

In addition to developing a program combining cognitive training and compensatory strategies, dementia patients often require a more holistic approach to the management of lifestyle factors such as mood, stress management, exercise, sleep, and nutrition that have the potential to adversely impact cognition. While in no way a substitute for consultations with specialists in their respective disciplines (i.e., psychotherapist or nutritionist), neuropsychologists are often the 'first-line' providers in informing patients about free or low-cost resources available to augment their existing treatment program. A small sample of such resources includes:

Apps for Stress Management:
- **My Mood Tracker** [111]
- **Self-Help Anxiety Management** [112]
- **Breathe2Relax** [113]
- **Happify** [114]
- **Headspace** [115]
- **Gratitude Journal** [116]

Websites/Organization for Stress Management:
- **The American Institute of Stress:** www.stress.org [117]
- **Foundations for Well Being:** www.thefoundationsforwellbeing.com [118]

Exercise Resources:
- **Your Everyday Guide from the National Institute on Aging:** https://www.nia.nih.gov/health/publication/exercise-physical-activity/introduction [119]
- **World Health Organization's Global Strategy on Diet, Physical Activity and Health:** http://www.who.int/dietphysicalactivity/factsheet_olderadults/en/ [120]
- **The American Heart Association's Easy Tips to Get Active: Get Moving** [121]
- http://www.heart.org/HEARTORG/HealthyLiving/PhysicalActivity/GettingActive/Get-Moving-Easy-Tips-to-Get-Active_UCM_307978_Article.jsp#.WWklNuTruP8

Sleep Resources:
- **Relax Melodies (App)** [122]
- **Sleep Genius (App)** [123]
- **National Sleep Foundation:**
  - https://sleepfoundation.org/ [124]

Nutrition Resources
- **Nutritional Psychiatry: Your Brain on Food:**
  - http://www.health.harvard.edu/blog/nutritional-psychiatry-your-brain-on-food-201511168626 [125]
- **Food & Nutrition: Useful Tips for a Healthy Brain:**
  - https://healthybrains.org/pillar-nutrition/ [126]

Case Example

Ms. ENL, a 60-year-old, right-handed, married woman, experienced a sudden onset of severe dyspnea upon exertion; an atrial myxoma was discovered requiring immediate treatment and excision. Following successful cardiac surgery, the patient was placed on prophylactic anticoagulation therapy with Coumadin. After 15 days of

treatment, the patient suffered an intracranial hemorrhage (ICH), requiring a hemicraniectomy, a medically induced coma, and, ultimately, a ventriculoperitoneal (VP) shunt placement and cranioplasty. Upon stabilization of her condition, the patient received occupational and physical therapies at bedside to treat hemiparesis of the upper- and lower-left extremities. Upon neurological exam, she was found to have decreased tone, facial droop, complete homonymous hemianopsia, upper- and lower-left hemiparesis, ptosis, blunted affect, and aprosodia. Upon discharge from the medical floor of the hospital, she was sent to inpatient rehabilitation for two additional months. Approximately three months after the ICH, the patient began experiencing episodes of left arm and leg shaking, which were ultimately diagnosed as partial motor seizures. She was subsequently treated with lamotrigine and levetiracetam. EEG findings were consistent with right hemispheric cerebral dysfunction, which was maximal anteriorly. A CT completed shortly after the event reportedly revealed a large hematoma in the right frontal lobe with significant surrounding vasogenic edema, resulting in parenchymal expansion and herniation of the cortex through the craniotomy site. The parenchymal hematoma was decompressed into the lateral ventricles, and the blood was seen to layer dependently in the left occipital horn.

Approximately two years prior to the patient's diagnosis of myxoma, ICH, and seizure, Ms. ENL had first presented to neurological attention secondary to complaints of inattention, distractibility, and overall "slowed thinking." An MRI completed at that time was significant for the presence of: "patchy T2 hyperintensities within the periventricular region and beyond which is suggestive of microvascular ischemia that was greater than expected for patients of similar age." Due to the patient's cognitive symptoms, multiple vascular risk factors (i.e., diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, coronary artery disease s/p stent placement), and ischemic change on MRI, the patient's neurologist was suspicious of the presence of vascular-related cognitive impairment and suggested more aggressive management of lifestyle risk factors. Weight loss and increased cardiovascular exercise were attempted. Family medical history is remarkable for dementia (mother) and vascular related risk factors (father).

Ms. ENL received comprehensive neuropsychological evaluation 15 months post-ICH. A professional woman with a graduate degree in Applied Mathematics, Ms. ENL's estimated premorbid levels of premorbid abilities were believed to fall at least within the high average range or above. In contrast, a decline from estimated premorbid levels of functioning was noted on tasks of visuoperception/visuoconstruction, learning, and memory. Learning and memory deficits were characterized by reduced initial encoding and storage, confabulation, and reduced discriminability on recognition memory paradigms. Executive dysfunction was the most salient feature of the evaluation and was characterized by diminished working memory, poor set shifting, reduced psychomotor speed, slowed verbal fluency, and impaired verbal and visual abstract reasoning. Preserved functioning was shown on tasks of word knowledge, verbal abstraction, confrontation naming, and narrative memory.

Functionally, she required the use of a cane to ambulate, was dependent on a catheter for genitourinary retention, and necessitated assistance for all activities of daily living (ADLs). Medication administration and finances were handled solely by family and a home-health aide. Based on her neurocognitive and functional impairments, a trial of cognitive rehabilitation was recommended. She later completed one year in an outpatient intensive rehabilitation program where she received outpatient OT, PT, and a brief, unsuccessful trial of "visual scanning therapy"; the latter was discontinued due to limited rapport with the therapist. The patient and family were open and receptive to reinitiating CTR if a "good fit" could be secured with a new therapist.

In terms of psychiatric history, though Ms. ENL reported experiencing varying degrees of affective distress throughout her lifetime, she became increasingly anxious and distressed since

the ICH. She briefly attended supportive psychotherapy to facilitate her adjustment to disability and subsequently sought cognitive behavioral therapy to improve coping strategies in stressful and/or anxiety-provoking situations.

A goal-setting session was undertaken with the patient and her husband. Family goals included increased length of sustained attention, multitasking, visual scanning, and improving functional independence, particularly with regard to her schedule and calendar management. Although the patient expressed great interest in returning to work and to resume driving, it was clear that she did not yet possess full insight and understanding of the range and scope of her residual neuropsychological deficits at 15 months post-injury.

A comprehensive holistic training approach to cognitive rehabilitation was taken, specifically, structured in-session exercises, follow-up "homework" with real-world applications, a memory notebook, and the use of a computerized cognitive enhancing program and apps related to stress management. Owing to Ms. ENL's marked deficits in attentional and executive dysfunction (i.e., sustained and divided attention, task vigilance, and freedom from distractibility), these aspects of cognition were addressed first, as their improvement would enable the patient to be more fully receptive to other aspects of remediation. Attention process training [84] is a highly structured intervention that focuses on improving attention using repeated, hierarchically organized tasks which activate multidimensional attentional systems through manualized exercises of sustained, selective, alternating, and divided attention.

Direct retraining of Ms. ENL's visuospatial difficulties was then undertaken. The underlying theory of this approach is that cognitive systems will improve through direct stimulation, specifically, through pencil-and-paper or computerized exercises; the increase in cognitive ability would, by extension, improve aspects of the patient's daily life [127]. Like the approach utilized by Roca et al. [71], intervention strategies included visual scanning training requiring the patient to fixate on a certain point, search for a target embedded among distractors, and reach for a target. The patient was also provided with rehabilitation in the tactile direction of movements, where Ms. ENL was encouraged to compensate for her difficulties in this area to direct movement using tactile, and not visual information.

The last major component of Ms. ENL's remediation included interventions for problems that she was experiencing in her everyday life, such as leaving ample time to travel between appointments. The patient's substantial difficulty with planning, organization, problem-solving, and insight were all apparent barriers, as was her frequent loss of items critical to her appointments (e.g., eyeglasses, medications, doctor's address). In a series of outpatient sessions, Ms. ENL was given progressively more difficult scenarios requiring her to "work backwards" from her arrival time at an appointment to a logical departure time from her home and simultaneously factor in potential impediments to her progress (i.e., traffic). To practice this technique in a real-world environment, Ms. ENL's family and home health aide were instructed to allow her to plan the daily schedule and then counsel her about any flawed logic or reasoning. Each of these attempts was recorded in the patient's memory notebook and discussed during the subsequent session.

After 15 months of treatment, Ms. ENL was again evaluated by another neuropsychologist (the treating remediationalist deferred testing secondary to a clear conflict of interest). Findings revealed considerable improvements in the areas of verbally mediated short-term memory, visual-spatial perception and memory, and right-sided fine motor coordination. Her encoding of newly learned verbally-based information was especially improved, now falling in the high average to superior range, which is likely secondary to attentional gains following treatment with APT.

Although Ms. ENL did not begin cognitive remediation until more than 16 months after ICH and ~40 months after the onset of symptoms consistent with vascular-related cognitive impairment, she improved considerably on both testing and in her day-to-day life. Her husband noted steady gains in cognition. Perhaps equally as important, Ms. ENL required less oversight by her home health aide, whose hours were

ultimately lowered from full time to part time. She also resumed working in an advisory role and passed both off- and on-road driving evaluations. As a result, her health-related quality of life and, by extension, her mood improved considerably, much to the delight of her friends and family.

Clinical Pearls

- Developing good rapport, trust, and mutual respect with the patient is key to successful training and rehabilitation. The job of a remediationalist is to identify a patient's weaknesses and to continually address them each week in sight of a greater, long-term goal. Once success is achieved, the difficulty of the task is usually gradually increased. This process is often frustrating for patients, particularly those with underlying neuropsychiatric conditions or emotional dysregulation. Having a good therapeutic alliance with the patient is critical so that they understand that the fleeting successes are not an attempt of the clinician to "be mean," but rather to facilitate future gains. Also, although it is easy to focus on the individual's neurocognitive weaknesses and developing strategies to assist with these, it is equally important to remember that the person's strengths can be used to facilitate positive change.
- When disseminating information to patients with memory disorders, it is important that the information be given in a simple, concrete form and repeated as many times as needed. Patients should then be encouraged to re-state what they have learned in their own words ("verifying" the information).
- Set realistic expectations with the patient and their families prior to treatment onset. Patients and families should be explicitly counseled that cognitive retraining and rehabilitation cannot and does not "cure" neurodegenerative processes. Rather, goals should be aimed at maintaining current abilities for as long as possible and optimizing the patient's day-to-day functioning.
- Patients should be encouraged to bring in real-world examples of daily struggles so that they can be incorporated into the session and have a greater likelihood of being generalizable.
- The patient should be reminded that the process of cognitive therapies is a collaborative one between them and their remediationalist, so it is important for them to be ever-involved in the process through goal-setting, vocalizing positives and negatives, and being open and honest about the use of these exercises outside of the session.
- The goals should be continually reassessed by the patient, his or her family, and the neuropsychologist and adapted based on patient's disease progression or evolving needs.
- The patient should be continually reminded of the goals of rehabilitation and explicitly told how each exercise (or each session) is aimed at achieving that ultimate goal.
- Relating activities to a functional goal or benchmark is often useful at improving or maintaining motivation. For example, making the comparison of a complex visual attention exercise to a patient's desire to return to drive can be useful.
- To improve the likelihood of an exercise's generalizability to day-to-day tasks, it is important that at-home assignments include tasks that have "real-world" applicability. To illustrate, encourage patients to employ a mnemonic strategy taught during the session at a family gathering.
- A patient's progress should be continually reassessed by both cognitive metrics and family report of adaptive functioning. This combination of subjective and objective rating scales provides complementary information that obviates many of the limitations of cognitive training and rehabilitation (i.e., "teaching to test" or diminished generalizability).
- For older adults with memory difficulties, include a trusted family member or friend within the session to be assured that the strategies/psychoeducation provided can be transferred once out of the office.

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Environmental Design for Cognitive Decline

25

Rosemary Bakker

Environmental design is an underutilized yet effective treatment option in helping patients with cognitive decline maintain function with fewer behavioral problems [1]. In this chapter, key design solutions (e.g., memory aides, interior design, and smart home technologies) will be explored that can help patients and their caregivers lead safer and more satisfactory lives. Environmental design cannot stand alone as a therapeutic modality; therefore, the importance of the psychosocial environment, with guidelines on how caregivers can best elicit cooperation and trust from their loved ones, will be addressed. Table 25.1 highlights environment-related changes in function and perception commonly associated with dementia.

Caregiver Challenges

Fluctuation in Skills and Behaviors

Patient skills, behavior, and memory can fluctuate from day to day or even within a single day, making it difficult for individuals or families to know how to intervene. Robert C took his wife for testing as he could no longer cope with her changes in memory and judgment; she was regularly flooding the apartment, forgetting that the bath water was running. An accomplished cook for 50 years, she had recently roasted a frozen chicken in the oven without removing the plastic wrapping. Yet he reports, there are days when she still seems "normal."

Unusual Behaviors

Patients may engage in unusual or unsafe behaviors that are particularly challenging to cope with, like hoarding or wandering. Mistaken perceptions can occur in low-light levels and in shadowy areas, sometimes leading to calls to the police due to "strangers in the room." Low-stress thresholds that are common and seemingly minor events, such as the noise of a loud television or dishwasher, can act as a trigger for an extreme reaction. It is not surprising that more than 40% of caregivers of persons with cognitive decline rate the emotional stress of caregiving as high or very high [2] and that 34% of caregivers report needing more help with keeping the person safe at home [3].

Lack of Insight

Patients with cognitive decline often have limited insight that there is anything wrong, making it difficult for the clinician or family member to

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Table 25.1 Environment-related changes of function and perception in dementia patients

Visual/spatial	Hearing
Problems with visual/spatial perception if foreground and background are not color contrasted (e.g., reduced food intake can occur if food and plate are the same color)	Inability to focus due to excessive background noise
Perceptual distortion caused by highly patterned flooring, seating, or wall covering	Confusion or agitation in noisy environments
Inability to recognize their own image (e.g., in the mirror or in a bare reflective window)	Loss of ability to interpret sounds accurately; underlying hearing disorders can also predispose a person toward auditory misperceptions (e.g., sound of telephone perceived as small dog barking)
Visual misinterpretations in low lighting	
Problems with object recognition with similarly shaped objects (e.g., waste basket mistaken for toilet bowl)	
Mobility	*Memory/judgment*
Difficulty in walking caused by changes in gait and balance, especially if area carpets and door sills are present	Problems with sequential tasks
Stair-climbing difficulties Lack of handrails Only one handrail, if patient has a one-side weakness due to a stroke Risers and steps in the same color	Problems with short-term memory (e.g., forgetting food cooking on stove) Inability to focus Way-finding issues and getting lost, even within the home Inappropriate judgment (e.g., putting clothes in the microwave to dry)
Forgetting they cannot walk unassisted	
Forgetting to use their walker or inability to learn how to use it	
Restricted access due to narrow doorways or lack of stair alternatives during wheelchair usage in the late stages	

openly discuss dementia or safety issues for fear of upsetting the patient. For example, the patient may not remember that he or she has been leaving the stove on or getting lost on the way home from a shopping excursion. As a clinician, you may need to broach performance of daily activities gently, noting any resistance, and get permission from the patient to speak privately with the caregiver later on, if necessary.

Cognitive Decline or Poor Design?

When a patient has impaired function, it is commonly assumed that the problem is cognitive decline rather than the interaction between the patient and the environment. Consider the following example: On a very hot summer day, the author reported to the assisted-living staff that her mother was in her room—agitated and without air conditioning; the staff replied that her Alzheimer's had progressed, and she could no longer operate her air conditioner. Upon further investigation, however, the lack of function was not due to dementia. Rather, her mother simply could not read the lettering on the air conditioner's control panel because the font was too small and the contrast between the font and the background color too low. She was not able to understand the problem, but she did express her frustration over the poor design as the discussion ensued. "Why do they do that? Why do they make your brain work so hard?" Applying an On/Off label in a large black font against a white background quickly restored her function—and her well-being.

An environment that is suited for individuals with cognitive impairments does not happen spontaneously; it takes understanding and planning. Without understanding the environment's effect on a patient's behavior, many caregivers blame declining abilities on the disease and may not engage in preventive measures. In some cases, the interventions are too restrictive, not allowing for meaningful participation by the patient. For example, if a patient forgets a couple

of steps in the bathing process due to problems with sequential tasks, the caregiver may take over all steps, which often causes resentment on both sides.

Finding out What Works

Clinicians should stress to caregivers that design and behavioral strategies need to be individualized and continually reassessed; strategies that are effective for some may only work briefly or not at all in different situations. Throughout this chapter, individualized approaches to challenging situations will be highlighted, to illustrate the wide variety of responses in this population.

Ongoing Safety and Design Issues

Caregivers should keep in mind that providing for the safety of their loved ones is an *ongoing challenge as the disease progresses*. As one caregiver recently remarked, "Even when you think you have resolved a problem, you have no clue as to what is going to hit you in the face the next day." To help reduce challenging behaviors when adapting the home environment, changes should be phased in gradually whenever possible, and caregivers should be instructed to observe how the person responds and switch course when and if necessary. If the caregiver is planning on keeping their loved one at home for as long as possible, consideration should be given to increasing the home's accessibility (e.g., wider doorways, ramps, walk-in showers, etc.).

The Environment as a Therapeutic Modality

Reducing Environmental Triggers of Agitation

It is common for caregivers to report that their loved ones are easily agitated, but when the patient's behavior is explored in greater detail, there is usually a specific event preceding the agitation that acts as a trigger for that behavior. If a patient presents with a new history of agitation, ask the caregiver to think back to the activity or conversation that took place prior to the behavior. For example, if a caregiver states that their loved one becomes agitated during bathing, ask them to document exactly when the agitation begins. Was the patient uncomfortable while disrobing, fearful of getting into or out of the bathtub, or anxious when the water was turned on or when their body was washed? Caregivers can be advised to keep a journal and document the behavioral incidents. If the cause is external, whether it is precipitated by environmental factors or by caregiver interaction, the caregiver can then act to change or modify the trigger(s) and the associated agitation [4–7].

Common triggers for agitation include environmental factors and caregiver interaction, including:

- Noise
- Room temperature
- Standard bathing techniques
- Lack of stimulation
- Overstimulation
- Denial of access
- Tasks too complicated for person's current abilities
- Caregiver tone of voice
- Caregiver behavior (e.g., controlling)

Monitoring the Effects of Interventions

It is not always clear if a person can safely engage in an activity, and balancing risk and freedom is an ongoing challenge for caregivers. At some point, the caregiver may need to set certain items or areas of the household off-limits. Most standard home safety checklists recommend denying access to "safety hazards" but do not mention that sometimes the solution causes a new problem. Patient A may simply walk away if they can no longer turn the stove on (after removal of the knobs) or open a newly locked cabinet door, but patient B may become so frustrated that they attempt to remove the lock or the door or even tear the room apart. Ron G removed the knobs

and installed child safety covers on the stove before he went to work so that his mother would not cook when he was not at home; this is a common home safety recommendation. Left alone all day, his mother became so agitated that she dismantled the stove and emptied the kitchen cabinets onto the floor and countertops. Ron G was overwhelmed by this severe reaction and felt he had no choice but to place her in a nursing home. This outcome may have been prevented, or at least postponed, if he had been warned of the potential for negative outcomes and had been able to monitor the situation.

Memory Aides for Earlier Stages

In the early to mid stages, depending on the extent of the cognitive loss, reminder signs with simple language, large-sized text, and personalized images act as an "external brain," giving needed instruction for daily living. The image and text used *must* be customized for the person and large enough to capture their attention, or the intervention will not be effective [4]. Here are a few successful examples:

1. Cecilia G remembered to brush her teeth if simple instructions were placed in her direct view:
   (a) Put toothpaste on toothbrush.
   (b) Brush teeth.
2. Arlene S identified her room when a photo of herself from her earlier days was placed on the door. But for Ed T, a former corn researcher, it was a dried corn arrangement, not a personal portrait, which enabled him to recognize his apartment door.

Finding Lost Items

Losing and searching for belongings is a common and frustrating activity; organizational strategies may be helpful for those experiencing mild cognitive decline. For example, a patient may be able to learn to place their keys in one location, especially if it is visually easy to identify, as in a bright red bowl on an uncluttered foyer table. A sign (text and icon) reminding the patient to place the keys in the bowl can help reinforce the new behavior. Electronic finder devices can also reduce distressing time spent on finding objects. The patient may not be able to learn how to use the device or may misplace the device, but caregivers have successfully used locator devices for some patients with good results [5]. As one caregiver said, "I used to get so anxious when I visited my dad, as we would spend a lot of time searching for his keys and then we would both be in a bad mood. Now, when I visit, I use the locator device, which I keep on my key ring and within minutes, I find his keys. Now we spend more time on enjoyable activities."

Visual Misperceptions and Visual Dysfunction

Problems with Depth Perception

Many patients experience visual dysfunction when there is lack of contrast, causing significant problems with depth perception. Lack of contrast makes it harder or impossible to identify objects that are set against a background of similar colors. For example, a patient may walk right past a white toilet on a white wall and continue to search for the toilet, but a color-contrasted toilet seat can enhance object recognition and may help the person remain continent for a longer period of time [6]. Patterned carpeting or carpets with dark contrasting borders may also be difficult for patients with visuospatial difficulties; some individuals may not perceive the floor to be level and may attempt to jump or step over patterns or borders.

Misperception and the Environment

Some individuals have difficulty differentiating objects, especially those that have similar shapes, such as a patient who mistakes the wastebasket (oval shape) for the toilet bowl (oval shape). Others may be unable to recognize themselves in a mirror or misperceive what's there. For example, he or she may see a stranger and not

themselves in the mirror or think that their own reflection in a dark window at night is a stranger. And some may see frightening shapes, like a crouching person in a large houseplant in dim lighting or animals in a swirling, patterned fabric or carpet. Others have difficulty differentiating reality from representation. They may perceive people in photographs as real and refuse to undress or even get upset if the photograph does not respond when spoken to. If a violent TV show is on, they may think the event is actually happening right in their room. The person may become so frightened that they call the police.

The following interventions can reduce or eliminate the misperceptions, depending on the cause:

- Remove wastebaskets from bathrooms.
- Remove or cover mirrors.
- Turn photographs around (or remove, if necessary).
- Close blinds or drapes early at night.
- Increase light levels.
- Control TV viewing.
- Replace patterned furnishings.

Lighting and Function

Appropriate lighting can improve overall quality of life for people with dementia, though this is often overlooked. It can reduce the environmental misperceptions that occur in low-light conditions. Appropriate lighting can also significantly improve visual function due to age-associated visual loss [7]. Mark P regularly led the congregation during prayer service, but when he began stumbling over words, everyone thought it was due to the progression of his dementia. But after a new overhead light was installed, his reading skills went back to normal.

Mobility and Falls

Patients with dementia fall two to three times more often than individuals without cognitive impairments [8]. Patients experience not only normal age-related vision and mobility changes that increase fall risk but also dementia-related challenges that increase the incidence of unsafe situations. Table 25.2 lists common dementia-related risk factors for falls.

Table 25.2 Common dementia-related risk factors for falls

Inability to housekeep, *maintain a home*, *or hoarding behavior* can create mounds of clutter and other home hazards
Reduced attention and/or depth perception can make certain objects, like doorsills and low tables, less noticeable and are common causes for tripping
Lowered stress thresholds and becoming easily agitated; storming off or possibly striking out and losing balance
Fear of falling and, *consequently*, *not walking much*, which further increases fall risk; reduced exercises leads to weakened muscles and stiff joints
Impaired memory and judgment can cause risky behaviors, such as descending steep stairs in the dark, searching for a mother or adult child the person believes is still in his/her care
Changes in perception and balance can cause problems, such as not knowing where to place one's feet going up- or downstairs, walking with a shuffle, and getting one's foot caught on area rugs or doorsills, or holding onto unsteady furniture

Strategies to Reduce Falls

There are a variety of environmental strategies to employ depending on the patient's fall risk factors. Below is a list of key interventions:

- Remove area carpets and doorsills, especially if patient shuffles.
- Clear clutter (crates and baskets can be used to store clutter outside of walkways if patient is upset at removal).
- Remove low tables, especially glass.
- Provide for accessibility:
  - Ramps
  - Walk-in showers
  - Bath and shower chairs
  - Use compensatory measures
  - Highlight edges of steps for better visibility
  - Color-contrasted seating, bedding, and toilet seat to the floor
- Monitor high-fall areas with sensors or weight-sensitive chair, bed, or floor pads to

alert caregiver when person attempts to transfer or use stairs independently when it is no longer safe to do so.

Challenges with Stair Climbing

At some point, the individual may have difficulty climbing stairs, especially if there are no handrails. One-sided handrails can be problematic for an individual with weakness on the side as the handrail (e.g., due to a stroke). Risers and steps that are similar in color can also pose a challenge. If the patient is unsure of their step or becomes agitated when climbing stairs, a 2-in. strip of bright tape applied along the edge of the step may help them better distinguish the tread from the riser [9]. When it is too dangerous for someone to use the stairs without supervision, the caregiver needs to limit access. A monitoring device, such as a motion sensor, should be used. A motion sensor with a remote alert can notify the caregiver, even in another room, when the patient approaches the staircase. Advance notice may give the caregiver the time they need to be at the patient's side to offer assistance. A baby monitor may or may not work, depending on the amount of noise a person makes walking across a room. Denying access to the stairs using gates or locked doors may be necessary at times, but it should be done with caution and frequent monitoring, especially when the person is accustomed to using the stairs freely. Child safety gates are specifically designed for children, not for the strength or height of an adult. Some individuals may simply turn around and walk away when faced with a child safety gate, but others may attempt to open the gate or, worse, climb over it.

Electric Stair Lifts

Sometimes people ask if a patient with dementia can use an electric stair chair lift. There is little research on this topic, but problems with fear of falling should be expected, as most patients have little or no experience with using a "chair" that automatically moves up and down the stairs. Step-by-step instructions *before starting the chair lift* could help reduce fears. It may also be a good idea for the caregiver to walk behind the person and offer support, telling their loved one that they are safe and they will not fall.

Wandering

Wandering and getting lost are serious problems for patients with dementia, especially since these happen so unpredictably. A patient can wander off unexpectedly, even when the caregiver thinks they are safe. It is not unusual that someone with dementia may leave their home in an effort to get to a job they no longer have or they may go searching for someone they truly believe is still in their care, such as a child who is now fully grown. They may leave home desperately searching for their "real" home because they no longer recognize where they are living. The patient may pace and constantly move about, increasing their chances of getting lost. Finally, they may become agitated and storm off; they may be bored, disturbed by too much noise, or upset by side effects from certain medications.

What makes wandering difficult is that most people are so accustomed to leaving home whenever they wish, and individuals with dementia are no exception. At some point in the disease, the patient *will* get lost if they go out alone, and we cannot predict when that moment will come. Wandering typically occurs during the middle stages of AD, when many other disease symptoms are present. However, caregivers have brought their loved ones in for testing only *after* a serious wandering episode, stating that there was no warning that there was anything to be concerned about. It can be a shocking way to learn that the dementia process has begun.

There has been little research on which wandering solutions work best in different situations and environments, so trying to find the best strategies to deal with wandering can be challenging. How well any intervention works depends on a number of factors, including the patient's temperament, the stage of the disease, their environment, and, of course, the product or strategy employed. For example, a patient may become very agitated by locked doors, refuse to carry a tracking device like a cell phone, or wear a special monitoring device on their wrist. Further, GPS and other tracking devices do not work in all environments. Since no *single* strategy will work in all situations, it is best to recommend that the caregiver try several to see which ones work best for their situation. Combining several strategies

is preferred for backup safety, for example, using both an ID bracelet and a monitoring device that alerts the caregiver to an open door.

Pilot studies of a nighttime home-wandering monitoring system, consisting of room and bed occupancy sensors, door alarms with remote alerts, and a communication panel at the caregiver's bedside, showed potential for improved caregiver well-being and quality of sleep [10], reduced injuries, and unattended home exits by persons with dementia [11]. *Redirecting* an individual's attention from leaving home to a preferred activity is a powerful preventive tool. Many patients have decreased initiation but can participate if someone else can initiate the activity for them. Going outside when the weather permits can also reduce "cooped up" feelings and associated agitation. Refer to the section on wandering at ThisCaringHome.org for prevention strategies; there are also reviews and descriptions of electronic devices that can help find the patient if they wander and cannot find their way home.

Chair and Bed Transfers

Assisting an adult in the sit-to-stand transfer is one of the most difficult and dangerous tasks for a caregiver, putting them at risk for injury [12]. Caregivers, especially novice caregivers, often provide more physical help than is needed, not knowing how else to proceed, and physical support is usually not performed in an ergonomically correct manner [13]. Difficulties with transferring are usually due to a combination of factors, including furniture design, the individual's health, memory, and response to the caregiver (e.g., many patients do not respond favorably to a caregiver's request to get up from a chair or bed).

Chairs

For most people with adequate strength and function, it is much easier to get up from an ergonomic chair (not too low or deep, with an opening under the seat and side arms) than from a sofa or an easy chair, because the necessary body movements are much easier on the joints and muscles. Even individuals with Parkinson's disease who are rigid and frequently lean forward can get in and out of a good chair, especially if they rock back and forth and rise on the count of three.

Motorized, lift-up chairs can be extremely helpful when the person has severely limited movement or refuses to sleep in bed, as the chair can be put in a reclining position. Caregivers should be forewarned that a lift-up chair is best used with a caregiver present, as the controls are typically difficult for persons with dementia to use. A fall could occur if a person attempts to climb out of a chair that is in the reclining position. Additionally, some patients become frightened when the chair starts to move without warning, so the caregiver should tell the person what is going to happen *before* they lower or raise the chair, even if they think the person will not understand.

Beds

A mattress with the appropriate degree of firmness will be comfortable for the patient to sleep on and easier to push off from when getting out of bed. For many individuals, the most suitable bed height for a comfortable transfer is 18 in. Before attempting to help a person out of bed, instruct the caregiver to give a good reason to get up. In addition, a warm, gentle voice can do wonders. The right type of bed handle can help a person get out of bed and stand, as it offers a stable surface to hold onto and push off from and it can also help with balance. To use a bed handle safely, the person still needs good upper body strength and the ability to stand and bear weight. The bed handle should attach *securely* to the bed frame.

Impact of Memory Issues on Transfers

Although it may be hard to imagine, people with dementia sometimes forget how to get out of a chair or bed, therefore providing instructions may be helpful. Gloria T had been physically helping her husband to get up from his chair and bed but was experiencing significant back problems. The author recommended that

her husband be assessed for function to see if he still had adequate ability to help with transferring. A physical therapist's assessment showed that he had adequate transfer function and taught Gloria T "coaching" techniques to replace her physical assistance. She now offers simple step-by-step instructions, including visual cueing, like tapping the edge of the seat or bed, and physical cues, like placing one hand on his lower back and one on his shoulder to gently guide him forward. The caregiver's attitude and physical approach is an important aspect of the person's willingness to get up. Approaching the patient with a positive attitude and offering an inviting reason to get up can provide needed encouragement. To reduce feelings of intimidation and "power struggles," the caregiver should be advised to be at eye level with the patient (e.g., sit next to patient or kneel down at bedside) while inviting the patient to an enjoyable activity.

Meal Preparation, Cooking, and Dining

Organizational Strategies and Cues

Although many patients may no longer be able to cook a full meal, most can participate in a limited way with the proper instruction and kitchen organization. It is hard for anyone to find items in a cluttered environment, especially, if the storage areas are not well marked. Patients in the early stages or their caregivers can be advised to group similar items together (e.g., breakfast food items). If the patient forgets to look inside the cupboards or drawers, signs and pictures can be put up on the outside to help him locate objects behind closed doors or drawers. If this does not work, a cupboard door can be removed. The most used items can also be left on the countertop, in see-through containers, labeled in large letters to help alert the patient as to their contents. Gregg T was able to prepare his breakfast on his own, but only when his wife set out all ingredients beforehand and left simple instructions.

Cooking Challenges

Use of cooking appliances when an individual's memory is impaired is a major safety concern [14]. Devices that automatically turn off appliances left on inadvertently can proactively help to avert crises and extend a patient's ability to cook, as long as the patient still has good stove skills and judgment. For example, Jon B installed a device to turn off the stove for his wife's nighttime cup of tea. He felt she was safe cooking independently but wanted assurance that if she were to forget and leave the stove on, it would automatically shut off after a set period of time (he chose 3 min, long enough for the kettle to boil). Alternatively, cooking appliances are available that may be safer to use for a certain subgroup of patients, including electric teakettles that automatically turn off after the water boils and microwaves with easy one-button cooking.

Not everyone, however, will be able to use a new appliance or learn a new way of cooking, *no matter how minor*. Caregivers who have replaced a gas stove with an electric stove are sometimes shocked to discover that their loved one cannot learn how to use it. Smart devices and safer household appliances can be very helpful, but they do not replace caregiver oversight. Caregivers should be advised to *frequently* assess the patient's cooking skills and judgment, for example:

- Do they still know which cookware is safe to use or do they put plastic containers on lit burners or metal containers in the microwave?
- Might an electric teakettle be placed on a hot burner?
- Do they know that paper plates that are safe to use in the microwave oven are not safe in the toaster oven?

Eating and Nutritional Status

Nutritional status can be affected by a myriad of factors, including lighting, table and tableware, food choice and appearance, cueing, and

tablemates (for those living in a facility). Often, eating challenges can be overcome with a bit of trial and error.

Inadequate lighting and lack of color contrast can lead to reduced nutritional intake [15].

- High contrast between the dinnerware and the tabletop is now included in design regulations for dementia-specific units in some assisted-living and nursing home residences.
- Printed tablecloths decorated with fruit may cause the cloth to be picked at instead of the actual food; therefore, plain tablecloths and placemats are recommended.
- A person's food or liquid intake can be inadequate if the drinking glass or utensils cannot be easily grasped; built-up handles and appropriate-sized glasses are the key.
- Choice of food items, texture, portion, and arrangement are critical for encouraging appetite. Some individuals will refuse to eat from a plate piled high with food or if more than one food is served at one time.
- Many patients have changes in olfactory and taste perceptions; unusual flavor combinations or excessive desire for sweets is not uncommon [16]. Caregivers report that their loved one's appetites have increased when they added sauces to dishes, including salsa, honey mustard, maple syrup, or ketchup. The choice of flavors and their combination is very individual, so it is important that the caregiver experiment to see what the patient responds to most favorably.
- Verbal cueing (e.g., "place the fork in your hand") and physical cueing (placing a fork in their hand) may encourage greater independence.
- Some individuals who can no longer manipulate utensils may be able to eat independently if finger foods are offered (e.g., baked fries or fish sticks). A key to success is to serve only foods that require like utensils at a given time; otherwise confusion can occur over which food items require the use of a utensil.

Hygiene

Bathing and Agitation

Bathing a person with dementia is one of the most stressful activities for a caregiver. It can also be an emotionally demanding experience for the patient, who may be stressed by fear of running water, discomfort in a cold drafty room, embarrassment at being seen undressed, fear of falling (especially when moving in or out of the tub), or confusion due to memory problems. The person may think he or she has already bathed or may be simply overwhelmed by the bathing process itself, no longer understanding what to do or how to do it. Dementia-friendly bathing techniques can be highly effective in reducing bathing agitation. In the video, *Bathing Without a Battle*, nursing home residents who previously yelled, hit, and cursed during a standard bath are shown relaxing and thanking the aide for their help after the aide had received specialized training [17, 18]. If a patient refuses to bathe or experiences agitation during bathing, consider referring the caregiver to techniques such as:

- Warming up the room before the bath (feeling cold can be a stressor)
- Using a specially designed bathing privacy outfit (lack of privacy can be a stressor)
- Using a handheld shower and avoiding spraying water onto the head and facial area (overly sensitive areas in many patients with dementia)
- Placing a color-contrasted towel on the bath chair for enhanced depth perception and using a color-contrasted bath mat in the tub for a full immersion (so the person can judge the depth of the tub to reduce fear of drowning)

Toileting

Some individuals become incontinent simply because they cannot find the bathroom. They may not be able to distinguish the bathroom door from

the surrounding doors, or they may have completely forgotten the bathroom's location [4]. If they are in the early to mid stage, the patient may be able to find the bathroom using the following techniques:

- Placing a large sign on the door
- Painting the door a bright color
- Leaving the light on in the bathroom or hallway

Another common problem is forgetting to use toilet tissue. Increased odor and infection risk are key concerns. Reminder notes and verbal prompts can be helpful for some but do not work for everyone. Bidet toilet seats have been used as a substitute for paper in Continental Europe and Asia for many years. There are separate units or those that attach to an existing toilet, with push button controls for washing and drying, allowing the user to wash after each use. Bidet toilet seats can increase the person's cleanliness, but they are expensive, and they require a caregiver present as operating new controls and a new way to toilet would be beyond the skills of most patients with cognitive loss.

Dressing

Patients with cognitive decline commonly experience clothing and dressing problems [19]. For example, the individual may no longer be able to organize and sort clothing and, therefore, leave piles of clothing scattered about or mix dirty clothes with clean clothes. At some point, dressing may require more skills than the patient possesses. For example, they may forget the order in which to put on various clothing items, they may wear too little or too many layers of clothing, or they may refuse/forget to change clothing when needed. Often, the patient may resist help and become terribly agitated when the caregiver tries to intervene. Here are a few simple strategies that have helped other caregivers in similar situations:

- Label drawers with words or pictures of the content (e.g., blouses, pants, underpants).
- Leave out the clothes to be worn that day, in the order in which they are to be worn either on a wall hook or on the bed.
- Buy two or three of the same clothing item. When the patient is bathing, the caregiver can quickly swap the dirty set for the fresh.

Smart Devices and Monitoring Systems

In the last decade, there has been a significant increase in the availability of home monitoring products to help extend independent living for those with cognitive decline. These systems allow caregivers to monitor the activity of a family member who is living alone, so they can check in on them from a remote location and offer support as needed. Smart devices can be used "off the shelf" for specific activities, or entire home systems can be installed. Monitoring can help to identify problems as they occur so that the caregiver can intervene before they become a full-blown crisis. For example, there are medication reminders that attach to a standard phone line and will send the caregiver an alert if the person does not remove pills from a medication box. There are also devices that detect extreme changes in room temperature and can send the caregiver an alert if the home is too hot or too cold. Dan G visited his mother in Wisconsin in early winter and was alarmed to discover how cold the home was. His mother had inadvertently turned off the furnace switch and was not cognizant that there was any problem. A monitoring device could have detected the drop in temperature and sent the son an alert; then the son could have called a neighbor to check in on the mother and turn the furnace back on. Fortunately, the son visited his mother before any serious problems occurred.

Home "Behavioral" Systems

These monitoring systems work by using discreet wireless sensors placed in key locations around the home, like the bedroom, kitchen, medication areas, and bathroom. The sensors keep track of the patient's normal routines and send the

designated caregiver(s) alerts regarding unusual situations or departures from the norm. For example, depending on the system, the caregiver can receive alerts if the person opens the outside door at 5:00 am instead of their usual 10:00 am time or gets out of bed at night and does not return. Pilot studies show these systems can be helpful for the right person, who can still live safely on their own, but need daily monitoring and some backup support to do so [20–22].

Conclusion

Clinicians can serve as a valuable resource to patients and their caregivers by providing them with advice and information on how to avoid excess disability through dementia-appropriate design. By understanding the environment's effect on a person's behavior, caregivers have the opportunity to create a therapeutic environment that promotes more positive outcomes, allowing them and the person they care for lead safer, more satisfied lives.

Clinical Pearls

- Caregivers should keep in mind that providing for the safety of their loved ones is an *ongoing challenge as the disease progresses.*
- Reminder signs can act as an "external" brain for those in the earlier stages helping a person function more independently. Use simple language, large-sized text, and/or photographs.
- Usually there is a *specific* event preceding agitation that acts as a trigger for that behavior (e.g., noise, cold interior temperature, water flowing onto the face during a shower.) Advise the caregiver to find the "trigger" when the person is agitated so that he or she can act to change or modify the trigger(s) and the associated agitation.
- Before denying access to appliances, rooms, or exit and entrance doors, monitoring technologies (e.g., motion sensors, remote door alarms, automatic turnoff devices) should be tried first whenever possible. If locks need to be installed (e.g., cabinets, front door) or the stove knobs removed, advise the caregiver to monitor the person's reaction, as some patients become agitated when access is denied.
- Interventions should be *frequently* reassessed since strategies may not continue to be effective as the symptoms of the disease progress or if the environment changes.
- Salient interior features and household items should be color-contrasted from their background to enhance function (e.g., increase food intake by using a strongly contrasting plate color to the food, reduce tripping on stairs by highlighting the edges of steps with 2-in. color tape).
- To reduce environmental misperception, patterns should be kept to a minimum, and lighting levels should be abundant and glare-free, with no dark areas in a room.

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Additional Resources

ThisCaringHome.org, a project of Weill Cornell Medical College, is multimedia web site that offers caregivers innovative ways to learn research-based strategies that reduce caregiver stress and enhance the safety and Well-being of loved ones with Alzheimer's disease or other types of dementia.

Epilepsy and Aging

26

Anna Rita Giovagnoli

Background

Seizures and Epilepsies

Epilepsy is a chronic neurologic condition marked by the recurrence of seizures. A seizure is a sudden, transitory event characterized by positive or negative mental or physical symptoms associated with neuronal discharge and electroencephalographic (EEG) changes. Seizure types vary across the life span, with more challenging diagnostic demands in older adults. In 1981, the International League Against Epilepsy (ILAE) classified two major categories of seizure type, characterized by either partial or generalized onset [1]. In 1989, epilepsy was defined by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause [2] and divided into idiopathic (generally have a genetic basis and onset during childhood), symptomatic (caused by brain lesion), and cryptogenic (unknown cause) [2]. The new 2017 ILAE classification of the epilepsies [3] and ILAE classification of seizures [4] take into account seizure type, epilepsy type, and epilepsy syndrome, including etiology and their therapeutic implications at each diagnostic step. The new classifications have introduced new terms replacing old definitions, such as generalized, cryptogenic, and psychic, have combined acquired and genetic structural lesions, and have reformulated definitions of awareness and consciousness. A single unprovoked seizure does not constitute epilepsy, nor do isolated febrile seizures, neonatal seizures, or acute symptomatic seizures provoked by acute systemic illness, intoxication, or substance abuse or withdrawal [5].

Epidemiology

Epilepsy accounts for a significant proportion of the world's disease burden ranking fourth after tension-type headache, migraine, and Alzheimer's disease [6, 7]. Among neurological diseases, epilepsy accounts for the highest disability-adjusted life year rates both in men and women. Anywhere, epilepsy affects from 0.5% to 3% of the population. The worldwide annual incidence of epilepsy ranges from 16 to 51 per 100,000 [7]. The age-specific incidence tends to vary significantly; it is high in children and adolescents (70 per 100,000), stabilizes in adults (30 per 100,000), and increases in the elderly (100 per 100,000) [8]. The age-specific prevalence is also different in children and adolescents (4.5–5 per 1000), adults (6 per 1000), and old people (7 per 1000). Older adults now have the highest prevalence of epilepsy per decade of any age group [9]. Gender-specific disparity in incidence

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and prevalence (higher in males than females) is small [10], and most studies show shifting rates between the sexes in different age groups [11, 12]. Finally, the prevalence and incidence of epilepsy vary across the world due to variations in diagnostic definition, socioeconomic status, access to health care, and environmental exposures [7] and may be underestimated in geographic areas where epilepsy is greatly stigmatized. The Task Force of the 2013 European Forum on Epilepsy Research stated that 6 million people are affected by epilepsy in Europe (mean prevalence 6.5 per 1000 people); the median prevalence before 2010 was 5.3 per 1000 including all ages, 4 per 1000 including children and adolescents, and 6.5 per 1000 including adults and elderly [13]. In Latin America, the median lifetime prevalence in all countries was 17.8 (range 6–43.2) per 1000 people, and the range for incidence was 77.7–190 per 100,000 people per year, with no differences between rural and urban areas, sexes, age groups, ascertainment methods, or years of study [14]. Very limited data are available about the incidence of epilepsy in low- and lower middle-income countries, although the incidence rate is higher in the developing countries than industrialized countries [15, 16].

Seizures and Epilepsy in Older Adults

The number of older adults with epilepsy is rising because the world's population is aging, and the risk of acute symptomatic seizures and status epilepticus (SE) is highest in older adults [17–21]. By the year 2025, greater than 30% of the population of many developed countries will be older than 60, and the aged population is expected to account for a high percentage of all new-onset seizures [22, 23]. This is due in part to increases in long-term survival after acute neurological insults and the likelihood of correct diagnosis compared to past decades. In the United States, epilepsy affects nearly 1.5% of those ≥65 years old, and the prevalence is higher in nursing homes; therefore it has been described as a substantial public health problem [9, 18, 20, 24–32]. Nevertheless, epilepsy and aging issues have received limited attention in both human and animal research [33–35]. While the study of epilepsy in children and young adults has led to major advances in neuropsychology [36, 37], epilepsy and aging are thought to be one of the most neglected areas of research within the field of neuropsychology [38]. This pattern is likely to change with the advancing wave of interest in cognitive functions with aging and improving diagnosis of geriatric seizures.

Etiologies

Older adults with epilepsy may have had epilepsy since earlier in life or experience the onset of epilepsy at an advanced age in the context of either an acute medical or neurological illness or a non-acute setting including the aging process itself [17, 19, 20, 34, 38]. Whereas across the life span, the majority of seizures are unrelated to brain lesion, 33–50% of seizures have an unknown etiology in the elderly [7, 39]. These figures may decrease as diagnostic procedures improve [18, 27, 28, 40]. A fundamental distinction is made between epileptic seizures and non-epileptic seizures that occur due to other neurological attacks such as migraine, sleep-related disorders, and narcolepsy or to a medical condition such as cardiac syncope, paroxysmal abdominal pain, metabolic derangement, respiratory compromise, or alcohol abuse [41]. Cerebrovascular disease, dementia, tumor, and head trauma are the brain disorders most often associated with new-onset epilepsy in older adults.

Cerebrovascular Diseases

Stroke is the most common cause of new-onset seizures and epilepsy in older adults, accounting for 30–50% of all epilepsies in this group. Stroke-related seizures can be divided into early onset and late onset, which reflect different etiopathogenesis. The 5-year risk of developing a poststroke seizure is roughly 10%, and about one-third of those with seizures will develop epilepsy [42–45]. The risk of poststroke seizures might be higher after a longer follow-up period [20, 29]. Seizure risk is highest in severe, disabling strokes, in hemorrhagic strokes, and in those with cortical involvement [26, 32, 40, 43].

Further, the relationship between stroke and epilepsy is bidirectional, in that individuals with late-onset seizures are at higher risk of an initial stroke, owing to a coexistence of vascular risk factors such as hypertension, ischemic heart disease, diabetes, and antiepileptic drug (AED)-related alteration of folate metabolism. When a late-onset seizure occurs after a stroke, the possibility of a new cerebrovascular accident should be investigated. Older adults with a combination of stroke and dementia were four times as likely to have epilepsy as those without either condition [27]. The possibility of a decline in cognition also should be investigated, especially in the case of late-onset recurrent seizures or SE [46]. Older adults with new-onset seizures should therefore undergo a thorough cerebrovascular workup and neuropsychological assessment [29].

Mild cerebrovascular disease may cause epilepsy in some patients [17, 20, 21, 28]. Transient ischemic attacks (TIAs) are rarely associated with seizures. TIAs usually can be differentiated from seizures, because negative motor phenomena such as hemiparesis are quite uncommon in seizures. However, "inhibitory seizures" do occur, most often characterized by aphasia or dysarthria. An aphasic disturbance that has a sudden onset and then remains stable until its subsequent gradual resolution is more likely to be a TIA [21]. A normal EEG is expected in TIA, whereas the EEG is likely to be abnormal in "inhibitory seizures," showing diffuse slowing or intermittent rhythmic delta activities. In about two-thirds of inhibitory seizure patients, the negative symptoms are associated with some degree of confusion or a subsequent partial retrograde amnesia for the event, whereas focal vascular insults do not usually produce confusion [21, 46].

Alzheimer's Disease and Other Neurodegenerative Diseases

Alzheimer's disease (AD) and other neurodegenerative conditions represent the presumed etiology for 10% of new-onset epilepsy in patients older than 65 [47, 48]. Patients with AD have up to tenfold increased risk of developing seizures and epilepsy in comparison with healthy adults of the same age. Seizure incidence at ages beyond 70 is elevated threefold over patients of a similar age without AD [18, 49]. Prospective and retrospective clinical studies have reported great variability in the prevalence of seizures, with rates ranging from 1.5% to 64% [50]. However, a multi-site study of 453 patients indicated that unprovoked seizures are a "quite uncommon feature" in AD, although more common than in the general elderly population [51]. Another prospective study with long follow-up and large sample size estimated the incidence of seizures in AD at 1 per 200 patient-year, a rate that was also lower than in previous investigations [52]. The studies with pathological confirmation often have small patient numbers. Out of these, one study reported that 10–17% of patients with autopsy-confirmed AD presented with unprovoked seizures after onset of dementia [53].

Early age of AD onset relating to gene mutations is associated with greater risk of seizures [26, 29, 47, 51, 54]. Increasing dementia severity is the other reliable risk factor for seizures in AD, with a greater frequency in the later stages of the disease. The frequency of seizures is also high in patients with AD and Down syndrome, affecting up to 56% of cases [55]. An additional factor is the potentially proconvulsant effect of acetylcholinesterase inhibitors and memantine, which are used in the treatment of dementia [56].

Focal seizures, including those with loss of consciousness and secondary generalization, are the most common type of seizure in patients with AD [47, 51]. It is possible that focal seizures with loss of consciousness are underdiagnosed because these patients may be unaware of sudden changes or not able to report subjective symptoms, while caregivers may not distinguish behavioral alterations caused by seizures and fluctuations in vigilance and attention related to dementia [51]. Patients with dementia sometimes exhibit orofacial movements, outbursts of temper, wandering, fluctuating confusion, and memory lapses that are not necessarily seizure related [21]. Seizures frequency may therefore

be underestimated or overestimated in demented patients, although in general they seem infrequent. The role of EEG and its prognostic value in predicting seizures in patients with AD has not been adequately explored. In the absence of specific studies, the choice of AED treatment is mostly empirical and based primarily on side effect considerations [50].

Experimental studies have shown that high levels of β-amyloid, the main constituent of AD plaques, and the apolipoprotein ε4 allele, a genetic risk factor for AD, are associated with seizures [57], supporting the clinical evidence of association between AD and epilepsy. The accumulation of β-amyloid peptides may trigger synaptic degeneration, circuit remodelling, and abnormal synchronization within neural networks. Since neuronal hyperexcitability amplifies the synaptic release of β-amyloid, seizures can create a never-ending circle accelerating cell death. Experimental models in mice have shown the presence of subclinical seizures and confirmed the pathophysiological cascades. In non-AD patients, seizures starting in the medial temporal lobe can damage the hippocampal circuitry, leading to progressive memory loss. In patients with AD, the combination of β-amyloid-related excitotoxicity and seizure-related hyperexcitability in the hippocampus makes epilepsy a very important issue for diagnosis and treatment of cognitive decline [58].

Dementia with Lewy bodies (DLB) can be associated with seizures [59]. Reports on EEG in DLB have been conflicting, but recent diagnostic guidelines indicate EEG abnormalities are supportive of the diagnosis. In one study that examined EEG abnormalities, a "Grand Total EEG" index was derived from six variables: rhythmic background activity, diffuse slow-wave activity, reactivity, paroxysmal activity, focal abnormalities, and sharp-wave activity. The patients with DLB had a higher index than patients with AD, and DLB was identified with a sensitivity of 72% and a specificity of 85% using an EEG cutoff score. The association between DLB and this EEG abnormality was independent of age and Mini Mental State Examination (MMSE) [60].

Frontotemporal lobe dementia (FTD) appears to be rarely associated with seizures [47, 54, 61]. However, a family has been reported with a novel phenotype characterized by a combination of early-onset and rapidly progressive FTD, parkinsonism, and epileptic seizures [62]. Although seizures do not feature in the diagnostic criteria of FTD, they have been reported to have a similar prevalence to AD [63]. Other neurodegenerative dementias such as Huntington's disease and prion disease may be rarely associated with seizures [63].

Brain Tumors, Alcohol, Drugs, Head Trauma, and HIV/AIDS

Seizures are the first sign of a brain tumor in 50% of older patients [29]. In the case of head trauma, age (65 years or greater) is one of the factors that increases the risk of posttraumatic epilepsy. The peak incidence of initial seizures related to alcohol withdrawal occurs late in life [31]. About 10% of seizures in older adults are associated with use of alcohol or prescription drugs, and seizures sometimes occur after withdrawal from certain sedative medications following chronic use [20]. A sizable minority of individuals with HIV or AIDS is more than 50 years old, and this percentage is increasing. Seizures in this group usually occur later in the disease process, resulting from mass lesions of various etiologies or due directly to cerebral HIV infection [20].

Clinical Issues

Diagnostic Challenges

The diagnosis of epilepsy mainly rests on a patient's history and should be considered in any patient who suffers from recurrent attacks of consistently or relatively stereotyped involuntary behavior or subjective experience. Classically, the first step is to define a critical symptom or fixed combination of symptoms (seizure diagnosis), the second is to establish the nature of the

seizure (epileptic versus non-epileptic), and the third is to determine the cause of seizures or epilepsy. The new 2017 ILAE classification of the epilepsies [3] indicates three levels of diagnosis: (a) seizure type (as defined by the new ILAE seizure classification) [4]; (2) epilepsy type, including focal epilepsy, generalized epilepsy, combined focal and generalized epilepsy, and unknown epilepsy; and (c) epilepsy syndrome. This classification incorporates etiology at any step of diagnosis, taking into account six etiology subgroups and their therapeutic implications: structural that is linked to a brain lesion visible on neuroimaging that may be genetic (e.g., polymicrogyria) or acquired (e.g., tumor), genetic, infectious, metabolic (often with a genetic basis such as porphyria), immune, and unknown, therefore eliminating the term cryptogenic [3].

Focal refers to the anatomic location where a seizure starts, although focal seizures may rapidly engage bilateral neural networks with an apparently generalized onset. Generalized means that a seizure is generalized since the onset. Retained awareness, defined as knowledge of self and environment, is a marker of preserved consciousness during a seizure, allowing to distinguish focal seizures with or without loss of consciousness, although this may be difficult on a clinical ground and consciousness may be even preserved in the very early phase of generalized seizures [4].

The new seizures classification [4] includes new terms such as cognitive that replaces psychic, indicating specific cognitive phenomena (e.g., aphasia) or positive cognitive symptoms (e.g., déjà vu), and emotional that refers to focal seizures with emotional or affective subjective manifestations. The new epilepsy classification has also replaced some terms such as idiopathic epilepsy that is now named genetic generalized epilepsy.

Seizures are both underdiagnosed and overdiagnosed in specific subgroups of older adults [17, 26, 28]. Unnecessary treatment with antiepileptic drugs (AEDs) can lead to deleterious side effects, while lack of appropriate treatment in undiagnosed geriatric epilepsy patients can have dire consequences. In many older patients, new-onset seizures are not diagnosed, or there is a significant delay to diagnosis, with a mean time to correct diagnosis in one study of more than 18 months [17, 21, 25–28, 64]. In general, reasons for difficulty in securing a seizure diagnosis in older adults include (1) atypical or nonspecific presentation or semiology of focal seizures; (2) absence of classic symptoms; (3) infrequency of tonic–clonic seizures; (4) coexisting cognitive impairment that may lead to an incomplete history, underreporting of events, or failure to recognize transitory confusional states; (5) absence of witnesses due to patient living alone or being retired; (6) low sensitivity or specificity in diagnostic investigations such as interictal EEG or ECG; (7) decreased continuity of patient/physician relationships; and (8) the absence of specialists in the diagnostic process [26, 28, 32, 61, 65, 66]. It is also important to keep in mind that two or more different disorders may coexist in the same patient [67].

The etiology, semiology or clinical presentation, and prognosis of a seizure disorder often differ between younger and older patients. In fact, "novel diagnostic paradigms" have been recommended because of the diverse etiologies and atypical presentations of seizures in older adults [21, 26, 28, 61, 64]. Tables 26.1 and 26.2 [61] present some common characteristics of seizures in older adults and clues to the diagnosis, respectively. Generalized tonic–clonic seizures can occur in older adults, including primary generalized seizures that reemerge in old age after initial occurrence in early life [28]. About

Table 26.1 Characteristics of epilepsy in older adults

Focal epilepsy is most common
New-onset frontal lobe seizures more common than temporal lobe seizures
Motor or sensory symptoms more common than psychic symptoms
Auras less common than other symptoms and may present in a nonspecific way (e.g., dizziness)
Automatisms less common than in young adults
Secondary generalization less common than in young adults
Prolonged postictal state can occur
Status epilepticus appears to be more common than in young adults

Table 26.2 Clues to the possibility of epileptic seizures in older adults [61]

Confusional state with sudden onset and end
Rhythmic muscular contractions in a focal territory
Paroxysmal behavior disorder with or without a focal neurological sign
Impairment of consciousness
A prior history of epilepsy
Focal slow waves on interictal EEG

two-thirds of geriatric seizures have a focal onset, with or without secondary generalization. Although there are no specific guidelines for epilepsy in older adults, consistent recommendations can help clinical management [17, 25].

Focal Seizures

Focal motor seizures are the most frequently reported type of focal seizure. However, this may reflect not only a real occurrence but also the difficulty in collecting details about the seizure semiology in older people who may fail to report cognitive and emotional symptoms [68]. Focal seizures with loss of consciousness account for about 40% of all seizures in the aged population [20, 21, 25, 28, 69, 70].

Focal seizures with a mesial temporal lobe onset are less common in older than in young adults and are often associated with an aura, disturbance of consciousness, behavioral arrest, orofacial and limb automatisms, and a period of postictal confusion of seconds to minutes. Secondary generalization also is relatively frequent, and widespread volumetric changes on imaging and cognitive deficits are common in this group [71]. Older patients with long-standing temporal lobe epilepsy (TLE) are expected to show impairment in more domains than memory. While new-onset temporal lobe seizures can occur quite late in life [72], new-onset focal seizures in older adults are most likely to be extratemporal, often originating in the frontal lobe. This is at least in part due to the link between anterior frontal cortical areas and stroke.

There is often a lack of specific clinical signs of epilepsy in older adults. In a study of individuals older than 60 years who had a mean duration of focal epilepsy of 44 years, many demonstrated progressively less elaborate and briefer seizures over the course of their lives [73]. Auras are uncommon and often nonspecific, and automatisms and secondary generalization also are relatively uncommon. A disturbance of consciousness accompanied by a blank stare may be the only manifestation of a focal seizures in an older adult [18, 21, 28]. Postictal symptoms result from seizure-induced reversible alterations in neuronal function. Both the postictal focal motor deficits and confusional state can be prolonged in older patients, with the former lasting for hours and the latter for days. The prolonged postictal confusion may even be mistaken for dementia [21, 26, 28, 29, 32, 38].

Ictal and postictal disturbances of consciousness can be particularly difficult to ascertain in older adults who are cognitively compromised because they may be unresponsive for long periods of time. In this regard, the new seizures classification [4] has not adopted responsiveness but knowledge of self and environment as a marker of awareness. A person who has retained awareness during a seizure can recall and validate awareness after the seizure.

In older adults, a particular diagnostic challenge is represented by transient epileptic amnesia (TEA) in clear awareness whose definition as focal seizure requires a meticulous documentation by an expert observer [74]. TEA, also called epileptic amnesic syndrome, is characterized by abrupt, transient, and severe anterograde memory disturbance (median duration 30–60 min). It tends to occur upon awakening and sometimes is associated with other temporal lobe symptomatology such as olfactory hallucinations, oral automatisms, or brief unresponsiveness. However, cognition is otherwise generally intact during the attack, and transient amnesia may be the sole ictal symptom. TEA is a probably underdiagnosed type of TLE that tends to have a late onset [75–78] usually in the sixth or seventh decade of life. It may be associated with an abnormal EEG, especially a sleep-deprived EEG, and is almost always responsive to an AED such as carbamazepine. Interictal memory impairment is commonly reported by TEA patients and may not resolve with treatment. Although standard

memory testing might reveal only subtle difficulty, some TEA patients report considerable problems with remote memory loss and accelerated long-term forgetting (ALF). In the latter, information tends to be recalled normally for a day or more but then fades at an accelerated rate compared to healthy controls. The subjective report of this phenomenon by a subset of TEA patients has been confirmed by means of memory assessment over long intervals [79]. ALF may reflect a problem with a late stage of memory consolidation and perhaps a disturbance restricted to the hippocampus bilaterally. Thus, epilepsy should be ruled out in patients with credible reports of intermittent and clear-cut amnesic attacks, ALF, or isolated retrograde amnesia [75, 76, 78, 80]. Transient global amnesia (TGA) is not an epileptic event and so is associated with a normal EEG or slowing only, tends to last longer than TEA, and is usually a one-time event [75, 76]. Table 26.3 lists characteristics of TEA versus TGA and TIA.

Status Epilepticus

It is noteworthy that 30% of first seizures in older adults present as SE [81], defined as any seizure lasting more than 30 min or intermittent seizures lasting for more than 30 min during which the patient does not regain consciousness [82]. Stroke is the most common etiology of SE in older adults [43]. Two main types of SE are distinguished: generalized (convulsive, nonconvulsive) and partial (simple, complex). Incidence of SE is substantially higher in older adults in comparison to younger adults, and mortality is elevated in older adults, particularly in patients with brain anoxia [83, 84]. SE is often underdiagnosed. In particular, nonconvulsive and partial complex SE can present as prolonged confusion or unusual behavior such as lethargy, agitation, automatisms, or mild personality change, which may prevent a timely diagnosis in elderly patients. When nonconvulsive SE is suspected, an EEG should be performed so that, if it is confirmed, treatment can be provided quickly [81].

Non-epileptic Paroxysmal Syndromes

There is a range of disorders with symptoms that can cause or mimic a seizure, including cerebrovascular, cardiovascular, endocrine/metabolic, infectious, sleep, migraine, and psychiatric conditions. The main differential diagnosis in older adults is convulsive syncope. Syncope is loss of consciousness due to an acute decrease in cerebral blood flow, and if it is prolonged, convulsions may occur. This type of seizure may result from a cardiac cause (heart block, ventricular tachycardia, ventricular fibrillation, asymmetric septal hypertrophy, aortic stenosis), carotid sinus hypersensitivity, or vasovagal attack. Clinical observation (e.g., heart rate, blood pressure, skin vegetative signs) facilitates diagnosis. Whether or not an attack is observed, diagnosis is aided by simultaneous EEG and electrocardiography (ECG).

Other causes of non-epileptic seizures include sleep-related disorders such as sleep attacks (irresistible episodes of sleep), cataplexy (sudden loss of postural tone sparing consciousness, often stimulated by strong emotions such as fear), sleep paralysis (lasting a few minutes on awakening or when falling to sleep), hypnagogic

Table 26.3 Differential diagnosis of transient epileptic amnesia (TEA), transient global amnesia (TGA), and transient ischemic attack (TIA)

	TEA	TGA	TIA
Duration	<1 h	4–6 h	Variable
Ictal amnesia	Retro-anterograde	Dense anterograde, variable retrograde	Not well characterized
Other symptoms	Sometimes olfactory hallucinations, automatisms, brief loss of awareness	Headache, nausea	Focal neurological deficits
Recurrence	~monthly	Rare	Not well characterized
Interictal memory	Includes accelerated long-term forgetting, remote memory loss	No permanent deficits	Risk of permanent deficits from strokes

Note: Adapted with permission from Zeman and Butler [75]

hallucinations, and REM behavior disorders. Diagnosis is based on a characteristic history and the typical EEG pattern showing sleep-onset REM. Another differential condition is migraine which may cause sudden loss of consciousness owing to brainstem vasomotor changes. Clinical history and EEG may easily discriminate epilepsy and migraine, although patients with migraine may show EEG epileptic abnormalities and some patients can be affected of course by both disorders.

Psychogenic Non-epileptic Seizures

After Charcot's definition of hystero-epilepsy and later terms such as pseudo-seizures or hysterical seizures, the term psychogenic non-epileptic seizures (PNES) has been preferred. PNES are sudden involuntary attacks of sensation, movement, autonomic alteration, anesthesia, or complex behavior, such as crying, bizarre postural changes, hyperventilation, or sudden fear expression, that are not caused by cortical discharges but may mimic epileptic seizures [85]. In general, PNES may be longer than average epileptic seizures (>2 min), have motor features with a gradual onset and a fluctuating course, and be associated with thrashing, violent movements, side-to-side head movements, asynchronous movements, and closed eyes. Other possible signs of PNES include crying or speaking during seizures, noninvolvement of the face during generalized movements, no seizures during sleep, stronger seizures when the staff is present, resistance when trying to open the patient's eyes, and frequent hospitalizations. A history of multifaceted symptoms and features that are unusual for epilepsy and an absence of incontinence, tongue laceration, and self-injury support this diagnosis. PNES patients also are more likely to recall details from the unresponsive period compared to patients with epilepsy [21]. Diagnosis of PNES requires differentiation not only from epileptic seizures but also other forms of non-epileptic episodes. Video-EEG recording documenting the absence of epileptiform discharges during an event is the gold standard for diagnosis of PNES. In the absence of ictal EEG, no single symptom, clinical sign, or demographic variable allows for the diagnosis of PNES. Differential diagnosis is important to prevent unnecessary AED treatment, iatrogenic complications, and delayed referral to adequate psychiatric treatment.

PNES appear to be about as common in older as in younger adults and sometimes can have an onset late in life [64, 86, 87]. Some studies suggest that PNES represents approximately one-half of the non-epileptic seizures identified during video-EEG monitoring in patients over age 60 [86, 88]. In younger adults, approximately 75% of PNES patients are women, but this ratio may decrease significantly in late-onset (>age 55) patients [89, 90]. In addition, it appears that a history of sexual abuse, which is relatively common in early-onset PNES patients, is rare in late-onset patients, who are more likely to have severe physical health problems (e.g., cardiovascular illness) and report health-related traumatic experiences. Older onset patients also seem to be less likely to have baseline psychiatric disturbances [90].

PNES are linked to heterogeneous etiology, cognition, psychopathology, and emotion processing style determining different responses to psychophysical distress and varied neurological and psychiatric pictures. The phenotypic presentations of PNES have been explained by complex interactions between the cognitive and emotional systems, presuming that an internal or external stimulus can destabilize the cognitive-emotional system causing an aberrant behavior [91].

Neuropsychological studies have provided equivocal results showing that PNES patients perform similarly, better, or worse in comparison with epilepsy patients. Attention and cognitive control are the most frequently impaired functions, while memory and naming deficits seem comparable to those observed in TLE patients [92]. In young adults with PNES, neuropsychological impairment is often a function of suboptimal motivation during the assessment or an emotional disturbance. For example, PNES patients tend to perform worse than those with epilepsy on the Portland Digit Recognition Test and Word Memory Test. Assessment of personality measures and symptom validity tests provided more help with differential diagnosis, although there is no single psychological profile that dif-

ferentiates PNES from epilepsy. The Minnesota Multiphasic Personality Inventory (MMPI-2/MMPI2-RF) and the Personality Assessment Inventory (PAI) differentiated PNES from epilepsy: the PAI had an overall diagnostic accuracy at 74% compared to MMPI's accuracy at 69%. On the MMPI/MMPI-2, the conversion profile was the most common in PNES patients [93]. Extreme scores on the Hypocondrias and Hysteria scales of the MMPI-2 are more common in PNES patients [89, 94]. The Somatic Complaints on the MMPI2-RF correctly classifies about two-thirds of epilepsy and PNES patients. Two supplementary scales (PNES Physical Complaints and PNES Attitudes) have provided slightly better accuracy in correctly classifying 73% of patients [95]. Careful assessment of cognition, personality, psychopathology, emotional–behavioral distress symptoms, pre-illness life and medical events, personal resources, and coping attitudes plays a role in determining the origin of PNES according to the integrated cognitive-emotional model [92]. An integrated cognitive and psychobehavioral battery can also help to define epilepsy-related psychological disorders which in relatively rare cases can result in coexistence of non-epileptic seizures.

Diagnostic Techniques

Diagnostic techniques include neuroimaging, EEG, ambulatory electrocardiography (ECG), orthostatic blood pressure measurement, tilt table testing, hematological and biochemical profiles, and thyroid function testing [69].

EEG recordings cannot absolutely confirm or exclude epilepsy unless the registration of epileptiform discharges is contemporaneous to seizure symptoms. Discharges on EEG are not rare in older patients without epileptic seizures, and interictal epileptiform activity is present on routine EEG only in a minority of patients with onset of seizures after age 60 [96]. Benign EEG variants that are most common in older adults include subclinical rhythmic electrical discharges of adulthood (SREDA), wicket spikes, and small sharp spikes [66, 81]. Nevertheless, EEG often can be helpful in the diagnostic process [61, 65, 72, 97], including extended/ambulatory EEG and long-term inpatient video-EEG monitoring. The latter tends to be underused in older adults, as they account for about 5% of video-EEG inpatient admissions [64, 66]. Long-term monitoring (typically lasting 3–5 days) can be cost effective and especially valuable in diagnosing recurrent spells, classifying epilepsy, and determining candidates for epilepsy surgery [28, 63, 64, 81, 87, 98, 99]. Long-term video-EEG does require precautions to be in place for prevention of falls and prompt detection and treatment of adverse events; tertiary epilepsy centers generally offer the highest level of experience and care [99].

In recent years, brain imaging has become more sophisticated, allowing for various structural and functional studies. For the most part, these techniques have been applied for the diagnosis of younger, drug-resistant epilepsy patients or to experimental study designs. Age-related changes on brain imaging are common and not necessarily related to onset of epilepsy. For other abnormalities, computerized tomography (CT) scans can reveal tissue contrasts such as the presence of blood, calcified lesions, and encephalomalacia, whereas magnetic resonance (MRI) is more effective in identifying subtle changes in tissue density such as glial tumors or hippocampal changes [17, 20, 25, 38, 87]. CT- and MRI-detected brain lesions are not a necessary or sufficient criterion for epilepsy. However, in older patients, the detection of a focal brain lesion represents a significant diagnostic criterion that supports diagnosis when typical clinical and EEG signs are present [61]. In particular, in older patients with SE or prolonged behavior/mental symptomatology of uncertain origin (e.g., nonconvulsive SE versus metabolic failure), CT and MRI are important emergency measures [100].

Treatment of Seizures and Epilepsy in Older Adults

Antiepileptic Drug Treatment

AEDs are the most common treatment for epilepsy, while other approaches may be applied in patients with drug-resistant seizures. Major drug

selection criteria (i.e., the seizure type to be treated and side effects) are considered in the context of individual patient characteristics in order to determine the probable relative efficacy and tolerability of a drug. This process has become more complex as many new AEDs have been introduced to clinical practice in the last few decades, requiring systematic trials to determine efficacy in the individual patient. Epilepsy usually is diagnosed after two or more unprovoked seizures occur [20]. The question of whether a physician should begin treatment with an AED immediately after a first seizure is controversial. Studies have demonstrated that deferring treatment until more than one seizure has occurred does not adversely affect the long-term remission rate. However, it has been recommended that treatment be instituted after a single unprovoked seizure, especially in the context of a history of stroke, because of the high risk of subsequent seizures and their potential serious consequences, including falls, fractures, etc. [28, 41, 43, 46]. Fortunately, up to 80% of patients who develop epilepsy in old age are rendered seizure free with AED treatment [28, 40], with better outcome when an AED is started within 2 years of the first seizure compared to after 2 years [69].

Taking into account the selection criterion of the seizure type, the narrow-spectrum AEDs (e.g., carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine), which are typically effective in focal seizures with or without secondary generalization, are primary choices in the treatment of late-onset epilepsy in older adults. However, broad-spectrum AEDs (e.g., lamotrigine, levetiracetam, rufinamide, topiramate, valproate, zonisamide), effective both in focal and generalized seizures, are useful when diagnosis is uncertain. Older adults are more likely than younger patients to become seizure free with low AED doses [18]. Characteristics of AED use in older adults are listed in Table 26.4.

AEDs rank fifth among all drug categories in capacity to elicit adverse side effects in older adults. In a recent survey, 64% of a sample of community-dwelling older adults with intractable focal epilepsy listed medication side effects as an illness-related concern [101]. AED adherence among elderly patients often is suboptimal, and this is associated with increases in both seizures and health-care costs [102]. It is worth keeping in mind that compliance may be affected by the ability to afford an AED [32, 86, 101, 103]. Medication side effects may be dose dependent or drug specific, and the spectrum of side effects may differ from that seen in younger patients. The pharmacokinetics (absorption, distribution, and metabolism) and pharmacodynamics (receptor function) of AEDs generally are different in older adults, who are more susceptible to the adverse side effects of these drugs and toxicity, as well as interactions with other types of medications. Older adults are often more susceptible to AED-induced cognitive side effects, ataxia, and dizziness, with a secondary increased tendency to confusion and falls. The coexistence of various medical (e.g., cardiac, hepatic or renal failure, obesity), neurological (e.g., sleep-related disorders, migraine), or psychiatric comorbidities (e.g., depression, psychosis, anxiety) may be a factor in choosing a particular AED. For instance, valproate and pregabalin are associated with weight gain; valproate and topiramate may be effective in migraine; levetiracetam, primidone, phenobarbital, topiramate, and zonisamide may contribute to worsen depression; levetiracetam, phenobarbital, and primidone may cause behavioral reactions; carbamazepine and valproate may have positive psychotropic effects; and many AEDs (in particular phenobarbital, primidone, topiramate) may cause cognitive deficits. Detailed discus-

Table 26.4 AED use in older adults

AED selection depends on comorbid conditions, co-medications, and expected side effects
Age is associated with increased vulnerability to side effects and toxicity
Increased likelihood of failing medication trials due to adverse effects in older adults
Slower, more gradual titration and lower dosage recommended
Serum drug concentrations tend to vary
AED combined with another medication may amplify adverse effects common to both

sions of AED risks and benefits in older adults are provided elsewhere [20, 25, 28, 29].

Comorbidities in older adults, and the use of other medications, may implicate pharmacological interactions and co-toxicities. Other drugs can alter the absorption, distribution, and metabolism of AEDs, effects which increase the risk of either toxicity or therapeutic failure [86]. Common medications that interact with AEDs include warfarin, digoxin, theophylline, cyclosporine, and corticosteroids. Because depression and anxiety are common in patients with epilepsy, the proconvulsive properties of tricyclic antidepressants have to be considered. All tricyclic antidepressants can lower seizure threshold; seizures caused by these drugs typically are generalized tonic–clonic [26]. It has been estimated that 33% of the pharmaceutical expenditure by older adults is for over-the-counter products. Some over-the-counter allergy, weight loss, and memory aids may also have proconvulsive properties [20, 26].

In line with the conclusions of the ILAE [104], a low dose of lamotrigine, gabapentin, or carbamazepine has been recommended for treatment of poststroke seizures [46]. A few recent studies have described the effectiveness and tolerability of AEDs in patients with AD, suggesting no difference in clinical efficacy between phenobarbital, levetiracetam, and lamotrigine but minor side effects for levetiracetam [105]. Levetiracetam has been demonstrated to be safe in the treatment of older patients with focal or generalized SE [106]. Use of phenobarbital and phenytoin is advised against in older adults, in part due to risk of sedation and falls (for a combination of reasons, epilepsy doubles the risk of fractures), but phenytoin remains commonly prescribed in this age group, in part because it is relatively inexpensive and its properties are well known [18, 20, 24, 25, 28, 29, 38, 40, 107].

It should be noted that the cutoff of 65 years of age to designate older age is arbitrary, with no particular biological significance, because the gradual health changes associated with aging manifest themselves at different times in different people. Thus, older adults are "not a single cohort" [20, 41, 86]. In addition to chronological age, a patient's biological age, based on a physician's clinical judgment, is an important factor when medication choices are made [20, 25]. Attempting to minimize AED side effects while also controlling seizures is a delicate balance [28, 71, 108, 109]. When a seizure is caused by electrolyte imbalance, febrile illness, or hypoglycemia or hyperglycemia, chronic AED treatment is not required after the condition is successfully treated [26, 86].

Epilepsy Surgery

Surgery is a potentially curative treatment for disabling, medically refractory epilepsy, and in TLE in particular, it is the standard of care in selected patients [110, 111]. There have been few studies of epilepsy surgery in older adults, and no consensus exists on an upper age limit for epilepsy surgery candidates [112]. The overall findings from a small series of studies of epilepsy surgery in patients greater than 50 years old [113, 114] and two recent studies addressing surgery in those more than 60 years old [110, 115] suggest older patients often are viable candidates for epilepsy surgery. One study [115] described postsurgical seizure and neuropsychological outcome in TLE patients with a mean age of 56 and a mean duration of epilepsy of 33 years. Seizure outcome after temporal lobe excisions was not significantly different in patients older than 50 years compared to a sample consisting of patients younger than 50. In fact, even a subset of patients greater than 60 years old ($n = 11$) had an outcome similar to the younger group. Although surgical and neurological complications were infrequent, they were significantly higher in the >50 age group. In addition, the >50 age group was more likely to show significant decline when assessed about 12 months after surgery on an index of attention, and the >60 years group was especially vulnerable to decline in verbal memory, even though 91% of them underwent a right-sided surgery. This report [115] concluded that, although there is modestly increased risk of complications and neuropsychological decline, epilepsy surgery is effective in older TLE

patients. Another report that reviewed results from seven patients who underwent temporal resection after age 60 also concluded that surgery in this group generally is safe and effective [110]. Similarly, based on studies of patients with a mean age in the early to mid-50s, other authors concluded that neither chronological age nor duration of epilepsy should necessarily exclude patients from consideration for epilepsy surgery [112, 114]. While recognizing that the risk of any operative procedure is higher in elderly patients and that there may be obstacles to surgery for some, these authors emphasized the potential benefits of surgery in the context of possible medication intolerance, persisting seizures, and corresponding physical injuries, loss of independence, cognitive decline, and psychiatric disorders in the absence of surgery. More research is needed about cognitive outcome and quality of life after epilepsy surgery in older adults.

Neurobehavioral Disturbances

The total number of people with neurobehavioral disorders worldwide has been estimated 35.6 million and has been projected to nearly double every 20 years, with an estimate of 10 million cases in Europe [116]. Together with AD, stroke, FTD, and PD, epilepsy is one of the most frequent conditions of disabling cognitive and behavioral changes. Neurobehavioral disturbances associated with epilepsy often precede seizure onset perhaps due to common underlying brain pathology [117]. Despite seizures control with pharmacological or surgical treatment, these disturbances may persist lifelong. Twenty percent to 88% of patients with epilepsy have psychosocial problems [118], and 60% of them suffer from memory, attention, and executive impairments [119] that add to chronic disability and costs of epilepsy that may be underestimated due to a difficulty to distinguish the costs of comorbidities from those related to seizures [13].

Older age and socioeconomic background are associated with factors that raise the risk of cognitive decline [120]. A poor social network can increase the risk of dementia by 60%. Vulnerability may be amplified by epilepsy causing cognitive decline [121]. Chronic psychosocial distress and cumulative traumatic events associated with epilepsy may be further causes of cognitive decline. However, little is known about the cognitive outcomes in older patients with early-onset epilepsy. Loneliness, a critical aspect of social marginalization, social isolation, and social exclusion, has been shown to have functional neuroimaging correlates in the ventral prefrontal cortex [122]. Epilepsy in the context of aging can represent a potent risk factor of brain dysfunction and vulnerability.

Cognitive Impairments

Abnormalities in cognition are relatively common in older adults with epilepsy [71, 123–125]. New-onset epilepsy in older adults sometimes may cause cognitive decline leading to an incorrect diagnosis of dementia. Further, AED treatment (e.g., valproate) may provoke reversible cognitive impairment that can also be misdiagnosed as dementia [126]. Thus, if onset of cognitive impairment and epilepsy is linked in time, both epilepsy and side effects of AED treatment should be considered in the differential diagnosis of cognitive decline.

In adults with epilepsy, memory and word-finding difficulties are predominant [127]. These complaints are also common with normal aging, and are likely to be frequent among older epilepsy patients, who may be concerned about the possibility that they are developing dementia. At the group level, older people with partial epilepsy show a variety of cognitive impairments as compared to healthy subjects matched for gender, age, and education [123–125, 128]. For example, abstraction, divided attention, word fluency, and episodic memory were impaired in this group, although between-group differences generally were not large [124, 125]. In one study, results remained stable over a 3-year period [123], although there was failure to benefit from a test–retest effect. Poorer neuropsychological functioning in the general population of patients with

epilepsy has been associated with earlier age of onset, a known etiology, duration, number of years taking medications, number of medications taken, and lifetime number of generalized tonic–clonic seizures [109]. Other factors associated with cognition are brain lesion, genetic abnormalities, seizure frequency, type of seizure, SE, and surgery [129].

Although variables such as age of onset and duration of illness are associated with manifestation of cognitive deficits [124], recent cross-sectional studies suggest that cognitive deficits characteristic of early-onset TLE are established early in life and tend to remain relatively stable with aging [130, 131]. In older patients with focal epilepsy, AED polypharmacy appears to be the strongest determinant of cognitive performance, regardless of whether seizures are controlled or refractory [124, 125], with effects on initiation, shifting, attention, and memory. In one study, older epilepsy patients on AED polypharmacy were impaired in comparison to patients with amnesic MCI, whereas those on AED monotherapy showed a comparable cognitive profile to the MCI group [128]. Before AED treatment, almost 60% of older patients with new-onset epilepsy of different types have shown executive deficits, whose main determinants were cerebrovascular pathology and neurologic comorbidities [132]. A recent study found that a history of cardiovascular disease or SE and a below-average educational level are risk factors for accelerated cognitive aging characterized by impaired information processing and spared higher cognitive/intelligence functions, similar to what occurs in normal aging [133]. See Table 26.5 for a summary of the results of studies of cognition in older adults with epilepsy.

Quality of Life and Mood

On generic measures of health-related quality of life (QoL), scores for both physical and mental health status tend to be lower in epilepsy patients than in the general population, particularly for those with uncontrolled seizures. The few studies of elderly epilepsy patients suggest they also have significantly lower QoL compared to the general population [103, 134]. On epilepsy-specific QoL measures [109, 135], elderly patients with epilepsy generally do not experience poorer QoL compared to younger patients, but QoL can suffer in those with new-onset epilepsy, especially those diagnosed after retirement [134, 135]. As just one example of the potential long-reaching impact of the illness, veterans with epilepsy were about 1.5 times more likely than those without to report getting no regular exercise which, among other things, may lead to decreased muscle mass, falls, hip fractures, and frailty [134].

Young and old epilepsy patients share many of the same QoL concerns [124], but the impact of an epilepsy diagnosis on QoL is potentially different in older adults. For example, it may lead to premature admission to a nursing home or other long-term care facility [25, 69], and the diagnosis of epilepsy in the context of existing age-related physical and cognitive changes may lead to a debilitating sense of loss of control or a fear of losing one's mind [26, 38, 136]. Also, some senior citizens may be distressed by their own recall of a time when there were limited treatments for epilepsy, people did not understand why seizures occurred and were afraid of them, and families sometimes sent people with seizures to institutions or kept them isolated from others [137–139]. Different epilepsy-specific QoL measures have not been compared in an elderly population [35]. It may prove useful to develop a QoL instrument specifically for older adults and their caregivers [35, 103].

A few studies show that age is not always a significant predictor for QoL in patients with epilepsy [140]. The impact of epilepsy on the aged population may be more complex than on younger groups because health and perceptions of life success have different definitions that are dependent on the modified perspectives, aims, and physiological ability associated with aging. In the general population, the main determinants of successful aging include absence of disability, arthritis and diabetes, and being a nonsmoker and, to a lesser extent, social interaction, physical activity, and absence of cognitive impairment and

Table 26.5 Results of neuropsychological studies of older patients with epilepsy

Study sample	Cognitive domain investigated	Neuropsychological tests	Findings	Reference
26 Epilepsy pts	Overall cognitive abilities	Dementia rating scale	Epilepsy pts impaired with respect to healthy controls. Epilepsy pts on AED polytherapy more impaired than MCI pts	Griffith et al. [128]
26 MCI pts	Immediate and long-term memory	Wechsler memory scale-III logical memory subtest		
26 Healthy older controls	Lexical ability	CFL word fluency test		
40 Epilepsy pts	Selective and divided attention	Attentional matrices, trail making tests	Epilepsy pts impaired on all tests, with the worst deficits in those on AED polytherapy	Piazzini et al. [125]
40 Healthy older controls	Abstraction	Raven CPM		
	Memory, learning	Short story, paired words test, Rey complex figure		
	Language	Verbal fluency test, token test		
25 Epilepsy pts	Overall cognitive functioning	Mattis dementia rating scale	Epilepsy pts impaired on all tests. Pts on AED polytherapy more impaired than pts on monotherapy	Martin et al. [124]
27 Healthy older controls	Immediate and long-term memory	Wechsler memory scale-III logical memory subtest		
17 Epilepsy pts	Overall cognitive functioning	Dementia rating scale	Epilepsy pts impaired on all tests, with stable pattern over 3 years	Griffith et al. [123]
17 Older controls		Wechsler memory scale-III logical memory subtest		
95 pts with epilepsy and AD treated with phenobarbital, levetiracetam, or lamotrigine	Overall cognitive functioning	Mini-mental state examination Alzheimer's disease assessment-cognitive	At 1-year follow-up, levetiracetam was associated with seizure decrease and improved attention, short-term memory, and verbal fluency; lamotrigine with mild cognitive decline; and phenobarbital with significant worsening	Cumbo and Ligori [105]
68 Controls				
257 Untreated pts with new-onset mixed epilepsy	Executive functions	EpiTrack	58% of the patients showed impaired executive functions	Witt et al. [132]
27 pts with mixed epilepsy treated with AED	Fluid and crystallized intelligence	Wechsler adult intelligence scale	Significant deterioration on the full scale IQ and performance IQ but not on verbal IQ	Breuer et al. [133]

Pts patients, *IQ* intelligence quotient

depression [141]. The impact of epilepsy on QoL in older adults may depend on a combination of such determinants, as well as on the subjective perception of aging and personal resources. The subjective perception of epilepsy, stigma, loneliness, low self-esteem, poor mastery, and disease-related distress and, on the other side, life fulfillment and coping abilities interact in the individual patient, explaining 20–35% of the variance of QoL [142]. Spiritual aspects may also contribute to determine overall well-being, irrespective of age [140]. Addressing factors that enhance QoL (e.g., physical exercise, calorie restriction, cognitive and social stimulation, and psychological support) may combat the deleterious effects of epilepsy in older adults [143].

Depression is common in older epilepsy patients and is associated with poor subjective QoL [144]. Suicide risk is elevated in people with epilepsy and in older adults [145, 146], occurring more frequently in patients with chronic long-lasting epilepsy and medical and psychiatric comorbidities. Other disabling mental health symptoms also are common among people with epilepsy [118]. More research is needed to understand QoL issues and the causes and consequences of depression and other psychiatric disorders in geriatric epilepsy [18].

Framework for Neuropsychological Assessment

Neuropsychologists can make a key contribution to the care of older adults with suspected epilepsy, cooperating to the assessment of cognitive and behavioral impairments as well as to the understanding of social or psychological problems that are caused not only by epilepsy-related brain dysfunction but also by chronic pathology, environmental, and demographic conditions of vulnerability and aging itself [14, 24, 75, 108, 109, 147, 148]. A thorough assessment of cognitive functions is essential in discriminating epilepsy-related impairment from dementia and aging-related physiological decline and should be conducted prior to the initiation of treatment for newly diagnosed seizures [28, 40].

The neuropsychological approach to epilepsy, often assumed as a model to test patients with focal brain lesions, aims to produce a functional map of impaired and preserved functions, highlighting the interactions between weaknesses and strengths and contributing to determination of the type and severity of brain damage. Other aims are clinical monitoring, in particular the follow-up of AED changes and surgery, and the determination of baseline cognitive and emotional status. The neuropsychological approach to presurgical assessment is evolving in the face of advances in the duration of long-term outcome and spectrum of cognitive functions [149–151]. The monitoring of theory of mind and social cognition may be particularly useful in older epilepsy patients who can be vulnerable to the effects of social isolation and loneliness as consequences of both epilepsy and aging [152]. Aspects of the therapeutic assessment model can be applicable in geriatric neuropsychology, including the tenets of addressing the patient's presenting concerns and the potentially threatening nature of the assessment, treating the patient as a collaborator, and providing feedback relevant to the individual's questions and everyday functioning and circumstances [153, 154]. It is a common experience that older patients affected by similar brain pathology may be heterogeneous at the physical, mental, and behavioral levels. This suggests to take into account individual features when assessing cognitive failures and strengths.

Neuropsychological data reflect a combination of fixed factors, such as neuropathology and its localization; disease course factors, including history of recent SE or epilepsy surgery; and potentially remediable factors, such as medication effects, fatigue, mood, and perceived cognitive self-efficacy [149, 153, 155]. When cognitive status is in question, neuropsychologists can help determine a patient's ability to understand the rationale for medications, the written instructions about the regimen, the use of dosing trays, and the potential need for close involvement of a family member and interaction with a multidisciplinary health-care team. The treatment goal for an epilepsy patient is not only to achieve seizure freedom with minimal AED

side effects but also to maintain or improve QoL, freedom from psychosocial epilepsy burden, and alleviation of neurobehavioral comorbidities. Since no ideal AED exists and AEDs cannot achieve all of these goals [25, 32, 69], interdisciplinary efforts can strive for application of an integrated pharmacotherapy and non-pharmacological treatment and maximization of QoL.

Health-care professionals and epilepsy advocacy groups have worked together to publish specific recommendations concerning driving applicable to people with epilepsy [156], yet formal driving restrictions vary widely across different states and countries [157]. Neuropsychological assessment may play a role in advising about driving restrictions related to aging and epilepsy. In particular, a careful neurocognitive and psychobehavioral profile can provide information about a patient's awareness of cognitive impairments and risks for driving and about the status of the main cognitive resources that are important to complex driving behavior (e.g., visuospatial functions) [158]. This baseline information may be helpful during other examinations relevant to fitness to drive, including structured assessment of driving performance (e.g., driving simulation test).

Exclusion of cognitive decline requires at least two examinations, usually separated by 8–10 months. Especially at advanced ages, variability in cognitive reserve may lead to quite different individual trajectories of cognitive change. Stern [159] defined cognitive reserve as "the ability to optimize or maximize performance through differential recruitment of brain networks, which perhaps reflect the use of alternate cognitive strategies", suggesting that, as neural recruitment is a normal response to increased task demands, cognitive reserve is present in healthy and brain-damaged persons (Chap. 2). A more efficient capacity to use and alternate neural networks would correspond to a greater cognitive reserve. On the clinical ground, mental reserve may be considered the difference between the cognitive functioning that is expected by a patient and their actual performance, with greater reserve in patients performing better than predicted by brain damage. Cognitive reserve, as a product of intelligence level, education, lifestyle, social stimulation, personal experiences, and motivation, can modify or buffer the impact of aging and epilepsy on cognitive functions.

Cognitive functions may reflect previous neural and functional reorganizations, resulting in selectively impaired or preserved function irrespective of epilepsy. This underlines the importance of obtaining a comprehensive neuropsychological profile in older patients with epilepsy and assessing in detail different cognitive abilities. In adult epilepsy patients, the mental control, episodic memory, inhibition of interference, set-shifting, lexical-semantic competence, constructive praxis, and theory of mind may show different trajectories [150]. In older healthy persons, the understanding of social situations, in particular, might be relatively preserved in comparison with memory and executive functions [160]. A neuropsychological battery sensitive to epilepsy- and aging-related variables should assess multiple domains, but the battery should be cognizant of fatigability and fluctuating compliance. The tests should not be redundant or excessively time-consuming. In addition to the necessary psychometric properties, the tests ideally should have alternative forms for serial assessment and be sensitive at the lowest levels of performance, allowing for detection of small changes.

There is no consensus neuropsychological test battery for older patients with epilepsy. The neuropsychology subcommittee of the NINDS Epilepsy Common Data Element (CDE) Project published a recommended test battery for adult epilepsy patients that could be adopted for older adults [161, 162]. The subcommittee recommended that when WAIS-IV or WASI short forms are used, the Vocabulary and Block Design tests should be administered, at a minimum. The entire battery, depending on whether an IQ short form or the optional tests are used, should take from 2 to 3.5 h [162]. The CDE recommendations emphasize that the tests do not have to constitute a "fixed battery." Alternative or novel measures can be included to maintain continuity within an existing program or to advance the field [162, 163]. As just a few examples, additions might

include measures of planning, theory of mind, semantic knowledge, and visual perception. The battery listed here does not include psychiatric measures, but the Epilepsy CDE also does provide a list of recommended psychiatric scales [162]. For more on the recommended test battery, see Chaps. 4, 10 and 18, in this volume.

Self-Evaluation of Cognitive Functions

Decades ago, a review of the self-report memory questionnaire literature led to the conclusion that it is "prudent to employ memory questionnaires with caution" [164]. Basic studies found no close correlation between self-reported memory ability and objective test results across patient groups [165]. Presurgical adult TLE patients, the most consistently studied epilepsy group, most often overestimate their degree of memory impairment [163]. Complaints of recent memory dysfunction may be associated with a number of factors, including a stable chronic deficit, increased seizure activity, medication side effects, mood, or a combination of these factors [147], with depression and anxiety playing a central role in self-perception of memory [71, 165, 166]. Little is known about self-report of non-memory functions. A recent study estimated awareness of different cognitive functions and the predictors of self-report in patients with mixed epilepsy diagnosis [166]. Results showed that 39% of the patients had full awareness of their cognitive capacities (as expressed by the concordance between assessed and perceived functions), while 32% and 28%, respectively, overestimated and underestimated their functions. Self-report was predicted by neuropsychological performance in aware patients and by depression and seizure frequency in unaware or incompletely aware patients, while the type of epilepsy had no effect. Epilepsy patients may appear unaware of their cognitive abilities due to negative affect and clinical burden. Clarifying cognitive awareness and the causes of self-report can help plan treatment for neurobehavioral disturbances.

Non-pharmacological Treatment of Cognitive Decline in Old People with Epilepsy

The nervous system is able to adapt its functional and structural organization in response to pathological changes, as well as to environment, internal stimuli, and stressors, resulting in increased connectivity and gray matter density in the prefrontal and parietal cortex, thalamus, and hippocampus [167]. The organization of the brain cortex can change substantially as a result of practice and experience, cooperating to the elaboration of compensatory abilities overcoming the impaired functions, compensating cognitive, mood, or relational alterations. Studies of healthy people reveal evidence of functional and structural changes in the adult brain following cognitive or psychomotor training [168]. There is also evidence of brain modifications after repeated experiences and exercises aimed to stimulate cognition, behavior, or mood in healthy elderly [169] and in subjects with mild cognitive impairment [170]. Cognitive treatment can improve QoL perception in the elderly [171]. Cognitive stimulation, cognitive training, and cognitive rehabilitation are the main non-pharmacological cognitive therapies that can respond to different necessities, such as compensating cognitive impairment, addressing psychosocial problems, and enhancing the benefits of pharmacotherapy and neurosurgery. Cognitive rehabilitation refers to a tailored approach that helps patients and their families to identify personal goals and strategies to overcome cognitive, psychological, and behavioral failures. Cognitive training is a guided practice that uses standardized tasks involving memory, attention, or problem-solving, aiming to improve, maintain, or restore the impaired functions. Cognitive stimulation and reality orientation therapy are non-structured approaches that may have a general influence on cognitive functions and QoL in patients with mild cognitive decline, brain injury, stroke, or AD [172]. Although cognitive rehabilitation tends to favor memory and executive functions, there are no evidence-based cognitive

treatments for epilepsy patients. A randomized study showed that cognitive rehabilitation may increase attention in some epilepsy patients [173]. A recent evidence-based review [174] selecting 18 studies (2 reviews, 4 papers on the principles and efficacy of rehabilitation in epilepsy, a methodological paper, a single-case report, a multiple-case report, 9 experimental studies), most involving TLE patients, has suggested that a holistic cognitive rehabilitation approach may be more useful than selective interventions for memory or attention disturbances. Objective cognitive impairments and subjectively perceived cognitive failures can affect QoL of adult epilepsy patients [155]. In older patients with epilepsy, cognitive rehabilitation may cooperate to the treatment of neurobehavioral comorbidities and impaired self-efficacy and QoL [175]. However, the modalities of treatment and outcome end points are important concerns of clinical care and research. The lack of sound results on the effectiveness of non-pharmacological therapies on impaired cognition in epilepsy patients may reflect the lack of agreed core outcome sets. Recommendations from the ILAE Neuropsychology Task Force may help to determine core outcome sets in older epilepsy patients candidates to cognitive training or rehabilitation [176]. Identification of mood problems during a neuropsychological evaluation may lead to effective psychiatric or psychological treatment and reassurance that a feared dementia is not present. Insights from cognitive training and mental stimulation improving executive functions and memory and subjective cognitive functions in healthy older adults without cognitive decline [169, 177] may help elaborate modalities of treatment for older epilepsy patients.

Information for Patient and Family

Information acquired from patients and family members may help determine the severity of the problem in everyday life and understand patient's needs. While clinical and laboratory workup can answer questions concerning diagnosis and treatment of seizures, careful evaluation of the cognitive and psychosocial patterns can provide an important approach to neurobehavioral comorbidities in terms of impairments, mental reserve, psychosocial environment, and daily function. A comprehensive report of the results of neuropsychological assessment is not only a due feedback to the patients but also a source of information for tailored therapy, yielding indications for cognitive or psychological interventions or educational program, alleviating the patient's worries and uncertainty.

Guides that may be helpful for patients and families include those published online by the Epilepsy Foundation, the Epilepsy Project, and the Epilepsy Action [178–180]. For additional sources of information, see Loring, Hermann, and Cohen [181]. As noted above, the term epilepsy may have unfortunate connotations and stigma associated with it for some older patients, and so it may be best to avoid the term in those cases [17]. Family members and caregivers can be taught about the signs of AED toxicity to help prevent falls and other consequences [19]. A 7-day pillbox aids adherence to AEDs, and some patients may benefit from having a family member fill the pillbox once per week. A visiting nurse also may enhance AED adherence.

Clinical Pearls

- Older epilepsy patients might require more explanations than younger adults about assessment of cognitive and psychological disturbances and may be incompletely aware of their seizures, epilepsy diagnosis, and neurobehavioral changes.
- The neurologist and neuropsychologist should take long time to clarify the nature of the symptoms, distinguishing epileptic seizures from non-epileptic events and interictal cognitive failures from ictal cognitive symptoms.
- Interview of a collateral source is important in acquiring information about seizure type(s) and frequency, the patient's level of everyday cognitive functioning, medical comorbidities, AEDs and other medications, previous brain

pathologies, head trauma, alcohol use, family history of dementia, etc.
- Neurodegenerative disorders represent the etiology for 10% of new-onset epilepsy in older patients.
- Transient ischemic attacks (TIAs) are rarely associated with seizures. TIAs usually can be differentiated from seizures, because negative motor phenomena such as hemiparesis are quite uncommon in seizures.
- Seizures are the first sign of a brain tumor in 50% of older patients.
- The risk of posttraumatic epilepsy following head trauma increases with age.
- In addition to a comprehensive cognitive battery, clinicians should assess for depression, anxiety, suicidality, and QoL, including driving restrictions.
- Compare cognitive impairments and mental reserve, looking for potentialities of cognitive training or rehabilitation.
- Remember that social isolation, loneliness, and poor social networks are risk factors for cognitive decline and can increase the psychophysical vulnerability of older persons.
- Both the patient and spouse may benefit from psychosocial support and psychoeducation.

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27 Neuropsychological Assessment of Older Adults with a History of Cancer

Mariana E. Bradshaw and Jeffrey S. Wefel

Adults over the age of 65 have a 9.1 times greater risk of cancer diagnosis and 17.9 times greater risk of cancer-related mortality. In fact, it is estimated that 53.3% of cancer incidence and 69.4% of cancer-related mortality occur in individuals aged 65 or older [1]. The US Census Bureau predicts a rapid rise in the number of individuals in the United States who are over the age of 65. In 2012, it was estimated that there were 43.1 million people aged 65 or older; this number is projected to almost double, rising to 83.7 million by the year 2050 [2]. As a result, cancer is likely to become an even greater public health concern. Significant advances have been made in multimodal drug therapy and have resulted in increased success in the management of many cancers. However, since many anticancer therapies are not highly specific, healthy tissues are also placed at risk. This can have potential untoward impacts on cognitive functioning, which may be of particular importance for an aging population whose members are at increased risk for cognitive decline and toxicities related to cancer therapies.

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Cancer-Related Cognitive Impairment

In order to determine whether or not cancer therapies impact cognitive functioning, one must first understand the presence and pattern of cognitive symptoms prior to the initiation of treatment. This prevents misattribution of posttreatment cognitive impairment to a specific treatment, when in fact it might have been associated with the cancer itself. Patients with brain tumors may present with a variety of cognitive deficits as tumors destroy, crowd, and infiltrate brain tissue; the nature and severity of cognitive impairments vary in association with lesion location and lesion momentum [3, 4] or the rate at which tumors grow. Cancer-related cognitive dysfunction is not limited to central nervous system (CNS) cancers. Several studies have demonstrated cancer-related cognitive dysfunction in non-CNS cancers as well. For example, cognitive dysfunction in at least a subgroup of women with breast cancer has been demonstrated prior to initiation of chemotherapy, with estimates ranging from 11% to 35% of patients [5–8]. The first of these studies revealed particularly frequent difficulties (18–25%) on measures assessing learning and memory [5]. Pretreatment cognitive dysfunction has also been found in other patient populations, including acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS), with

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pretreatment impairments in learning and memory (41–44%), cognitive processing speed (28%), aspects of executive dysfunction (29%), and upper extremity fine motor dexterity (37%) [9]. Animal models provide some hypotheses regarding the mechanisms responsible for these changes. Mice with peripheral tumors showed significant increases in memory impairment and depressive behavior as the tumors progressed, with alterations in hippocampal function thought to be secondary to reduced neurogenesis, reduced levels of brain-derived neurotrophic factor and cyclooxygenase-2, and increased circulation of pro-inflammatory cytokines [10].

Patients with small cell lung cancer have also been shown to exhibit pretreatment cognitive impairments. Meyers et al. [11] demonstrated that 70–80% of patients with small cell lung cancer exhibited memory deficits, 38% had deficits in executive functions, and 33% showed impaired motor coordination *before* treatment was initiated. The high prevalence and relatively specific memory disorder in this population are believed to be associated with paraneoplastic processes that have been identified in small cell lung cancer as well as several other non-CNS cancers [11, 12].

Treatment-Related Cognitive Impairment

In addition to the potential for cognitive impairment related to cancer itself, cancer therapies, including surgery, radiation, chemotherapy, immunotherapy, and hormonal therapy, may have an untoward impact on cognitive functioning. The cognitive deficits associated with brain tumors are often specific to lesion location; however, the pattern of treatment-related cognitive decline tends to be suggestive of frontal-subcortical dysfunction. This pattern includes impairments in executive functioning, speed of processing, and speeded motor coordination, as well as inefficiencies in learning and memory retrieval in the context of relatively well-preserved memory consolidation processes [13]. These impairments typically manifest in complaints of difficulty with short-term memory, such as forgetting the details of recent conversations and events as well as misplacing possessions. Complaints often include problems with sustained attention, organization, and multitasking.

Surgery

Undergoing surgery and associated exposure to anesthesia may carry differential risk for older patients, who appear to be more vulnerable to developing postoperative cognitive dysfunction, or POCD, affecting memory, attention and concentration, and speed of processing [14]. We are not aware of any data to suggest that the surgical resection of non-CNS cancers carries any greater risk than other non-CNS surgeries. However, in patients with brain tumors, surgery may result in damage to normal tissue interdigitated with tumor or tissue that surrounds the tumor. This can engender relatively focal cognitive impairments or more diffuse impairments secondary to disconnection of brain networks.

Radiation

It is well known that radiation to the brain may be associated with the development of neuropsychological dysfunction both during and after treatment. The acute phase (during treatment) is characterized by transient symptoms of headache, fatigue, fever, and nausea, as well as exacerbation of preexisting neurologic deficits. Early-delayed toxicity typically develops 2–5 months after completion of radiotherapy and has been associated with declines in information processing speed, attention, learning efficiency and memory retrieval, executive functioning, and fine motor dexterity; these symptoms may resolve spontaneously. Late-delayed toxicity can occur months to years after completion of radiation therapy and includes progressive dementia, personality changes, and leukoencephalopathy. Unlike acute and early-delayed effects, late-delayed toxicity tends to be irreversible [15]. Proposed mechanisms for radiation-induced

neurotoxicity include vascular damage, altered neurogenesis, loss or damage to mature neurons, and signaling changes. These processes may begin relatively early after radiation and may persist over time, combining to result in irreversible neuronal deficits [16]. Numerous risk factors for developing radiation-induced cognitive dysfunction and necrosis have been identified and include age over 60 years, greater than 2 Gy dose per fraction, higher total dose, greater total volume of brain irradiated, greater dose to the hippocampal region bilaterally, hyperfractionated schedules, shorter overall treatment time, concomitant or subsequent treatment with chemotherapy, and the presence of comorbid vascular risk factors [17–19]. Current practice utilizes lower doses of radiation and more precise delivery techniques in an attempt to reduce exposure of the surrounding healthy brain tissue. Continued advances in treatment modalities (i.e., intensity-modulated radiation therapy, whole-brain radiation with hippocampal sparing, and proton therapy) should further improve the therapeutic ratio and limit incidental brain irradiation, thereby minimizing associated neurobehavioral complications. The risks and benefits of focal versus whole-brain radiation for the prevention or treatment of brain metastases are still being debated. However, recent evidence has consistently shown that in patients with 1–3 newly diagnosed brain metastases, treatment with stereotactic radiosurgery plus whole-brain radiation resulted in better tumor control but more frequent declines in cognitive function, particularly learning and memory, compared to treatment with stereotactic radiosurgery alone [20, 21]. The most profound adverse effects of radiation treatment tend to emerge over time. Therefore, careful monitoring of cognitive function in patients over time remains necessary.

Chemotherapy

The majority of research regarding chemotherapy-related side effects has been conducted in patients with breast cancer; cognitive dysfunction has most frequently been observed in learning and memory, attention, executive function, and processing speed, with estimates of dysfunction ranging from 13% to 70% [6, 7, 22–28]. Posttreatment follow-up has revealed that a subset of these women fails to achieve complete recovery [28]. More recent studies have also raised concern for ongoing, progressive cognitive decline after completion of chemotherapy, which may be of particular concern for older individuals who are already at increased risk for cognitive decline secondary to noncancer-related factors [29]. A dose-response effect appears to be present. In patients with breast cancer, cognitive function was found to be progressively worse with cumulative exposures to chemotherapy, even after controlling for baseline cognitive status, age, education, and mood [30]. In a study of older adults treated for early-stage breast cancer, approximately half exhibited cognitive decline after treatment; the oldest patients, especially those treated with docetaxel, were particularly vulnerable [31].

Many chemotherapies are administered clinically in combinations (i.e., regimens) making it difficult to establish if a particular agent is associated with more or less risk of neurotoxicity. However, some preliminary evidence suggests that anthracycline-based chemotherapy regimens may carry more risks to cognitive functioning in patients with breast cancer. Patients with breast cancer who were treated with regimens that included an anthracycline exhibited lower verbal memory performance and greater disruption of connectivity in the left precuneus compared to patients treated with non-anthracycline-based chemotherapies or no chemotherapy [32].

Several other non-CNS cancer populations have been studied with evidence of cancer therapy-related cognitive dysfunction including nonseminomatous germ cell tumors of the testis [33], ovarian [34], prostate [35], and myeloma [36].

Cognitive and emotional dysfunction associated with hematopoietic stem cell transplant (HSCT) has also been reported by a number of investigators and is thought to result from the intense treatment regimen utilizing high-dose chemotherapy and total-body irradiation during pretransplant conditioning [37, 38]. Studies in this group of patients are limited by small sample

size and cross-sectional designs; however, the available prospective neuropsychological assessment data suggest a decline in executive functions [38] and memory [39] following HSCT.

There may be multiple mechanisms at play in the development of chemotherapy-related neurotoxicities, including neuroinflammation, release of damage-associated molecular patterns, and change in cellular metabolism secondary to alteration of mitochondrial function (for a review of these potential mechanisms, please see Vichaya et al. [40]).

Biological Response Modifiers

Biological response modifiers (BRMs; also known as immunotherapies) are aimed at modifying the immune response of cancer patients in hopes of yielding a therapeutic effect [41]. Such agents include a wide variety of treatments, including cytokines, vaccines, monoclonal antibodies, thymic factors, and colony-stimulating factors [42]. In normal, healthy controls, a single dose of only 1.5 million international units of the cytokine interferon alpha (IFN-alpha) worsened reaction time at 6 and 10 h after injection. When used as a treatment for cancers such as chronic myelogenous leukemia and melanoma, IFN-alpha is delivered at much higher doses for longer periods of time. Posttreatment cognitive impairments have been documented on measures of memory, psychomotor speed, and executive functioning, especially when used in combination with chemotherapy [43, 44]. In addition, IFN-alpha has been associated with depression [45] and the so-called dysphoric mania, characterized by extreme irritability or agitation that is often accompanied by poor insight and does not respond to treatment with antidepressants [46]. Although antidepressants may be used prophylactically for symptom prevention/reduction in some patients, pretreatment screening in combination with close serial monitoring of a patient's mood may help avoid unnecessary medications and potential side effects [36, 47]. Interest in and development of immunotherapies for the treatment of a variety of cancers have increased rapidly in the last several years. Along with a number of dramatic successes have come some unique neurotoxicities. At this point, little is known about specific neuropsychological effects of these agents. Perhaps the most profound neurologic dysfunction has been seen in association with chimeric antigen receptor T-cell therapies in which the development of a cytokine release syndrome is ubiquitous, and frank neurologic impairment including aphasia, delirium, somnolence, and even death has been reported [48]. Interestingly, there are anecdotal reports indicating that at least some of these adverse effects may be temporary and resolve after cessation of therapy.

Hormonal Therapies

Estrogen and testosterone have been found to impact cognitive functioning [49, 50], and treatments affecting these hormones are commonly used in the care of breast and prostate cancer patients. Studies in breast cancer have investigated both selective estrogen receptor modulators (SERMs) such as tamoxifen (TAM) and aromatase inhibitors such as anastrozole or exemestane. Patients receiving TAM, anastrozole, or a combination of those therapies performed more poorly than noncancer controls on measures of memory and processing speed [51]. One year of treatment with TAM was associated with declines in memory and executive functioning, whereas no such decline was observed in patients treated with exemestane [52].

In prostate cancer, LHRH agonists such as leuprolide and goserelin have been found to be associated with alterations in visuospatial processing, including visual memory, and executive functioning, with contradictory findings with regard to verbal memory performance [50]. While group analyses of mean change often fail to demonstrate a statistically significant effect, reliable change index-based analyses have demonstrated cognitive decline in up to 50% of men treated with an LHRH agonist in some studies [53] and with no increased incidence of cognitive decline other studies [54].

Cancer in Older Adults

Prognosis is impacted more by characteristics of the tumor than by age [55]. However, older age is an unfavorable prognostic factor in acute myeloid leukemia, non-Hodgkin's lymphoma, and primary brain tumor. In contrast, older age is associated with more favorable tumor biology in breast cancers. In non-small cell lung cancer (NSCLC), research has found no impact or a favorable impact of age on prognosis. Of note, older adults are generally less likely to be included in clinical trials for cancer, despite an equal willingness to participate in trials when offered, and this appears to potentially be due to age bias and toxicity concerns [56]. Indeed, older adults are more likely to have comorbid conditions which may make them ineligible for many trials as well as more vulnerable to treatment-related toxicity [57]. Age is associated with reduced renal function and bone marrow reserves, as well as increased anemia, which could influence the way chemotherapies are tolerated [55]. As a result of comorbid conditions and greater toxicities, older patients are less likely to receive optimal doses of chemotherapy [58, 59].

Although concerns regarding increased risk of toxicity should not be dismissed, it has been demonstrated that older adults do benefit from cancer treatment. In a recent study, patients aged 70 years or older with newly diagnosed glioblastoma and a poor performance status treated with chemotherapy (temozolomide) alone were found to have an acceptable toxicity profile and increased survival as compared to supportive care, and an improvement in functional status was observed in 30% of cases [60]. Studies using a combination of chemotherapy (temozolomide) and radiation therapy have also revealed a survival benefit and acceptable rates of toxicity in adults over the age of 65 [61–63]. This suggests that more studies should consider inclusion of older adults.

It has been suggested that evaluation of comorbid conditions is a more appropriate surrogate for life expectancy than chronological age and should be taken into consideration over and above age when making treatment decisions for older adults [57]. The European Organization for Research and Treatment of Cancer (EORTC) elderly task force recommends design of specific trials for older patients, with separate trials for those patients considered fit, vulnerable, and frail. The task force also advocates for inclusion of geriatric assessment in clinical trials, such as the Comprehensive Geriatric Assessment (CGA), which evaluates functional, nutritional, and mental status, as well as the presence of comorbid conditions, use of associated pharmacologic interventions, and the individual's level of social support. In addition, the task force suggested consideration of "elderly-specific" outcomes, such as functional independence, time to progression, or a combination of efficacy and toxicity, as well as close monitoring and early intervention for toxicities to which older adults are more vulnerable, including myelotoxicity, anemia, mucositis, diarrhea, and dehydration [55].

Cognition in Older Adults With a History of Cancer

While the above data regarding the ability of older adults to tolerate and benefit from cancer therapies is promising, it is noted that those studies did not include formal measures of cognitive functioning. Few studies have investigated the impact of cancer and cancer therapies on cognition in older adults, despite the higher incidence of cancer diagnosis and potential increased risk of treatment-related morbidity in that population. The majority of studies investigating the impact of chemotherapy on cognition in patients with breast cancer have been performed in younger women, despite the fact that the majority of breast cancers occur in women over the age of 65 and aging is the number one risk factor for breast cancer [64]. This tendency to focus on younger adults is prevalent across cancer types; only 17% of studies investigating cognition in cancer patients that were identified in a recent literature review included patients whose mean or median age was 65 or above; of these, 27% utilized the MMSE as a measure of cognitive status [65].

Data available from the limited number of studies that have investigated the presence and pattern of cancer and cancer treatment-related cognitive symptoms in older adults suggest that, similar to younger adults, a subset of older adult cancer patients exhibits cognitive impairment prior to the initiation of treatment. For example, in older men diagnosed with prostate cancer, 45% scored ≥1.5 standard deviations below the normative mean on at least two neuropsychological tests prior to beginning androgen ablation therapy [66]. The proportion of patients with breast cancer who exhibit pretreatment cognitive impairment is higher among older women than in younger women [67].

Posttreatment cognitive changes have also been documented in older adults. In one of the few prospective studies focusing on chemotherapy-related cognitive dysfunction in older adults, patients aged 65–84 with a diagnosis of breast cancer underwent neuropsychological and geriatric assessment prior to the initiation of chemotherapy and 6 months after treatment. Consistent with research performed in younger women, results revealed a subset of patients who demonstrated posttreatment cognitive decline, most often in the domains of memory, psychomotor speed, and attention [8]. A more recent study found that breast cancer patients in the older age group (60–70) performed more poorly on a measure of processing speed than younger patients or healthy controls [68].

Hormonal therapies also appear to impact older adults in a manner similar to that observed in younger adults. Older women (≥65) treated with TAM were found to perform significantly worse than healthy controls on measures of memory and information processing speed [52]. In older men treated with LHRH agonists for prostate cancer, patients who scored in the average range or above on cognitive tests at baseline displayed improvements in visuospatial planning and phonemic fluency posttreatment; those who performed below expectation at baseline displayed no significant change in cognition. It was hypothesized that this lack of improvement (presumably due to practice effects) may in and of itself be representative of impairment [66].

Cancer and Dementia

It has been suggested that there may be a link between cancer and the development of dementia, particularly Alzheimer's disease (AD). This concern was raised in a retrospective study of Swedish twin pairs discordant for cancer history, which reported that twins with a history of cancer were more likely to be classified as cognitively impaired based on a telephone mental status screening measure [69]. However, as was highlighted in an editorial response to that study, screening measures are inadequate to make such a conclusion. Further, there was no statistically significant difference in the rate of clinician-determined dementia between twins with and without a history of cancer [70]. Controversy also exists regarding whether or not treatment with androgen deprivation therapy (ADT) for prostate cancer is associated with increased risk of dementia; while two retrospective cohort studies using text processing analyses found an increased risk of dementia associated with previous treatment using ADTs [71, 72], a third study found no such increased risk [73]. Results of another study indicate that AD is actually associated with a reduced risk of cancer and that a history of cancer is associated with a reduced risk of AD [74]. It was suggested by another investigator that this finding might reflect underdiagnosis of cancer in AD patients [75]; however, the same study that found a reduced risk of cancer in AD patients found no association between cancer and vascular dementia, and the authors point out that underdiagnosis, if present, would be just as likely to exist in this patient group as in AD patients [74]. A longitudinal study confirmed a slower rate of cancer development in individuals with a preexisting diagnosis of AD; the authors hypothesize that this may reflect a protective relationship between the two conditions or that they may share a common biological mechanism which affects the vulnerability of cells to apoptosis, which is excessive in AD and may be insufficient in cancer [76]. The Framingham Heart Study also found an inverse relationship between cancer and AD, controlling for survivor bias in sensitivity analyses [77]. Neither breast cancer nor chemo-

therapy for breast cancer was associated with a greater risk of a diagnosis of dementia, even in older women [78, 79]. In fact, for those patients treated with tamoxifen, a 17% lower risk of dementia was reported as compared to those without [78]. Three out of four retrospective studies using data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database found no increased risk of neurodegenerative dementia in chemotherapy-exposed versus non-exposed patients [79–82]. Patients with cancer requiring radiation to the brain should be considered separately, as they are at an increased risk of treatment-related dementia. As noted above, in patients who have been treated with whole-brain radiation (WBRT), late effects of treatment are of concern, and progressive dementia secondary to WBRT is more likely to emerge in patients who survive at least 6–12 months following radiation [83]. Severe dementia requiring full-time caregiving was documented in 10% of anaplastic glioma patients treated with accelerated radiotherapy followed by chemotherapy [84].

Cancer as Accelerated Aging

Though cancer may not be associated with an increased risk of dementia per se, the data presented above provides clear evidence of cognitive impairment associated with cancer and its treatments. Aging itself may provide a theoretical framework from which to understand these changes, as common biological underpinnings may exist for both cancer-related cognitive impairment and age-related cognitive impairment including neuroinflammation, oxidative DNA damage, genetic variations (including APOE and COMT), vascular factors, and cellular senescence (see Mandelblatt et al. [85], for a review).

Several hypotheses have been proposed regarding the potential for cancer and its treatments to either mirror or accelerate aging. It has been further suggested that those cancer patients with lowest reserve/greatest frailty have the steepest cognitive decline [86]. Support for the latter hypothesis comes from research in patients with breast cancer treated with chemotherapy compared to non-chemotherapy-treated patients and controls; patients age 60–70 with lower baseline cognitive reserve and treated with chemotherapy performed significantly worse on tests of processing speed. This was not true for patients with high cognitive reserve [68].

Imaging studies reveal similar changes in brain structure after cancer/treatment and after normal aging, providing further support for potential overlap of underlying mechanisms. Structural MRI has revealed reduced total and gray matter volume. Loss of total brain volume has been observed in patients treated for glioblastoma [87] and in survivors of breast cancer treated with chemotherapy. The extent of loss noted in the latter sample was comparable to approximately 4 years of normal aging [88]. Diminished white matter integrity has also been noted both in aging and after breast cancer [89]. Less efficient functional connectivity may also represent a commonality [90]. Functional imaging studies have shown reduced connectivity, with the default mode network proposed as a potentially sensitive biomarker [91].

Neuropsychological Assessment of Older Adults with a History of Cancer

Occasionally, older adults are referred for neuropsychological evaluation prior to undergoing cancer treatment to help with decision-making regarding appropriate therapies. Most commonly, patients are referred during or after their cancer treatment with complaints of memory loss. Some of the most common considerations for differential diagnosis are listed in Table 27.1. In addition to the untoward impact of cancer and cancer treatments or metastatic disease, alternative etiological considerations include those seen in older adults without a history of cancer, such as neurodegenerative dementias, potentially reversible metabolic or electrolyte imbalances, and cognitive change secondary to mood disturbance.

Table 27.1 Common etiologies for memory loss in older adult patients with a history of cancer

Cancer- and treatment-related toxicity
Brain metastases
Dementia including
Cerebrovascular disease
Alzheimer's disease
Lewy body dementia
Frontotemporal dementia
Potentially reversible conditions including
B12 deficiency
Thyroid abnormalities
Electrolyte abnormalities
Complications of mood disturbance and fatigue

Baseline evaluations of neuropsychological functioning allow for the identification of even subtle treatment-related neurotoxicities; such information can prevent misclassification of patients who do experience clinically and functionally meaningful declines in cognitive function but continue to perform within normal limits relative to normative standards. For example, in a prospective, longitudinal study, Wefel et al. [28] found that classifying posttreatment cognitive performance as impaired using a conventional classification criterion (e.g., 1.5 SDs below the normative mean), without consideration of their pretreatment baseline level of performance, resulted in false-negative classification errors (i.e., concluding no cognitive change/impairment occurred when review of longitudinal testing in fact demonstrated cognitive decline) approximately 50% of the time. While baseline cognitive evaluation is critical for research, it is rarely available as a point of comparison for clinicians, who are most often asked to address referral questions in the absence of baseline data and in the aftermath of cancer and cancer treatment.

Thus, as with any evaluation, one must conduct a thorough interview investigating the premorbid level of functioning, including information regarding educational and occupational attainment and any developmentally based weaknesses, as well as the use of neuropsychological tests to estimate premorbid functioning. Information regarding medical comorbidities and the type of cancer treatment received should also be obtained during the clinical interview and can be of particular importance when the obtained cognitive profile and clinical correlates, such as imaging studies, may be ambiguous. For example, a patient's cognitive performance may reveal a pattern suggestive of frontal-subcortical dysfunction, and imaging studies might reveal white matter changes, which could be secondary to vascular disease or may reflect leukoencephalopathy secondary to treatment with certain cancer treatments such as methotrexate. Knowledge regarding the presence or absence of risk factors for cerebrovascular disease and the type of cancer therapy utilized may therefore elucidate the underlying etiology of observed cognitive impairments. The clinician should also determine the onset and course of cognitive symptoms and how that timeline relates to cancer diagnosis and treatment. In the most straightforward case, patients and their family members are likely to describe cognitive difficulties that had onset during treatment or became noticeable shortly thereafter, when the patient was presented with increased cognitive challenges. These difficulties are often described as nonprogressive. Greater challenges arise when cognitive problems are perceived prior to initiation of treatment and are exacerbated during treatment or are only appreciated long after completion of treatments traditionally thought not to cross the blood brain barrier.

Appropriate neuropsychological assessment of patients with cancer includes careful selection of reliable and valid measures that are sensitive to subtle changes in functioning and are robust to practice effects [14]. In this patient population, there is often a heavy emphasis on tests assessing frontal-subcortical network functioning. Additional test selection may vary in association with cancer diagnosis; for example, tests of visuospatial functioning are likely less sensitive to treatment-related cognitive decline in women with breast cancer but may be critical in the assessment of treatment-related cognitive decline in men with prostate cancer. Similarly, test selection for patients with brain tumors may vary somewhat depending on lesion location.

In addition to the above considerations, a thorough neuropsychological examination includes

an assessment of fatigue, pain, and affective distress, which can have an untoward impact on cognitive performance, particularly with regard to aspects of attention and memory. It is important to note that in cancer patients, self-report of cognitive complaints has been shown to correlate more strongly with fatigue and mood disturbance than with objective evidence of cognitive dysfunction, as assessed by standardized neuropsychological tests [92]. Thus, a thorough assessment may be needed to elucidate whether perceived difficulties are secondary to cancer- and treatment-related cognitive dysfunction and/or affective distress and fatigue.

Case Examples

Ms. A, Ms. B, and Ms. C are college-educated women in their mid-70s who have a history of breast cancer and were treated with standard dose adjuvant chemotherapy including fluorouracil, Adriamycin, and cyclophosphamide. All three women presented with similar complaints, namely, problems with recent memory characterized by difficulty remembering recent conversations, forgetting to pay bills, and difficulty with medication management. Ms. C and her family members also described word-finding difficulty. As a result of these complaints, the women were referred for evaluation of their cognitive functioning in an effort to determine whether cognitive symptoms reflected the impact of cancer and associated treatment or whether there was concern for an additional neurodegenerative process.

Neuropsychological evaluation of Ms. A revealed a pattern consistent with frontal-subcortical dysfunction and characterized by mild impairments in memory retrieval (in the context of intact memory consolidation processes), working memory, and bilateral fine motor dexterity. The latter impairments were believed to reflect her peripheral neuropathy, which is commonly associated with the chemotherapies she received. The observed pattern of performance, and the fact that her reported functional difficulties had onset during her chemotherapy and developed simultaneously with her peripheral neuropathy, is consistent with the untoward impact of her breast cancer and cancer treatment.

Ms. B's cognitive profile was very similar to that of Ms. A's; however, in Ms. B's case, the etiology of her cognitive impairments is less clear, as her medical history was also notable for numerous cerebrovascular risk factors, including hypertension, hypercholesterolemia, and a previous transient ischemic attack. Thus, it is possible that the observed cognitive impairments result from cerebrovascular disease, from her cancer and chemotherapy, or from a combined effect of vascular burden and treatment effect.

Finally, Ms. C's neuropsychological evaluation revealed moderate to severe impairments in learning and memory, with little to no benefit from the provision of retrieval cues. In addition, she evidenced disorientation, dysnomia, and impairments in processing speed and visuoconstruction. Basic attention span and reasoning skills remained relatively preserved. The severity and pattern of the observed difficulties exceeded that which might be expected secondary to breast cancer and associated treatment alone; in addition, it was noted that while her cancer diagnosis and treatment were quite remote, her cognitive difficulties had more recent onset and, per her family's report, had been gradually progressive. This was worrisome for a neurodegenerative process. The patient was therefore referred to neurology for a further diagnostic work-up.

Prevention and Treatment of Cognitive Sequelae of Cancer and Cancer Therapy

Risk factors for treatment-related cognitive dysfunction (i.e., high dose, agent, and schedule of administration) can be adjusted to reduce neurotoxicity while maintaining adequate disease control [93, 94]. Hippocampal avoidance during whole-brain radiotherapy was associated with less decline in memory and preservation of quality of life [95] and is being further investigated in larger phase III trials. The addition of

memantine during WBRT has been shown to delay time to cognitive decline [96]. Pharmacologic interventions targeted at specific underlying mechanisms of some neurotoxic side effects have also been investigated; it remains unclear whether these interventions are differentially effective for older versus younger patients. Psychostimulant medications have shown promise in addressing fatigue in some cancer patients [97–103], but better study designs are needed to clarify their efficacy [104]. Patients with cardiovascular diseases may not be ideal candidates for these medications, as stimulants have been associated with increased blood pressure and elevated heart rate. As with patients of all ages, medical comorbidities must be taken into account when considering the appropriateness of this and other pharmacological interventions. Other medications that have been used in oncology populations include donepezil to combat difficulties with cancer-related fatigue, attention, and memory [105, 106]. The use of high-dose vitamin E has been shown to be beneficial in patients with nasopharyngeal carcinoma who had imaging evidence of unilateral or bilateral temporal lobe necrosis, such that patients who were treated with vitamin E demonstrated greater improvement on measures of learning, memory, and cognitive flexibility than non-treated controls [107]. Unfortunately, most intervention studies targeting cognition or fatigue have been small, of variable quality, and require replication.

In addition to making adjustments to primary treatments and using pharmacological interventions to combat cognitive inefficiencies and fatigue, goal-focused compensatory interventions and behavioral strategies may be useful in minimizing the impact of neurobehavioral symptoms on daily life in patients with cancer. Physical exercise has been linked to improvements in at least some aspects of cognitive functioning in patients with mild cognitive impairment and Alzheimer's disease [108, 109] and has been associated with increased patient self-reported quality of life, including cognitive functioning, in cancer patients [110]. Several studies have associated improvements in self-report of cognitive function with exercise including yoga, resistance training, and Qigong [111–113] in cancer patients. In older cancer patients, self-report of memory loss was lower in those who exercised during treatment than in controls [114]. Breast cancer and lower-grade glioma survivors who participated in speed of processing exercises or compensatory strategy training demonstrated benefit [115–118]. Similarly, combined physical activity/cognitive training intervention in breast cancer survivors was associated with improved cognitive function [119].

Knowledge gained from traditional rehabilitation disciplines treating survivors of traumatic brain injury or stroke has yielded important information regarding evidenced-based compensatory strategies that may be applicable to patients with cancer-related cognitive dysfunction. Such multidisciplinary therapeutic interventions, provided by a team of psychologists, speech/language pathologists, occupational therapists, and vocational specialists, were found to improve community independence and employment outcomes in brain tumor patients at a significantly lower cost and shorter treatment length than was typical of survivors of traumatic brain injury who took part in the same program [120]. Training in the use of compensatory strategies and attention retraining has also shown promise in addressing both cognitive complaints and mental fatigue [118]. Compensatory tools might include external memory aids such as memory notebooks, user-programmable paging systems, and medication reminder systems to assist neurologically impaired patients compensate for difficulties with forgetfulness. Older adults, particularly those with multiple comorbidities, may require adjustments to their environment and increased support to make certain that demands do not exceed capacity while maintaining safety and ensuring treatment compliance.

Recently, preclinical investigations have helped to identify both potential mechanisms underlying cognitive changes in cancer patients as well as therapeutic strategies with translational potential. For example, animal studies show exer-

cise was demonstrated to be a protective factor against cancer treatment-related cognitive side effects, with daily running after WBRT associated with reduced decline in spatial memory in mice [121]. Additional potential pharmacologic interventions have also been identified. For example, the severe memory impairment observed in rats treated with chemotherapy was fully prevented by supplementation with an antioxidant, *N*-acetyl cysteine [122]. The small molecule drug KU-32 may also be neuroprotective; rats treated with the chemotherapy 5-fluoruracil (5-FU) plus KU-32 exhibited stronger temporal discrimination as compared to those treated with 5-FU plus saline [123]. The addition of metformin to a cisplatin chemotherapy regimen prevented cognitive impairments in mice [124]. Following treatment with docetaxel, administration of the PDE-4 inhibitor rolipram led to recovery of chemotherapy-induced impairments in spatial memory as well as depressive and anxious behavior in mice [125]. Similarly, administration of the peroxisomal proliferator-activated receptor-γ agonist pioglitazone prevented memory disturbance associated with whole-brain irradiation in rats [126]. Radiation-induced memory loss was also attenuated via transplantation of human embryonic stem cells into the rat hippocampus [127]. Siegers and Fardell recently reviewed these preclinical efforts [128]. As with any promising preclinical experiment, translating these promising leads into clinical trials in humans is needed.

Conclusion

Older adults are at increased risk for developing cancer; thus the incidence of cancer is predicted to increase with an aging population [1, 2]. Despite the possibility of treatment-related cognitive declines for some patients, these treatments remain a critical component in the management and eradication of many cancers. Thus, the potential side effects of these therapies must be considered in the context of the overall health benefit they provide. Continued research into the mechanisms of treatment-related cognitive dysfunction may afford opportunities for the development of neuroprotective therapies, effective adjuvant supportive therapies, or modification of primary treatments. Advances in behavioral interventions will help minimize the impact of cancer and cancer therapy on cognitive function, mood, quality of life, and functional abilities. It appears that older adults can benefit from cancer treatments; as with younger adults, medical comorbidities, cognitive status, and social support are important clinical considerations. To date, older adults have often been excluded from studies investigating the impact of cancer and cancer therapies on cognitive functioning, and more research is needed to determine whether older adults are differentially affected.

Clinical Pearls

- Cognitive changes can result from CNS and non-CNS cancers, even prior to the initiation of treatment.
- Treatment-related cognitive changes may result from surgical intervention, radiation, chemotherapy, immunotherapy, and hormonal therapy.
- Treatment-related cognitive declines most often occur during or immediately after surgery, chemotherapy, immunotherapy, and hormonal therapy. In contrast, late-onset cognitive decline can occur and is more likely to be progressive, after treatment with radiation.
- The neuropsychological profile of treatment-related cognitive decline often suggests frontal-subcortical dysfunction.
- Screening measures such as the MMSE are insufficient to detect cognitive changes often associated with cancer and cancer treatment.
- Neuropsychological assessment should include measures that are sensitive to frontal-subcortical network dysfunction; test selection may vary depending on cancer type, location of brain tumor, or treatment received.
- The risk of cognitive dysfunction or cancer increases with age. It is unclear if the develop-

ment and treatment of non-CNS cancer increases risk for cognitive dysfunction in older adults compared to younger adults; however, older individuals with comorbidities appear to be at greater risk for adverse effects of treatments. Whether or not late effects of treatment for non-CNS cancers confers an increased risk of dementia remains a matter of active investigation.

- A limited number of pharmacologic interventions for cancer treatment-related cognitive impairment have been identified to date. The use of compensatory strategies is the most common intervention to assist individuals with cancer treatment-related cognitive decline in maximizing their daily functioning.

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Part III

Late Life Cognitive Disorders

Differentiating Mild Cognitive Impairment and Cognitive Changes of Normal Aging

28

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Introduction

Normal Cognitive Aging

As people live longer, scientists are given greater opportunity to improve their knowledge of the structure and function of the aging brain. In the United States, the current life expectancy at birth is 76 years for men and 81 years for women, and approximately 13% of US citizens are 65 years and older [1–3]. The US Census Bureau's projections estimate that about one in five citizens will be seniors by the year 2030 and the oldest old (85 years and older) is the fastest-growing segment of the population. Given these statistics, there is a great need for clinical services and research focusing on normal and pathological cognitive aging.

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It is generally accepted that some degree of cognitive decline associated with aging is inevitable, with a great deal of variability as to when these changes begin [4]. Interindividual variation in cognitive performance in areas such as memory and fluid intelligence increases with age. Thus, with advancing age, there becomes an increase in the proportion of elderly persons who show normative age-associated cognitive decline [5–8]. It can become difficult to parse out "normal" cognitive aging versus pathological cognitive decline in the absence of neuropsychological testing with normative comparison data.

Some aspects of cognition remain relatively intact with normal aging, including implicit memory, vocabulary, and storage of general knowledge [5, 8, 9]. The cognitive decline that typically accompanies normal cognitive aging involves decreased efficiency in information processing in several areas, including speed of processing, reaction time, working memory capacity, short-term memory, executive control (e.g., inhibitory functions), and verbal fluency [5, 10–12]. Visuoperception, visuoconstruction, and spatial orientation also decline with age [13, 14].

Slowed processing speed is a key cognitive change in the aging brain. It has been widely found, for example, that visual-motor tracking, sequencing, and set-shifting slow with age [15–17]. Reduced processing speed is suspected of mediating cognitive efficiency by restricting the speed at which cognitive processes can be executed

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[9, 11, 18, 19]. Reduced processing can also affect the quality and accuracy of performance due to the decreased quantity of information processed that is necessary for completion of the task [19]. Further, products of earlier processing may be lost by the time later processing occurs, rendering integration of relevant information difficult or impossible. The consequences of reduced processing include decreased working memory capacity because less information can be processed within a given time, as well as impaired higher-order cognitive functions such as abstraction or elaboration, because the relevant information is no longer available in working memory or storage [19].

Age-related changes in working memory are likely due to reduced inhibitory mechanisms of selective attention [20]. That is, older adults show decreased ability to effectively suppress the processing of irrelevant, or marginally relevant, stimuli and thoughts. This leads to a generalized attentional dysregulation that is also thought to account for age-related deficits in various aspects of executive performance, including shifting cognitive set, suppressing responses, and response competition [9]. Cognitive aging is also associated with poorer effortful or controlled processing, while automatic processing remains relatively intact [21]. Older adults retain relatively good memory for "gist" or familiar stimuli, while source memory and recollection of contextual details decline [12].

Normal age-related changes in language function include increased inefficiency in phonological retrieval, resulting in word-finding difficulties that are often referred to as the "tip of the tongue" phenomenon [22]. The literature shows that confrontation naming performance declines with age, with the rate of decline accelerating in older age groups [23–25]. Semantic fluency or the ability to retrieve words associated with a particular category under time constraints also declines with age, as does lexical fluency (i.e., the ability to rapidly retrieve words from declarative memory that begins with a particular letter or sound) [26]. However, it is suspected that the age-related decline in verbal fluency is at least partly due to the substantial contributions of auditory attention and verbal memory abilities to the tasks, rather than simply a primary degradation of semantic or lexical networks [27].

Structural Brain Changes

Numerous changes in brain structure accompany normal aging, including volumetric shrinkage, decreased white matter density, loss of dopaminergic receptors, and the emergence of neurofibrillary plaques and tangles. The greatest degree of cortical thinning and volumetric brain shrinkage across the lifespan occurs in the hippocampus, caudate, cerebellum, and calcarine (i.e., occipital) and prefrontal areas [28, 29]. Ventricular volume also increases in old age [30]. Decreases in white matter density and other white matter abnormalities are particularly evident in the frontal and occipital regions of the brain [31, 32]. White matter changes may be the primary culprit for age-related cognitive slowing, as white matter's main function is to facilitate transmission of signals to and from different areas of the brain via myelinated axons. As myelin integrity degrades with age, so does the speed of cognitive processing. Together with findings on cortical volume and thinning, studies on age-associated white matter changes point to significant alterations in frontal networks [31, 32].

Loss of dopaminergic receptors occurs with age and is thought to contribute to the attentional dysregulation, executive dysfunction, and difficulty with contextual processing that accompanies normal cognitive aging [33–35]. It has been proposed that context processing involves using internally represented task-relevant information in a way that influences processing in the pathways responsible for task performance [36]. For example, performance on the Stroop task is dependent upon the ability to use the context of task instructions (i.e., inhibit reading color-named words while saying the printed ink color) in order to maintain attention toward ink color rather than the printed word. Braver and Barch (2002) postulated that contextual representations are affiliated with the dorsolateral prefrontal

cortex and are regulated by dopamine projections to this area. The mechanism of context processing subserves cognitive functions such as attention, working memory, and inhibition by affecting the selection, maintenance, and suppression of information relevant (or irrelevant) to the task, accounting for the decline in these abilities with age [36].

An autopsy study on clinically nondemented oldest old (age ≥ 85 at death; $n = 9$) found neurofibrillary tangles (NFTs) in one or more limbic regions in all study participants [37]. The most affected regions included the entorhinal cortex, amygdala, subiculum, CA1 field of the hippocampus, and inferior temporal regions. Midfrontal, orbitofrontal, and parietal regions were less affected, and occipital regions were minimally affected in clinically nondemented persons. Senile plaque (SP) formation also was observed in this group and was found to affect all brain regions equally, with the exception of relative sparing of the occipital cortex. Participants who were clinically nondemented at death showed significantly less NFTs and SPs than participants with mild cognitive impairment (MCI) and dementia. Pathological lesion density was significantly related to cognitive status. However, two of nine participants who were nondemented in the few months prior to death met *pathological* criteria for Alzheimer's disease, suggesting individual variability in the relationship between brain pathology and cognitive presentation. One explanation for this variability is the notion of cognitive reserve, a hypothesized degree of protection against disease or injury whereby one is behaviorally unaffected by pathology sufficient to cause dementia in someone with less cognitive reserve. The construct of cognitive reserve is discussed more fully elsewhere in this volume (see Chap. 2).

Functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow for the examination of blood flow and oxygenation to particular brain structures, in participants as they engage in cognitive tasks. Comparisons of older and younger adults reveal an increase in bilateral activation with age, whereby tasks associated with focal, unilateral activation in younger adults (e.g., verbal memory) become associated with bilateral activation in older adults [38, 39]. Further, bilateral activation in older adults is associated with *better* performance on cognitive tasks, including working memory, semantic learning, and perception [40–43]. This suggests that the older brain engages in more widely distributed compensatory processing by activating the contralateral hemisphere to achieve greater cognitive benefits [9].

Theories of Aging

In a process termed "dedifferentiation," sensory function (i.e., visual acuity and audition) has been shown to predict performance on a wide range of cognitive tasks in older, but not younger, adults [44, 45]. It has been proposed that abilities that are relatively independent earlier in life, such as sensory ability and cognition, become more interrelated with old age. Functionally, this can be thought of as a decrease in neural specificity, whereby regions that respond selectively in younger adults change to respond to a wider array of inputs in older adults. Similarly, in older adults, increased prefrontal activation is associated with decreased parahippocampal activation and hippocampal volume shrinkage [46, 47]. Whereas activation in the parahippocampal regions is associated with learning new material in younger and middle-aged adults, increased prefrontal activation is instead observed in older adults, suggesting greater frontal activity may be a compensatory mechanism for decreased mesiotemporal activation [9, 46].

Salthouse proposed the processing-speed theory of cognitive aging, which assumes that a wide range of cognitive task performances are limited by the imposed constraints on the speed of processing [19]. Slow processing speed dampens cognition in two ways: (1) cognitive operations are executed too slowly to be successfully completed in the available time and (2) the amount of simultaneously available information, necessary for higher-level processing, is reduced,

as early processing is no longer available when new processing occurs. Complex operations are most affected by slow processing speed since they are dependent on the products of simpler (and earlier) operations, and often, the accuracy of performance is dependent on the number of operations that can be carried out in a given time period (e.g., associations, rehearsals). The amount of simultaneously available information may also be reduced due to disruptions in the synchronization of neural signals and activation patterns [19].

The *scaffolding theory* of aging and cognition proposes that structural brain changes associated with aging are accompanied by effort on the part of neural networks to maintain homeostatic cognitive functioning in the face of these changes [9]. This leads to changes in brain function through "strengthening of existing connections, formation of new connections, and disuse of connections that have become weak or faulty" (p. 175). Scaffolding is described as the brain's "normal response to challenge" (p. 183), and the theory can be used to explain the process of acquiring a novel skill. The initially engaged neural networks shift from broad and dispersed to a specific and honed circuit of neural regions. While the more specific regions assume dominant control over functions, the initial broad networks continue to be minimally active, suggesting that they remain available for compensatory processing [46]. In the aging brain, scaffolding is thought to maintain healthy cognitive function in the face of neural degradation. These circuits can provide supplementary, complementary, or alternative ways to complete a cognitive task and are thought to reside largely within the prefrontal cortex, consistent with findings on overactivation of frontal networks with age [9]. Scaffolded networks, however, are less efficient and more prone to error than honed circuits, which are highly functionally interconnected. According to scaffolding theory, this results in the observable and measurable cognitive decline seen in older adults. The need for compensatory scaffolding exceeds the available networks, resulting in a more profound decline in functioning in the oldest old.

Individual Factors in Cognitive Aging

Given the considerable variation in cognitive performance in older persons, particularly in the oldest old, examination of individual difference factors related to the cognitive aging process is warranted [5, 6]. Factors shown to contribute to cognitive reserve or to be related to cognitive decline in clinical studies include education, occupational complexity, physical health, and diet [48]. It is suspected that cognitive reserve is represented biologically by a number of processes, including (1) richer interconnectivity and organization of neural circuits; (2) alterations in synaptic efficiency, marked by changes in neurotransmitter release, receptor density, and receptor affinity; (3) and changes in intracellular signaling pathways [48].

Physical health status is arguably one of the more important factors to consider when predicting performances on cognitive assessment in noncognitively impaired elderly. Clinical and subclinical medical disorders have been found to be better predictors of neuropsychological performance than chronological age, and these disorders include hypertension, hypercholesterolemia, obesity, and white matter lesions [49]. Cardiac arrhythmias [50], sensory loss [51], pulmonary function [52], and other measures of biological age [53] have also been associated with poorer cognitive functioning.

Higher education has been associated with preserved cognitive performance over time (i.e., less decline) in aging adults [54, 55], though not all research has supported this outcome [56]. Occupational complexity is shown to be related to relatively better cognitive functioning with age, above and beyond the benefits afforded by higher levels of education [57]. More specifically, cognitive ability in older adults was found to be related to the degree of complexity of one's work with people but not to occupational complexity with data or things [57]. In particular, participants who held jobs with high complexity of work with people demonstrated better cognitive performance on measures of verbal skills, spatial skills, and processing speed than participants with low occupational complexity with people.

No differences in memory performances were found. The cognitive benefit received from high occupational complexity ceased following retirement, suggesting that once these occupational skills are no longer being practiced, they fail to retain their effectiveness in bolstering cognitive ability.

Mild Cognitive Impairment

Defining Mild Cognitive Impairment

Neuropsychological referrals are often made on the basis of a patient's or their family's perceived (i.e., subjective) report of a decline in cognitive ability. An integral part of the neuropsychologist's role is to determine whether a patient's complaints or their family's observations of cognitive decline are due to the normal cognitive aging process or if they instead represent an objective impairment in cognitive functioning relative to the patient's same-age peers. The construct of MCI represents a decline in cognitive performance greater than would be expected for the person's age but not sufficient to meet criteria for a diagnosis of dementia [58]. Petersen described MCI as interposed between normal cognitive changes associated with aging and the very early stages of a dementing process [59]. It is therefore conceptualized as a pathological condition and not merely a manifestation of the normal aging process. Incidence and prevalence rates vary as a consequence of study details, including diagnostic criteria, assessment procedures, and sample characteristics (e.g., community versus clinic, age, education, gender, race, health comorbidities). Within the general population, prevalence rates have been found to range from 1% to 35% [60, 61].

The original criteria for MCI proposed by Petersen et al. [58] are as follows:

1. Presence of a memory complaint
2. Normal activities of daily living
3. Normal general cognitive function
4. Abnormal memory for age
5. Not demented

These criteria are particularly useful for patients who have impairment in the memory domain but intact cognitive performance and functioning in all other domains. Such patients would be labeled as having amnesic MCI (a-MCI). Revised criteria were proposed by a multidisciplinary, international group of experts, in light of the heterogeneity of MCI clinical presentations reflected in the literature [62]. For example, some patients have a primary impairment in the memory domain only, whereas others have memory impairment in addition to other domain impairment(s). Still others have impairments in single or multiple nonmemory cognitive domains. These heterogenous clinical presentations may have multiple etiologies, including degenerative, vascular, metabolic, traumatic, psychiatric, etc. [59, 62].

The most updated clinical diagnostic criteria for MCI are recommended by the National Institute on Aging and Alzheimer's Association workgroup [63]. The diagnostic criteria for MCI in a clinical setting are as follows:

1. Concern regarding change in cognition: There is evidence of concern for change in the patient's cognitive status as compared to his/her previous level. This concern may be on the part of the patient, an informant who knows the patient well, or from a skilled clinician who has observed the patient.
2. Impairment in one or more cognitive domains: There is evidence of lower performance in one or more cognitive domains that is greater than what would be expected for the patient's age and educational background. Impairment may be in a variety of domains, including memory, attention, language, executive function, and visuospatial skills.
3. Preservation of independence in functional abilities: The patient generally maintains his/her independence of function in daily life without considerable aids or assistance. However, patients may have mild problems performing complex functional tasks (e.g., paying bills, preparing meals, shopping), whereby they may be less efficient, take more time, and make more errors than in the past.

4. Not demented: These cognitive changes are sufficiently mild so that there is no evidence of significant impairment in social or occupational functioning. A diagnosis of MCI requires evidence of intraindividual change. If the patient has been evaluated only once, change will be inferred from the history and/or evidence that cognitive performance is impaired beyond what is expected for that patient. Practical application of these criteria will be considered below in the Assessment section.

Subtypes

We have already mentioned *single-domain amnesic MCI* (*a-MCI*), which is a useful category for patients who have impairment in memory but intact cognitive performance in all other domains and in daily functioning. As research on MCI has advanced to include cognitive impairment in domains other than memory, several other subtypes of MCI have been proposed [59]. Some patients display impairment in a single nonmemory cognitive domain (e.g., executive function) but perform normally in other domains, including memory. These patients would be given labels of single-domain non-amnesic MCI (na-MCI). Still other patients present with impairments in multiple domains while continuing to display relatively intact activities of daily living (ADLs) and general cognitive functioning; these patients would be classified generally as having multiple-domain MCI. More specifically, in the event that a deficit in memory is present, a patient is given a diagnosis of multiple-domain MCI with amnesia (md-MCI + a); if memory impairment is not evident, then a diagnosis of multiple-domain MCI without amnesia (md-MCI-a) is appropriate.

Etiology and Prognosis

In addition to different subtypes, there also are multiple etiologies for MCI. Petersen suggested four main etiologies: (1) degenerative (e.g., Alzheimer's disease), (2) vascular (e.g., cerebrovascular disease), (3) psychiatric (e.g., depression), and (4) traumatic (e.g., head injury) [59]. Of course, a host of other potential etiologies should always be considered in the differential diagnosis, including medication side effects and other toxic factors, metabolic factors (e.g., thyroid dysfunction, vitamin B12 deficiency), or infection. Particular subtypes of MCI are reported to be more commonly associated with certain etiologies. For example, patients with a-MCI are more likely to convert to Alzheimer's disease than patients with na-MCI [58, 64–66]. An impairment in episodic memory, i.e., the ability to learn and retain new information, is most commonly seen in MCI patients who later convert to Alzheimer's disease [63]. Additionally, a longitudinal decline in cognition provides additional evidence for a likely etiology of Alzheimer's disease [63]. Those with impairments in nonmemory domains such as executive function and visuospatial skills may be more likely to convert to dementia with Lewy bodies [59]. Persons with na-MCI in one study were least likely to convert to any form of dementia [63].

Follow-up data from the initial Petersen et al. study on MCI using patients (N = 220) from the Mayo Alzheimer's Disease Center/Alzheimer's Disease Patient Registry (ADC/ADPR) demonstrated a rate of progression from MCI to dementia of 12% per year [58, 59]. At a 6-year follow-up, approximately 80% of MCI patients in the same study were reported to have progressed to dementia. Other studies have found conversion rates of 10–19% per year from MCI to Alzheimer's disease [65, 67]. In comparison, 1–2% of the general population develop Alzheimer's disease per year, providing evidence that MCI places one at increased risk for future dementia above the rate that is expected for a person's age [58]. Persons diagnosed with a-MCI were found in one study to have a fourfold greater risk than noncognitively impaired individuals to develop Alzheimer's disease over a 2-year follow-up period [68]. When considering a general diagnosis of MCI (i.e., not taking into account subtype), patients are found to have a three times greater risk of developing Alzheimer's disease (average follow-up of 4.5 years) [69].

At the same time, however, many persons with MCI remain stable with this diagnosis or revert to normal. For example, in a clinical sample, 41% remained stable over an average 3.5-year follow-up, and 17% returned to normal cognitive status [70]. These data suggest that for some patients, MCI represents an intermediate point on the continuum from normal cognition to dementia, while for others, MCI is a transient period of cognitive decline that resolves with time. The latter may be seen in patients with reversible causes of cognitive dysfunction, such as metabolic abnormalities or substance use. Those with na-MCI are most likely to revert to normal or improve their cognitive status over time [64].

Pathophysiology and Neurodiagnostic Findings

Neuroimaging data lends further support for MCI as a unique diagnostic entity, separate from both normal cognitive functioning and dementia states. Retention of Pittsburgh compound B (PIB), used to image beta-amyloid plaques in neuronal tissue, has been examined using positron emission tomography (PET) in persons with normal cognition, MCI, and Alzheimer's disease (AD) [71]. In their study, Forsberg et al. found that PIB retention in MCI patients is higher than that of normal controls but lower than in AD patients. Additionally, the MCI patients who converted to AD within the 2–16-month follow-up period had higher mean PIB retention than the MCI patients who remained stable during follow-up periods. Magnetic resonance imaging (MRI) has been used to examine trajectories of volumetric brain loss in a healthy aging sample over a 15-year period [30]. Ventricular expansion was found to be faster in persons developing MCI years prior to the emergence of clinical symptoms. An increasingly rapid expansion occurred approximately 2 years prior to the clinical diagnosis of MCI.

Neuroimaging studies show that subjects who progressed to AD within an 18-month follow-up period had greater volume loss than a stable MCI group and a control group in areas consistent with volume loss in AD (i.e., medial and inferior temporal lobes, temporoparietal neocortex, posterior and anterior cingulate, precuneus, and frontal lobes) [72]. Autopsy studies reveal that subjects who died with a classification of a-MCI showed the early pathologic changes seen in subjects diagnosed with AD prior to death with greater density of temporal lobe neurofibrillary tangles [73–75]. Annual increase in ventricular volume as assessed by serial MRI has revealed the greatest volume increase in AD subjects, followed by an intermediate increase in a-MCI subjects, and the smallest change in cognitive normals. Further, a-MCI and AD subjects with APOE-ε4 genotype show the greatest increase in ventricular volume. These findings also correlate clinically with concurrent change in cognitive and functional status [76]. Specific and distinguishing MRI abnormalities also have been identified in MCI subjects who ultimately convert to AD, vascular dementia, and Lewy body dementia, lending support for MCI as a prodrome to multiple dementing processes [77].

Assessment

Referrals

Referrals for neuropsychological evaluation when MCI is a diagnostic consideration may come from a variety of sources. Neurologists are likely to be one of the most common referral sources, along with primary care physicians, psychiatrists, and self-referral (initiated either by the patient or a family member). One study of male patients with MCI receiving care at a Veterans Affairs hospital found that, generally, either patients or their families prompted the consultation for memory loss [78]. In many cases, patients may be seen first by neurologists who then provide a neuropsychological referral for a more comprehensive cognitive evaluation. Most typical referral questions from other medical professionals in the context of an evaluation for MCI will pertain to differential diagnosis and etiology. Typical differentials will include normal cognitive aging versus MCI versus dementia, as well as

Table 28.1 MCI differential diagnosis

Normal cognitive aging
Dementia (e.g., Alzheimer's, vascular, frontotemporal dementia, Parkinson's plus syndromes)
Depression/"pseudodementia"
Delirium
Other potentially reversible causes for cognitive dysfunction (e.g., metabolic abnormalities, substance use, obstructive sleep apnea, concussion)

depression or "pseudodementia" versus MCI or dementia. Etiology of cognitive impairment also is a common referring question and usually involves a question of Alzheimer's disease pathology versus other causes such as vascular cognitive impairment, frontotemporal dementia, a Parkinson's plus syndrome (e.g., Lewy body dementia, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration), or metabolic causes. Table 28.1 shows a list of common differential diagnoses for MCI. There are other associated issues that may be relevant to referring physicians, such as beginning an appropriate cognitive-enhancing medication or psychotropic drugs for treatment of mood disorders. The neuropsychological evaluation is often requested to serve as a baseline for subsequent serial evaluations in order to track the trajectory of cognitive decline or improvement following treatment. Assessment of functional independence may be requested based on cognitive testing, such as whether the patient is completely independent or requires in-home assistance as part of their daily functioning. Cognitive testing may also help form an opinion as to whether the patient may require a formal driving evaluation. Assessment of driving abilities is detailed elsewhere in this volume (see Chap. 15).

Clinical Interview

An important component of the clinical interview when assessing patients with MCI involves obtaining an accurate picture of the emergence of cognitive symptoms and any functional difficulties. For this reason, it is ideal to have a collateral informant present at the interview to provide his or her insight into the patient's behaviors and functional status. The informant is typically a spouse, child, sibling, or other close family member or friend who is knowledgeable about the patient's history and can provide information about changes in cognitive and functional status.

One of the diagnostic criteria of MCI is the presence of a subjective cognitive complaint. Patient complaints may be corroborated by the collateral informant, whereas in some cases, the friend or family member's report is the only evidence for subjective cognitive change. This may occur in cases where the patient has little to no insight into their cognitive changes. It is important to obtain a thorough history of the emergence of cognitive symptoms, including examples of cognitive problems the patient is experiencing in everyday life. For example, the early and prominent emergence of language symptoms may be indicative of a primarily aphasic dementing process, whereas early memory difficulties may signal mesial temporal lobe involvement, the area initially and primarily affected in Alzheimer's disease. Evaluating functional abilities also is essential when considering a diagnosis of MCI. Functional independence is the key factor in the differential diagnosis of MCI or early dementia. Patients with MCI are considered to have intact basic activities of daily living (ADLs), with predominantly intact instrumental ADLs. An assessment of functioning should include questions about the patient's ability to care for his or her basic needs, such as hygiene, dressing, and feeding oneself, as well as his or her more instrumental needs, such as making and keeping appointments, financial management, driving abilities, and medication management.

The patient and his or her informant should also be questioned about changes in behavior or personality, which are often early indicators of a primarily behavioral dementing process, such as frontotemporal dementia. Behaviors to consider include those indicative of apathy, disinhibition, perseveration, or behaviors that are out of the ordinary for the person. In addition, irritability often accompanies symptoms of cognitive decline. Patients should be questioned about

emotional symptoms and psychiatric history to assess for the presence or increase in symptoms of depression, anxiety, or other salient psychological problems. This is particularly important because approximately 35–75% of patients with MCI endorse at least one neuropsychiatric symptom at a prevalence rate that is higher than same-age non-MCI peers [79–82]. The most commonly endorsed symptoms include depression/dysphoria, apathy, anxiety, and agitation [83, 84]. Commonly reported symptoms of depression in MCI include poor concentration, inner tension, pessimistic thoughts, lassitude, reduced sleep, thoughts of death, inability to feel, and reduced appetite [85]. There is some evidence for higher rates of depression in a-MCI versus na-MCI and in multiple-domain MCI versus single-domain MCI patients [79, 83]. Given evidence for elevated rates of mood symptoms in persons with MCI, it is imperative that patients are screened for clinical and subclinical symptoms of depression, anxiety, apathy, and irritability.

The clinician should obtain a thorough medical history and assessment of the patient's current health status. Results should be obtained from any completed neurodiagnostic studies (e.g., MRI, CT, EEG) for consideration in the differential diagnosis. Evaluating the presence of vascular risk factors such as hypertension, hypercholesterolemia, and diabetes is essential when considering etiology of cognitive decline. An assessment of the patient's sleep quality is important, including whether he or she has been diagnosed with sleep apnea, which has known effects on executive cognitive functioning, vigilance, and memory [86, 87]. A review of the patient's current and recent medications is also critical in order to consider medication-induced cognitive changes. It is important to obtain not only a list of the patient's medications but also a careful chronology of when each potentially psychoactive medication was introduced in relation to the chronology of cognitive symptom emergence. A review of the patient's use of recreational substances is necessary to rule out preventable causes for cognitive changes. Finally, family history of dementia should be assessed, including approximate age of onset of cognitive difficulties in family members.

Functional Impairment

In assessing whether ability to carry out activities of daily living (ADLs) is essentially normal (a diagnostic criterion for MCI), a thorough history from the patient (and ideally an informant) should be obtained. Self-report or clinician-administered ADL scales can also be employed but do not replace a careful detailed interview, since many of the ADL scales do not pick up on subtle changes in functioning. Petersen noted that minor inconveniences in a patient's daily functioning may be present, but they are not sufficient in severity to constitute a major disability in functioning [59]. Patients with MCI tend to report some degree of decline in their ability to handle daily tasks, whereby they feel they are more forgetful, are less able to multitask, and have difficulties with planning and organization [88]. These inefficiencies can manifest in a variety of ways, such as problems remembering where one has placed objects, forgetting new names, difficulty completing two tasks at once, and trouble remembering shopping items, recalling conversations, or prioritizing tasks by importance. It is often the ability to learn, retain new information, and perform higher-order executive skills that is dampened in persons with MCI, resulting in somewhat less efficient daily functioning [88–90]. Persons with MCI tend to make errors in performing tasks accurately and efficiently while still remaining able to complete tasks [91]. This is in contrast to dementia patients, who tend to also make these errors in addition to omitting major portions of tasks.

Poorer memory performance on cognitive testing has been found to predict future difficulties in financial management in patients with MCI, and impaired memory and psychomotor speed are the cognitive domains most strongly related to functional abilities [92]. Other research suggests that attention and executive functioning, but not memory, are associated with difficulties

managing multiple-step financial tasks, such as bill payment and preparation and management of bank statements [93]. Persons with MCI tend to show subtle functional declines in driving abilities when compared to noncognitively impaired persons, though their overall performances are not at the level of frank driving impairments [94]. Instead, they are less likely than their cognitively normal peers to perform certain driving routines seamlessly (e.g., left-hand turns, maintaining lane control), and their performances are more often rated as "less than optimal." Although some dampening in functioning is observed in MCI patients, it is much less severe than the functional decline seen in patients with dementia. MCI patients tend to perform functionally on a level intermediate between persons with normal cognition and dementia patients [91]. MCI patients are still able to function independently, albeit perhaps less efficiently and with the use of compensatory strategies.

Cognitive Impairment

Criteria for diagnosing MCI include not only self- or family report of cognitive decline but also objective measurements of deficits in cognitive functioning. An exact cutoff for what constitutes "mild" impairment has not been set in stone, but traditionally, a cutoff score of 1.5 SD below age norms has been used based on Petersen et al.'s original study [58]. In that study, the MCI group performed, on average, 1.5 SD below age-matched controls. However, Petersen emphasizes that this was not intended to serve as a cutoff score and that it is ultimately left up to clinician judgment whether or not a patient displays objective memory impairment relative to his or her baseline [59]. The most recent consensus criteria note that scores on cognitive tests for patients with MCI are typically 1–1.5 SD below the mean for age- and education-matched peers on culturally appropriate normative data [63]. It is emphasized that these ranges are to be used as guidelines and not cutoff scores.

Selecting neuropsychological instruments for evaluating MCI should include an evaluation of the patient's performance in all major cognitive domains (i.e., memory, attention, processing speed, language, executive functioning, visuospatial skills, motor functioning) in order to ensure a comprehensive assessment. Typically, a dementia screening measure is also administered and ideally an estimate of premorbid functioning (e.g., word reading). A comprehensive assessment approach that employs detailed neuropsychological assessment is advocated to improve the reliability and stability of the MCI diagnosis [95]. Although all major neurocognitive domains should be validly sampled, it is of particular importance to obtain multiple measures of memory, as this domain is typically the presenting subjective complaint and is essential for differential diagnosis. Because there are multiple possible etiologies of MCI, it would be inappropriate to focus only on memory testing and a global screening measure. Assessment of other areas, including executive, attentional, and motor abilities in assessing for a vascular etiology, as well as visuospatial functioning in assessing for Lewy body pathology, allows for the most comprehensive approach to determining etiology, a common referral question. Careful examination of memory profile patterns is also helpful in this regard. Given that a significant proportion of MCI patients present with neuropsychiatric symptoms, it is important to also include self-report measures of mood functioning, such as assessments of depression and anxiety symptoms. Table 28.2 provides a sample test battery for a comprehensive neuropsychological evaluation when MCI is considered in the differential diagnosis. Other measures and test batteries may be chosen, but the guiding principles of test selection should be comprehensive sampling of cognitive domains, appropriate norms for age and other patient demographic factors, and wide range of measurement between the floor and ceiling captured by the measures, and whenever possible, measures with alternate forms for retesting over time should be used.

Table 28.2 Sample core neuropsychological battery for assessment in MCI

Mini-Mental State Exam [96]
Repeatable Battery for the Assessment of Neuropsychological Status [97]
Wechsler Adult Intelligence Scale IV [98] or Wechsler Abbreviated Scale of Intelligence [99]
Wide Range Achievement Test 4 (Reading subtest) [100]
Trail Making Test A and B [101]
Stroop Color-Word Test [102]
California Verbal Learning Test II [103] or Hopkins Verbal Learning Test—Revised [104]
Rey Complex Figure Test [105, 106] or Brief Visuospatial Memory Test—Revised [107]
Wechsler Memory Scale III (Logical Memory) [108]
Boston Naming Test [109]
Controlled Oral Word Association [110] and Semantic Fluency (i.e., Animal Fluency) [111]
Wisconsin Card Sorting Test [112]
Clock Drawing and Copy [113]
Finger-Tapping Test [114]
Grooved Pegboard [115]
Geriatric Depression Scale [116] *or* Beck Depression Inventory, Second Edition [117]
State-Trait Anxiety Inventory [118]

Common Neurocognitive Deficits

The most common neuropsychological impairment seen in MCI patients who ultimately convert to Alzheimer's disease is a decline in episodic learning and memory early in the disease process [119, 120]. This is thought to be consistent with early involvement of structures in the medial temporal lobes (e.g., hippocampus, entorhinal cortex) in the progression to Alzheimer's disease (AD). Memory profile patterns in a-MCI tend to display reduced learning, rapid forgetting, poor recognition discrimination, and elevated intrusion errors [119, 121].

In terms of overall cognitive profiles, MCI patients have been found to show clearly defined memory impairments with only mild impairments in other domains, such as executive functioning [122, 123]. While a-MCI patients may show some difficulty in planning and problem-solving, md-MCI patients show the most severe impairments [124]. It is unclear whether md-MCI patients' cognitive profiles are more impaired due to different disease etiologies (e.g., vascular) or whether differences are due to md-MCI patients being further along in the disease process.

Although visual confrontation naming impairment is a hallmark symptom of AD, patients with a-MCI have not been found to differ from controls on such tasks, suggesting that the breakdown in semantic knowledge does not typically occur at the MCI stage [125]. At the same time, however, MCI patients have been shown to have poorer performance than controls on tasks of semantic memory, receive less benefit than controls when semantically cued on memory tasks, and use less semantic clustering strategies on verbal learning tasks [69, 126, 127]. It may be the case that these deficits in semantically related learning are due at least in part to dampened executive functioning processes that affect categorization or semantic organization [128].

In the attention domain, MCI patients who ultimately convert to AD demonstrate poorer immediate serial recall and divided attention than their MCI counterparts who remain cognitively stable [129]. This subgroup demonstrates the early stages of attentional impairment seen in AD, suggesting that such attentional impairments slowly decline over the course of the disease.

Vascular MCI has been less extensively studied in the research literature, though data suggest that patients with vascular disease or significant vascular risk factors demonstrate poorer attention, executive function, visuospatial performance, and slower processing speed than patients without vascular risk factors [130, 131].

Diagnosing MCI Subtypes

Once a diagnosis of MCI is established based on diagnostic criteria, selecting an MCI subtype is based on the results of the neurocognitive profile. In amnesic MCI (a-MCI), there is a single deficit in the learning and memory domain with

preserved cognitive functioning in all other domains. Other patients have impaired learning and memory in addition to impairment in another domain (oftentimes, executive functioning, but any other domain is possible), and these patients would receive a diagnosis of multiple-domain amnesic MCI (md-MCI + a). Patients who have a single nonmemory domain impairment (again, often executive dysfunction or attention/processing speed) are given the diagnosis of non-amnesic MCI (na-MCI). A subset of patients demonstrates impairment in two or more nonmemory domains and would be diagnosed with multiple-domain non-amnesic MCI (md-MCI-a).

Feedback and Recommendations

When reporting a diagnosis of MCI to a patient and possibly his or her family members, it is important that the clinician clearly explain the nature of the MCI diagnosis. Important information to highlight includes the degree of cognitive impairment associated with the diagnosis (i.e., greater than normal for the patient's age but not severe enough to warrant a diagnosis of dementia). Equally important to convey sensitively is the patient's increased risk for converting to dementia in the future, particularly for patients given an amnesic MCI diagnosis (single or multiple domain), which has the greatest association with future conversion to dementia, typically Alzheimer's disease [64, 68]. Patients should be made aware of their particular areas of difficulty (e.g., memory, executive functioning) and the real-world implications for these deficits. At the same time, cognitive and other personal strengths should be highlighted in the context of developing compensatory strategies for dealing with objective cognitive deficits and the functional difficulties that often accompany such deficits. If a-MCI is diagnosed, given its heightened association with a progression to Alzheimer's dementia, retesting may be recommended in 1 year. For other types of MCI, it may be more appropriate to recommend retesting as clinically warranted, if further cognitive changes are suspected by the patient, family, or referring clinician.

Useful information for clinicians disclosing an MCI diagnosis, including the meaning and impact for the patient, can be gleaned from a unique analysis of qualitative interview data from a small clinical sample of MCI patients ($N = 12$, diagnosed 3–6 months prior) [132]. The authors examined patient's experiences of living with and making sense of an MCI diagnosis. Interestingly, over 40% ($n = 5$) of their sample used positively valenced words to depict their emotional reactions to the diagnosis. Narrative accounts typically revealed satisfaction in finding professional validation for their subjective symptoms, as well as relief associated with a negative dementia diagnosis. Given evidence that MCI often is a precursor for dementia, this raises the issue of whether patients with MCI are adequately explained their increased risk of developing dementia in the future. Only 2 of 12 participants expressed a negative reaction to their diagnosis, and this occurred in the context of a perceived looming dementia diagnosis. Several participants did mention awareness of the possibility of further decline in cognitive status, often in the context of being unsure whether a decline would occur. Oftentimes, a current state of relief occurred simultaneously with tension surrounding an uncertain dementia prognosis. Around half of the participants related MCI as part of the normal aging process. Taken together, these findings suggest that there are varying interpretations of an MCI diagnosis, which the investigators pointed out have the potential to impact health behaviors, including returning for follow-up cognitive testing or planning for future states of decisional incapacity.

Recommendations for patients diagnosed with MCI may include follow-up with the patient's neurologist or psychiatrist to discuss potentially beginning a trial of anti-dementia medication, such as an acetylcholinesterase inhibitor. If the patient does not already have established medical care within these specialties,

an appropriate referral should be made, particularly if baseline neurodiagnostic studies (e.g., MRI, EEG) have not yet been completed. Management of risk factors associated with cognitive decline, such as medical comorbidities (e.g., vascular risk factors such as hypertension, diabetes, hyperlipidemia, sleep apnea, metabolic levels), should be recommended. Similarly, patients should be encouraged to participate in a physician-approved exercise regimen and maintain a healthful diet. Numerous studies have documented improvements among MCI participants in terms of cognitive abilities (particularly executive functioning), as well as decreased levels of pro-inflammatory cytokines and other neurodegenerative biomarkers. Moreover, research indicates that consumption of a healthy diet, including a Mediterranean-based diet, may prevent initial development of MCI symptoms and may also prevent conversion of MCI to AD [133–135]. Given that mood factors can exacerbate symptoms of cognitive impairment, appropriate monitoring of depression, anxiety, or other psychological factors is necessary. In some cases, a psychiatric or psychotherapy referral is warranted to assist in managing symptoms pharmacologically or cognitively/behaviorally. Patients should be encouraged to remain cognitively and socially active and to continue to complete daily tasks as independently as possible.

In terms of functional abilities, it is important for patients and their families to continuously monitor functional status, particularly with regard to potentially dangerous tasks such as driving. A change in functional status may be the simplest way for families of patients with MCI to recognize advancing cognitive decline, and they should be encouraged to assist the patient in monitoring instrumental activities of daily living (IADLs) such as financial management, driving, medication management, and higher-level organizational abilities. A decline in the ability to manage and perform IADLs is likely to represent a concordant decline in cognitive status and may alert the patient and family that neuropsychological reevaluation is warranted to assess for progression to a dementia syndrome.

With regard to neuropsychological retesting, it is difficult to establish a universally appropriate time for follow-up evaluation. Whereas a significant proportion of MCI patients will ultimately convert to dementia, many will also remain stable with the diagnosis or will revert to normal, depending on etiology. In those patients who ultimately receive a dementia diagnosis, the course of cognitive decline may be quite variable, with some patients remaining in the MCI category for years after initial evaluation and others converting to dementia rather rapidly. Patients present for their initial neuropsychological evaluation at various points on the continuum, further complicating an estimate for possible dementia conversion. Two points of reference can be helpful in determining a follow-up evaluation: (1) the severity and number of domains impaired and (2) the patient's functional status. It is likely that patients with relatively more severe cognitive impairments are further along in their disease progression and patients with multiple impaired domains may reach a dementia diagnosis sooner. Similarly, patients who show relatively greater impairment in daily functioning may be closer to a dementia diagnosis. Perhaps the safest benchmark for retesting is a 1-year follow-up period, in conjunction with the recommendation that the patient return for testing earlier should he or she (or family members) notice a significant decline in cognitive ability or functional status prior to the 1-year mark.

In conclusion, accurate clinical discrimination between normal cognitive aging and MCI is an important diagnostic challenge. This discrimination will become increasingly critical as new interventions are developed to target the very earliest manifestations of incipient brain disease.

Clinical Pearls

- A significant proportion of MCI patients will ultimately convert to dementia, although many will remain stable or will revert to normal, depending on the etiology of the cognitive disturbance.
- The most recent consensus criteria indicate MCI is associated with cognitive test scores that are typically 1–1.5 SD below the mean for age- and education-matched peers; it is emphasized that these ranges are to be used as guidelines, *not cutoff scores*.
- Although memory complaints of some kind are typically the most common presenting reason for evaluation, it is important to carefully assess the nature of the complaint since other aspects of cognition may actually underlie the perceived deficit.
- Assessment of mood/personality functioning is critical since subjective memory complaints tend to be more strongly correlated with negative affect than with objective memory performance.
- In addition to taking a general medical history, be sure to inquire about pain, sleep, and substance use in the context of the cognitive complaints.
- Assessing impact on activities of daily living (ADLs) requires careful clinical judgment. Be certain to clarify how ADLs are impaired by *cognitive* factors as opposed to physical or emotional factors. Ask the collateral source if the patient would still be *capable* of performing activities (e.g., driving, managing finances) that other family members are conducting.
- Memory complaints such as forgetting what you went into a room for or difficulty recalling names are common in older adults and may not be clinically significant. However, collateral reports suggesting repetitive speech/questioning or trouble navigating a familiar environment are more likely to be clinically relevant.
- The examiner should get the patient's consent to obtain collateral information from a well-known source. The congruence, or lack thereof, between patient self-report and collateral report is clinically informative in terms of lack of insight/awareness of deficits or a tendency to amplify complaints

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Assessment of Alzheimer's Disease

29

Rosie E. Curiel, Arlene Raffo, and David A. Loewenstein

Introduction to Neuropsychological Assessment

The human brain is comprised of an estimated 40–100 billion neurons with trillions of interconnections, easily making it the most complex organ in the human body [1]. Neuropsychology is the formal study of brain-behavior relationships. The clinical neuropsychologist seeks to assess the integrity of the brain's functions through the use of sensitive tests that measure a wide array of cognitive abilities and functional capacities that can provide information about the individual's strengths and weaknesses in executing the complex demands that are encountered in the real world. In addition, the impact of psychological distress on cognition and behavior is also of great interest to a neuropsychologist; thus, a neuropsychological evaluation often entails a careful assessment of an individual's psychological state.

All human behavior is directed and influenced by the brain; however, cognitive performance may be affected by other factors, including the integrity of sensory systems, as well as fatigue and motivation [2]. There are many reasons for poor cognitive performance including low educational attainment, anxiety or depression, lack of effort, the effects of medical conditions, and the influence of different medications [2]. One of the primary challenges when interpreting neuropsychological tests is to identify other variables that may have impacted cognitive performance.

As with all assessment, it is essential to keep in mind the reason for the evaluation. In general, there are five primary purposes to perform a neuropsychological assessment which include (1) to provide objective data that can determine the presence or absence of cognitive impairment, (2) to tap a broad array of cognitive domains (i.e., memory, language, attention, executive function, visuospatial abilities) that can be related to the integrity of brain function, (3) to provide evidence supporting the presence or absence of different neurological or neuropsychiatric conditions, (4) to serve as a baseline by which to monitor treatment effects, and (5) to assist in developing plans for management of care and treatment strategies.

The complexity of establishing brain-behavior relationships is one of the reasons that clinical neuropsychologists are required to have doctoral-level training in brain anatomy, cognitive neuroscience, as well as psychometrics. Neuropsychologists also require an extensive knowledge base of clinical and abnormal psychology and psychiatry to rule out the influences of many different conditions on behavior. For these reasons, advanced postdoctoral clinical

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training is required well beyond general doctoral-level training and coursework.

The neuropsychological assessment of the older person can be particularly challenging. Normal age-related changes in cognition occur over time, which must be differentiated from cognitive deficits that signal pathological brain changes that can lead to dementias such as Alzheimer's disease (AD). In general, crystallized intelligence, which includes general fund of knowledge, language usage and syntax, as well as vocabulary, remains relatively stable as a person ages [3]. Information processing speed, reaction time, and activities requiring more fluid processes such as novel, complex problem-solving may diminish with age [2, 4]. In addition to normal age-related cognitive decline, there are also expected changes with auditory and visual acuity that accompany aging and make it more difficult for the older adult to process information in their environment. Finally, older age is associated with an increase in medical conditions that may influence cognition, as well as the use of more medications to manage both chronic and acute conditions [2]. Against this backdrop, the clinician who is evaluating the older adult needs to make a determination as to whether an obtained pattern of results is indicative of brain impairment or, instead, represents the single or combined influences of many other factors.

A Focus on Alzheimer's Disease

Alzheimer's disease (AD) is a devastating illness, affecting over 5.5 million adults in the United States. Worldwide, an estimated 46.8 million people have Alzheimer's disease or a related dementia [5], and only one in four people has been diagnosed. The costs of caring for patients with Alzheimer's disease in 2016 was estimated to be $236 billion dollars [6]. Given the aging trend, accurately diagnosing AD has become the focus of growing clinical research since the prevalence of this disorder is expected to nearly double to 71 million by 2030 and has been forecasted to reach epidemic proportions if no cure is generated [7].

Overview of the Neuropathological and Clinical Course of Alzheimer's Disease

Alzheimer's disease (AD) was first discovered in 1906, but the causes of this devastating disorder were not better understood until recently. The characteristic neuropathology of AD is the presence of senile plaques and neurofibrillary tangles upon autopsy. It is thought that plaque formation in AD begins with the abnormal deposition of a protein called beta-amyloid (Aβ) which causes toxic amyloid fibrils up to 20–30 years before any clinical symptoms are manifested. These abnormal proteins continue to aggregate, particularly in the frontal lobes, anterior cingulate and posterior cingulate cortices, precuneus, and striatum until the burden results in a cascade effect that leads to difficulties with the phosphorylation of the microtubule-associated protein (MAP) tau which results in neurofibrillary degeneration [8] and can be visualized as neurofibrillary tangles. These changes lead to synaptic disruption and neurodegeneration of brain structures such as the hippocampi and the entorhinal cortices that can eventually be visualized early in the disease process as atrophy on structural magnetic resonance imaging (MRI).

Because of early neurodegeneration in medial temporal lobe structures, the first clinical manifestations of AD are typically seen as the disruption of short-term memories. As the disease progresses, there are typically more pronounced memory difficulties evidenced by misplacing possessions, forgetting appointments, repetitive conversations, and worsening ability to recall recent events. The patient may begin to have difficulties with word finding, may get lost while driving, and begin to evidence problems with judgment. This reflects the increasing involvement of the cortical regions of the brain such as the frontal, temporal, and parietal lobes. Over time, the patient becomes less able to manage their affairs and loses greater ability to perform activities of daily living at their usual level. The progression of the illness is quite variable from several years, to as many as 20 years, but eventually leads to total disability and eventual death [1].

At the present time, there is a reluctance by some to seek early evaluation given that present treatments for Alzheimer's disease, such as cholinesterase inhibitors, are merely palliative and do not treat the underlying pathology of AD. However, a recent advance in knowledge suggests that emerging treatments will be most effective in the earliest stages of AD before the advent of multi-system degeneration [9]. Moreover, accurate diagnosis can ensure that the patient and family receive proper counseling and advice to better manage their lives and plan for the future. Conversely, neuropsychological methods can help reassure persons with unimpaired cognitive function and can provide a valuable baseline to compare future results for those at risk. Finally, there are a number of conditions that may mimic the symptoms of AD where neuropsychological assessment can be an important part of differential diagnosis.

Clinical Diagnostic Criteria for Alzheimer's Disease

The clinical diagnosis of probable AD offered by the NINCDS-ADRDA [10, 11] was updated in 2011 when a working group was established by the National Institute on Aging (NIA) and the Alzheimer's Association to revise and update the 1984 diagnostic criteria for AD. The working group ensured the revisions would be pragmatic for use by all levels of practitioners, without mandating access to neuropsychological testing, neuroimaging, or biomarkers to diagnose. Generally, this task force retained the overall structure of "probable AD dementia" from the 1984 criteria convened by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [10, 11], which required (a) memory impairment and impairment in at least one other cognitive domain, (b) dementia as evidenced by impairment in social and/or occupational function, and (c) ruling out any other possible causes of the dementia syndrome. However, on the basis of modernized biological knowledge and findings, empirically documented progressions were made to the 1984 diagnostic criteria. Seven key areas were updated to reflect current knowledge of the biology and clinical indicators of AD. The first update reflects the histological pathology of AD, which is now understood to encompass a comprehensive clinical spectrum including those with mild cognitive impairment (MCI), those with dementia, and even the cognitively healthy. The second revision updated the current knowledge base of distinguishing features of other dementia typologies such as dementia with Lewy bodies [12], vascular dementia [13], frontotemporal dementia [14], and primary progressive aphasia [15]. The third point discusses the necessity of combining biomarkers such as magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, and cerebrospinal fluid (CSF) in differential diagnoses by clinicians. Recognition that memory is not always the prominent feature in every case of AD represents the fourth key update. The fifth change of the 1984 criteria addressed the abundance of genetic testing and data available for previewing. Specifically, three gene mutations were implicated to cause early-onset heritable AD: amyloid precursor protein, presenilin 1, and presenilin 2 [16, 17]. The sixth point recommended updated age cutoffs for the diagnosis of AD dementia. Two decades of research has concluded the AD process in an older individual is the same process for those less than 40 years of age with early onset, although the latter is more likely to have a family history and genetic risk factors [18]. The last key revision addressed the wide-ranging heterogeneity of a "possible" AD dementia type. Under current research, this diagnosis would include those individuals who are considered to have mild cognitive impairment [11]. Subsequently, the committee proposed classification criteria for the AD-type dementia as the following: (1) probable AD dementia, (2) possible AD dementia, and (3) probable or possible AD dementia with evidence of the AD pathophysiological process. It was the committee's intentions that the first two would be used in clinical settings, with the latter applicable for research purposes [11].

The *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) was published in 2013 and is the current standard for clinical diagnoses in the United States. The DSM-5 uses the following terminology for dementia due to Alzheimer's disease: major or mild neurocognitive disorder due to AD. To meet criteria for a major neurocognitive disorder due to AD, one must meet the general core criteria for a major or mild neurocognitive disorder and portray an insidious onset and gradual progression in at least two or more cognitive domains. A diagnosis of probable AD is given if evidence of a contributory AD genetic mutation from familial history (from genetic lab results) is specified. Alternatively, probable AD is justified if all three of the following criteria are present: evidence of a decline in memory and learning with a decrease in at least one other cognitive domain; proof of a gradual, progressive decline without any gaps; and no evidence of comorbid etiology. If the three clinical symptoms are not present or there is no evidence of genetic mutation, then possible AD should be diagnosed [19]. The DSM-5 criteria parallel the recommendations of the NIA and the Alzheimer's Association working group.

Neuropsychological assessment is recommended as a means of confirming the presence of different cognitive deficits. While the accuracy of the clinical criteria for probable AD generally exceeds 85% in most specialized memory disorders centers, a final diagnosis of the disorder can only be rendered upon examination of the density of senile plaques and neurofibrillary tangles upon autopsy [9].

In the neuropsychological assessment of AD, there is nothing more important than establishing the presence or absence of cognitive impairment, which can be related to the integrity of specific brain systems. In cases where an individual is moderately or severely impaired, the clinical assessment is less ambiguous, and the clinician is able to arrive at a clinical impression without substantial testing. However, there are a significant number of cases where the cognitive deficits can be quite mild and even difficult to detect by experienced clinicians. Persons with high cognitive reserve, for example, can employ other cognitive and brain resources to mask any overt deficits. It is not uncommon to see family members completely unaware of the substantial cognitive deficits that are only uncovered by a comprehensive neuropsychological evaluation.

Mild Cognitive Impairment (MCI)

It has been increasingly recognized that the clinical manifestations of Alzheimer's disease (AD) occur well before the manifestation of a dementia syndrome and a clinical diagnosis of the disorder. Petersen [20–22] coined the term mild cognitive impairment (MCI) as an intermediary state between a normal cognition and dementia. The criteria for MCI are as follows:

(a) Subjective memory complaint made by the patient or preferably a knowledgeable informant
(b) Objective evidence of memory impairment confirmed by neuropsychological testing, typically 1.5 SD below expected levels
(c) Intact intellectual functions and global mental status as defined by an MMSE score of 24 or above
(d) No sufficient cognitive impairment to cause significant impairment in social and/or occupational function

Implicit to this characterization was the notion that amnestic difficulties do not represent a static state of affairs, but rather reflect a decline from premorbid levels of function that heightens the probability of progression to probable AD [21]. In clinical settings, the rate of progression from amnestic MCI to dementia was 10–15% per year [20, 21, 23, 24] with 100% subjects diagnosed with MCI found to progress to dementia over a 9.5-year period and 84% receiving a neuropathological diagnosis of probable AD [25]. In contrast, the progression to dementia among subjects with MCI is considerably less in community settings where the base rates of MCI are lower [9, 26].

Subsequently, Petersen [22] proposed that MCI did not have to be confined to only an amnestic impairment but could also be defined by non-memory impairments. Different types of MCI included amnestic MCI single domain, amnestic MCI multiple domains, non-amnestic MCI single domain, and non-amnestic MCI multiple domains. The degree of impairment for both amnestic and non-amnestic measures is associated with the likelihood that individuals with MCI will progress to dementia, versus reverting to a normal state over time [27]. Alexopoulos et al. [28] found that 25% of subjects with amnestic MCI, 38% of subjects with non-amnestic MCI, and 54% of individuals with mixed amnestic and non-amnestic impairment progressed to dementia over a 3.5-year follow-up period. Roundtree et al. [29] found no differences in the rates of progression between those with amnestic MCI (56%) and those with non-amnestic MCI (52%) over a 4-year follow-up. Manly and associates [30] found that impairment in more than one cognitive domain was most predictive of progression to dementia over a 4.5-year period. In a more recent study, Loewenstein and associates [27] showed that those with multiple memory impairments, multiple non-memory impairments, or a combination of non-memory impairments had a much greater likelihood that their deficits would remain or progress over a 2- to 3-year period. Those with the greatest likelihood of progression to dementia included the multiple memory impairment group, followed by the mixed memory and non-memory group. Subsequent longitudinal studies have also shown that persons diagnosed with MCI multiple domain have a much greater likelihood of progression to dementia [31].

In 2011, Dr. Marilyn Albert and colleagues, along with the NIH and the Alzheimer's Association, led a working group to gather a consensus understanding for the diagnosis of the pre-dementia phase of AD, defined as mild cognitive impairment (MCI) due to AD. Further refinement of MCI due to AD is considered critical to further our understanding of the early subtle symptoms inherent to AD and to integrate them into clinical and research practices [32].

The Clinical Neuropsychological Interview

A key element of a comprehensive neuropsychological assessment is a detailed clinical interview with the patient and a collateral informant who is very familiar with the patient's activities of daily living. It is generally most effective to interview the patient and the caregiver separately so that they feel free to speak honestly about their concerns. Many informants, particularly spouses and children, are reluctant to share sensitive information about cognitive and functional deterioration in front of their loved ones. The informant may be particularly reluctant to disclose information in front of a patient who is in denial about their symptoms or who tends to react negatively to any suggestion of impairment.

During the clinical interview, it is important to initially gather information about the current cognitive difficulties experienced by the patient. It is especially helpful to determine whether the symptoms that are reported are primarily associated with loss of memory or whether they also represent language, executive, attentional, or visuospatial disturbances. Most individuals with early Alzheimer's disease have recent memory deficits but remain able to recall information from the distant past. This is related to the disease's predilection to affect the medial temporal lobules, specifically in the hippocampal and entorhinal cortices, which interfere with the storage and consolidation of new information.

While memory impairment is a hallmark feature of the disease, individuals may initially present with deficits in other cognitive domains, namely, language, visuospatial, and executive functions. Sometimes, the cognitive symptoms of AD will first become apparent in the face of stressful life events which tax an individual's cognitive reserve (e.g., the loss of a loved one, physical illness, depression). These underlying symptoms may abate with time as the person marshals cognitive resources to compensate for these deficits or as these stressors are no longer present. Unfortunately, the neurodegenerative process continues to progress to the point where successful compensation is no longer possible.

Occasionally, the first deficits exhibited by patients with AD (particularly those 70 years or younger) will be characterized by a language disturbance, such as a reduced ability to retrieve words. Some patients present with primary deficits in judgment, reasoning, and other aspects of executive function. In younger patients, when the predominant symptoms are language and executive dysfunction (such as disinhibition), the clinician must consider the possibility of a frontotemporal dementia versus AD. On the other hand, diffuse Lewy body disease must be considered if there are predominant concerns of impaired attention, cognitive slowing, visuospatial disturbance, and executive dysfunction, particularly in the presence of parkinsonian features, psychiatric disturbances such as visual hallucinations, and/or rapid eye movement (REM) behavior sleep disorders. REM sleep disturbances are evidenced by dream-enacting behaviors such as punching, kicking, or jumping while asleep.

It is also critically important to determine whether there has been a sudden onset of cognitive symptoms (often observed in vascular or other non-AD neurological disorders) or whether the cognitive disorder has a slowly progressive course with a gradual worsening of symptoms that is typically seen in AD. While the clinical interview often begins with open-ended questions so that the clinician can obtain as much information in the patient's and caregiver's own words, there are often a follow-up series of questions (listed in Table 29.1) that can be helpful in elucidating the exact nature of cognitive symptoms.

The clinical interview allows the examiner to ascertain the premorbid function of the patient, determine the nature and extent of cognitive decline, and determine the extent to which observed deficits interfere with social and/or occupational functions. It also provides an opportunity to determine the effects of anxiety and depression on the patient's functioning and also to assess the effects on cognition that are caused by medical conditions and/or current medications. The clinical interview also provides an opportunity to determine the effects of premorbid factors such as learning disabilities, attention deficits, a lack of formal education, and previous or current behaviors that might affect cognitive performance such as alcohol and drug abuse. The general importance of the clinical interview is that it provides a context in which to view and interpret neuropsychological findings.

Table 29.1 Questions that help elucidate cognitive symptoms

1. Does [patient] have difficulties remembering recent events (i.e., conversations, activities)?
2. Is [patient] misplacing possessions?
3. Does [patient] have trouble remembering the names of familiar persons, or does he/she often forget the names of persons recently met?
4. Does [patient] get lost while driving, become lost in a public place, or get lost even in their own neighborhood?
5. Is there repetitive questioning?
6. Is there a decline in [patient] ability to drive, operate a computer, or use common household objects?
7. Does [patient] have difficulty finding the correct word or words in free speech?
8. Is there a decline in [patient's] ability to understand what he/she has read in a newspaper, magazine, or book?
9. Does [patient] have difficulties remembering what was seen on television or the movies?
10. Have cognitive issues caused [patient] to withdraw from their usual activities such as work, playing cards, or social clubs?
11. Has there been any changes in [patient's] ability to manage their finances (i.e., write a check, balancing a checkbook)?
12. Has [patient] increasingly demonstrated poor judgment in work and social situations?
13. Has there been a change in personality (disinhibition, ability, apathy)?

Neuropsychological Assessment of Preclinical AD and Dementia

The most sophisticated neuropsychological batteries assess different aspects of neuropsychological functioning at baseline and ensure that their measurements have sufficient range to longitudinally track changes across different cognitive domains. The optimal neuropsychological battery assesses (1) learning and retentive memory, (2) executive functioning, (3) language, and

(4) visuospatial skills. It is also beneficial to have measures of attention and processing speed, as these are frequently impaired by a variety of brain disorders and may serve as a more general marker of impairment.

Identifying individuals who are at risk for Alzheimer's disease (AD) early on in the AD continuum is essential for the development of preventive and early targeted therapeutics that can be administered before the brain has been significantly compromised. Detecting cognitive changes is critical because cognitive changes are used to detect and track disease progression over time from MCI to early AD. Traditional and widely used assessment paradigms, such as delayed recall and rate of forgetting, are not well suited to identify the subtle changes in cognition that manifest during the preclinical stages of AD and early MCI [9]. Moreover, typical neuropsychological measures are traditionally administered in optimal conditions such as a quiet environment that minimizes any potential distractors. This is at odds with demands in the real-world environment in which persons are forced to allocate attentional resources, multitask, and deal with a welter of competing stimuli. Accordingly, it has been observed that in the "optimal" testing environment associated with traditional neuropsychological tasks, a number of persons are able to employ cognitive reserve and individualized compensatory strategies to mask actual underlying neuropsychological deficits [33] or, conversely, use learning strategies that may hinder their optimal performance. These, and other aspects of traditional neuropsychological paradigms, often result in modest sensitivity to preclinical AD states, making it exceedingly difficult to detect the earliest cognitive deficits and track changes over time [9, 34].

To address some of these issues, Loewenstein et al. [35] have developed "cognitive stress tests" (CSTs) that are not as susceptible to individual variability in learning strategies or compensatory mechanisms and are sensitive to the earliest behavioral manifestations of brain impairment related to AD. CSTs are specifically designed to stress the cognitive system and minimize the impact of individualized strategies that might mask subtle memory or other cognitive deficits. This is analogous to an exercise electrocardiogram, which is often much more effective than a resting-state electrocardiogram for detecting underlying cardiac deficits that are only identified when stress is applied to the system. Some of these CSTs, along with traditionally employed assessments, will be described below.

Assessment of Memory

There is a plethora of cognitive measures that have been developed and validated for the assessment of memory. In evaluating an individual for the presence of MCI or early dementia, the most commonly employed memory assessments have focused on list-learning paradigms that examine different aspects of memory. This includes but is not limited to the storage and consolidation of to-be-remembered information, contrasting immediate with delayed recall, and recognition of target stimuli. Other memory paradigms have assessed immediate and delayed memory for story passages, paired associate learning, and retention of simple and more complex geometric designs. The advantage of such measures is that it provides an assessment of learning over several trials that can evaluate the effects of proactive and retroactive interference and provide measures of delay recall. Recognition memory and cued recall can also be assessed. Each of these components is important in the evaluation of AD. Difficulties with delayed recall and rate of forgetting were historically seen as hallmark features of AD [37, 38], but there is evidence that not all AD patients exhibit these deficits [39]. Furthermore, while these procedures have proven valuable in the assessment of conditions such as traumatic brain injury, cerebrovascular impairment, and dementia, it has become apparent that they are largely insensitive in capturing the early prodromal or preclinical stages of AD and other neurodegenerative disorders [40, 41]. A list of commonly used list-learning measures is presented in Table 29.2.

The choice of memory test depends on the circumstances of the evaluation. The California

Table 29.2 List-learning and other memory tests for the assessment of AD

Loewenstein-Acevedo Scales for Semantic Interference and Learning (LASSI-L) [42]
Short-Term Visual Memory Binding Test [43]
California Verbal Learning Test (CVLT-II) [44]
Hopkins Verbal Learning Test- Revised (HVLT-R) [45]
Rey Auditory Verbal Learning Test [46]
Modified Fuld Object Memory Evaluation [47, 48]
Semantic Interference Test [49]
Logical Memory; Wechsler Memory Scale – 4th Edition (WMS-IV) [50]
Visual Reproduction; WMS-IV [50]
Verbal Paired Associates; WMS-IV [50]
Brief Visual Memory Test [51]

Verbal Learning Test – Second Edition (CVLT-II) [44] is a comprehensive test, presenting the older adult with 16 items that encompass 4 semantic categories. The patient has five trials to learn the to-be-remembered targets and is then administered a second list of 16 items to assess the potential effects of proactive interference (old learning interfering with new learning), retroactive interference (presentation of the new list interfering with learning from the old list), and the use of semantic cues to facilitate recall. Delayed memory is assessed across free and cued recall trials after a 20-min delay, followed by a recognition memory test. Even though a shorter CVLT-II list is available for older adults, the standard edition for the evaluation of early patients is preferred. There are numerous indices for learning and memory that can be very helpful in diagnostic determination. An alternative to the CVLT-II is the Rey Auditory Verbal Learning Test (AVLT) [46, 52], which is similar to the CVLT-II, but does not make use of semantic cues or different semantic categories. For subjects that are depressed or anxious, a list-learning task across five learning trials is relatively lengthy to give and may be experienced as overwhelming. An excellent alternative is the Hopkins Verbal Learning Test – Revised (HVLT-R) [45], which requires the older participant to learn 12 words across only 3 learning trials. When issues such as very low education or significant hearing deficits are present, a modified three-trial Fuld Object Memory Evaluation [47, 48] can be quite useful. This requires the individual to select ten common objects from a bag and to recall the objects after a verbal fluency distracter task. The participant is then selectively reminded of those items that were not recalled, and then another distracter task is administered for a total of three recall trials. Loewenstein and colleagues [48] modified the three-trial Fuld Object Memory Evaluation paradigm by having subjects recall a second list of items that are all semantically similar to the original to-be-remembered targets (i.e., ring versus bracelet). Reduced recall for the second list compared to the first list was thought to be due to competition from the previously presented targets on the first list (proactive interference), while reduced recall for the first list after recall of the second list was thought to be related to retroactive interference. The Semantic Interference Test (SIT) [49] evidenced high sensitivity and specificity in distinguishing normal elderly subjects from subjects with MCI and early dementia. Moreover, vulnerability to proactive interference was most associated with those MCI subjects who progressed to dementia over a 2- to 3-year period [52].

This work led Loewenstein and colleagues to develop a more refined scale, the Loewenstein-Acevedo Scales of Semantic Interference and Learning (LASSI-L) [42], which demonstrated high test-retest reliabilities for both amnestic MCI and CN subjects. While the LASSI-L measures learning and the effects of semantic interference among MCI patients with suspected early AD, shared semantic cueing across both lists produced significant numbers of semantic intrusion errors. In fact, on the initial List B cued recall, 52.9% amnestic mild cognitive impairment (aMCI) patients and 72.5% of AD patients, but only 6.3% of CN elders, had an *equivalent or greater number of semantic intrusions for List B targets than correct cued recall of the targets themselves* [42, 54]. In fact, a combination of cued recall measures tapping maximum storage and susceptibility to proactive interference on the LASSI-L differentiated between aMCI and normal elderly subjects with 87.9% sensitivity and 92.5% specificity. Because the design of the LASSI-L cued recall condition magnifies semantic interference effects, it has

shown to have greater sensitivity and specificity to detect very early and subtle cognitive impairment among asymptomatic older adults with apparently normal cognition.

It has long been recognized that binding of associations (name-face) and other associative memory is impaired in conditions such as AD. With regard to list-learning tasks, *memory binding* refers to associative binding of targets on multiple lists through the use of a common semantic cue. The lack of such memory binding may reflect an early sign of presymptomatic memory impairment [42, 54]. Buschke's Memory Capacity Test, also known as the Memory Binding Test (MBT) [54], involves the learning of an initial list of 16 targets, which was associated with a distinct category cue at encoding. The same category cues are then employed to recall a different list of 16 targets. For example, the semantic cue "fruit" may be associated with "strawberries" on the first list and "pears" on the second list. Associative binding can be assessed through this type of paradigm, which is something that cannot be done with widely employed traditional memory measures.

Another type of memory binding paradigm is Parra-Rodriguez's Short-Term Visual Memory Binding Test (SVMBT) [42]. This measure relies on feature detection embedded in a recognition paradigm. In this test, memory binding effects can be tested for using polygon shape and color combination, contrasted to memory for polygon shape alone or polygon color alone. The SVMBT, which utilizes feature binding as opposed to semantic binding, has been shown to be very sensitive in detecting memory deficits in early AD [55], as well as changes in E280A single presenilin-1 mutation and asymptomatic carrier AD patients [56], and can differentiate mild AD from depression and other non-AD disorders [55].

There are also a number of measures that tap other aspects of memory functions, such as logical memory for story passages, paired associate learning, as well as immediate and delayed recall of simple and complex geometric designs. Some of the memory tests that we have found useful in our clinical laboratory are listed in Table 29.2.

Assessment of Non-memory Functions

The assessment of *language functions* includes both an evaluation of both expressive and receptive language functions. Confrontation naming and word retrieval skills can be assessed by measures such as the Boston Naming Test [57]. Access from semantic lexicon can be evaluated using a category fluency test for animals, fruits, and vegetables [58]. In contrast, letter fluency is a more orthographic memory task that requires retrieval from phonological stores and is sensitive to frontal lobe dysfunction [59]. We also obtain a brief reading sample, a writing sample, as well as repetition of phrases. Receptive language can be assessed by having the subject perform simple and more complex commands, such as those on the Token Test [60].

Common elements of *executive function* tests are the ability to plan, solve problems, engage in concept formation, and shift cognitive sets. One of the most sensitive measures for executive dysfunction is the Wisconsin Card Sorting Test [61], which provides an excellent measure of concept formation, perseverations, and the ability to shift cognitive sets. Unfortunately, since this is a test of novel learning, this is not an optimal measure for repeated testing. Trails B of the Trail Making Test [62, 63], a test of simple visual scanning abilities that requires alternation between numbers and letters and cognitive set shifting, is a widely used measure of executive functioning. Since there are so many cognitive processes required for this test of complex visual scanning abilities, Trails B is very sensitive to cerebral dysfunction in general, although observed deficits may not be specific to executive impairments. *Visual-spatial disturbances and constructional praxis* can be ascertained by constructional tasks such as the Block Design subtest of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) [64]. When it is important to distinguish between a perceptual disturbance from the inability to construct figures based on that perception, tests such as Judgment of Line Orientation [65], or Hooper Visual Organization Test [66], may be useful.

Praxis is the ability to perform skilled motor movements. Simple measures of ideational praxis may be carried out by instructing the patient to prepare a letter for mailing, while simple tests of ideomotor praxis instruct patients to demonstrate how to blow out a match and use scissors or a hammer.

Attention may be assessed by tests of digit span or continuous performance tests which require vigilance and a response when certain stimuli flashes across a computer screen. *Psychomotor speed* may be assessed by Trails A of the Trail Making Test in which a patient connects numbers spread out across a page as quickly as possible, by employing tests of simple or choice reaction time on the computer, or by manual finger tapping.

When Should Neuropsychological Tests Be Administered?

Neuropsychological testing should be administered to any older adult in which it is important to establish the presence or absence of cognitive deficits or where the clinician is unsure about the nature and the extent of cognitive deficits. Examining different patterns of neuropsychological deficits may also help the clinician in diagnostic formulation and provide an objective baseline in which to monitor progression and response to treatment. Finally, neuropsychological test results can highlight patterns of strengths and weaknesses that can be helpful in patient management.

Consider the example of an 85-year-old woman born in Lithuania with a fifth-grade education who is presenting with significant depression in an outpatient setting. On her mental status evaluation, she gives the wrong day of the week and is able to recall two of three objects. One of her sisters insists that she had cognitive decline, whereas another sister insists that there has been no change in cognitive function. In this case, the clinician is unsure of the diagnosis and orders a neuropsychological evaluation. The neuropsychologist can test memory, language, executive functions, and attention by using objective normative data that is appropriate to the patient's age, education, and background, as well as comparing test results in different domains. This can greatly assist with determining the presence or absence of cognitive impairment and diagnostic determination.

There are some cases that, even with the most sensitive neuropsychological assessment, results will be equivocal. In this case, the neuropsychologist may conduct serial assessments in 6–9 months. Sometimes, the neuropsychologist will use parallel forms when available to reduce the possibility of practice effects. The neuropsychologist may also use reliable change indices to determine the extent to which changes on certain other tests reflect true differences, rather than resulting from chance. It should be noted that neuropsychological test results provide a snapshot of a person's performance at one point of time but that longitudinal assessment may be required to more accurately define the parameters of a particular condition.

Summary and Future Trends in Neuropsychological Assessment

Neuropsychological assessment has an important role in distinguishing between the cognitive effects of normal aging and deficits related to cerebral dysfunction. The objective nature of the tests, the ability to relate results to appropriate normative data, and the comparison of patterns of strengths and weaknesses all contribute to important information that can improve clinical decision-making. As efforts are made to detect AD in its earliest stages, it will become even more important for the field of neuropsychology to develop tests that are sensitive to specific deficits in utilizing semantic cues, the effects of semantic interference, and evidence of subtle executive dysfunction. With the increased reliance on biomarkers for early detection of AD, there will also be a need to develop algorithms that incorporate both cognitive variables and biomarkers. To this point, a recent investigation has revealed that measures of episodic memory and combined FDG-PET scans together

predicted progression from MCI to AD better than either measure alone [67]. In their review of the literature, Brooks and Loewenstein et al. [9] propose that the diagnosis of early AD is greatly strengthened by evidence of amyloid deposition in the brain by PET imaging; CSF evidence of amyloid or tau levels suggestive of AD, being homozygous for the ApoE4 allele (two E4 alleles); or atrophy of the hippocampus, entorhinal cortex, and other medial temporal structures on MRI. However, confirmation of memory and other cognitive deficits will always be essential in characterizing the disease, in providing continuous measures to monitor progression over time, and in developing effective management strategies. Finally, as new treatments are developed, cognitive and functional measures will be at the forefront as a means to measure outcome.

Clinical Pearls

- Neuropsychological tests should not be interpreted in the absence of a comprehensive clinical interview. The clinical history by the neuropsychologist is a critical part of the examination. A reliable collateral informant should be used to gather information regarding premorbid cognitive function and to determine the extent to which cognitive complaints represent a change in cognitive function.
- The primary goals of neuropsychological assessment are to (a) determine the presence or absence of cognitive impairment; (b) determine the nature and extent of cognitive deficits; (c) determine whether the pattern of observed deficits is consistent with cerebral impairment and different etiological conditions; (d) inform decisions about management, interventions, and care; and (e) establish a baseline by which to assess change over time.
- The hallmark features of Alzheimer's disease (AD) are deficits in delayed recall and rate of forgetting. However, some patients with AD will evidence their greatest deficits in learning information across multiple trials.
- In preclinical AD, proactive semantic interference, and the failure to recover from semantic interference, may be more useful to detect meaningful changes in cognition and represents cognitive markers that are correlated with biological markers of AD pathology.
- List-learning tests are optimal for memory evaluations because they assess the ability to learn new information across multiple trials and also assess delayed recall and rate of forgetting.
- It is desirable to assess memory for both verbal and nonverbal information (i.e., immediate and delayed visual reproduction).
- The patient with Alzheimer's disease may, on occasion, present with primary impairments in language, visual-spatial skills, or executive dysfunction. Therefore, it is important to assess these domains.
- Amnestic mild cognitive impairment (aMCI) is a risk factor for Alzheimer's disease and related memory disorders. In specialty memory disorder clinics, the rate of progression to dementia and a diagnosis of probable AD ranges from 12% to 15% per year, while the rate of progression in other settings where the base rates may be lower is considerably less.
- The clinical diagnosis of probable AD requires a dementia syndrome by DSM-5 criteria, and cognitive impairment must be sufficiently severe to interfere with social and/or occupational functions. A new diagnosis of dementia cannot be made in the presence of a delirium.
- A clinical diagnosis of AD is greatly strengthened by evidence of medial temporal lobe atrophy on MRI (particularly in the hippocampus and entorhinal cortex), CSF findings of Aβ-42/Aβ-40 ratios or Aβ-42/tau40 ratio suggestive of AD, blood tests showing two apolipoprotein E4 alleles, positron emission tomography (PET) scans showing abnormal beta-amyloid imaging on PET imaging, or hypometabolism in temporal and parietal cortices.
- Parkinsonian signs and symptoms, REM sleep behavioral disturbance, and fluctuations in cognitive abilities such as attention, memory,

visual-spatial, and executive functions should raise the possibility of diffuse Lewy body disease.

- Early language disturbances and/or predominant changes in personality (i.e., disinhibition), in addition to an earlier onset of symptoms, should raise the possibility of frontal-temporal dementia (FTD). These individuals typically have predominant frontal-temporal atrophy on structural MRI, a high degree of executive dysfunction, and characteristic patterns of decreased metabolism or blood flow in the frontal and temporal lobes on functional neuroimaging, such as PET or SPECT.
- Serial testing is recommended in cases where the presence or the extent of cognitive deficits is unclear or when it is important to monitor potential improvement or worsening over time.
- It is critical to use neuropsychological tests that have been appropriately validated for patients of different ethnic and cultural backgrounds. Test results must be applied against normative data that is appropriate with regard to age, education, cultural background, and gender.
- Denial of symptoms is commonly observed in AD, yet some patients with early AD are aware of changes, which may lead to significant levels of depression and anxiety. Although pseudodementia is relatively uncommon in outpatient settings, the clinician should be aware of the effects of anxiety and depression in decreasing performance on neuropsychological tests.

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Vascular Cognitive Impairment

30

Robert Paul and Lauren Salminen

Introduction to Vascular Cognitive Impairment Nomenclature

Approximately 800,000 individuals experience a cerebrovascular event on an annual basis in the USA. Worldwide, the number is close to 15 million. Unfortunately, the vast majority of individuals who experience a stroke will develop cognitive symptoms secondary to neuronal injury. There is no cure for vascular cognitive impairment (VCI) or intervention capable of fully arresting the underlying disease process. As such, VCI represents a major global health concern.

VCI refers to the full spectrum of cognitive dysfunction associated with cerebrovascular disease (CVD). The recently updated Diagnostic and Statistical Manual (DSM)-5 [1] criteria for major neurocognitive disorder does not require a primary memory disorder (see Table 30.1). The evolution away from an Alzheimer's disease (AD)-centric diagnostic system is still relatively new, and the nomenclature has yet to be fully adopted in the scientific literature. Rather, the majority of research refers to VCI as vascular dementia (VaD), vascular cognitive impairment-dementia (VCID), subcortical ischemic disease (SID), and subcortical ischemic vascular dementia (SIVD). VCI and VaD are often used to describe cognitive impairment regardless of whether the vascular injury involved cortical or subcortical brain regions. By contrast, SID and SIVD refer specifically to cognitive impairment secondary to ischemia in the white matter or subcortical gray matter. To simplify the terminology for this chapter, we refer herein to the full spectrum of cognitive impairment as VCI and vascular injury limited to the subcortical regions as SIVD. Mild VCI is used to describe cognitive impairment without disruption in activities of daily living (ADLs), and VaD is used to refer to cognitive impairment with disruption to ADLs. When appropriate, reference to DSM 5 nomenclature is noted.

Risk Factors for Vascular Cognitive Impairment

The risk of occlusive or hemorrhagic stroke exists across the lifespan, but the incidence is inherently tied to advanced age. Samples of community-dwelling elders reveal CVD on structural neuroimaging in the majority of individuals [2].

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Table 30.1 DSM-5 Criteria for Major Neurocognitive Disorder [1]

A.	Significant cognitive decline[a] from a previous level of performance in one or more cognitive domains
	Learning and memory
	Language
	Executive function
	Complex attention
	Perceptual motor
	Social cognition
B.	The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications
C.	The cognitive deficits do not occur exclusively in the context of a delirium
D.	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

[a]Evidence of decline is based on concern of the individual; a knowledgeable informant, or the clinician; and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

Endothelial dysfunction, reduced vascular plasticity, atherosclerosis, hypertension, diabetes mellitus, and hyperlipidemia are important risk factors for CVD. Heart disease is especially critical, as emboli often emerge from the heart as a consequence of underlying CVD, thus increasing the risk of occlusive stroke.

Lifestyle factors are implicated in the development of age-related vascular pathophysiology. Smoking, obesity, lack of exercise, and poor nutrition separately, and collectively, correlate with cardiovascular risk factors. Lifestyle variables do not fully account for the development of CVD, but as modifiable risks, they represent prime therapeutic targets. Medications (e.g., antihypertensives) and behavioral interventions (e.g., smoking cessation, weight loss) reduce the risk of recurrent stroke, but no intervention completely halts the progression of cardiovascular or CVD with advanced age. Further, recent work suggests that the optimal therapeutic window may be many years before the expression of clinical symptoms. For example, blood pressure, atrial fibrillation, and prior myocardial infarction predicted the incidence of stroke in 47–55 year-old males followed for an average of 11 years [3]. These findings highlight the importance of managing risk factors long before the onset of clinical symptoms.

Neuroimaging Markers of Vascular Cognitive Impairment

Common neuroimaging markers of SIVD include lacunes and subcortical hyperintensities (SH). Neuroimaging scans readily demarcate lacunes as small cerebrospinal filled cavities in the white matter and SH as bright white areas. These markers are best visualized on T2-weighted fluid-attenuated inversion recovery (FLAIR) scans because this sequence suppresses the signal generated by cerebrospinal fluid in the ventricles. The enhanced visual contrast is akin to turning off the glow of city lights in order to visualize stellar constellations in the night sky (Fig. 30.1).

The presence of SH or lacunes on neuroimaging does not equate to VCI. Nearly all individuals display these vascular markers at some point in older adulthood, and many individuals with clear ischemic changes on imaging perform within the normal range on cognitive testing. However, it is important to note that "normal" performance here is based on the age of the participant, not optimal function. Erroneously described as "silent" infarcts, these ischemic imaging markers of CVD almost certainly represent a substrate of age-related cognitive decline. The total volume of SH and lacunar burden correlates only modestly with cognitive performance, and debate continues on the relative importance of lacunar count, volume, and location of the lesion. The lack of correspondence is at least partially accounted for by the limited sensitivity of available imaging techniques. Studies using diffusion tensor imaging (DTI) reveal significant alternations in the microstructural integrity of "normal appearing white matter," particularly in regions adjacent to ischemic infarcts [6]. Further, vascular-related abnormalities (e.g., hemosiderin deposits) visible using 7 Tesla MRI are not visible at the more common 3 Tesla strength [7]. These studies highlight that vascular lesions

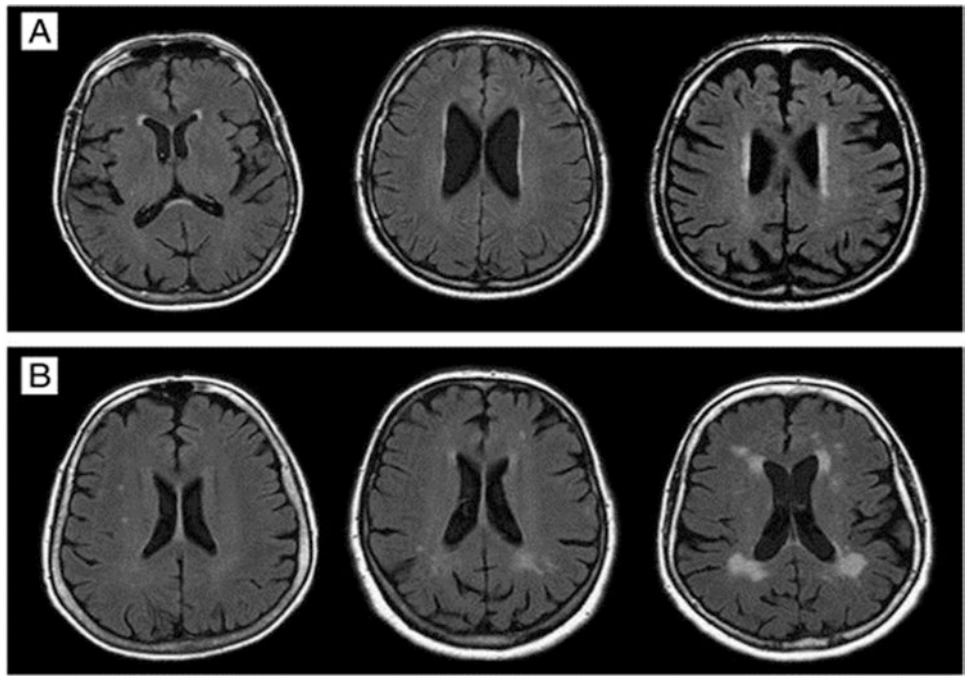

Fig. 30.1 White matter lesions on a T2-weighted FLAIR MRI scan. Images are extracted from work by Freudenberger and colleagues [4] (**a**) Example of typical progression of age-related periventricular white matter lesions in a "healthy" older adult. From left to right: periventricular caps, lining, and halo. (**b**) Typical progression of deep white matter lesions in an adult with cerebrovascular disease (CVD). From left to right: punctate, patchy and early confluent, and confluent [5]

on MRI may contribute to the expression of cognitive impairment, but many vascular-related neuroimaging abnormalities go undetected in routine clinical practice.

The absence of a standardized rating system in radiology further complicates the diagnostic landscape of CVD. Previous efforts to define thresholds based on the volume of infarcted tissue (e.g., 25% of the white matter, or lacunes greater than 10 cm) proved unhelpful. New research methods using data driven models such as machine learning/deep learning have potential to create more accurate predictive algorithms capable of directing personalized patient care. Clinical brain science has moved at a glacial pace in the development and application of these models, but momentum is building in the field of VCI. Recent work reveals high diagnostic accuracy for cardiovascular disease [8], and nearly perfect accuracy in the prediction of acute changes in cerebral blood volume and hemodynamic decompensation [9]. Advances in this space will emerge rapidly as multiple groups, including ours, harness the strength of these algorithms to build predictive models of VCI that integrate neuropsychological, demographic, and neuroimaging input features.

Neuropsychological Phenotype of Vascular Cognitive Impairment

The potential for any branch of the cerebrovascular network to become occluded or to hemorrhage creates a massive range of vulnerable brain regions. Stroke location and stroke volume have long been revered as the primary determinants of symptoms. A stroke in the nondominant association cortex might produce minimal symptoms, whereas a stroke of the same volume in the thalamus or the hippocampus is capable of causing profound impairment.

The neuropsychological phenotype of VCI is directly related to both location and size of the underlying infarct(s). The most common site of vascular damage involves the middle cerebral artery (MCA), which tracts to the lateral surface of the brain after completing a near 90-degree turn. This course correction creates an anatomical vulnerability for embolic occlusion, resulting in temporary (transient ischemic attack; TIA) or permanent (stroke) occlusion of the lumen. The MCA perfuses a large geographic region of the lateral surface as well as deep subcortical brain regions via the lenticulostriate arteries.

When the larger vessels perfusing cortical regions are primarily involved, individuals experience a sudden onset of aphasia, agnosia, paralysis, etc. (see Table 30.2), with "stepwise" decline in function over time. Neuropsychologists working in a rehabilitation setting are most likely to encounter these cases, yet they do not represent the most common subtype of VCI. The most common form of VCI involves subcortical ischemia and strategic subcortical stroke without prominent cortical involvement. These cases have an insidious onset, with a slow and progressive clinical course. Neuropsychologists working in outpatient settings are more likely to see these cases in order to assist the clinical team with differential diagnosis and treatment recommendations. This form of VCI (commonly referred to as SIVD) represents a diagnostic challenge because the history of symptom onset and progression mirrors that of AD, and neuroimaging cannot establish causal links to the cognitive symptoms. Here the potential for misdiagnosis is high. The neuropsychologist is uniquely positioned to guide the clinical process by following a theoretically driven integration of neuropsychological data, patient history, and neuroimaging results to render a highly probable diagnosis of VCI.

The neuropsychological profile of SIVD is typical of a "subcortical profile" [10]. This term does not fully integrate modern perspectives of whole-brain networks and cognition, yet the concept holds value in test interpretation and diagnostic etiologies. Neuropsychological testing of SIVD reveals poor performance in multiple aspects of executive function, verbal retrieval, learning efficiency, and psychomotor speed [10–14]. Lexical fluency is more impaired than semantic fluency (the opposite of AD), but patients frequently perform below average on both due to impaired response fluency. Symptoms of apathy and depression are prevalent, the former possibly due to damage within the subcortical

Table 30.2 Common Stroke Sites and Corresponding Clinical Features

Large vessel stroke site	**Clinical features**
Middle cerebral artery (MCA)	Hemiplegia, aphasia, homonymous hemianopia, contralateral hemianesthesia
Anterior cerebral artery (ACA)	Paraplegia, incontinence, abulia, executive dysfunction, personality changes
Posterior cerebral artery (PCA)	Homonymous hemianopia, alexia with or without agraphia, visual agnosias, color anomia, Balint's syndrome, prosopagnosia
Basilar artery	Ophthalmoplegia, motor deficits, ataxia, dysmetria, vertigo, nausea/vomiting, coma, cranial nerve IV palsy, contralateral decreased sensation to pain and temperature, Horner's syndrome, ipsilateral deafness
Lacunar stroke site	**Syndrome**
Posterior limb of internal capsule (PLIC), basis pontis, cerebral peduncle	Pure motor: Contralateral hemiparesis
PLIC, deep white matter, thalamus	Sensorimotor: Contralateral weakness and numbness
Posterior thalamus	Pure sensory: Loss of contralateral sensory function
PLIC, basis pontis, thalamus	Ataxic hemiparesis: Unilateral weakness disproportionate to contralesional hemiparesis and ataxia
Anterior limb/genu of internal capsule, basis pontis	Dysarthria-clumsy hand: Weakness of contralateral hand and decline in fine motor abilities, slurred speech
Subthalamic nucleus	Hemiballismus/hemichorea: Contralesional limb flailing, dyskinesia

mesolimbic system/tracts and the latter more commonly linked to functional impairments (especially language) following thalamic or MCA infarcts [15, 16].

Significant impairment in functional status due to cognitive impairment equates to a diagnosis of dementia (or major cognitive disorder: DSM 5). VaD most commonly results from extensive white matter ischemia, one or more strategic subcortical strokes, large vessel cortical infarcts, or combination involving the mantle and the subcortex. More rare, VaD can also occur from lesions in the cerebellum. In one memorable case evaluated by our team, VaD developed soon after a cerebellar stroke that damaged the occipitofrontal fasciculus. The patient exhibited profound executive dysfunction in addition to cerebellar-mediated motor abnormalities. The neuropsychological phenotype of VaD is similar to VCI with prominent executive and psychomotor speed deficits, but a global pattern is also possible when patients present with both large cortical infarctions and extensive subcortical ischemia [17]. Physical signs of extrapyramidal and pyramidal disruption are more common in cases of severe vascular disease. Similarly, individuals who meet criteria for VaD may present with imbalance or incontinence that mimics normal pressure hydrocephalus (NPH).

Clinical Course of Vascular Cognitive Impairment

Up to 80% of individuals with first-ever stroke exhibit cognitive impairment [18], and one third of individuals who experience a large vessel stroke meet criteria for VaD within 12 months [19]. Survivors of first-ever stroke are at increased risk for additional vascular events. Prospective studies reveal that nearly 50% of individuals with early stage VCI progress to dementia within a 5-year period [20]. Even more alarming, a recent study revealed that MRI perfusion changes following a TIA predicts subsequent stroke [21]. These studies suggest that the natural history of VCI is characterized by a linear progression from CVD without cognitive complications to dementia.

Diagnosis of Vascular Cognitive Impairment

The most common diagnostic systems for VCI in the research literature include the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN) criteria [22]. The ADDTC and NINDS-AIREN systems require neuroimaging evidence of CVD for a probable diagnosis. Cognitive impairment is also required, though the NINDS-AIREN criteria mandate evidence of episodic memory dysfunction, whereas the ADDTC criteria are more flexible. As noted previously, the DSM 5 criteria for major neurocognitive disorder no longer require a primary memory disorder, but the criteria have not yet been integrated into the VCI literature.

Differential Diagnosis of Vascular Cognitive Impairment

Both patients and referring parties express specific concern about the diagnostic differentiation between VCI and AD. Some groups have argued this differentiation is not possible given that postmortem data reveal a high frequency of mixed dementia and a low frequency of pure VaD. However, in vivo imaging studies demonstrate that most individuals with SIVD show limited or no cortical binding of ^{11}C-Pittsburgh compound B on positron emission tomography [23]. As such, while autopsy studies suggest that both AD and vascular disease are related substrates to dementia, it is very likely that more pure cases of each condition exist in the early stages of disease, years before the development of comorbid pathology. Described previously in this chapter, the frequency of SIVD means that the clinical course will not aid the diagnostic process. However, impairment in executive function and psychomotor abilities without evidence of amnestic memory loss (percent of information lost from last learning

trial to retention trial or discrimination memory on a recognition trial) argues against AD. Additional diagnostic considerations include frontotemporal dementias (FTDs) and NPH. Patients with FTD often present at clinic with acute changes in personality or isolated aphasia early in the course of the disease and before age 65. By contrast, major personality changes are not common in VCI, and aphasia is more typical of advanced VaD or strategic subcortical infarct. NPH presents a unique challenge because the cognitive phenotype mirrors that seen in VCI. NPH usually includes more prominent gait disturbance and urinary symptoms (urgency, frequency, or incontinence). However, older males with cardiovascular disease, prostate hypertrophy, and arthritis report the same cluster of symptoms, further emphasizing the importance of a carefully conducted patient interview.

Clinical Evaluation: Interview and History

The interview provides a prime opportunity to evaluate receptive and expressive language skills during conversation. Further, interview questions targeting clinically relevant demographic and medical histories allow the clinician an organic opportunity to assess whether memory failures resemble "tip of the tongue" retrieval deficits or amnestic loss of information. Reflexively we query the patient and the family about the clinical course, but this rarely proves valuable. When a history of sudden onset and stepwise decline is present, the diagnosis is nearly already known by the referral source, and the purpose of the evaluation is focused on characterizing strengths and weaknesses.

Neuropsychological Assessment

Proper neuropsychological evaluation of VCI requires a combination of breadth and depth. Screening tools, such as the Mini-Mental State Exam (MMSE), lack sensitivity to mild VCI [24, 25]. The Montreal Cognitive Assessment (MoCA) provides greater coverage of executive processes, but the scope remains inadequate. More comprehensive options are summarized in Table 30.3. It is important that the selected battery includes comprehensive tests of executive function (working memory, response

Table 30.3 Neuropsychological Protocol Recommendations

Domain	Harmonization 30-min protocol[a]	Harmonization 60-min protocol[a]	Additional considerations
Global	MMSE	MMSE	MoCA
Executive function/ activation	Animal fluency Letter fluency Digit Symbol Coding	Animal fluency Letter fluency Digit Symbol Coding Trail Making	Letter-Number Sequencing Stroop test
Psychomotor speed			Grooved Pegboard Test
Language		Boston Naming Test	
Attention/reaction time		Simple and choice reaction time	Digit Span
Visuospatial skill		Rey Complex Figure Test	
Memory	Hopkins Verbal Learning test—Revised	Hopkins Verbal Learning Test—Revised or California Verbal Learning Test-2	Brief Visual Memory Test—Revised
Neuropsychiatric/ Depressive symptoms	Mood questionnaire (BDI II, CES-D)	Neuropsychiatric Inventory Mood questionnaire (BDI II, CES-D)	

[a]Adapted from NINDS and Canadian Stroke Harmonization Network Protocol Recommendations (Hachinski et al.) [24]
[b]Additional considerations
Abbreviations: *MMSE* Mini Mental State Examination, *MoCA* Montreal Cognitive Assessment, *BDI II* Beck Depression Inventory II, *CES-D* Center for Epidemiological Studies Depression

inhibition, cognitive flexibility, planning, and organization), motor, learning, retention, and recognition discrimination, and language. Poor test coverage in these domains will undermine the process to differentiate cortical and subcortical cognitive phenotypes.

Neuroimaging Corroboration

Neuropsychologists are not routinely trained to interpret neuroimaging scans, so the degree of vascular burden must be extracted from the radiology report. This is unfortunate because these reports do not rely on a standardized system to rate severity. A binary approach may be the only option when expert input is unavailable. Within this framework, vascular disease of any severity (even "age-related vascular disease") would be supportive of VCI, whereas the complete absence of vascular disease would argue against VCI. This "winner take all" strategy is admittedly over simplified and only recommended when trained expert input is unavailable.

Clinical Case Example

Here we describe an example of a typical VCI assessment with baseline and 12-month follow-up results. Neuroimaging input is provided verbatim. The case was modified to remove personal identification.

Background and History

Mrs. Smith (fictional name) is a 71-year-old, right-handed, married female who was referred for neuropsychological evaluation by her neurologist secondary to cognitive difficulties identified by the patient. During the interview, Mrs. Smith reported a history of TIAs, "stroke," and memory loss that began approximately 5 years prior to the evaluation. She reported a TIA-like event a year prior followed by a "stroke." She was unable to provide further details regarding the reported stroke, but she did note that she elected to stop driving 2 years ago after developing tingling sensations in both hands.

Mrs. Smith described a 2-year history of short-term memory loss, characterized by repeating herself and difficulty remembering names of people she recently met; she reported no difficulty recalling familiar names. She independently manages her medications (list provided) and all other basic and instrumental ADLs. She denied hallucinations, fluctuating symptoms, urinary incontinence/urgency/frequency, significant visuospatial abnormalities, and changes in personality.

Mrs. Smith's medical history includes high cholesterol, high blood pressure, TIAs, and adult-onset seizures. Psychiatric history is unremarkable. She completed college with a degree in business education, and she worked as a high school business teacher for many years. Mrs. Smith and her husband now live in an independent senior community where they enjoy an active lifestyle. Her husband was unavailable to participate in the interview. She does not smoke or drink alcohol. She reported no family history of dementia. A brain MRI report dated 3 weeks prior was remarkable for "periventricular white matter low attenuation related to chronic small vessel ischemia consistent with generalized age-related cerebral volume loss."

There was no evidence of abnormal gait, posture, physical asymmetries, tremor, or rigidity. During the interview, her conversational speech was fluent and goal-directed. She exhibited appropriate prosody, and there was no evidence of paraphasias. Receptive speech was intact, and there was no clear difficulty comprehending simple or complex material. She was very friendly and cooperative. Her mood was euthymic, and she remained engaged throughout the evaluation.

Baseline Neuropsychological Evaluation

Baseline neuropsychological data are presented in Table 30.4. Mrs. Smith recalled 23 words across 3 learning trials on a verbal learning measure. After a brief delay, she recalled 6 out of 12 target words (low-average performance). Her performance was less strong on a recognition trial, as she tended to endorse semantically related foils. She appeared confused on this aspect of the test compared to the free recall portions. On a test of learning and memory of prose passages, she exhibited intact learning and retention of information, and she performed one standard deviation above average on the delayed trial, suggesting no rapid loss of information. Further, her recognition memory was adequate. Performance on a test of visual learning and memory was significantly impaired in terms of learning and retention, though her recognition memory was intact.

On a measure of semantic fluency, she performed within expectations for her age, naming 17 animals within 1 min. By contrast, on the letter fluency test, she produced only 20 words across all 3 letter cues in 3 min, resulting in below-average performance. She correctly named only 47/60 items on the Boston Naming Test (below-average performance) and incorrect items included both

Table 30.4 Baseline and 12-month follow-up neuropsychological data for case example

Test	Baseline (raw)	12-month (raw)	Outcome
Attention			
WAIS-III Digit Span	14	10	Decline
Executive function			
Trail Making Test, B	Timed out[a]	Unable to complete due to confusion[b]	Decline
Clock drawing	Unable to draw accurately	Concrete setting	Stable
Psychomotor speed			
Trail Making Test, A	77[a]	141[b]	Decline
WAIS-III Symbol Search	12[a]	11[a]	Stable
WAIS-III Digit Symbol	25[a]	27[a]	Stable
Pegs, dominant	145	155[b]	Decline
Pegs, nondominant	123	133[a]	Decline
Activation/language			
Semantic fluency	17	17	Stable
Letter fluency	20[a]	16[b]	Decline
Boston Naming Test	47[a]	48[a]	Stable
Visuospatial			
Rey Figure copy	15.5[a]	18.5[a]	Decline
Memory			
HVLT-R learning	23	17[a]	Decline
HVLT-R delay	6	6	Stable
HVLT-R recognition	6[b]	9	Improve
BVMT-R learning	10[b]	16[a]	Improve
BVMT-R delay	3[b]	7	Improve
BVMT-R recognition	100%	100%	Stable
WMS-III, LM I	40	36	Stable
WMS-III, LM II	26	24	Stable
Mood			
BDI II	4	3	Stable

[a]Mild impairment
[b]Moderate impairment. Abbreviations not previously defined: *WAIS-III* Wechsler Adult Intelligence Scale – 3rd ed., *WMS-III LM* Wechsler Memory Scale 3rd ed. Logical Memory

high- and low-frequency words. Her copy reconstruction of a Rey Complex Figure was impaired. She did not appear to grasp the gestalt of the design, and her placement of details was poorly planned and organized.

Mrs. Smith's ability to repeat a string of digits in forward sequence was intact. Her performance on a test of visual scanning and psychomotor speed was moderately impaired. Though she successfully completed the practice trial of the Trail Making Test, Part B, she became very confused on the test trial, which she was unable to complete. This suggests significant problems with cognitive flexibility. Mild to moderate difficulties were noted on tests of psychomotor speed and visual scanning. When asked to construct a clock and set the hands to a specified time, she drew a clock with the numbers in the reverse order on two separate efforts. When a clock was drawn for her and she was then asked to set the hands of the clock to a specified time, she was unable to complete the task. Psychomotor speed on the Grooved Pegboard Test was moderately impaired for the dominant hand, but performance on the nondominant hand was stronger, with a score in the borderline normal range. Mrs. Smith's total score on the Beck Depression Inventory II was not suggestive of current depressive symptoms.

Based on the neuropsychological test results, clinical history, and neuroimaging data, it appeared that Mrs. Smith meets DSM 5 criteria for minor neurocognitive disorder, vascular origin.

12–Month Follow–Up Evaluation

Mrs. Smith returned for a follow-up examination after 12 months. Performances declined on tests of executive function and psychomotor speed. Her performance also declined on a test of learning efficiency, but she improved on visual learning, and there was no change in retention on either test. Overall, the lack of decline in retention or other major cognitive domain argues against a new diagnostic formulation. Her MRI report dated 11 months after the first MRI revealed "mild to moderate diffuse punctuate T2 and FLAIR hyperintensities within the left and right frontal parietal periventricular subcortical white matter and more confluent increased T2 and FLAIR signal within the left and right parietal periventricular white matter suggesting mild to moderate small vessel ischemic changes. There may be mild diffuse cortical atrophy with prominent sulci bilateral cerebral hemispheres."

Case Summary

The case example includes common issues in the evaluation of VCI. First, the patient's age and medical history raise the probability of a vascular origin. Second, the neuropsychological pattern was typical of a "subcortical" phenotype, with impairment in learning, executive function, and motor skills. The patient performed poorly on the recognition trial of learning test, but this was not accompanied by a loss of information. Finally, her brain MRI reports were congruent with her history and neuropsychological pattern of VCI.

Clinical Pearls

- The clinical course of VCI can be abrupt with stepwise decline or slow, insidious, and progressive.
- The pattern of neuropsychological deficits associated with vascular burden is dependent on the location of damage. Executive impairment is usually dominant but not universal, and is not necessary for diagnosis.
- For differential diagnosis, impairment in executive function and psychomotor abilities without evidence of amnestic memory loss (percent of information lost from last learning trial to retention trial, or discrimination memory on a recognition trial) argues against AD. Additional diagnostic considerations include frontotemporal dementias (FTDs) and NPH.
- Integration of neuroimaging results is mandatory to diagnose VCI.
- The progression of VCI can be influenced by healthy lifestyle interventions.

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Primary Progressive Aphasia

31

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Introduction

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by an insidious onset and gradual, progressive loss of language abilities. PPA is considered one of the two main frontotemporal dementias (FTD) which are (1) language variant FTD and (2) behavioral variant (bvFTD). PPA is distinguished from other neurodegenerative conditions by an exclusive impairment in language during the first 2 years of the disease. In some cases, impairment may remain confined to the domain of language for as many as to 10–14 years. While impairments in additional cognitive domains can become apparent as the disease progresses, language deficits remain the most prominent feature [1]. Specific aspects of language that are commonly affected in PPA include abilities such as word finding, object naming, word comprehension, semantic knowledge, and speech fluency [1, 2].

Early conceptualizations of PPA emerged in the 1890s, at which time the disorder was described as a progressive decline in language associated with atrophy in frontal and temporal brain regions within the left hemisphere [3, 4]. Examination of individuals with PPA in the years since has elucidated the heterogeneous nature of this clinical syndrome and led to the classification of three primary variants of PPA: (1) the nonfluent/agrammatic variant, (2) the semantic variant, and (3) the logopenic variant. Significant focus has been placed on characterizing the defining presentations and etiological determinants (e.g., neuroanatomical changes, genetic contributions, biomarkers) of each of these subtypes [1, 2, 5], which will be described in greater detail through this chapter (Fig. 31.1).

These PPA variants together comprise the language variant of FTD. Approximately 40% of FTD cases are estimated to be language variant, with behavioral variant FTD accounting for the other 60% of FTD patients [6]. Although the age at onset for PPA ranges from 40 to 80 years old, PPA tends to begin earlier than other dementias, most commonly presenting between the ages of 55–65 [1] with the average age of onset in the late 50s [7]. It is estimated that approximately 60% of FTD cases (including both behavioral variant and PPA) occur within the 45–64-year-old age range [8].

Estimates of the incidence and prevalence of PPA are limited and often based on overall estimates of the frequency of FTD. According to Onyike and Diehl-Schmid [6], epidemiological studies of the incidence and prevalence of FTDs have been difficult to pursue for a number of reasons, including the high level of expertise necessary for diagnosing behavioral variant FTD

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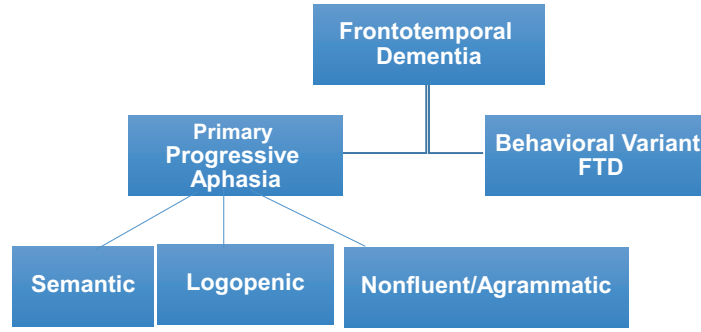

Fig. 31.1 Overview of frontotemporal dementias

and PPA, the relative rarity of FTDs (compared to more common cases of Alzheimer's dementia, for example), and the wide range of potential age at onset. Prevalence rates for FTD are estimated to be in the range of 2.7–15 per 100,000, and annual incidence is estimated to be 2.2–3.5 per 100,000 persons/year [9]. Knopman and Roberts [8] estimate a prevalence of 15–22 per 100,000 within the 45–65-year-old range specifically and estimate that between 20,000 and 30,000 persons in the USA have FTD. Although a greater preponderance of PPA among males has been previously suggested [1], more recent reviews suggest an equal gender distribution [6, 9].

Diagnosis

Typical Clinical Presentation

Diagnosis of PPA should be made when there is (1) gradual onset of language deficits or aphasia with (2) progressive worsening over time and (3) when language difficulties are the primary presenting complaint as well as the main barrier to performing instrumental activities of daily living and (4) there is no other identifiable cause for the language impairment such as vascular disease (stroke) or neoplasm [1]. Neuropsychological testing is critical for diagnosing PPA and, in particular, determining the PPA variant. Cognitive test results should be interpreted with caution given that many tests have verbal instructions and require verbal responses. For example, a patient with PPA may do poorly on a verbal memory test or verbal reasoning task due to language deficits but have no problems recalling recent events or demonstrating good reasoning skills in daily life.

The goal of the neuropsychological evaluation is to assess for aphasia or more subtle language deficits, clarify diagnostic subtype, determine relatively intact cognitive functions, and provide treatment recommendations. Assessment of PPA often requires the administration of neuropsychological tests of language that go beyond those employed in a typical dementia evaluation. Such specialized tests may include the Boston Diagnostic Aphasia Examination [10], Western Aphasia Battery [11], Pyramid and Palms Test [12], or Test of Irregular Word Reading Efficiency [13], for example.

Subtypes of PPA

Report of language problems will differ across PPA subtypes, but all patients with PPA and their caretakers typically report gradual decline in speech fluency, word finding, or object knowledge as the first and worst symptom.

Nonfluent PPA: From Hughlings Jackson to Wernicke and Broca, the distinction between fluent and nonfluent aphasias has been long recognized as important for anatomical localization. Dysfluent speech disorders are associated with anterior dominant hemisphere lesions, and fluent aphasias are associated with posterior dominant hemisphere lesions [14]. Nonfluent PPA is also known as the agrammatic variant or progressive nonfluent aphasia. The

hallmarks of nonfluent PPA are effortful speech and agrammatic language production. At least one of these two features must be present for clinical diagnosis.

Agrammatism is characterized by short phrase lengths and omission of grammatical morphemes [2]. For example, there is loss of function words such that speech becomes telegraphic due to simplification of grammatical forms. A patient with suspected nonfluent or agrammatic PPA may complain of difficulty with speech fluency or problems with pronouncing or articulating words. Fluency is assessed by examining or observing (1) prosody or the melody of speech which includes inflection, timbre, pitch, and rhythm, (2) phrase lengths or lengths of utterances which is the number of words in a word grouping between pauses, (3) rate of speech (defined as less than 50 words per minute), and (4) effortfulness of speech. Effortfulness is the articulatory agility or facility of speech [15]. Early dysfluent speech may start as aprosodic (monotone or robotic sounding), have shorter phrase lengths (e.g., less than seven words prior to a pause), be halting, labored, or present as an apraxia of speech (problems with the control of the oral motor apparatus) with distortions, deletions, or transpositions of speech sounds. At initial presentation, speech may be halting, slow and monopitch or have imprecise articulation [16]. Of note, in the early phase of nonfluent PPA, the patient may produce normal scores on classic language measure such as object naming, repetition, or language comprehension tests with the only deficit being on verbal fluency/word list generation tasks.

As the nonfluent PPA progresses, comprehension of grammatically complex sentences becomes impaired, whereas single-word comprehension and object knowledge remain intact. Comprehension of syntactically complex sentences can be tested by asking the patient to point to the picture in response to the prompt "The boy calling his mother has a red shirt" or similar items from the Boston Diagnostic Aphasia Examination Syntactic Processing subtest [10]. Deficits in grammatical comprehension and expression are found in both reading and writing. Nonfluent PPAs develop apraxia of speech and progress to mutism [17].

Semantic PPA: Semantic memory includes acquired information about words, objects, people, abstract concepts, names, and language that essentially comprises all our declarative knowledge of the world [18]. Patients with semantic PPA, also called semantic dementia, show impairments in comprehension of single words, naming difficulty, and degraded object knowledge [19]. On testing, they demonstrate severe impairments in confrontation naming and single-word comprehension (particularly for low-frequency words) but have intact speech production and repetition. Eventually they lose not only the object names but also the knowledge of the meaning or use of an object—degraded semantic representations and object knowledge [19]. Because of their difficulty with object naming and gradual loss of semantic knowledge, they may present with empty or circumlocutious speech. Surface dyslexia and dysgraphia (inability to read or write words with irregular pronunciation) can also be seen. In surface dyslexia, the patient sounds out words phonetically and has difficulty pronouncing words that do not follow regular pronunciation rules like "colonel," "yacht," or "pint" but can read nonwords fluently [20]. Visual object concepts seem to be more difficult than abstract concepts for patients with semantic PPA [21]. Repetition and motor speech are spared. Speech is fluent, phonetically accurate, and syntax and prosody are normal.

As the loss of semantic knowledge progresses, speech becomes increasingly vague and generic with substitution of superordinate terms such as "animal" for "camel" or "food" for "grapes" with increasingly semantically impoverished speech [22]. Semantic PPA goes beyond a visual agnosia because while the semantic PPA patient cannot recognize objects, they also cannot answer questions that require object knowledge such as naming in response to an auditory cue (e.g., "jewelry for the finger") or recognizing sounds. Because

of the loss of object knowledge, semantic PPA patients will have difficulty determining if an object is presented in the correct color, if a tool matches an object for which it is used, or answering true or false to semantic probes such as "bananas are yellow." They become incapable of drawing the defining features of specific animals, for example, drawing a trunk on an elephant. Figure 31.2 shows drawings of various animals or objects made by a patient with semantic PPA. Note the lack of defining features, suggesting loss of subordinate semantic level representations. Table 31.1 shows the patient's responses to questions assessing semantic knowledge.

Logopenic PPA: Patients with logopenic PPA have impairments in single-word retrieval in conversation and on testing of naming to confrontation or to auditory cues. In addition, to meet criteria for logopenic PPA, patients must have impaired repetition of sentences and phrases [2]. Speech may be slow with frequent word-finding pauses, but this differs from the halting, agrammatic, and aprosodic speech that characterizes nonfluent PPA. Paraphasic errors tend to be more phonological (substituting words with similar sounds) than semantic. It is possible that some clinicians will perceive speech output as nonfluent, but on formal testing that focuses on articulation and grammar, these patients are likely to score as "fluent." Logopenic PPA is thought to be a phonological loop [23] (a component of auditory working memory) disorder as supported by deficits on digit/letter/word span tasks and neuroimaging findings [24]. If a patient presents with the same features as logopenic PPA but repetition is intact, consider an anomic aphasia subtype of PPA. The anomic subtype may progress to include features of either logopenic or semantic PPA. If there are impairments in grammar and word comprehension early in the course, consider the mixed subtype [25].

Although patients with PPA may not be able to verbally communicate their thoughts, explicit memory is relatively intact. Poor verbal memory scores may be seen in PPA patients because the language deficit interferes with online encoding

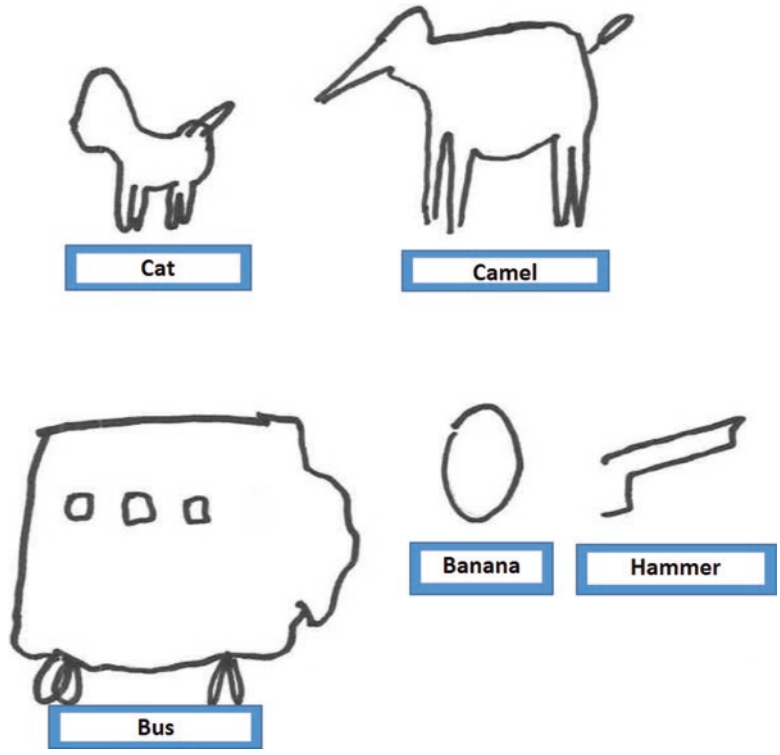

Fig. 31.2 Animal and object drawings by a patient with semantic PPA showing lack of defining object features suggesting loss of subordinate semantic level representations

Table 31.1 Responses to semantic probes by a patient with semantic PPA

Following commands:
Hold your hand out with your palm up ("What's a palm?") (poor comprehension due to semantics)
Semantic probes:
Does a hyena like to laugh? ("What's a hyena?")
Does a deer have antlers? ("I know what a deer is, but what are antlers?")
Naming to semantic descriptions:
Bird that drills holes in trees ("I don't know")
Farm animal that gives milk ("that's easy, we see them so often, it's not a frog, it's not a horse")
Vehicle with pedals and has two wheels ("I know what you mean, you can ride it")
Largest animal in the ocean ("we just saw them in Hawaii")
Reading phonetically irregular words (i.e., surface alexia):
Said "dow" instead of "dough"
Said "yakt" instead of "yacht"
Said "coop" instead of "coup"

due to language rather than medial temporal lobe dysfunction. Executive functioning, visuospatial skills, and social comportment are initially preserved but can decline as the disease progresses. During the middle or late stages of PPA, widespread cognitive deficits, behavioral changes, and abnormal motor functioning are likely due to the close anatomical proximity to regions important for such functions [25]. As with other neurodegenerative conditions, differential diagnosis becomes more challenging in the moderate to late stages.

Neuroimaging and Clinical Pathological Correlates

Understanding the neuroimaging correlates and histopathological basis of PPA is key for advancing future targeted treatments. Specific variants of PPA are preferentially associated with different underlying pathological findings, but finding an underlying pathology is not diagnostic of a specific variant of PPA. Table 31.2 shows the behavioral features and typical neuroimaging correlates of each PPA variant.

Nonfluent PPA is most often associated with frontotemporal lobar degeneration FTLD-tau-positive (Pick bodies) or less frequently FTLD-TDP (ubiquitin) pathological changes. Imaging changes in nonfluent PPA include left inferior frontal gyrus, insula, premotor, and supplementary motor areas [5]. Semantic PPA is most commonly associated with FTLD-TDP pathological changes [26] and anterior temporal lobe atrophy. Logopenic PPA is most commonly associated with Alzheimer's disease pathology [27], and voxel-based morphometry shows a pattern of atrophy in the left perisylvian, inferior parietal, temporoparietal junction and left posterior superior and middle temporal gyrus [5, 24, 28].

Differential Diagnosis

The clinician must make a concerted effort to rule out other possible causes of aphasia or language disturbance prior to diagnosing PPA. Most notably, the clinician will need to rule out static causes for aphasia such as a stroke to the language dominant hemisphere. For strokes, the onset of language impairment is abrupt. Motor and sensory symptoms may be seen, and the course is one of improvement rather than decline over time. Transient conditions such as akinetic mutism could mimic an advanced nonfluent PPA. The course of PPA is slower than that of a neoplasm [29]. Neuroimaging is useful to rule out lesions or masses in the dominant hemisphere, and quantitative MRI with volumetrics can identify focal brain atrophy that would point to a specific variant of PPA [30–32]. Other conditions that can cause progressive decline in speech must also be considered such as motor speech deficits (e.g., dysarthria, dysphonia, and hypophonia in patients with myasthenia gravis, multiple sclerosis, or Parkinsonism). Most patients with PPA have similar biomarkers to those which characterize frontotemporal dementia (FTD) or Alzheimer's disease (AD), but there are regions of brain atrophy that are specific to individual PPA variants that are not classic of behavioral variant FTD (bvFTD) and AD [2]. Patients with bvFTD can experience language impairment,

Table 31.2 Behavioral and neuroimaging correlates the PPA subtypes

PPA variants			
Determine the course and presentation of symptom onset	**Nonfluent/ agrammatic**	Behavioral features	Agrammatic language production
			Nonfluent speech characterized by effortful, halting speech with inconsistent paraphasic errors
			Possible impaired comprehension of syntactically complex sentences
Difficulty with language should be the most prominent clinical feature and deficit at symptom onset and for the initial phase of the disease			Spared single-word comprehension and object knowledge
		Neuroimaging	Left posterior fronto-insular atrophy or hypoperfusion or hypometabolism on SPECT or PET
	Semantic	Behavioral features	Impaired object knowledge, particularly for uncommon items
Language deficits impair activities of daily living			Impaired confrontation naming
			Impaired single-word comprehension
			Surface dyslexia or dysgraphia
Amnestic disorders can occur later in the course but are not the presenting feature			Spared repetition and speech production ability
		Neuroimaging	Predominant anterior temporal lobe atrophy or hypoperfusion or hypometabolism on SPECT or PET
	Logopenic	Behavioral features	Impaired word retrieval in spontaneous speech and object naming
			Impaired repetition of sentences and phrases
			Phonological errors on speech production tasks with absence of frank agrammatism
			Spared single-word comprehension and object knowledge
		Neuroimaging	Predominant left posterior perisylvian or parietal atrophy or hypoperfusion or hypometabolism on SPECT or PET

though the primary presenting complaint is behavioral or social comportment changes. Patients with Alzheimer's disease often have impairment in naming, but memory decline occurs in tandem with anomia. In posterior cortical atrophy, generally considered an atypical variant of AD, the presenting complaint is difficulty with reading, visual agnosia, oculomotor apraxia, optic ataxia, and simultanagnosia [33, 34]. Individuals who have neurodegenerative motor syndromes, such as amyotrophic lateral sclerosis, are at greater risk for developing FTD, so such syndromes should not necessarily be exclusionary for diagnosing PPA. Clinicians may prefer to use the term "PPA-plus" for cases in which the primary presenting *cognitive* complaint is language decline that occurs *after* other noncognitive symptoms emerge in the degenerative condition [25]. For example, patients with ALS may develop nonfluent PPA along with weakness, fasciculations, and muscle wasting [35]. Individuals with progressive supranuclear palsy have a gait disorder and vertical gaze palsy and may develop nonfluent PPA. In cortical basal degeneration, a Parkinson's plus syndrome, the patient may have rigidity, limb apraxia, alien hand, and a nonfluent aphasia. Table 31.3 presents conditions associated with language impairment that can aide the clinician in diagnostic considerations.

The Clinical Evaluation

As with any comprehensive neuropsychological assessment, the clinical interview is a critical component of assessing for possible PPA and can play a key role in differential diagnosis of the PPA variants. In addition to providing the patient with a chance to describe their specific

Table 31.3 Differential diagnosis of PPA

Course of language deficit	Possible diagnoses
Longstanding with no report of decline	• Early neurologic insult affecting the dominant hemisphere • Developmental language disorder • Reading disorder • Disorder of written expression
Slow, insidious with primary complaint of language decline	• PPA (semantic, logopenic, nonfluent/agrammatic)
Slow, insidious, or *stepwise* with primary complaint of other cognitive impairment or motor dysfunction	• Amyotrophic lateral sclerosis • Corticobasal degeneration • Progressive supranuclear palsy • Alzheimer's disease • Posterior cortical atrophy • Behavioral variant of FTD • Retrieval-based word-finding problems related to vascular cognitive impairment, Parkinson's disease, normal pressure hydrocephalus, etc.
Acute or *rapid*	• Stroke • Seizure • Neoplasm • Traumatic brain injury

concerns, the clinical interview provides a rich opportunity for observing the patient's spontaneous language abilities and areas of impairment in casual conversation. For example, examiners should be attuned to an individual's fluency of speech, which includes phrase length, rate of speech, prosody, and effortfulness. Attention should be paid to paraphasic errors, syntactic errors, agrammatisms, and issues with language comprehension. Such behavioral observations can be as important, or even more so, than explicitly reported concerns. Input from a co-informant such as a family member or close friend who has regular contact with the patient can also be highly beneficial, particularly when a patient's degree of language impairment or other cognitive deficits may impede their ability to communicate.

To aid in accurate diagnosis, it is also important to gain an understanding of the onset and course of any language difficulties during the clinical interview. First, obtaining a clear characterization of the patient's current impairments, as well as their premorbid level functioning, is necessary, as a diagnosis of PPA is predicated on a decline from previously intact premorbid language abilities [1]. Second, a gradual onset and progressive decline in language are characteristic of PPA, whereas a more acute onset and/or stepwise decline may signal a different etiology for a patient's aphasic symptoms (e.g., a vascular etiology; see Differential Diagnosis for further considerations).

Furthermore, the clinical interview should include questions regarding perceived deficits (or the lack there of) in domains beyond language. In instances where the condition has been present for some time, interview information is useful for determining whether the criteria of exclusive impairment in language during the early years of the disease have been met. While standardized neuropsychological tests play a critical role in PPA diagnosis, many tests rely heavily on comprehension of verbal instructions, require patients to provide verbal responses, or require covert verbal reasoning, which may result in apparent deficits in nonlanguage domains that are actually driven by the patient's core language deficits [1]. As such, a detailed clinical interview can be highly beneficial for teasing apart difficult aspects of differential diagnosis.

Language Assessment Battery

Consideration of the different cognitive processes that are disrupted in the three variants of PPA guides test selection. While not an exhaustive list, below are selected tests that many practicing neuropsychologists have access to and can be readily implemented for assessing PPAs (Table 31.4).

Figure 31.3 provides a list of cognitive tests by language process that can also be used to guide the clinician when choosing a battery of tests.

Table 31.4 Test lists for assessing the PPA subtypes

PPA subtype	Deficit	Measures for assessment
Nonfluent-grammatic	Agrammatic language	BDAE: cookie theft card
	Speech apraxia/poor articulation	Verbal fluency measures; BDAE: oral agility, verbal agility, automatized sequences
	Impaired syntax for complex sentences	BDAE: syntactic processing; MAE: token test; Woodcock-Johnson: understanding directions
Logopenic	Dysnomia with spared object recognition	BDAE: BNT, cookie theft
	Phonological paraphasias on speech production tasks, phonological dyslexia, or dysgraphia	Woodcock-Johnson: word attack, letter-word identification, spelling, spelling of sounds, sound awareness-rhyming; BDAE: word and nonword repetition; WIAT: pseudoword decoding
	Impaired repetition of sentences and phrases	MAE: sentence repetition: BDAE: sentence repetition
Semantic	Impaired object knowledge, particularly for uncommon items	BDAE: BNT, cookie theft, complex ideation, praxis, semantic probe, word comprehension by categories; Woodcock-Johnson: reading vocabulary, oral comprehension, passage comprehension; WAIS-IV: information; category fluency; Pyramid and Palms or Camel and Cactus
	Impaired confrontation naming	BDAE: BNT, cookie theft
	Impaired single-word comprehension	BDAE: word-picture matching
	Surface dyslexia or dysgraphia	Test of Irregular Word Reading Efficiency

Key: test names and citations
Boston Diagnostic Aphasia Examination (BDAE-3) [10]
Camel and Cactus Test [36]
Multilingual Aphasia Examination: MAE [37]
The Pyramid and Palms Trees Test [12]
Test of Irregular Word Reading Efficiency [13]
WIAT III: Wechsler Individual Achievement Test [38]
Woodcock-Johnson III [39]

Information for Caregivers

Accurate diagnosis of PPA is important for various reasons, but what follows is specific to caring for patients with PPA irrespective of the variant. Education for patients and their primary support system is important for setting up expectations and making appropriate adjustments to facilitate communication. The neuropsychological evaluation is a great tool to use for education on deficits and areas of intact cognitive skills. For instance, family may think that the patient has memory impairment because they are "forgetting" the names of objects when, instead, the deficit is in verbal confrontation naming. Family members may describe the patient as confused when the patient is having language comprehension deficits that lead to tangential responses to questions. Helping caregivers understand the type of language impairment(s) faced by the patient will set the stage for discussing patient-centered recommendations. Using laminated cards, voice synthesizers, or other technological devices (e.g., tablet and smartphone) to facilitate communication can be helpful for certain patients with PPA [40–43]. Some patients with PPA can learn sign language and may benefit from speech therapy to determine the utility of other communication methods. Collecting information on local support groups and educational programs to provide to families and patients provides great resources. Below are some recommendations to consider.

Suggestions for caregivers:

- Try not to interrupt the patient and finish his/her sentences unless they appear visibly frustrated or request you to do so.
- Do not be quick to correct or point out language errors.

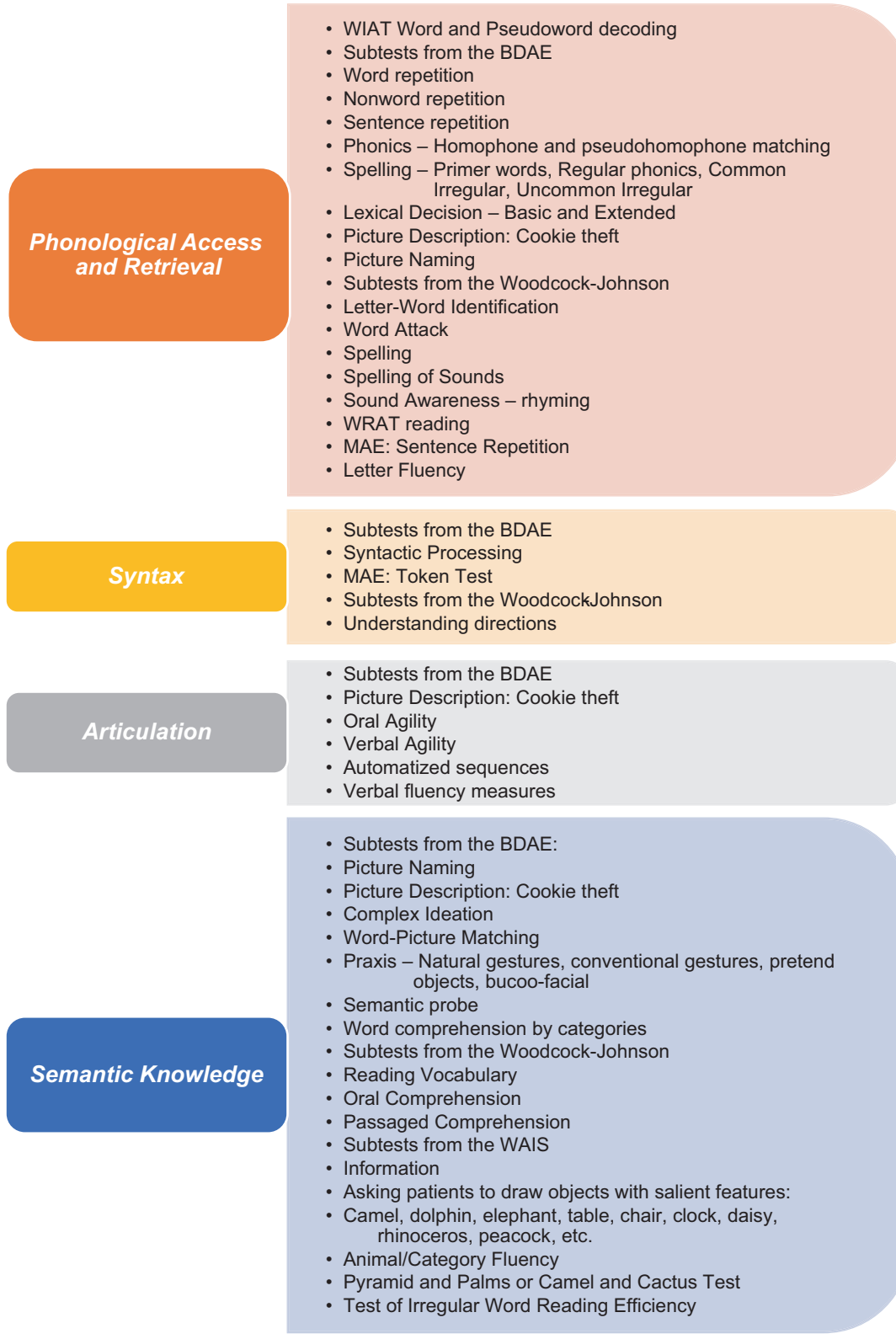

Fig. 31.3 Test list by language process

- It is okay to ask for clarification and help cue the patient if requested to do so or if the patient appears frustrated.
- Be supportive and adapt to the patient's communication needs.
- Speak slowly and simplify word choice to facilitate comprehension.
- Ask questions with two choices instead of open-ended questions.
- Try to limit distractions and noise when conversing.

Suggestions for patients:

- If you cannot find a word, try to talk around the word. Describe the word or find a substitute word.
- Use gestures and other nonverbal cues to help communicate.
- Take your time to convey a thought, and simplify the content of your message where needed.
- Electronic devices, a picture board, or cards with symbols, photos, or objects can be used as the disease progresses to help supplement or replace speech.
- For nonfluent PPA (adapted from [44]):
  - Make notes prior to important meetings or conversations including relevant vocabulary.
  - Rehearse a sentence mentally prior to speaking.
  - Plan important conversations at times of day where fluency is highest or allow a period of restorative silence prior to important conversations.
  - Avoid conversing in noisy or overstimulating environments.
  - When having trouble selecting a word during writing, run through choices by speaking aloud.
  - Use a voice recognition dictation software if speaking is less effortful than writing as this will eliminate spelling demands.
- Websites: The Association for Frontotemporal Degeneration (www.theaftd.org) and The National Aphasia Association (www.aphasia.org)

Case Report

A 74-year-old man presented to the neuropsychology clinic with a complaint of gradual decline in memory and dysnomia over the past 1.5 years. He reported minimal concerns with memory; however, his wife said that he tends to forget conversations. In terms of language, he described severe dysnomia and the need to use a computer for spell-checking. He reported no changes to his handwriting, problems with articulation, mispronouncing words, or problems with language comprehension. Brain MRI showed mild asymmetric volume loss in the left frontotemporal region with prominence of sulcal spaces including the sylvian fissure (see Fig. 31.4). He completed his Bachelor's Degree in Business and spent his career employed for a local utility company. He had a neuropsychological evaluation 1 year before, which showed significant problems with word knowledge, picture-naming, speeded word retrieval, and some tests of memory, with the exception of normal performance on a verbal list memory task.

During the interview, the patient was alert, responsive, and well oriented. He was a good personal historian and could easily recall recent news events; however, he had a difficult time finding specific words when describing events. For example, he struggled to find the word "microwave" when describing how he made dinner the night before and instead called it, "a box shape that you open and press keys, and it uses electricity." Phonemic cuing of the first half of the word, i.e., *micro*, was not helpful.

On testing, his neuropsychological profile was most notable for language impairment. Specifically, his speech was fluent with normal rate and prosody. He was severely dysnomic and was unaided by semantic or phonological cuing during casual conversation. His performance was severely impaired (1st percentile) on a picture-naming task, and he was only moderately aided by phonemic cuing (41% of missed trials). In comparison to his previous neuropsychological testing, his naming accuracy declined from 72% correct to 55% correct. He made several

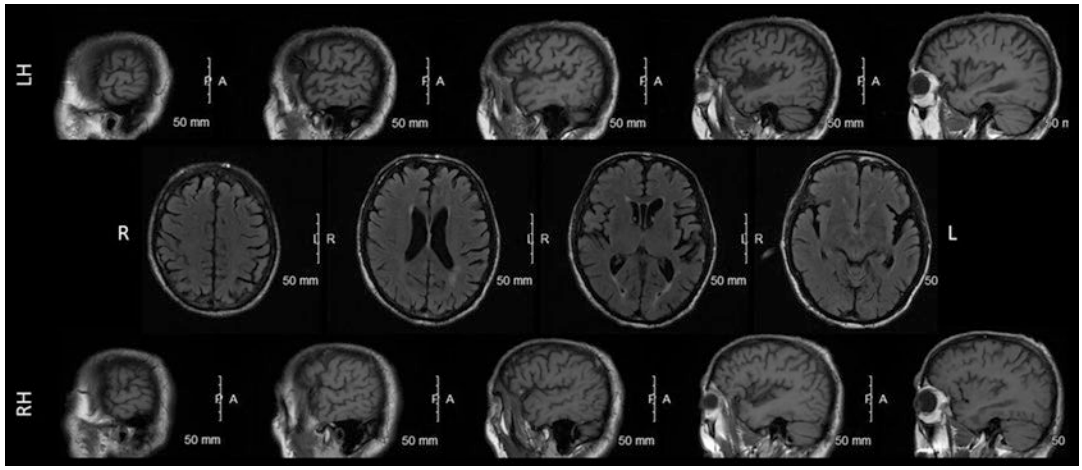

Fig. 31.4 Brain imaging for a patient with logopenic PPA. T1 MRI (sagittal views) and T2 FLAIR (axial views). Notice the increased sulcal spacing in the left hemisphere (LH: top row) in comparison to the right hemisphere (RH: bottom row)

phonemic paraphasic errors (such as saying the word *damp* for the target word *lamp*) when reading words and pseudowords (e.g., *bloy*). He was able to spell high-frequency basic primer words (i.e. *dog*) without difficulty but was unable to spell more complex regular words ("flage" for the word *flag*) and irregular words ("quire" for *choir* and "caurnal" for *colonel*). His relatively better performance for real words than pseudowords and low-frequency irregular words was characteristic of a phonological dyslexia and dysgraphia. His difficulty accessing the phonological codes for words was thought to be influencing his ability to successfully complete several other language-based cognitive measures. In terms of memory, he had borderline performance on a story memory test but average performance on a list-learning task. An important difference between these two tasks is the multiple presentations of the verbal list (read five times) in comparison to the story, which is presented twice. Thus, multiple repetitions of verbal information were beneficial to overcoming his phonological access impairment. Further support for a language-based impairment rather than a nonspecific amnestic presentation was the fact that he performed in the average range on a visual memory task that did not require language. In comparison to his previous neuropsychological test results, he did not demonstrate an appreciable decline in accuracy on memory tests, a finding that would be unusual if he had a primary Alzheimer's dementia diagnosis.

The patient was given a diagnosis of logopenic primary progressive aphasia based on neuroimaging showing cortical atrophy in the perisylvian region and the pattern of neuropsychological test results. More specifically, the patient meets criteria for imaging-supported logopenic variant PPA based on impaired single-word retrieval in spontaneous speech and naming, impaired phrase repetition, phonological errors in spontaneous speech and naming, spared single-word comprehension and object knowledge, spared motor speech and fluency, and the absence of agrammatism. The diagnosis is "imaging supported" because of the left perisylvian atrophy.

Clinical Pearls

- PPAs are considered a form of frontotemporal dementia even though the pathology of some variants is present outside of the frontal lobes such as semantic or logopenic PPAs.
- If word-finding problems and significant memory impairment are of similar duration, a garden-variety Alzheimer's disease is a more likely diagnosis than PPA.

- In the early phase of nonfluent PPA, the patient may produce normal scores on classic language measures with the only deficit being on word list generation tasks.
- If a patient no longer recognizes the meanings of objects, consider evaluating them for semantic PPA.
- Patients presenting primarily with complaints of an inability to read may have posterior cortical atrophy which is not a form of PPA.
- Patients who have robotic, halting, or aprosodic speech but largely normal scores on naming and language comprehension may be showing the early stages on a nonfluent PPA.
- Naming deficits can be seen in both semantic and logopenic PPAs, but in semantic PPA, the patient also loses the ability to provide semantic information about the object, such as how it is used.
- Repetition speech impairment is one of the hallmarks of logopenic PPA.
- A patient with semantic PPA may score poorly on verbal story memory measures because of his/her difficulty with the semantic aspects of the stories.
- Patients with logopenic PPA may score poorly on single-trial verbal list learning due to poor repetition and working memory that interferes with a recency effect as they are not able to hold recently presented words in mind.

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Assessment in Acute Stroke Rehabilitation

32

George M. Cuesta and Lisa Gettings

Background

Stroke is the fifth leading cause of death in the United States, killing more than 130,000 Americans each year, i.e., 1 out of every 20 deaths [1]. Someone in the United States has a stroke every 40 s; every 4 min, someone dies of a stroke [2]. Every year, nearly 795,000 people in the United States have a stroke. Of these, 610,000 are first or new strokes, and 185,000 are recurrent strokes [2]. As a consequence of the accelerated aging of the US population, stroke will remain a public health problem with adverse personal, societal, and economic implications. For example, stroke costs the United States an estimated $33 billion each year [2]. This total includes the cost of healthcare services, medicines to treat stroke, and missed days of work. Stroke is the leading cause of serious long-term disability [2]. It reduces mobility in more than half of stroke survivors age 65 and over [2].

The risk of having a stroke varies with race and ethnicity. For example, the risk of having a first stroke is nearly twice as high for blacks as for whites, and blacks are more likely to die following a stroke than are whites [2]. The risk of stroke for Hispanics falls between that of whites and blacks [2]. Native Americans, Alaska Natives, and blacks are more likely to have a stroke than are other groups [3].

While stroke risk increases with age, they can and do occur at any age. In 2009, for example, 34% of people hospitalized for stroke were less than 65 years old [4].

Stroke survivors represent the largest diagnostic category of referrals to acute rehabilitation hospitals [5]. According to Caplan (2010), rehabilitation services for stroke patients are typically provided to those in the middle range of impairment [6]. While those with milder strokes are frequently discharged directly to home with outpatient therapy or home care, those with more severe strokes who cannot tolerate inpatient rehabilitation are discharged to a long-term care facility with limited rehabilitation therapy services.

Neuropsychologists who work in acute stroke rehabilitation settings will find that providing assessment and intervention to this patient population demands a broad range of skills. They must be well trained, knowledgeable, and competent in neuropsychology, rehabilitation psychology,

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and health psychology in order to provide effective assistance to their three principal constituencies: stroke patients, their family caregivers, and the stroke rehabilitation treatment team. Neuropsychologists assist these constituencies with managing the physical, cognitive, behavioral, emotional, social, sexual, and vocational consequences of stroke. This chapter will provide a brief overview of the knowledge, skills, and competencies needed for neuropsychologists who work in an acute stroke rehabilitation setting.

What follows is information about stroke prevalence, incidence, definitions, stroke risk factors, clinical signs and symptoms of stroke, pathophysiology of stroke, diagnostic issues for the physician, neuropsychological assessment in an acute rehabilitation setting, neuroimaging issues, common referral questions for the neuropsychologist, suggested neuropsychological testing batteries, and clinical pearls from the author's experiences working in an acute rehabilitation setting.

Prevalence. An estimated 6,400,000 Americans, 20 years of age and older, have had a stroke (extrapolated to 2006 using National Center for Health Statistics/National Health and Nutrition Examination Survey 2003–2006 data). Overall stroke prevalence during the period from 2003 to 2006 was estimated at 2.9% [7]. According to data from the 2005 Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, 2.7% of men and 2.5% of women age 18 and greater had a history of stroke. Among these, 2.3% were non-Hispanic white, 4.0% were non-Hispanic black, 1.6% Asian/Pacific Islanders, 2.6% were Hispanic of any race, 6.0% were Native American Indian/Alaska Native, and 4.6% were admixed [8].

Incidence. On average, every 40 s, someone in the United States has a stroke. In the United States alone, more than 700,000 people suffer a stroke each year, and about 2/3 of these individuals survive and require rehabilitation [9]. The most recent data from the Heart Disease and Stroke Statistics 2016 Update, a report from the American Heart Association [2], indicated that each year about 795,000 people experience a new or recurrent stroke. About 610,000 of these are first attacks, and 185,000 are recurrent attacks. The age-adjusted incidence of first ischemic stroke per 100,000 was 88 in whites, 191 in blacks, and 149 in Hispanics, according to the data from the Northern Manhattan Study [10]. The stroke incidence rate is higher for men compared with women at younger ages, but not at older ages. The male-to-female incidence ratio was 1.25 in those 55–64 years of age, 1.50 in those 65–74 years of age, 1.07 in those 75–84 years of age, and 0.76 in those 85 years of age or greater [2].

On average, every 4 min, someone dies of a stroke. Mortality data from 2006 indicated that stroke accounted for approximately 1 of every 18 deaths in the United States. In the decade from 1996 to 2006, the stroke death rate fell 33.5%, and the actual number of stroke deaths declined to 18.4%. More women than men die of stroke each year due to the larger number of elderly women. Women accounted for 60.6% of stroke deaths in the United States in 2006. The 2006 overall death rate for stroke was 43.6 per 100,000. Death rates were 41.7 for white males, 67.1 for black males, 41.1 for white females, and 57.0 for black females [11].

Definitions. A *stroke* occurs when brain cells die as a consequence of inadequate blood perfusion. When blood flow is interrupted, brain cells are robbed of vital supplies of oxygen and nutrients. Fully 80% of strokes are caused by blockage of an artery in the neck or brain. These are referred to as *ischemic strokes*. In ischemic strokes, blood flow is insufficient to maintain neurologic function, and infarction occurs when ischemia reaches a threshold to produce cell death. The remaining 20% of strokes are caused by a blood vessel that bursts in the brain and causes bleeding into or around the brain. These are called *hemorrhagic strokes*. A *transient ischemic attack* is an acute transient neurological deficit that typically lasts less than 1 h and is without persistent neurological

abnormality or evidence of acute infarction on neuroimaging [12]. A *silent stroke* is a brain injury of vascular origin that is appreciated on neuroimaging, but is not associated with symptoms. Silent strokes are frequently found during diagnostic neuroimaging of an acute stroke in patients with no prior history of a stroke. A *lacunar infarct* is a small cavity caused by a small deep cerebral infarct and is most often associated with arterial hypertension. These appear predominantly in the basal ganglia, thalamus, and white matter of the internal capsule and the pons [12].

Risk Factors. Some risk factors for stroke are modifiable (e.g., hypertension, diabetes mellitus, atrial fibrillation, alcohol use, smoking) and are subject to external control by changes in lifestyle. Manipulation of modifiable risk factors may have dramatic effects on the incidence, prevalence, economic effects, and personal costs of stroke. Devasenapathy and Hachinski (2004) asserted that up to 75% of all strokes are preventable [13]. Other researchers have asserted that nearly 379,000 strokes could be prevented each year through treatment of atrial fibrillation, cigarette smoking, hypertension, heavy alcohol consumption, and physical inactivity [14].

However, some of the risk factors for stroke are not modifiable. These include prior stroke, age, gender, race, ethnicity, and heredity. Stroke risk increases with age. For example, the lifetime risk for stroke in adults over the age of 55 is greater than 1 in 6 and doubles with each successive decade after age 55 [15].

Clinical Signs and Symptoms of Stroke. In general, onset of stroke symptoms is acute. According to the National Institute of Neurological Disorders and Stroke (NINDS [16]), common presenting neurological symptoms include the following [16]:

1. Sudden numbness or weakness of the face, arm, or leg on one side of the body
2. Sudden confusion, trouble speaking, or understanding
3. Sudden trouble seeing in one or both eyes
4. Sudden trouble walking, dizziness, and loss of balance or coordination
5. Sudden severe headache with no known cause

Pathophysiology. There are many different types of strokes, each having a different cause. The two main types of stroke are *ischemic* stroke and *hemorrhagic* stroke. The following is a very basic description of these stroke types and the four most common causes of stroke (two of which are ischemic and two of which are hemorrhagic). For a more detailed description of the pathophysiology of stroke, the interested reader is referred to Barnett et al. [17].

The pathophysiology of *ischemic* strokes is widely known. They are the most common type of stroke, contributing to more than 80% of all stroke cases. They are caused by plaque buildup and blood clots that subsequently deprive parts of the brain from adequate perfusion or blood flow, oxygen, and nutrients; this results in damage and death of brain cells and tissue and stroke. There are many factors that affect the buildup of a blood clot that results in stroke. The most common cause of ischemia and the infarction that follows it is *atherosclerosis*. This is a noninflammatory, progressive disease that begins in childhood and peaks between the ages of 50 and 70 and can affect any artery in the body. Fatty deposits accumulate on the arterial wall. These deposits produce a *thrombus* that over time gradually narrows the arterial passage until the blood vessel becomes sufficiently occluded to produce a stroke. Permanent damage generally ensues with complete deprivation of blood flow beyond several minutes [6]. The likelihood of a stroke is largely affected by several main factors including age, family history, systolic blood pressure, smoking, alcohol use/abuse, diet, myocardial disease, diabetes, and atrial fibrillation. Of these, age and systolic blood pressure are the most influential factors in ischemic strokes.

Another type of ischemic event is the *lacunar stroke* that occurs when small penetrating branches of the major cerebral arteries become clogged and result in a thrombotic infarction. These types of strokes frequently affect the basal

ganglia, internal capsule, thalamus, and the pons. Location-specific syndromes can result from lacunar infarcts. These include pure motor or sensory stroke, dysarthric stroke, and hemiparesis with ataxia [6].

The *embolic stroke* is produced by an abrupt interruption of blood supply by pieces of thrombus that have broken loose from one part of the blood vessel system and later lodged in a narrower vessel downstream. This type of stroke mechanism causes rapid focal onset symptoms with little opportunity for compensation by collateral blood supply routes [6, 17].

Hemorrhagic strokes are caused by a blood vessel that bursts either within the brain or just outside it. These strokes frequently result in dramatic onset of symptoms. Hemorrhagic strokes are typically classified according to the anatomical location of the bleeding. Therefore, neuropsychologists may read in the patient's history and physical examination report that the hemorrhagic stroke was extradural, subdural, subarachnoid, intercerebral, intracerebral, or cerebellar. The main causes of hemorrhagic strokes are systolic blood pressure, age, and anticoagulation. High blood pressure is the main cause of both hemorrhagic and ischemic strokes. There are some less common causes of hemorrhagic strokes, and these include cranial trauma, tumors, hypertensive hemorrhages, and vasculitides, all of which lead to accumulation of blood around the brain causing hemorrhagic stroke.

The third most common cause of stroke after thrombotic and embolic strokes is the *primary intracerebral hemorrhage*. This hemorrhagic stroke results from degeneration and rupture of a penetrating cerebral artery, often due to hypertension. The blood rarely reaches the surface of the cortex but enters the cerebrospinal fluid in about 90% of the cases. Significant compression of the brain stem structures can be fatal [6, 17].

The fourth most common cause of stroke is the *subarachnoid hemorrhage* (SAH). This hemorrhagic stroke results from rupture of a saccular aneurysm. An aneurysm is a ballooning of an arterial wall due to congenital weakness in its structure. The ballooning further weakens the blood vessel's arterial wall making it prone to rupture and hemorrhage. In this type of hemorrhagic stroke, the blood leaks into the subarachnoid space between the external surface of the brain and the arachnoid meningeal layer. This type of stroke announces itself in an acute or gradual manner depending on the size of the affected blood vessel and the rupture itself. When onset is rapid, the consequences are often severe and life-threatening. The patient complains of a sudden and severe headache, and intracranial pressure dramatically elevates as a consequence of the injection of blood into the brain from the ruptured vessel [6, 17].

Diagnosis of Stroke. In general, diagnosis of stroke is beyond the scope of practice of neuropsychologists; nevertheless, knowing the decision-making process whereby physicians make a stroke diagnosis can richly inform neuropsychological practice. According to Yew and Cheng (2009), the history and physical examination remain the pillars of diagnosing stroke [18]. The most common historical feature of an ischemic stroke is acute onset; the most common physical findings of ischemic stroke are focal weakness and speech disturbance [19]. The most common and reliable signs and symptoms of ischemic stroke are listed in Table 32.1 [18–21]. In a community-based study of diagnostic accuracy, primary care physicians practicing in an emergency setting had 92% sensitivity for diagnosis of transient ischemic attack (TIA) and stroke [22].

Physicians must quickly assess persons with suspected acute ischemic stroke because acute stroke therapies (i.e., thrombolysis) have a narrow time window of effectiveness. One instrument that can assist the physician with rapid diagnosis of stroke is the National Institute of Health Stroke Scale (NIHSS [23, 24]). The NIHSS is available at http://www.nihstrokescale.org/docs/NIH_Stroke_Scale.pdf. This scale was designed to be completed within 5–8 min.

The physician must determine the exact time of symptom onset since it is critical for determining eligibility for thrombolysis. However, one community-based study found that clinicians agreed, to the minute, less than 50% of the time

Table 32.1 Most common symptoms and signs of stroke and their reliability [15]

Symptom or sign	Prevalence (%) [16]	Agreement among examiners (Kappa[a]) [17]
Symptoms		
Acute onset	96	Good (0.63) [17]
Subjective arm weakness[b]	63	Moderate (0.59) [17]
Subjective leg weakness[b]	54	Moderate (0.59) [17]
Self-reported speech disturbance	53	Good (0.64) [17]
Subjective facial weakness	23	–
Arm paresthesia[c]	20	Good (0.62) [17]
Leg paresthesia[c]	17	Good (0.62) [17]
Headache	14	Good (0.65) [17]
Nonorthostatic dizziness	13	–
Signs		
Arm paresis	69	Moderate to excellent (0.42–1.00) [17, 18]
Leg paresis	61	Fair to excellent (0.40–0.84) [17, 18]
Dysphasia or dysarthria	57	Moderate to excellent (0.54–0.84) [17, 18]
		Fair to excellent (0.29–1.00) [17, 18]
Hemiparetic or ataxic gait	53	Excellent (0.91) [18]
Facial paresis	45	Poor to excellent (0.13–1.00) [17, 18]
Eye movement abnormality	27	Fair to excellent (0.33–1.00) [18]
Visual field defect	24	Poor to excellent (0.16–0.81) [17, 18]

[a]Kappa statistic: 0–0.20 = poor agreement; 0.21–0.40 = fair agreement; 0.41–0.60 = moderate agreement; 0.61–0.80 = good agreement; 0.81–1.00 = excellent agreement
[b]Noted as "loss of power" [20]
[c]Noted as "loss of sensation" [20]
Information from References [19–21]

[20]. This finding suggested the need to corroborate time of symptom onset with a witness or a known event.

Neuroimaging must be completed in order to reliably distinguish between ischemic stroke and intracerebral hemorrhage. Both are characterized by acute onset of focal symptoms. However, patients with intracerebral hemorrhage typically have gradual worsening of symptoms after the abrupt onset. These worsening symptoms reflect the increasing size of the hematoma. Intracerebral hemorrhagic patients may also have decreased level of consciousness.

The primary purpose of neuroimaging in a patient with suspected ischemic stroke is to rule out the presence of other types of central nervous system lesions and to distinguish between ischemic and hemorrhagic stroke. Figure 32.1 provides examples of intracerebral and subarachnoid hemorrhages on computed tomography (CT) scans. CT scans are considered to be sufficiently sensitive at detecting mass lesions, e.g., brain masses or abscesses, as well as detection of acute hemorrhages. They may not, however, be sensitive enough to detect ischemic stroke especially when the stroke is small, acute, or in the posterior fossa (e.g., brain stem and cerebellum areas) [18, 25]. The purpose of CT scan is to rule out stroke mimics and to detect hemorrhage, however, not to rule in a diagnosis of ischemic stroke. A normal CT scan of the brain does not rule out the diagnosis of ischemic stroke. Multimodal magnetic resonance imaging (MRI) sequences, especially diffusion-weighted imaging, have better resolution than CT and, therefore, have better sensitivity for detecting acute ischemic stroke. Figure 32.2 is a dramatic illustration of this point.

Patients with subarachnoid hemorrhage present differently from intracerebral and ischemic stroke patients. The most common symptom described by the patient is having "the worst headache of my life." According to Suarez et al. (2006), other symptoms may include vomiting, seizures, meningismus, and decreased level of consciousness [26]. These patients may not exhibit focal signs due to bleeding that occurs

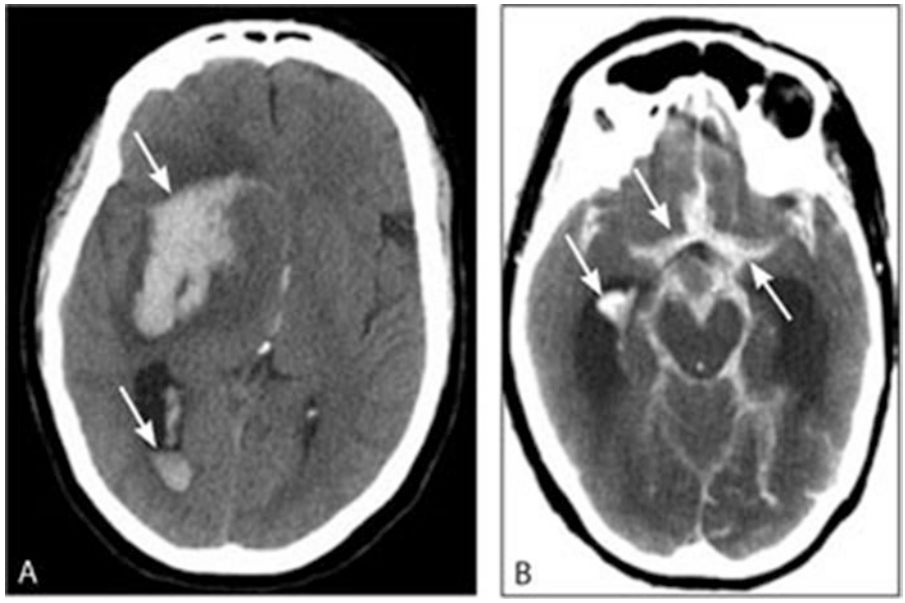

Fig. 32.1 Head computed tomography (CT) scans showing (**a**) intracerebral hemorrhages *(arrows)* and (**b**) subarachnoid hemorrhages *(arrows)*. Note that acute hemorrhage appears hyperdense *(white)* on a CT scan

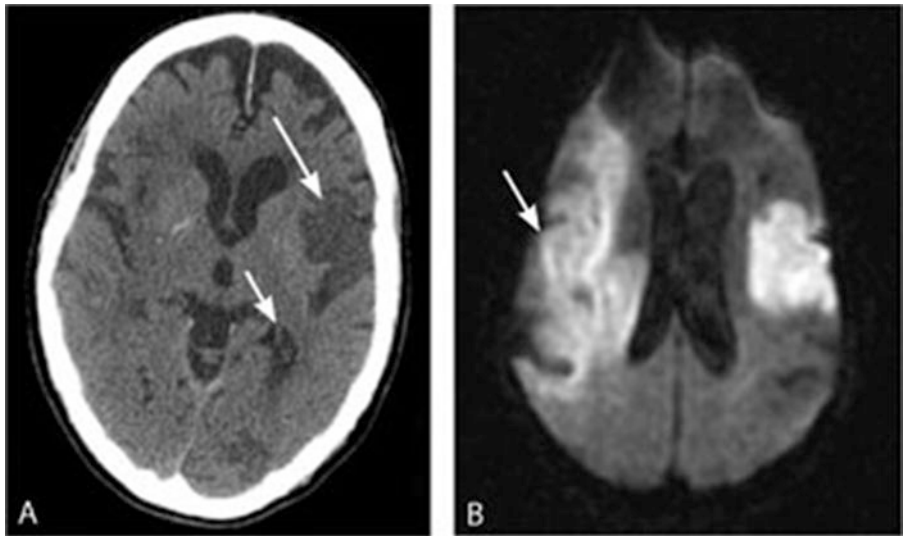

Fig. 32.2 (**a**) Noncontrast computed tomography (CT) scan showing two hypodense regions indicating old infarctions in the distribution of the left-middle cerebral *(long arrow)* and posterior cerebral arteries *(short arrow)*. (**b**) Diffusion-weighted magnetic resonance imaging scan obtained shortly after the CT reveals a new extensive infarction *(arrow)* in the right-middle cerebral artery distribution not evident on the CT. *Reprinted with permission from MedPix®*. Retrieved from http://rad.usuhs.edu/medpix

outside the brain. An exception to this is when an aneurysm bursts and bleeds into a focal location, e.g., a posterior communicating artery aneurysm that compresses the third cranial nerve.

Current guidelines for classification of early stroke severity recommend the use of the NIHSS [23]; however, no trial data currently exists that demonstrates that its use improves outcomes. It is one of the most common classification tools available and provides a structured neurological examination that has both diagnostic and prognostic value [23]. Yew and Cheng (2009) suggested that, in general, combinations of signs and symptoms are more useful than any single findings [18]. These authors presented a helpful algorithm for diagnosing stroke from several consensus sources, and these are presented in Fig. 32.3.

The Internet Stroke Center [28] has an excellent summary of the computed tomography (CT) and magnetic resonance imaging (MRI) criteria for infarction and hemorrhage; the interested reader is referred to that source for more detailed information.

Briefly, in CT imaging of *infarction*, the neuroradiologist will find a focal hypodense area in cortical, subcortical, or deep gray or white matter, following the vascular territory, or watershed distribution. CT imaging of *hemorrhage* will demonstrate a hyperdense image in white or deep gray matter, with or without involvement of the

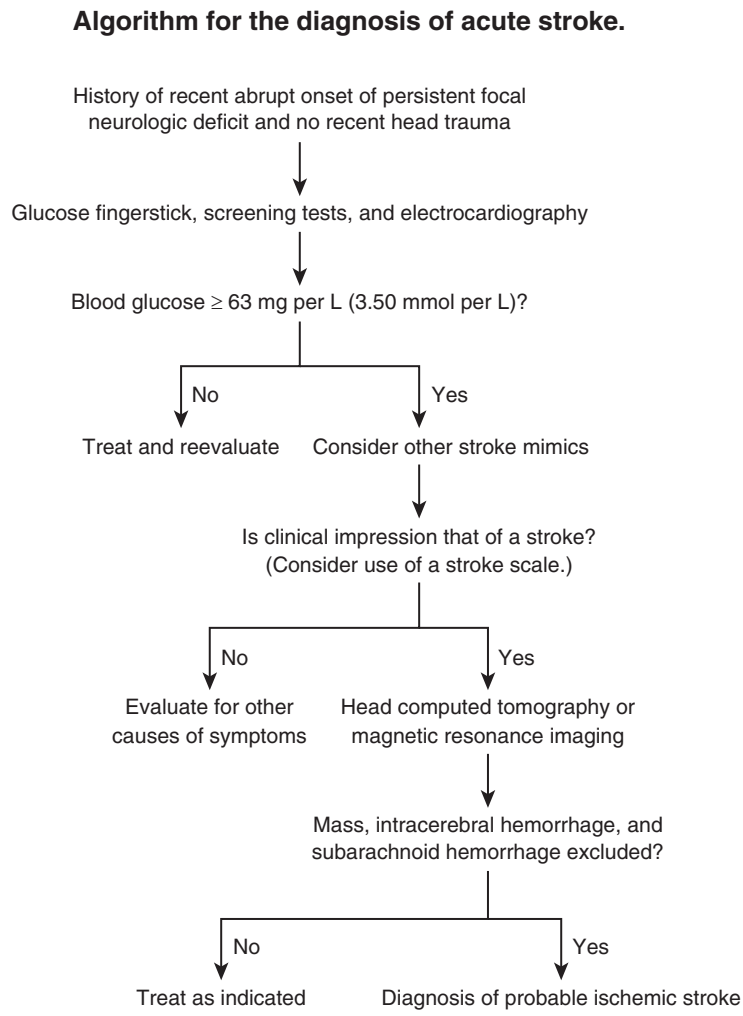

Fig. 32.3 Algorithm for the diagnosis of acute stroke. Information from References [20, 23, 27]

cortical surface. Hematoma refers to a solid, homogeneously hyperdense image [28].

In MRI imaging of an acute stroke, the clinician will find subtle low signal (or hypointense) on T1 imaging. According to the guidelines, this is often difficult to see at this stage. There is high signal (or hyperintense) on spin density and/or T2-weighted and proton density-weighted images starting about 8 h after onset, and it should follow vascular distribution. Mass effect is usually maximal at about 24 h and starts about 2 h after onset even in the absence of parenchymal signal changes. In subacute stroke, defined as 1 week or older, there is low signal on T1 and high signal on T2-weighted images and should follow the vascular distribution. Revascularization and blood-brain barrier breakdown may cause parenchymal enhancement with contrast agents. In old stroke, defined as several weeks to years, there is low signal on T1 and high signal on T2. Mass effect disappears usually after 1 month. There is loss of tissue with large infarcts and parenchymal enhancement fades after several months [28].

Poststroke Cognitive Impairment. Of primary concern to stroke neuropsychologists and other stroke rehabilitation specialists is the evaluation of cognitive impairment resulting from stroke. Up to 64% of persons who have a stroke will have some degree of cognitive impairment [29] with up to a third developing frank dementia [30–32]. Cognitive impairment that is caused by or associated with vascular factors has been called vascular cognitive impairment or VCI [33–35].

Prior to 2006, there were no commonly agreed upon standards for identifying and describing stroke patients with cognitive impairments, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment. In 2006, the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics, and clinical trials to recommend minimum, common, clinical, and research standards for the description and study of vascular cognitive impairment [36].

The Neuropsychology Working Group of this convention was charged with recommending test protocols that could be used in multicenter investigations of potential patients with vascular cognitive impairment (VCI). The protocols were dubbed the NINDS-CSN Neuropsychological Battery. Three different protocols were developed by the Neuropsychology Working Group to serve three different purposes. One protocol required about 60 min of administration time, the second required about 30 min, and the third required only 5 min of administration time. The 60-min protocol was developed for use in research studies. The 30-min and 5-min protocols were developed with clinical purposes in mind and will be further explained in the next section on Clinical Assessment. The interested reader is referred to the Hachinski et al. (2006) journal article for more detailed information [36].

Clinical Assessment

Diagnosis of acute ischemic stroke is often straightforward. The sudden onset of a focal neurologic deficit in a recognizable vascular distribution with a common presentation, i.e., hemiparesis, facial weakness, and aphasia, identifies a common syndrome of acute stroke. However, there are differential diagnostic problems because there are several subtypes of stroke, and some nonvascular disorders may have clinical pictures that appear identical to strokes. Table 32.2 provides a listing of common differential diagnosis of stroke as delineated by the Internet Stroke Center.

In an acute rehabilitation setting, by the time the patient arrives at the hospital, the diagnosis of stroke has usually been well established. Typically, the stroke event occurred in the community, while the patient was going about her/his normal everyday activities. The patient is taken to an acute care hospital where diagnosis is made by an emergency room physician and/or a stroke team, where available, and the patient is medically

Table 32.2 Differential diagnosis of stroke

Ischemic stroke
Hemorrhagic stroke
Craniocerebral/cervical trauma
Meningitis/encephalitis
Intracranial mass
Tumor
Subdural hematoma
Seizure with persistent neurological signs
Migraine with persistent neurological signs
Metabolic
Hyperglycemia (nonketotic hyperosmolar coma)
Hypoglycemia
Post-cardiac arrest ischemia
Drug/narcotic overdose

Source: American Heart Association. Basic Life Support for Healthcare Providers and Advanced Cardiac Life Support
From: *Acute Ischemic Stroke: New Concepts of Care* © 1998–1999 Genentech Inc. All rights reserved

stabilized. In consultation with the stroke team, a determination is made by family caregivers about whether the patient can manage the significant intensive intervention of an acute rehabilitation program. The patient is transferred to the acute rehabilitation hospital to begin orientation, assessment, and treatment intervention from a team of multidisciplinary professionals. The team typically includes a neurologist or physiatrist, nurses and nursing aides, social workers, occupational therapists, physical therapists, speech and language pathologists, recreational therapists, and the neuropsychologist.

From the day of admission, frequent anxiety-provoking concerns for family members/caregivers, rehabilitation team members, and clinicians are discharge planning and where the patient will go after they complete the trial of acute rehabilitation. Alternatives include short-term subacute rehabilitation (usually in long-term care facilities), home with home care services, home with day care services, or home with outpatient care. Ideally, all of these alternatives share in common varying degrees of frequency and intensity of occupational therapy, physical therapy, and speech therapy. The answer to the discharge placement question depends on the severity of the functional limitations (e.g., physical, cognitive, behavioral) produced by the stroke, the amount of functional recovery the patient makes during acute rehabilitation, and the resources (i.e., time, financial, emotional) available to the family. Neuropsychologists working in an acute rehabilitation setting are frequently consulted to evaluate the cognitive and behavioral limitations of stroke patients.

Common referral questions for the neuropsychologist working with stroke patients in the acute rehabilitation setting include:

1. Determining the cognitive strengths and weaknesses of the patient
2. Determining capacity to consent to treatment
3. Consultation regarding behavioral problems, e.g., agitation, aggression, and apathy

Cognitive Assessment: Regarding determination of cognitive strengths and weaknesses, family members and clinicians are frequently concerned about the patient's ability to manage activities of daily living and instrumental activities of daily living at home. The neuropsychologist can provide the rehabilitation team and the patient's caregivers with valid and reliable information from neuropsychological testing about the cognitive abilities that have been spared and the problem areas that remain. Rarely are these cognitive difficulties unaccompanied by behavioral issues. For example, a stroke patient may have impaired attention on neuropsychological testing that may be accounted for by destruction of attention pathways in the brain and exacerbated by the presence of post-stroke depression. The neuropsychologist can use any and every source of information available to her/him to determine impairments and strengths. Properly administered, scored and interpreted neuropsychological testing provides valid and reliable quantifiable information. However, in an acute rehabilitation setting, neuropsychologists work with teams, and these resources should be ethically exploited in order to obtain comprehensive information about the patient's functioning. For example, the neuropsychologist can observe the patient in occupational therapy during a cooking task or a dressing task

and make inferences about the patient's attention and memory functioning based upon these observations. Information from these observations can augment neuropsychological testing results. When these observations are consistent with neuropsychological testing results, they add to the ecological validity of the data.

Whenever possible, the neuropsychologist should, first, gather the facts about the stroke patient by reviewing her/his medical chart and then obtain feedback about cognition and behavior from the stroke rehabilitation team and from family caregivers. Additional key information to gather from collateral sources (e.g., family caregivers) includes a history of the patient's premorbid level of functioning (e.g., occupation, education, social support, temperament). Initially, a short visit with the patient might be helpful; in this visit, the neuropsychologist introduces her/himself, explains the reason for the visit, begins to build rapport, elicits the patient's informed consent for evaluation, and books a time to meet. The evaluation has already begun since the visit provides the opportunity for the neuropsychologist to start gathering preliminary information about the stroke patient's behavior, cognition, abilities, and challenges. During the evaluation, the neuropsychologist meets with the patient in a clean and quiet room with adequate space to accommodate a wheelchair. All the instruments the neuropsychologist plans to use in the evaluation should be readily accessible for efficiency and ease of administration.

When selecting the instruments she/he will use, the neuropsychologist takes care to consider the stroke patient's obvious impairments, e.g., right or left hemiparesis/plegia, right or left hemineglect/inattention, and receptive/expressive aphasia. Other patient conditions to be aware of, which can affect cognitive performance, are the patient's energy level and the presence of depression.

For the stroke patient unencumbered by aphasia with sufficient energy to withstand about 30 min of sustained cognitive activity, a standard neuropsychological screening assessment can include brief history taking and neuropsychological testing measures such as the one recommended by the Neuropsychology Working Group (i.e., NINDS-CSN Neuropsychological Battery) in Hachinski et al. [36]. The 30-min protocol suggested by the Neuropsychology Working Group included the following neuropsychological test battery: semantic and phonemic fluency, Digit Symbol-Coding, and the revised Hopkins Verbal Learning Test, in addition to the Center for Epidemiologic Studies-Depression Scale (CES-D) developed by the National Institute of Mental Health [37] and Neuropsychiatric Inventory. The Trail Making Test A and B and the Mini-Mental State Examination (MMSE) can supplement the battery.

When time is short and/or the patient is encumbered with decreased energy and/or short attention span, the neuropsychologist can use the 5-min protocol recommended by the Neuropsychology Working Group in Hachinski et al. [36]. The protocol consists of selected subtests from the Montreal Cognitive Assessment. This test is available with instructions in 34 different languages and normative data at www.mocatest.org (MoCA, [38]). It includes a five-word immediate and delayed memory test, a six-item orientation task, and a one-letter phonemic fluency test (the letter F). The MoCA may be used without permission, free of charge, for clinical or educational noncommercial purposes (Copyright Ziad Nasreddine, MD).

Medical test results (e.g., computed tomography or magnetic resonance imaging of the brain) are often included in the history and physical report completed by the attending neurologist or physical medicine and rehabilitation physician upon the patient's admission to the acute rehabilitation hospital. These results can be easily included in the neuropsychologist's initial report with reference to their source. Since diagnosis is typically already made by the attending physician, the neuropsychologist need not waste valuable time trying to come up with a diagnosis; rather, the information can be used to develop hypotheses about patterns of deficits that might be found on neuropsychological testing.

Consequently, neuropsychological testing results can either confirm or refute these hypotheses. These conclusions and, more importantly, their functional implications can be discussed in team meetings and recorded in the patient's evaluation reports.

Family members are a valuable source of information about the patient's premorbid (pre-stroke) functioning. Neuropsychologists can obtain information from reliable family members about the patient's social, academic, and occupational functioning. This information provides the neuropsychologist with a basis of comparison for their current functioning. It is suggested that the neuropsychologist integrate this information into the neuropsychological testing report. A portion of the history section of the report can be devoted to the patient's premorbid functioning with appropriate references.

Capacity Assessment: In acute rehabilitation settings, occasionally there will be patients who refuse to be treated or insist on going home, i.e., leave the hospital against medical advice. These patients might be depressed, frightened, and confused or possess characterological features that account for their behavior. Another variable for the neuropsychologist to consider is the energy level of the patient. Acute rehabilitation programs typically require 3 h a day of occupational therapy and physical therapy. On top of this requirement is about 45–60 min of speech therapy. Add to this regimen recreational therapy programs, nursing care, meals, visits from the neuropsychologist, family and friend visits, and you have one very tired stroke patient at the end of the treatment day! This regimen is too taxing for some patients who are already significantly physically and emotionally compromised by the stroke.

Treatment refusal and the desire to leave the hospital create stress not only for the treatment team but also for the family caregivers who typically want the patient to remain in the acute rehabilitation hospital for treatment. In these cases, the attending neurologist or physiatrist will often request a consult from the neuropsychologist to determine if the patient has the capacity to make treatment decisions for him or herself. Determining capacity to make treatment decisions can have the beneficial effect of respecting the autonomy of the patient, logically seeking a solution, and documenting the reasonable action taken in response to the problem. The details of how to conduct a formal capacity evaluation go beyond the scope of this chapter but in general include a careful review of the entire available medical record, a directed clinical interview with the patient, and/or the use of formal, structured assessment tools like the Aid to Capacity Evaluation (ACE [39]) and the MacArthur Competence Assessment Tool (MacCAT [40]). Grisso and Appelbaum (1998) developed an excellent formal structured assessment tool to evaluate capacity, and the reader is referred to that source for more detailed information.

In cases where it is determined that the patient has the capacity to make decisions for herself/himself and persists in their desire to leave hospital, then the rehabilitation team will have few options but to concede to these wishes even though it is thought by the team that continued treatment will be in the best interest of the patient. In an acute rehabilitation setting, this usually means the patient leaves the hospital against medical advice or due to lack of motivation for treatment is discharged to home or subacute treatment. In order to increase safety, the neuropsychologist can join with the attending physician, the social worker, and the nursing staff in providing the patient and the family caregivers with education about safety in the home, prohibiting driving and use of other mechanical equipment, medication administration/compliance, and prohibiting consumption of alcohol and other illicit drugs. The stroke rehabilitation team will also need to coordinate the assistance (e.g., home healthcare aide) and equipment (e.g., shower chair, wheel chair) that will be needed at home.

Behavioral Assessment: A common referral question for neuropsychologists working with stroke patients in an acute rehabilitation setting is consultation regarding behavioral problems. Poststroke depression, irritability, agitation, confusion, and aggression are just a few examples.

Neuropsychologists are called upon in these settings to provide assessment, treatment, and consultation about these difficult behaviors. One approach to assessment of these behaviors is multimodal. The neuropsychologist can obtain information about the patient's behavior from a number of sources. Feedback about the behaviors can be elicited from each of the stroke rehabilitation team members working with the patient. These include the occupational therapist, physical therapist, and speech therapist. Feedback from the nursing staff and nursing aides should not be overlooked. Sometimes there are inconsistencies in the patient's behavior in the therapy gyms vs. on the nursing floor. For example, patients might angrily insist on getting help from nursing staff for tasks they have demonstrated in the occupational therapy gym they are fully capable of completing independently. In addition to formal and informal interaction directly with the patient, neuropsychologists can observe the patient's behavior on the nursing floor and in the therapy gyms. A structured mental status examination combined with formal measures like the Beck Depression Inventory Fast Screen for Medical Patients (BDI-FS, [41]) or the Beck Anxiety Inventory (BAI, [42]) can be used to assess for depression and anxiety, respectively.

A factor that may complicate the clinical picture and present assessment and management problems is the presence of pre-stroke psychological diagnosis (e.g., posttraumatic stress disorder or PTSD). PTSD is a psychiatric illness that can affect individuals who have experienced or witnessed a life-threatening or traumatic event (e.g., combat exposure, physical or sexual assault, or natural disaster). The disorder is characterized by four distinct clusters of symptoms, including reexperiencing the traumatic incident (e.g., through nightmares or flashbacks), avoiding reminders of the event, experiencing persistent negative mood or changes in cognition, and heightened physiological arousal. According to data from the US National Comorbidity Survey Replication (NCS-R) collected from a nationally representative sample between February 2001 and April 2003, the estimated lifetime prevalence of PTSD among Americans over age 18 is 6.8% [43]. Similar to assessment of other psychiatric symptoms, patients can be evaluated for PTSD using the combination of a structured mental status exam and a formal measure such as the PTSD Checklist for DSM-5 (PCL-5; [44]). Common symptoms of PTSD that may present particular challenges for assessment and management in acute rehabilitation settings include mood disturbances such as anger, irritability, or depressed mood, mistrust of others, poor sleep, and a sense of foreshortened future.

A premorbid PTSD diagnosis for stroke survivors is particularly notable in light of past research demonstrating that patients diagnosed with PTSD are more likely to develop cardiovascular disease [45–47] and are at increased risk for stroke [48, 49]. Conventional wisdom would suggest that these findings are attributable to higher rates of certain risk factors for cardiovascular disease among patients with PTSD, including hypertension, dyslipidemia, diabetes, and tobacco use [50–52]; however, a review conducted by Edmondson and Cohen [53]; found that these risk factors do not fully account for the increased rates of cardiovascular disease and stroke in this population. More recent research by Grenon and colleagues [54]; provides a possible explanatory mechanism for this relationship. In a study of military veterans diagnosed with PTSD, researchers examined the relationship between PTSD and endothelial functioning, meaning the ability of blood vessels to fully dilate in response to stimuli. Consistent with previous research linking poor endothelial functioning with the development of cardiovascular disease, the study found that the blood vessels of veterans diagnosed with PTSD were significantly less reactive and did not dilate normally compared to those of veterans without PTSD. These findings suggest that reduced blood vessel dilation due to chronic stress may account for increased risk of heart attack and stroke in patients with PTSD, even after controlling for traditional risk factors.

An important aspect of the patient's experience for clinicians to consider when treating survivors of stroke is the psychological impact of the cardiovascular event, particularly with regard to the possibility of subsequent onset of posttraumatic

stress symptoms. A meta-analysis conducted by Edmondson and colleagues [55]; suggests that one in four stroke or transient ischemic attack (TIA) survivors develops significant PTSD symptoms secondary to these cardiovascular events. The overall prevalence of stroke- or TIA-induced PTSD among patients was found to be 13%, with 23% of patients developing symptoms within the first year following stroke and 11% reporting symptoms more than 1 year later. Notably, stroke survivors who develop PTSD have been found to be three times more likely to report medication nonadherence compared to survivors without PTSD, independent of other psychiatric or medical comorbidities [56].

These findings highlight the importance of thorough assessment and monitoring of psychiatric symptoms for stroke survivors during rehabilitation, as posttraumatic stress symptoms may influence engagement in secondary prevention behaviors that are critical for recovery and protection against additional cardiovascular events. For example, apathy and a sense of foreshortened future common in PTSD may negatively impact the patient's motivation to follow recommendations or accept care and assistance from others during the rehabilitation process. The patient's relationship with the treatment team may also be impacted by PTSD-related symptoms of anger and irritability, which may be expressed through minor expressions of annoyance with others or the environment, or through displays of verbal or physical aggression. In cases of premorbid PTSD, suffering a stroke or other cardiovascular event may exacerbate anxiety symptoms or serve to confirm previously held beliefs related to one's sense of safety or physical integrity (e.g., "Something bad could happen at any time," "The world is a dangerous place"). These symptoms can serve as significant impediments to fully engaging with treatment.

A patient's PTSD diagnosis, whether premorbid or poststroke, presents significant clinical challenges for the treatment team and merits special attention from neuropsychologists in acute rehabilitation settings.

One way the neuropsychologist can effectively use her/his time and the time of the stroke rehabilitation team is by having a once or twice weekly behavioral management team meeting. The team gathers at a specific time and place and discusses the problem behaviors of the patient. The neuropsychologist acts as the facilitator of the meeting and the consultant. Each member of the stroke rehabilitation team working with the patient provides their feedback on the behavioral problems as experienced in their respective disciplines. It is strongly recommended that nursing have representation in these meetings. It has been the author's experience that nursing aides provide valuable information about the patient's behavior since they work with them so intimately in otherwise very private activities such as personal hygiene, eating, bathing, toileting, etc. Each member of the team describes what interventions they have tried to alter the problem behavior. After each of the team members have described problem behaviors and attempted interventions, the neuropsychologist then makes other intervention suggestions based upon established guidelines. The author has found the practical guidelines from the Rehabilitation Institute of Chicago Publication Series to be very helpful [57].

What follows are some suggestions for neuropsychologists working with acute rehabilitation teams. These suggestions were lessons learned and developed from the author's own experiences working in an acute rehabilitation setting over a period of 13 years.

Case Example

James was a 42-year-old, right-hand-dominant, married, employed, domiciled, Caucasian man who was status post a right hemisphere stroke. He had a history of hypertension, hypercholesterolemia, diabetes, and smoking. He also led a somewhat sedentary lifestyle prior to the stroke. James was in the Army Reserves, and his unit was deployed to Iraq in 2003 for 12 months. While deployed, he experienced combat trauma and was diagnosed with PTSD by the local Veterans Administration Medical Center mental health treatment team. His most prominent symp-

toms included frequent nightmares, avoidance of crowds, mood lability, hypervigilance, and irritability. One day, while at work in his civilian job as a letter carrier for the post office, he fell ill and collapsed. Coworkers called 911, and he was taken to the emergency department of the local medical center. The emergency physicians in consultation with the acute stroke team diagnosed a right hemisphere ischemic stroke that left James with a left hemiparesis, left visual field neglect, and dysarthria. It was determined that onset of the symptoms of stroke was within 3 h, and, therefore, tissue plasminogen activator (tPA) was initiated to enhance blood flow. He remained in the acute care hospital for about a week and was determined to be a good candidate for acute rehabilitation. Some factors that determined his candidacy were relative youth, absence of aphasia, hemodynamic stability, good social support from his wife and family, and his own positive motivation to get better. Factors that were potential obstacles to progress were suspected onset of poststroke depression, exacerbation of premorbid PTSD symptoms, and lack of education about stroke and its consequences. He was medically stabilized and transferred to the acute rehabilitation center. James and his wife received orientation to the stroke rehabilitation unit. The first 48 h at the unit were dedicated to completing evaluations and assessments by the multidisciplinary team. The neuropsychologist met with the patient and his wife and provided orientation to the role of the neuropsychologist on the treatment team. A time was booked for a neuropsychological screening evaluation. When James first came to the office for the appointment, he began to sob uncontrollably. So, therefore, the time was spent focusing on treating his emotional well-being. Once he was able to compose himself, emotional support, encouragement, and education about stroke were provided to the patient. The neuropsychologist queried James about symptoms of depression and PTSD. The following symptoms of depression were acknowledged: early, middle, and late insomnia, loss of appetite with weight loss of about 10 pounds since stroke onset, lethargy, decreased concentration, anhedonia, dysphoric/depressed mood with affective lability, a sense of helplessness, and decreased self-esteem and confidence. The BDI-FS and BAI were administered, and he endorsed depression at a moderate level of severity and mild-moderate anxiety. With regard to PTSD, the PCL-5 was administered, and James endorsed significant exacerbation of premorbid symptoms specifically related to his well-being and safety, including increased hypervigilance to physical sensations due to fear of experiencing another life-threatening medical event. The neuropsychologist recommended, and James agreed, to consider the use of antidepressant medication, weekly individual readjustment counseling, weekly stroke education group, and weekly stroke support group. He also agreed to neuropsychological evaluation of his cognitive functioning later in the first week of his admission. His wife was very dedicated to him and was able to be present for the greater part of the treatment day; this support was positively influential in James' progress. She agreed to attend the weekly family/caregiver stroke education and support groups. On neuropsychological evaluation, James was administered the 30-min protocol described above. Effort was adequate on testing, and he was motivated to learn about his abilities and difficulties. His intelligence level was estimated to be in the average range. Cognitive impairments (greater than 2 standard deviations below the mean) were in the areas of attention, speed of processing, and visual hemi-inattention to the left side of space. Relative weaknesses (1–2 standard deviations below the mean) were in the areas of delayed recall of verbal and visual information. Cognitive remediation protocol was initiated. He initially responded well to some of the strategies he learned to compensate for problems with attention and memory. For example, he used external memory aids as described in Cuesta [58]. He was observed to reliably refer to his daily journal and written schedule to help him recall important events and appointments. However, his motivation to implement these skills was at times impacted by significant mood symptoms and negative expectations for the future. During his first 2 weeks on the unit, nursing staff also noted several bouts of irritability in

which James verbally lashed out in response to others' offers of assistance. The neuropsychologist emphasized the importance of adherence to the prescribed treatment regimen while also exploring the root of James's anger and frustration. Validation of James' emotional experience and psychoeducation on stroke-induced posttraumatic stress symptoms was provided to James and his wife. His depression and PTSD were monitored, and behavior was discussed in the weekly behavioral management team meeting. During the last week of his 4-week stay, the 30-min protocol was readministered to determine progress made since admission. A family meeting was convened with his wife, two young adult children, and his parents to provide them with feedback about functional progress made in rehabilitation and to discuss discharge planning issues. Also during the last week of his admission, the neuropsychologist made arrangements, in cooperation with the stroke rehabilitation team's social worker, for the patient to obtain individual psychotherapy for depression and PTSD. Also arranged was referral to a psychiatrist in the community for antidepressant medication management. Finally, arrangement for referral to a neuropsychologist in the community was made for follow-up neuropsychological evaluation 90 days poststroke.

Prognosis/Recommendations

As mentioned earlier, stroke is the third leading cause of death in the United States. In 2009, there were 135,952 Americans who died as a result of stroke. However, mortality rates are declining. During the first year, over 75% of patients survive a first stroke and over half survive beyond 5 years [59]. Those patients who suffer ischemic strokes have a much better chance of survival than those with hemorrhagic strokes. Among the ischemic stroke categories, embolic strokes pose the greatest threat to survival, followed by thrombotic and lacunar strokes. Hemorrhagic strokes destroy brain cells and pose other threats to survival like increased pressure on the brain or spasms in the blood vessels; both of these conditions can be very dangerous for the patient. However, studies suggest that those patients with hemorrhagic stroke have a greater chance for recovering function than those patients with ischemic stroke [60].

It is estimated that between 50% and 70% of patients recover functional independence after a stroke. However, between 15% and 30% of patients who survive either an ischemic or hemorrhagic stroke remain with some permanent disability [60]. The National Institutes of Health (NIH) devised a scoring system that helps predict stroke severity and outcome by scoring the following 11 factors: levels of consciousness, gaze, visual fields, facial movement, motor functions in the upper and lower extremities, coordination, sensory loss, problems with language, inability to articulate, and attention. In addition to the use of the NIH Stroke Scale (NIHSS), described above, measurement of brain injury using magnetic resonance imaging (MRI) and time (in hours) since onset of stroke symptoms to the time of the MRI brain scan are two additional factors used to predict stroke severity and outcome [60]. Up to 70% of patients with ischemic strokes who score less than 10 on the NIHSS have favorable outcome after 1 year. Only between 4% and 16% of patients have favorable outcome if their NIHSS score is more than 20 [60].

One question neuropsychologists frequently get from stroke patients and their families is "What are my chances of having another stroke?" The literature points out that the risk for recurrent stroke is highest within the first few weeks and months. Risk for recurrent stroke is about approximately 14% in the first year and about 5% thereafter. Specific risk factors for early recurrence include the following: older age, evidence of blocked arteries (i.e., history of coronary artery disease, peripheral artery disease, ischemic stroke, or transient ischemic attack), hemorrhagic or embolic stroke, diabetes, alcoholism, valvular heart disease, and atrial fibrillation [60]. When patients and their families are being educated about stroke recurrence, neuropsychologists can emphasize that preventive measures be implemented as soon as possible. These measures include encouraging patient compliance with

medication for hypertension, hypercholesterolemia, diabetes, and heart disease. Preventive measures also include encouraging the patient to make and maintain lifestyle choices like quitting smoking, quitting alcohol consumption, eating a more healthy diet, and getting more aerobic exercise. However, these behaviors are more challenging to change, and some may be physically impossible (e.g., exercise) for some patients to change after a devastating stroke.

In terms of follow-up, the neuropsychologist working with stroke patients in an acute rehabilitation setting will typically know the discharge disposition of the patient. Discharge alternatives include home with home care services, home with outpatient care or therapeutic day care, subacute rehabilitation in a nursing home, or skilled nursing facility. In cases where contact with the patient and family caregivers has been intensive, it is recommended that the neuropsychologist be involved with discharge planning and coordinating of neuropsychological rehabilitation services. For example, during the acute rehabilitation admission neuropsychological evaluation was completed, a trial of cognitive remediation begun, and psychological readjustment counseling initiated. The neuropsychologist, in cooperation with the social worker, can make recommendations and arrangements for the patient to obtain follow-up neuropsychological evaluation 90 days and 12 months poststroke to monitor progress. The neuropsychologist can also make recommendations and arrangements for continued cognitive remediation and counseling. In some cases, depending on time, third-party payment, and logistical constraints, the neuropsychologist may be able to provide these services on an outpatient basis.

Treatment/intervention recommendations include the following: follow-up (at 90 days and 12 months) neuropsychological evaluation to monitor progress made in cognitive and psychological functioning, readjustment counseling to continue to assist the patient with the psychological consequences of stroke, referral to a psychiatrist for prescription and management of psychotropic medication as indicated, and cognitive remediation to assist the patient with learning strategies to compensate for impairments. Specific techniques for remediation of memory have been suggested by Cuesta [58]: reinforcement of education about stroke and its consequences for both patient and family caregivers, recommendation and referral for respite care, and therapeutic consultation with the family caregivers, as needed. Neuropsychologists can be especially influential in improving the care of the patient by attending to the emotional and education needs of the family caregivers.

Summary and Future Directions

Neuropsychology work in an acute rehabilitation setting is a challenging, exciting, and meaningful work. Neuropsychologists who enjoy working with multidisciplinary teams will find the work rich and rewarding. The work requires the clinician to go beyond the comfort zone of the classic role of neuropsychological evaluation and consultation. The successful neuropsychologist working in an acute rehabilitation setting with stroke patients will learn and implement the competencies of rehabilitation psychology and health psychology.

Some, but by no means exhaustive, directions for future research include more precise determination of the predictive validity of neuropsychological measures. Increased precision in predictive validity of these tests can assist in establishing early prognosis and guiding treatment decisions [6]. Caplan (2010) suggested that a post discharge placement algorithm developed by Ween et al. (1996) can be strengthened with the addition of neuropsychological data [61].

Second, improving the discriminant validity of neuropsychological measures can aid with diagnostic accuracy. Some progress has been made related to this topic. For example, the three NINDS-CSN neuropsychological protocols mentioned earlier in this chapter have generated significant interest among researchers. For example, since the publication of the first version of this chapter, international effort has been made with validation studies completed from China [62],

France [63], Hong Kong [64], and Singapore [65] with promising results.

Third, improving the ecological validity of neuropsychological testing is another important area of future research. Neuropsychological tests with good ecological validity can aid in making reasonable and practical post discharge recommendations related to functional activities such as driving, handling personal finances, and returning to school and work. Research collaboration with other disciplines like occupational therapy and recreational therapy can be especially helpful in this endeavor.

A fourth important topic for future research is in the area of treatment efficacy for the emotional and behavioral problems associated with stroke, i.e., poststroke depression, anxiety, PTSD, and other behavioral disturbances that adversely impact on the rehabilitation potential of the patient. Behavioral/psychological treatment can be for individuals and/or groups and can take the form of psychoeducation, skills-building classes, and cognitive behavioral interventions.

Neuropsychologists are an important part of the multidisciplinary treatment teams working in acute rehabilitation settings with stroke patients. Awareness and recognition of the importance of the role of the neuropsychologist is increasing as evidenced by the work of a task force of the American Stroke Association [66]. Their report, "Recommendations for the Establishment of Stroke Systems of Care," explicitly recognized the place of neuropsychologists on the stroke rehabilitation team. Neuropsychologists must cultivate evidence that demonstrates that their competencies, skills, knowledge, and abilities are essential to acute rehabilitation multidisciplinary teams working with stroke patients.

Clinical Pearls

- The cultivation and development of respectful, cooperative, effective, and harmonious relationships with all members of the treatment team will ultimately benefit the patient and his or her family.
- Neuropsychologists should not see themselves as having exclusive dominion over the assessment and treatment of the patient's cognitive and behavioral problems. The different disciplines have their own assessment and intervention methods that are as valuable as the methods used in neuropsychology.
- In addition to assessment, neuropsychologists can provide valuable services to patients, their families, and the teams they work with including contributing to judgments about the patient's suitability for rehabilitation and capacity to make decisions, as well as monitoring psychological and social factors that affect recovery, advising other team members, educating patients and their families, and making recommendations for post discharge.
- Neuropsychologists should take the leadership in the behavioral management aspect of the acute stroke rehabilitation program.
- Nursing aides can provide extremely valuable behavioral observations about patients. They work closely and intimately with the patients when they are on the nursing unit, and they provide unique behavioral observations.
- The team can meet with the patient regarding maladaptive behaviors to communicate the adverse effect the behavior is having on the patient's rehabilitation and to make a plan for behavior management.
- It may be difficult or impossible to evaluate the affective state of an acutely ill, cognitively impaired stroke patient who cannot understand or reliably respond to interview questions. Woessner and Caplan [67], found that while behaviors or symptoms such as lethargy, sleep disturbance, and decreased appetite might signal depression or anxiety in otherwise healthy individuals, they may not have the same diagnostic meaning in a hospitalized stroke patient.
- The neuropsychologist's interactions with the patient's family are a golden opportunity to obtain collateral information about the patient's cognitive and behavioral functioning while alleviating anxieties and providing education about stroke and recovery.

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Assessment of Behavioral Variant Frontotemporal Dementia

33

Amanda K. LaMarre and Joel H. Kramer

Behavioral variant frontotemporal dementia (bvFTD) is one of the three neurodegenerative syndromes collectively referred to as frontotemporal dementia (FTD). Initially thought to be rare, we now know that it is equally as common as Alzheimer's disease in individuals under the age of 65 [1] and is the third most common dementia after Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) [2]. Precise estimation of the prevalence of FTD has been difficult as disease frequency is low and accurate diagnosis depends on expert evaluation. However, population-based studies in both the United States and United Kingdom estimate a sporadic occurrence at around 3.3–3.5/100,000 in individuals between 45 and 65 years of age [3, 4]. Age of onset is typically in midlife, though onset ranges considerably, from the 30s to 90s [1, 5, 6]. Survival rates vary depending on clinical phenotype, from 3 to 14 years [7]; however, median survival for all variants from diagnosis to death has been estimated to be approximately 7–13 years [8].

Clinically, FTD is expressed as three main variants [9]. BvFTD is characterized by profound and early changes in personality and behavior [9]. This phenotype is most common and accounts for approximately 70% of the clinical expression of the disease [10]. As such, bvFTD will be the focus of this chapter. The other two variants are subtypes of the Primary Progressive Aphasia (PPA) syndromes. The semantic variant (svPPA) is associated with the loss of word knowledge (e.g., semantic structure of language), while the nonfluent variant (nfPPA) is characterized by early disturbances in motor speech output and loss of syntax (e.g., grammatical structure of language) [9, 11]. These two variants account for approximately 15% and 10% of the phenotypic expression of the disease, respectively [10]. While some studies suggest that a gender distribution bias occurs by clinical syndrome (e.g., male bias in bvFTD and svPPA; female bias in nfPPA [1, 5, 6]), a recent review examining the prevalence and incidence of FTD suggests that males and females were equally as likely to be affected with FTD across all variants [12].

Earliest Signs of bvFTD

The earliest signs of disease in bvFTD are frequently subtle personality and behavioral changes that become increasingly pronounced as time goes on. These symptoms often include apathy or disinhibition, reduced emotional response, changes in personality or beliefs [13], poor

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judgment, and impairment in personal and social awareness [14–17]. These changes are often dramatic, resulting in the dissolution of the individual's former self, such that partners and families no longer recognize their loved ones [13]. For example, individuals may begin to make impulsive decisions or actions, including such behaviors as shoplifting, driving recklessly, or physically assaulting others [14, 16, 18, 19]. They might violate social norms by making inappropriate sexual comments [20] or become emotionally cold and self-centered such that they no longer respond to others' emotional needs or pain [21]. These changes often exist in sharp contrast to their cognitive ability, which may remain relatively intact for some time.

Diagnostic Criteria for bvFTD

In the past, diagnosis of bvFTD was most often made using the revised version of the Lund–Manchester criteria, which were then reformulated by a consensus of specialists in 1998 [9]. However, considerable advancements in our understanding of this disease over the last two decades has led to the development of new criteria, published in 2011 by the International bvFTD Criteria Consortium [22] (Table 33.1). With these criteria, diagnosis of possible bvFTD is based solely on clinical presentation. Patients must meet at least three of the six following criteria: (1) early behavioral disinhibition; (2) early apathy/inertia; (3) early loss of sympathy or empathy; (4) early perseverative, stereotyped, or compulsive behaviors; (5) hyperorality or dietary changes; and (6) a neuropsychological profile suggesting deficits on tasks of executive function with *relative* sparing of memory and visuospatial function. To meet the criteria for probable bvFTD, a patient must meet the criteria for possible bvFTD, exhibit significant functional decline, and show evidence of frontal and/or temporal atrophy on structural MRI or CT or hypometabolism on positron emission tomography (PET). Sensitivity of the new criteria has been demonstrated via retrospective chart review of pathologically confirmed cases in a multisite study, and findings suggest that the new criteria have greater sensitivity to the diagnosis of bvFTD, compared to the previous criteria (0.85 vs. 0.52, respectively) [22]. In addition, a study by LaMarre and colleagues has shown that the criteria demonstrate excellent inter-rater reliability for the diagnosis of both possible and probable bvFTD [23].

Neuroanatomy and Pathology of bvFTD

The hallmark symptoms of bvFTD strongly reflect initial areas of neurodegeneration. Structural neuroimaging analysis in patients in the earliest stages of bvFTD (Clinical Dementia Rating (CDR) scale = 0.5; mild dementia) suggests that initial degeneration occurs primarily in paralimbic structures such as the anterior cingulate cortex, frontoinsular region, dorsal anterior insula, and lateral orbitofrontal cortex [24], and disease staging of autopsy-confirmed cases of bvFTD are consistent with this finding [25]. These structures have been widely implicated in human social function and awareness of the self [26] and are part of a neural network thought to play a role in decoding the emotional salience (visceral, homeostatic, hedonic value) of a stimulus in order to facilitate appropriate action, i.e., "salience network" [27]. As the disease progresses, neurodegeneration occurs in widespread areas of the frontal and temporal lobes [28–32].

BvFTD is caused by abnormal aggregation of protein in the brain, referred to collectively as frontotemporal lobar degeneration (FTLD). The two most common pathologies associated with bvFTD are FTLD with tau-positive inclusions (FTLD-tau) and FTLD with TDP-43 positive inclusions (FTLD-TDP) [2, 33], with a handful of additional proteins accounting for approximately 10% of bvFTD cases [33]. Under normal conditions, both tau and TDP-43 play important roles in neuronal cell structure and function [34, 35]. Under pathologic conditions, however, these proteins aggregate and accumulate in the cytoplasm of neurons and glial cells and are associated with neuronal death and atrophy [2, 33].

Table 33.1 International consensus criteria for bvFTD [22]

I. Neurodegenerative disease
The following symptom must be present for any FTD clinical syndrome:
A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)
II. Possible bvFTD
Three of the following behavioral/cognitive symptoms [A–F] must be present to meet criteria. These symptoms should occur repeatedly, not just as a single instance
A. Early behavioral disinhibition
(a). Socially inappropriate behavior (b). Loss of manners or decorum (c). Impulsive, rash, or careless actions
B. Early apathy or inertia
(a). Apathy: Loss of interest, drive, or motivation (b). Inertia: Decreased initiation of behavior
C. Early loss of sympathy or empathy
(a). Diminished response to other people's needs or feelings: Positive rating should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings (b). Diminished social interest, interrelatedness, or personal warmth: General decrease in social engagement
D. Early perseverative, stereotyped, or compulsive/ritualistic behavior
(a). Simple repetitive movements (b). Complex, compulsive, or ritualistic behaviors (c). Stereotypy of speech
E. Hyperorality and dietary changes
(a). Altered food preferences (b). Binge eating, increased consumption of alcohol or cigarettes (c). Oral exploration or consumption of inedible objects
F. Neuropsychological profile: Executive/generation deficits with relative sparing of memory and visuospatial functions
(a). Deficits in executive tasks (b). Relative sparing of episodic memory (compared to degree of executive dysfunction) (c). Relative sparing of visuospatial skills (compared to degree of executive dysfunction)
III. Probable bvFTD
A. Meets criteria for possible bvFTD B. Exhibits significant functional decline (by caregiver report or as evidenced by CDR or FAQ scores) C. Imaging results consistent with bvFTD
(a). Frontal and/or anterior temporal atrophy on CT or MRI (b). Frontal hypoperfusion or hypometabolism on SPECT or PET
IV. bvFTD with definite FTLD pathology
Criterion A and either criterion B or C must be present to meet criteria
A. Meets criteria for possible bvFTD B. Histopathological evidence of FTLD on biopsy or at postmortem C. The presence of known pathogenic mutation
V. Exclusion criteria for bvFTD
Criteria A and B must both be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD
A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders, e.g., delirium, cerebrovascular disease, cerebellar disorder, systemic disorders (e.g., hypothyroidism), or substance-induced conditions B. Behavioral disturbance is better accounted for by a psychiatric diagnosis, e.g., depression, bipolar disorder, schizophrenia, preexisting personality disorder C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process (e.g., genetic mutations, extensive PIB finding, CSF markers)

Advancements in our understanding of the underlying pathology of FTD over the past 15 years have also demonstrated links with diseases not historically believed to be associated with changes in cognition and behavior [36–38]. For example, FTLD-tau includes cases fulfilling pathological diagnostic criteria for not only Pick's disease and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) but also for motor disorders such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [39, 40]. Similarly, cases found to have FTLD-TDP may present alone or in combination with motor neuron disease (e.g., amyotrophic lateral sclerosis (ALS)) [41, 42]. There is also a growing consensus that the behavioral syndrome of bvFTD can manifest in patients with PSP, CBD, and ALS [43–45].

Genetics

While sporadic cases are common in bvFTD, at least 30–40% of all cases appear to be genetic in nature [46], with rates of autosomal dominant pattern of inheritance ranging from 10% to 30% [47, 48]. At this time, genetic mutations known to cause familial FTD have been found on three different chromosomes (3, 9, 17) [49–51]. The first gene was discovered in 1998 and was found to be caused by mutations in the microtubule-associated protein ("MAPT") gene [52]. It is now known that *MAPT* codes for the protein tau, which as mentioned above, is a major pathological subtype of FTD [53]. Several years later, linkage analysis in the same region of chromosome 17 found that mutations in the gene coding for the growth factor progranulin also cause FTD (*PGRN*; [54]). Unlike *MAPT*, these cases display TDP-43 inclusions rather than tau [55]. Most recently, it was discovered that the most common cause of inherited FTD (and ALS) was caused by a GGGGCC hexanucleotide repeat expansion within the noncoding region of the chromosome 9 open reading frame 72 (i.e., *C9orf72* gene) [50]. While the minimum repeat length to confer risk is unknown, individuals with bvFTD and/or ALS can have anywhere from 100 to several thousand copies of the repeat expansion. Similar to *PGRN*, pathology typically shows TDP-43 inclusions [56]. Interestingly, any of the three clinical variants of FTD may occur in familial forms of the disease; however, certain variants are more likely to be expressed than others [10, 56, 57]. For example, *PGRN* mutation carriers tend to develop symptoms characteristic of bvFTD or nfPPA [58].[1]

Differential Diagnosis

Despite significant advancements in the field, diagnosis of bvFTD remains clinically challenging. Unsurprisingly, bvFTD is commonly misdiagnosed as early-onset AD. Many symptoms of the two diseases overlap, including neuropsychiatric disturbance and executive dysfunction [59, 60]. Patients with neurodegenerative motor syndromes may also exhibit symptoms consistent with a diagnosis of bvFTD (or an aphasia variant) [43–45]. As such, having a concomitant syndrome such as PSP or ALS should not be considered exclusionary for a diagnosis of bvFTD. Huntington's disease may also mimic many of the behavioral and psychiatric disturbances seen in bvFTD [61].

Patients with bvFTD may also be misdiagnosed with a late-onset psychiatric disturbance. Symptoms of disinhibition, euphoria, and poor judgment can mimic those of mania, while profound apathy and eating disturbance might be misconstrued as depression. Wooley and colleagues [62] completed a retrospective chart review of 252 patients with neurodegenerative disease presenting to an academic medical center specialty clinic. Of the patients with bvFTD, 51% of patients had received a prior diagnosis of a psychiatric disorder (e.g., major depression, bipolar disorder, schizophrenia) compared to 23% of patients with Alzheimer's disease (e.g., major depression, anxiety), suggesting that the symptoms of bvFTD may be misunderstood by mental health-care providers. That said, certain

[1] For a recent review on the genetics of FTD, please read Pottier et al. [56].

forms of the disease may actually cause outright psychiatric symptoms. For example, carriers of *C9ORF72* mutations frequently display psychiatric symptoms at disease onset, including those seen in psychotic, bipolar, and compulsive disorders [63–66]. As such, neurodegenerative disease should always be considered on the differential when new-onset psychiatric disturbance is present in older individuals.

A small subset of patients diagnosed with bvFTD have been characterized as "nonprogressive" or "bvFTD phenocopies" due to the presence of a behavioral disturbance in the context of lack of notable atrophy on imaging or cognitive decline over time [67–69]. The etiology of this syndrome remains unclear. For example, it has been demonstrated that some cases may actually represent psychiatric or personality disorders [70], while other cases may be due to a slowly progressive genetic form of the disease [71]. The importance of accurate differential diagnosis cannot be overstated. Treatments meant for a different diagnosis, such as AD, can potentially exacerbate bvFTD symptoms (Table 33.2).

Efforts to develop specific, disease-modifying therapies for FTLD are advancing rapidly, focusing on the major proteins currently known to be involved in the pathogenesis of the disease. Clinical trials aimed at manipulating tau, TDP-43, and PGRN levels have already begun. Testing the efficacy of these medications greatly depends on our ability to ensure homogenous samples in clinical trials. As there are currently no definitive methods for determining FTLD pathology prior to autopsy, predicting pathology antemortem remains a key challenge. Researchers are actively working to better understand the clinicopathologic correlations relevant to each protein currently believed to be involved in the development of FTLD.

Table 33.2 Disorders that may present with similar neurobehavioral features to bvFTD

Neurodegenerative diseases	Progressive supranuclear palsy
	Corticobasal syndrome
	Amyotrophic lateral sclerosis
	Alzheimer's disease
	Semantic variant primary progressive aphasia
	Huntington's disease
	Lewy body dementia
Psychiatric disorders	Bipolar disorder
	Major depression
	Psychosis
	FTD phenocopy
	Psychopathy
Neurologic disorders	Cerebrovascular accident
	Traumatic brain injury

Review of Neuropsychological Literature

Despite obvious impairment in the patient's behavior and judgment, researchers seeking to characterize a neuropsychological profile specific to bvFTD have not been highly successful. Research is plagued with a number of significant issues that likely contribute to discrepancies in the data, including lack of universally applied diagnostic criteria, variability in diagnostic terminology, lumping together of all three clinical variants of the disease, small sample sizes, and lack of reporting of disease severity or symptom duration [72]. Issues can also arise due to test selection and interpretation issues, including the possibility that impaired performance on tests are due to factors that are beyond what the test is meant to measure. For example, a study examining qualitative features of performance on neuropsychological testing in bvFTD and AD found that patients with bvFTD tend to perform poorly on tasks of visuoconstructive ability, not due to deficits in visual perceptive ability, but rather, due to perseverations and deficits in organizational ability [73]. Moreover, behavioral manifestations of the disease itself, including poor motivation and distractibility, may contribute to variability in cognitive performance scores.

Our current understanding of the neuropsychology of bvFTD lies largely within the context of research seeking to improve differential diagnosis between neurodegenerative diseases. In most cases, the cognitive profiles of individuals with bvFTD and AD are compared, though efforts to delineate specific tasks or cognitive facets that

will reliably differentiate the two have been unsuccessful. As such, *relative test score patterns* between domains appear to be most informative to differential diagnosis.

Memory

Compared to patients with AD who exhibit severe verbal and visuospatial episodic memory deficits [74–77], patients with bvFTD demonstrate a *relative* preservation in their episodic memory [73, 78–80], at least in the early stages of the disease [81]. The pattern is typically one of attenuated learning with a disorganized or inefficient approach. For example, Glosser and colleagues found that difficulty with serial-order recall was more common in individuals with bvFTD than in those with AD and svPPA [82]. Perhaps the most salient difference between bvFTD and AD is that bvFTD patients tend to retain information over delays, while AD patients exhibit rapid forgetting. Indeed, a recent study by Mansoor and colleagues found that individuals with pathology-confirmed bvFTD demonstrated significantly better consolidation of information over delays on a list-learning task when compared to individuals with AD [83]. Visual memory also appears to be relatively spared in bvFTD [78–81]. When both visual and verbal memory are within normal expectations, this may help strengthen diagnostic certainty that the patient does not have Alzheimer's disease.

These patterns of memory performance, however, are not specific to bvFTD. Disorders with frontal–subcortical involvement such as Parkinson's disease and PSP may also demonstrate similar patterns [84, 85]. Moreover, Ranasinghe and colleagues demonstrated that episodic memory declines longitudinally in both bvFTD and AD though mean scores at baseline were significantly different [81]. Nevertheless, relative preservation of episodic memory in bvFTD compared to AD remains one of the most reliable differences between these diseases.

Language

While individuals with bvFTD do not exhibit the same aphasia patterns that accompany PPA variants of FTD, notable declines in speech and language ability can occur. There are often reductions in spontaneous speech and decreased verbal output (single words or decreased phrase length) that can potentially progress to complete mutism [9, 86–88]. Reiterative speech disorders can also occur, such as palilalia, echolalia, verbal stereotypies, and automatic speech [9]. Despite these changes in verbal output, examination of semantic and syntactical knowledge using measures of confrontation naming, word/picture matching, and sentence comprehension suggests that these aspects of language remain relatively intact in bvFTD [73, 79, 89, 90].

There have been few studies that have directly examined differential language patterns between bvFTD and other diseases [87, 90, 91]. Rascovsky and colleagues [91] studied verbal fluency in pathology-confirmed cases of FTD and AD who were matched on age, education, and dementia severity. When converted to *z*-scores based on an age-matched control sample, scores on semantic fluency in the AD group were significantly lower than their scores on phonemic fluency, while the FTD patients performed poorly on both semantic and phonemic fluency.

Visuospatial

Although several studies have found that patients with bvFTD have visuoconstructional deficits on par with AD when the figure is very complex [78, 92, 93], the vast majority of research indicates that visuoconstruction and visual perceptual skills are better preserved in patients with bvFTD relative to AD [73, 86, 94–96]. Difficulties can arise for bvFTD patients when the task relies heavily on top-down control of spatial processing. For example, Possin and colleagues [97] demonstrated that figure copy performance was significantly correlated with right parietal cortex volume in patients with AD, but not with right

dorsolateral prefrontal cortex (DLPFC) volume. The opposite relationship was demonstrated in patients with bvFTD.

Attention/Executive Functions in bvFTD

While intuitive, the claim that attention and executive functions are broadly and disproportionately impacted in bvFTD lacks strong empirical support. Investigation of this domain using "traditional" tasks of executive function has led to largely conflicting findings. While some studies find impairments in this domain [79, 98–100], others do not [101–103]. One reason for this discrepancy likely relates to stage of disease at which patients are assessed. As neurodegeneration begins in the ventromedial aspect of the frontal lobe and moves dorsolaterally with disease progression [24, 27, 28, 104, 105], we would not expect to see executive deficits manifest until later in the disease. Moreover, some pathological subtypes of bvFTD do not necessarily exhibit significant DLPFC degeneration (e.g., TDP-43, Type II) [106]; as such, one might hypothesize that patients with this type of pathology will be less likely to demonstrate executive function deficits.

Another reason why findings have been inconsistent may be due to the fact that executive functions are a poorly defined construct that encompass heterogeneous facets of cognition such as working memory, inhibition, and set shifting [77, 107, 108]. Moreover, they depend heavily on lower-order aspects of cognition such as processing speed and visual perception. It appears that any number of tasks may be subsumed under this umbrella term and are often discussed as if interchangeable. Within the bvFTD neuropsychological literature, there is little consistency regarding which component of executive function might be particularly impaired in bvFTD (working memory vs. inhibition), or in the type of task chosen (e.g., Trail Making Test vs. Digit Span).

Overall, it appears that "traditional" clinical measures of executive function are not particularly sensitive early in the disease process. It is possible, however, that experimental measures of executive function may be more sensitive to subtle declines. For example, Krueger et al. [100] administered traditional tasks of executive function, as well as a computerized Flanker task (measuring cognitive control) to patients with bvFTD and healthy control subjects. Patients were dichotomized into those who scored within normal limits on standard tasks of executive function and those who did not, and their scores on the Flanker task were compared. Interestingly, *both* bvFTD patient groups showed a significantly larger congruency effect (e.g., longer latency on incongruent vs. congruent trials) compared to the normal control subjects [100]. These results suggest that even those patients who perform well on standard tasks of executive function may still have subtle yet perceptible deficits in cognitive control if measured by the appropriate method.

Another approach to measuring executive functioning in bvFTD has been to measure process-oriented features of performance such as errors. Kramer et al. found that overall error scores on tasks of executive function discriminated between patients with bvFTD and AD [79]. Rule violation errors may also be helpful in discriminating between AD and bvFTD. Carey and colleagues [109] found that despite similar achievement scores on the Delis–Kaplan Executive Function System Tower Task, patients with bvFTD made significantly more rule violations compared to patients with AD and normal controls. Similarly, Possin et al. (2012) have shown that despite similar scores on total number of correct designs generated, patients with bvFTD make a greater number of repetition errors compared to patients with AD [110]. Poor "online" detection of errors has also been shown to distinguish between bvFTD, CBS, and PSP [111].

Thompson et al. qualitatively analyzed error types between patients with AD and bvFTD on multiple tasks from several different domains of cognition, including language, memory, visuospatial, and executive function. While several tests were significantly different between the two groups, overall, differences in the types of errors

made were best able to distinguish between AD and bvFTD on regression analysis (e.g., spatial errors vs. perseverations on a drawing task) [73].

Examining errors is also important given that some researchers have found that patients with bvFTD often perform faster on measures of executive function (e.g., Stroop inhibition) than patients with AD but also make significantly more errors, indicating an imbalance in their ability to accurately make speed/error trade-offs [102, 103].

Social Behavior and Personality

The dorsolateral prefrontal cortex (DLPFC) degenerates in both AD and bvFTD, though this may occur at different stages in disease course [104]. This likely explains why large group differences in executive functioning are not regularly demonstrated between the two diseases [101, 112, 113]. Investigations into social and emotional function have produced more consistent results, likely due to the fact that they are mediated by more anterior and ventral aspects of the prefrontal cortex [114–117], areas selectively involved in bvFTD relative to other neurodegenerative disorders.

Studies examining social behavior in bvFTD have found that these individuals tend to demonstrate flat affect, reduced initiative, and more perseveration than patients with other neurodegenerative diseases [118]. Other studies have also found deficits in social pragmatics during conversation [87], worse judgment regarding social norms compared to patients with AD [119], and poor social judgment compared to patients with primary progressive aphasia [120]. Changes in personality facets related to interpersonal function have also been noted to occur in bvFTD. For example, Rankin et al. demonstrated that agreeableness (one of the Big Five personality traits) was not only decreased in bvFTD but also significantly related to right orbitofrontal cortex volumes [121].

Several researchers have found that patients with bvFTD have significantly less self-awareness regarding their current personality and behavioral deficits [21, 122–124] compared to patients with other neurodegenerative diseases, such as AD. This lack of awareness or concern may be due, in part, to the emotion-processing deficits that have been documented in bvFTD. While basic emotion processing such as the startle reflex has been shown to remain intact in patients with bvFTD [125], there are deficits in more complex forms of emotion such as self-conscious emotion, including embarrassment, [125, 126], emotional down-regulation [127], recognition of emotions in others [21, 128–131], and ability to empathize with others [120, 123, 132].

Complex Learning and Decision-Making

The ventral and orbital medial regions of the prefrontal cortex are also thought to be involved in self-advantageous decision-making and adaptive responses to changing emotional or social demands in the environment [115, 116]. Researchers have begun to create experimental paradigms which are thought to tap these processes, including tasks which measure risk taking via computerized gambling programs (e.g., Iowa Gambling Task) [133] and reversal learning tasks focused on reward and punishment [115]. Several studies have demonstrated impairments on these tasks in patients with bvFTD [98, 134–136]; however, these studies did not directly compare the performance of bvFTD to patients with other neurodegenerative diseases. More recently, several studies have demonstrated their utility in the differential diagnosis of bvFTD versus AD [137, 138]. Further research into the discriminatory ability of these tasks between different disease groups is warranted.

Summary of Neuropsychology Literature

While the "classic" pattern of impaired attention and executive function with relative sparing of memory, language, and visuospatial function can occur in bvFTD, this pattern is not

a constant and is just one of the six symptoms that define bvFTD (the other five being social or behavioral). As such, it is imperative that practitioners *do not* use evidence of this neuropsychological pattern as justification for diagnosis of the disease in the absence of other symptoms outlined in the International Diagnostic Criteria [22].

Clinical Assessment of bvFTD

A comprehensive evaluation of bvFTD should include a clinical interview, neuropsychological assessment, assessment of social and emotional function, and informant-based measures. Given that cognition can be relatively preserved in the early stages of the disease, the history, informant report, and observable behavior seen throughout the assessment will likely be the most helpful information you gather.

Interview

A well-structured clinical interview with a collateral source is critical. Patients typically lack insight into the social, emotional, or behavioral issues that are most germane to their caregivers and tend to deny problems. If the informant does not feel comfortable speaking frankly in front of the patient, one should consider conducting a separate interview. During the interview, important areas to cover include:

Onset and Progression

Has the onset been slow and insidious, or abrupt and explicit? Behavioral variant FTD is an insidious disease that may begin many years before changes become obvious. Moreover, because the age of onset of bvFTD tends to be in the late 50s, the personality and behavior changes are often misinterpreted as "midlife" troubles. While insidious change is common to most neurodegenerative diseases, abrupt onset changes in personality and behavior are less likely to be bvFTD.

Nature of Change

As evidenced in the International Criteria for bvFTD [22], changes in personality, emotionality, and social behavior are the most salient symptoms of bvFTD, and the six major symptoms of the International criteria can be used to structure the interview:

1. *Early behavioral disinhibition*. Has the person become socially, behaviorally, or cognitively disinhibited? Do they make inappropriate comments or engage in socially unacceptable behaviors (e.g., flatulence, nose picking)? Do they approach strangers and engage them in conversations or have new-onset gambling or stealing?
2. *Early apathy/inertia*. Does the patient demonstrate a significant loss of interest, drive, or initiation of behavior? For example, those patients who were once hardworking and spontaneous may become passive and indifferent to the surrounding environment. They may also become disengaged in others around them and show little interest in initiating or maintaining conversations.
3. *Early loss of empathy/sympathy*. Does the patient make hurtful or insensitive comments to others (e.g., make disparaging remarks about other's weight or looks), or seem not to notice the pain or distress of others, or lack emotional warmth?
4. *New-onset compulsive/stereotyped behaviors*. Patients with bvFTD can manifest complex compulsions, such as counting or checking rituals or hoarding of useless items such as paper napkins. They may also display simple motor or vocal stereotypies such as tapping, picking, lip smacking, and repeating nonsensical phrases.
5. *Hyperorality or dietary changes*. Changes in eating or hyperorality may occur as well, such that a person may begin to consume alcohol in large quantities, take up smoking cigarettes, or prefer to eat only fast food or sweets. Indeed, significant weight gain is common in bvFTD. Eating behaviors can also take on a

compulsive or rigid quality such as binge eating, eating only certain foods, or needing to be served meals at a particular time.

6. *Neuropsychological profile* (*executive deficits with relative preservation of memory and visuospatial function*). Does the patient seem to have trouble completing complex tasks, or doing two things at once, but can still drive, navigate around town, or remember conversations that occurred a few days earlier? As many patients will not have undergone neuropsychological testing prior to your assessment, pointed "real-world" questions regarding attention/executive functions vs. memory and visuospatial function can help get a better understanding of their cognitive profile.

Family History

Approximately 30–40% of all individuals with bvFTD have a strong family history of the disease. Unfortunately, clear family histories are often difficult to elicit. There may be vague recollections that one of their grandparents was "senile" or had been diagnosed with a psychiatric disorder later in life. However, if a history reveals family members who exhibited significant changes in personality and social behavior after the fifth decade or who had symptoms of motor disorder (e.g., ALS, PSP, CBS), these are potential clues that the individual may have a genetic form of the disease.

Neuroimaging

If the patient has had neuroimaging, it will be helpful to obtain the report or review the scan with a neuroradiologist or neurologist. Atrophy is often asymmetric (right > left) and, in the early to middle stages, confined to the medial frontal and anterior temporal lobes. With increasing disease severity, more diffuse areas of these brain regions degenerate, and more posterior areas including the parietal cortex become involved [25, 104, 105]. Of note, atrophy of the hippocampus also occurs in bvFTD [24, 25]; therefore, this finding should not be used to support a diagnosis of AD rather than bvFTD. Clinically, structural magnetic resonance imaging (MRI) is best for reviewing these findings, though positron emission tomography (PET) scans may also reveal hypometabolism of the frontal and temporal lobes. PET imaging that utilizes Pittsburgh Compound B (PIB), a radioligand which binds to amyloid in the brain, has been shown to be negative in bvFTD [104].

Cognitive Assessment

In general, tests of global cognition such as Folstein's Mini Mental Examination (MMSE; [139]), the Blessed-Roth Dementia Rating Scale [140], or the Montreal Cognitive Assessment (MoCA; [141]) can be insensitive to the subtle cognitive changes that occur early in bvFTD. Indeed, some bvFTD patients in our clinic score 30/30 on the MMSE, despite significant behavioral and social deficits. Nevertheless, inclusion of a measure of global cognition is standard practice in dementia assessment. With its greater focus on verbal fluency and executive functions, the MoCA may be better able to pick up on subtle deficits in bvFTD and is our measure of choice in this population.

We find that a short battery (approximately 1–1.5 h) that examines all major cognitive domains is a quick and useful way to help aid differential diagnosis without overtaxing the patient. While by no means invariable, the relative neuropsychological profile of a patient with bvFTD tends to be one of spared visuospatial and language function and relatively better performance than patients with AD on tests of episodic and semantic memory. Categorical verbal fluency is relatively better than phonemic fluency (though both may be attenuated due to economy of speech). We also recommend executive function tests that elicit and quantify performance errors such as rule violations, perseveration, environmental dependency, impulsivity, and distractibility since achievement scores have not been shown to reliably differentiate between bvFTD and AD.

Behavioral Observations

After neuropsychological evaluation, examiners at our center complete a brief behavior rating scale where patients are rated on a scale ranging from none, mild, moderate, to severe on the following observable behaviors: agitation, stimulus boundedness, perseverations, decreased initiation, motor stereotypies, distractibility, lack of social/emotional engagement, impulsivity, socially inappropriate behavior, and impaired or fluctuating levels of attention. Data from our center suggest that perseverative and inappropriate behaviors and lack of social engagement significantly discriminate between patients with bvFTD and AD. In addition to providing important diagnostic information, quantifying behaviors systematically can also be helpful in interpreting the neuropsychological data (e.g., Did the patient fully attend to the task, or were they distracted and disinhibited?).

Informant-Based Measures

The inclusion of informant-based measures in your assessment can yield important information which, for one reason or another, was not elicited on interview. These scales can provide invaluable information regarding social and emotional deficits experienced by the patient.

Neuropsychiatric Inventory [142]

The Neuropsychiatric Inventory (NPI) is a screening measure that is administered to the patient's informant by the clinician and is a well-validated measure of neuropsychiatric symptoms common in neurodegenerative disease. It was developed as a way to quickly and accurately assess the frequency and severity of 12 different neuropsychiatric behaviors that may occur in the context of dementia (e.g., anxiety, apathy, disinhibition, aberrant motor behavior). The informant is also asked to rate their level of distress by each symptom, which can be useful in helping structure feedback with the family. Extensive research investigating neuropsychiatric symptoms in dementia has been completed with the NPI [142]. Patients with bvFTD tend to have higher overall total scores on the NPI compared to AD, and the domains of apathy, disinhibition, aberrant motor behavior, and appetite/eating changes appear to best differentiate between bvFTD and AD [143–145].

Revised Self-Monitoring Scale [146]

This 13-item questionnaire measures an individual's sensitivity and responsiveness to social cues. While the measure was initially designed for self-report, this questionnaire is easily adapted to an informant-based questionnaire.

Interpersonal Reactivity Index [147]

The empathic concern (EC) and perspective taking (PT) subscales of the Interpersonal Reactivity Index (IRI) were designed to evaluate an individual's ability to empathize with others. The 7-item EC scale specifically measures an individual's emotional response which results from the perception of another's emotional state. The 7-item PT subscale measures an individual's tendency to spontaneously employ perspective taking in their typical social interactions. A recent paper by Dermody and colleagues (2016) demonstrated that while both AD and bvFTD patients displayed significantly worse scores on the Perspective Taking subscale of the IRI compared with healthy control participants, only patients with bvFTD displayed significantly worse scores on the Empathic Concern subscale, thus identifying a dissociation between AD and FTD patients in terms of cognitive versus affective facets of empathy [148].

Experimental Measures of Emotional/Social Function

There are a number of commercially available measures of emotional and social function that have been used to study deficits in bvFTD, but many of these tasks are too demanding for patients and do not provide reliable information. The following two measures were developed by Dr. Katherine Rankin at the University of

California, San Francisco (UCSF; krankin@memory.ucsf.edu). They are well tolerated by patients and provide diagnostically valuable information. If you would like to obtain copies, please contact Dr. Rankin.

Dynamic Affect Recognition Test

This test was designed to assess emotion recognition using dynamic, ecologically valid stimuli. Individuals are asked to watch 12 brief (20 s) vignettes of actors depicting one of the six basic emotions (happy, surprised, sad, angry, fearful, and disgusted) with a semantically neutral script and choose the correct emotion. Comparison of performance between patients with AD and bvFTD suggests that those with AD perform comparably to normal controls, while those with bvFTD have significant deficits in their ability to accurately recognize emotions [149].

Social Norms Questionnaire

This simple, 22-item yes/no questionnaire was developed as a way to determine the degree to which patients understand and can accurately identify implicit but widely accepted social boundaries dominant in the US culture. The social norms questionnaire (SNQ22) includes both inappropriate (e.g., "Cut in line if you are in a hurry," "Pick your nose in public," and "Wear the same shirt every day") and generally acceptable behaviors (e.g., "Tell a coworker your age," "Blow your nose in public," and "Eat ribs with your fingers"). Research suggests that compared to patients with AD, those with bvFTD rate many behaviors as appropriate that normal adults would say are inappropriate [119].

Case History

History of Presenting Illness

Mr. R is a 63-year-old, right-handed, retired policeman presenting for evaluation of personality and behavioral changes. While Mr. R denies any changes in his cognition or behavior, his wife and son provided additional clinical history.

Mr. R's symptoms began insidiously around the age of 58. Previously kind and even tempered, Mr. R became progressively more negative, sarcastic, and critical of others. He started to tell off-color jokes in mixed company and made loud derogatory remarks about overweight individuals standing nearby. He was more irritable and impatient when driving, lashing out verbally against other drivers for perceived infractions. There were no reported incidents of aggressive or violent behaviors. His family reported an overall emotional blunting, social withdrawal, and detachment from his family, losing all interest in their lives. The patient's wife reported that if she did not plan activities, Mr. R would stand and stare out the window all day. His son noted that his previously strong interest in the upkeep of his car had dissipated over the past 2 years. In addition, his diet drastically changed from healthy, low-fat foods to primarily junk food, candy, and large quantities of coffee. His family reported a weight gain of over 20 pounds in the past 5 years.

Mr. R's family also reported a significant decline in function, such that he became unable to follow through with paying bills, instead just leaving paperwork in piles around the house. His wife was not aware of this issue until they began receiving a series of notices. While previously handy around the home, Mr. R became unable to complete familiar projects, such as hanging doors, instead starting the job but then leaving it midstream. His family was also aware that Mr. R's job category at the police station changed once or twice in the 2 years before retirement for reasons that were unclear to them but which they now believe may have had to do with his impairments.

The patient's family noted that Mr. R had begun to engage in compulsive behaviors including emptying the recycling bin at home several times a day, checking the lint trap in the dryer repeatedly, and collecting paper napkins from restaurants. He also engaged in repetitive behaviors such as whistling and tapping his hands on

the table for prolonged periods of time. He compulsively scratches himself but no rash has been noted. He continues to display loss of empathy and will laugh when other people get hurt. He will often say repeatedly throughout the day, "everyone has lost their sense of humor!" or "where has your sense of humor gone?" He is restless and often wants to go somewhere; however, upon arriving at a new destination, he then wants to go back home. The family did not endorse any significant declines in his episodic memory, language, visuospatial, or motor function.

Mr. R's typical day consists of getting up, showering, and getting dressed. He requires reminders to bathe and groom. He will stand at a window for long periods of time and report that his son has gone by or that he is waiting for somebody to arrive. He appears insatiable and will eat for extended periods of time if he is not stopped.

Social/Medical History

Mr. R has been married to his wife for 44 years. They have four adult children. He completed a Master's Degree in Sociology. He worked in law enforcement for 30 years. According to his family, he performed his job in a professional manner and was well respected.

Past medical history is significant for a history of hypercholesterolemia. He has never been hospitalized nor had any surgery. He has no history of head trauma, severe febrile illness, or thyroid disease.

Family history is significant for a mother who developed signs of significant cognitive dysfunction around age 85 which was characterized mainly by memory loss and hallucinations. She died in 2007 with a diagnosis of dementia. His father died at age 59 of a heart attack. There is no other known family history of dementia, neurological or neuromuscular disorders, or psychiatric illness.

Neuropsychological Test Summary

Please see Table 33.3.

Neuropsychiatric Symptom Assessment

Examination of the NPI subscales indicates that the patient's wife endorsed frequent symptoms of agitation, apathy, disinhibition, aberrant motor behavior, and changes in appetite/eating behavior that cause her significant distress (NPI Total Score: 60).

Functional Evaluation

The patient's Clinical Dementia Rating Scale (CDR) total score was 1.0. His most significant impairments occurred in the domains of judgment and problem-solving, home and hobbies, and personal care.

Imaging Results (Fig. 33.1)

Impressions and Formulation

Mr. R is a 63-year-old, retired policeman with a 5-year history of significant personality and behavior changes marked by disinhibited and socially inappropriate behavior, irritability, apathy and social withdrawal, poor executive functioning, obsessive–compulsive activities, and hyperorality with a 20-pound weight gain in the past 5 years.

On neuropsychological testing, his affect was notable for emotional blunting and mild irritability. Overall, Mr. R demonstrated below-average performance on free recall measures of verbal and visual episodic memory. Verbal and visual recognition memory was within normal limits. His performance on measures of executive functioning varied, ranging from impaired to average.

Table 33.3 Neuropsychological test summary

Domain	Test	Raw score	Range
Global	MMSE	29/30	Within normal limits (WNL)
Attention/working memory	Longest digit span forward	7	WNL
	Longest digit span backward	5	WNL
Memory	CVLT-II-SF trial 1–4 total	23/36	Below average
	CVLT-II-SF 10-min delay	6/9	Below average
	CVLT-II-SF cued recall	7/9	Below average
	CVLT-II-SF recognition	9/9; 1 false positive	WNL
	Figure copy recall	10/17	Below average
	Figure copy recognition	YES	WNL
Language	Abbreviated BNT total	15/15	WNL
	Syntax comprehension	5/5	WNL
	Repetition	5/5	WNL
Visuospatial	Figure copy	15/17	WNL
	Object–number location matching	10/10	WNL
	Face perception	12/12	WNL
	Calculations	4/5	Below average
Executive function	Modified Trail making test (time)	64/120	Below average
	Modified Trail making test errors	4	–
	Design fluency	11	Average
	Design fluency errors	4	–
	"D" word fluency (60)	3	Impaired
	"D" word errors	3	–
	Animal fluency (60)	14	Below average
	Animal fluency errors	2	–
	Stroop interference total	54	Average
	Stroop interference errors	9	–
	Affect naming	9/16	Impaired

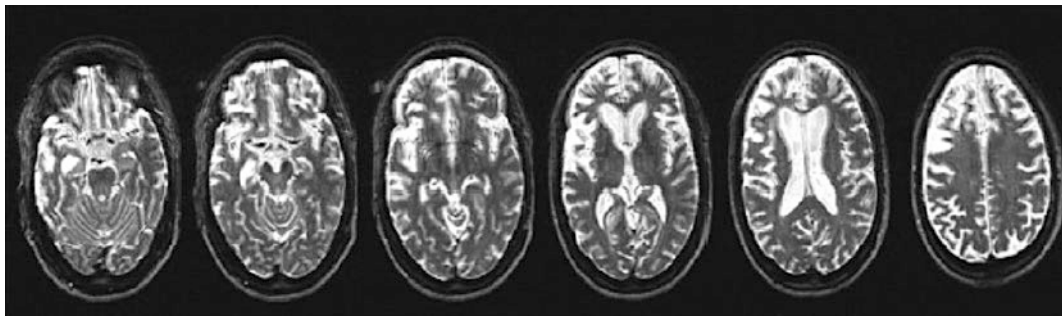

Fig. 33.1 T2-weighted structural magnetic resonance imaging (MRI) of Mr. R's brain. Note the significant volume loss in the frontal and temporal lobes bilaterally, worse on the right compared to left. (image is oriented according to radiological convention; e.g., left = right, right = left)

Of note, he made a total of 22 errors, which is well above average compared to others in his age range. Global cognition, attention/working memory, language, and visuospatial function remain largely intact.

Given his history of significant emotional and behavioral changes, error-prone pattern of performance on measures of executive function and neuroimaging findings of right > left degeneration of paralimbic frontal, temporal, and insular structures, his pattern of findings is most suggestive of a diagnosis of behavioral variant frontotemporal dementia.

In terms of treatment, Mr. R's primary care physician may want to consider prescribing treatment with a selective-serotonin reuptake inhibitor (SSRI) in order to target his obsessive–compulsive behaviors and irritability. However, anticholinesterase agents should not be prescribed, as these have been known to exacerbate the irritability seen in frontotemporal dementia. I also recommend that Mr. R begin a program of vigorous physical activity, as exercise has been shown to have neuroprotective properties. His entire family may want to consider attending a FTD caregiver support group. Finally, despite intact attention and visuospatial skills, it is strongly recommended that Mr. R discontinue driving.

Clinical Pearls

- FTD is first and foremost a disease that disrupts behavior and social function.
- Compared to AD, patients with bvFTD tend to have little insight into their condition and are more flat, perseverative, inappropriate, and emotionally dysregulated.
- Due to its pathological heterogeneity, bvFTD can present alone or in combination with other diseases such as PSP, CBD, and ALS.
- BvFTD is often misdiagnosed as late-onset psychiatric disease or early-onset AD.
- The presence of executive dysfunction in the absence of other major cognitive impairments is not specific to bvFTD.
- Neuropsychological testing should focus on *relative patterns* of performance vs. domain impairments.
- In the early stages of disease, process-oriented features of performance such as rule violations and errors appear to best discriminate between bvFTD and AD.
- Integration of history, behavioral observations, imaging, social/emotional function, informant questionnaires, and relative test scores in keeping with the disease are most important in coming to an accurate diagnosis.
- A multidisciplinary team approach, working with a neurologist and other health-care professionals, is most helpful in diagnosing this elusive disease.

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Movement Disorders with Dementia in Older Adults

34

Alexander I. Tröster and Angela Abbott

In old age, the most common dementias associated with movement disorders are Parkinson's disease (PD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). These conditions can be broadly grouped according to their characteristic neuropathologic features as synucleinopathies (DLB and PDD) or tauopathies (CBD and PSP). Clinical neuropsychological test findings by themselves are not diagnostic, and differentiation between synucleinopathies and tauopathies might be easier than distinguishing among synucleinopathies or among tauopathies. Indeed, the neuropsychological features of PDD and DLB are often indistinguishable even if subtle differences occasionally emerge [1] and for this reason are considered together within this chapter. Similarly, the tauopathies have considerable symptom overlap, and CBD can present clinically resembling PSP and vice versa (and both can present initially as a primary progressive aphasia). Despite neuropsychological overlap among dementias associated with different movement disorders, neuropsychological evaluation that carefully weighs test results, neuroimaging and neurological findings, interview information about disease course, emergence of various motor and non-motor symptoms (and their response to various treatments), and comorbidities can be helpful in supporting or ruling out a specific diagnosis. When patients with dementia and a movement disorder are referred for neuropsychological evaluation, the referral issue is often one of facilitating differential diagnosis and determining if additional factors (e.g., depression, medications, or medical conditions) are producing cognitive compromise. Other referral issues include patient selection for treatment (e.g., as in PD patients being considered for deep brain stimulation or DBS [patients with dementia are evaluated and typically excluded as candidates for DBS]), documentation of deficit progression with advancing disease (or improvement with treatment), and characterization of deficits to help determine potentially beneficial interventions and compensatory strategies.

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Epidemiology

Parkinson's Disease Dementia and Dementia with Lewy Bodies

Population prevalence rates of PD are about 0.01% under age 45 and 1.2% over age 65 [2]. Annual incidence of PD increases with age from 41 per 100,000 in 40–49-year-olds to as high as 1,903 per 100,000 in those older than 80 years [3].

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Table 34.1 Risk factors for dementia in Parkinson's disease [193]

Demographic variables	Disease variables	Neurobehavioral variables
Greater age	Later onset	Depression
Lower education	Disease duration	Poor performance on tests of
Lower socioeconomic status	Disease severity	(a) Executive/attention
Family history of Parkinson's dementia	Susceptibility to levodopa-induced psychosis or confusion	(b) Verbal fluency
	REM sleep behavior disorder	(c) Visuoperceptual
	Akinetic-rigid symptoms	(d) List learning

A population-based study in France reported an incidence of 263 per 100,000 person-years [4]. Dementia prevalence estimates in PD vary from 8% to 93%, depending upon diagnostic criteria, sampling, and case ascertainment methods used. The most rigorous studies reveal a dementia prevalence of about 25% among patients with PD [5]. Dementia incidence is about 3% for persons with PD younger than 60 years and 15% for persons with PD older than 80 years [6–8]. Advancing age, low education, and postural instability and gait disturbance (PIGD) have been associated with increased dementia risk in PD, among other factors (see Table 34.1).

DLB, as distinguished from PDD, is one of the most common dementias, accounting for between 0.3% and 24.4% of all cases of dementia when strict diagnostic criteria are used [9]. Prevalence estimates in the most rigorous studies range from 0.02 to 33.3 per 1,000 people, while incidence estimates range from 0.5 to 1.6 per 1,000 person-year [9]. One study reported an incidence of suspected DLB of 112 per 100,000 person-years [4]. A study in the USA using formal diagnostic criteria for DLB reported a similar incidence of about 0.1% in the population and 3% among dementia cases [10]. These numbers, however, may underrepresent true incidence rates [11] particularly in secondary care facilities where diagnostic accuracy may be improved [12].

Corticobasal Degeneration

Estimated to account for 4–6% of parkinsonism, CBD is considered a rare neurodegenerative disorder, for which prevalence and incidence rates have not been widely studied [13]. Prevalence in Japan has been reported to be about 2 per 100,000 [14] to 9 per 100,000 [15]. Incidence vary widely, from 1.4 to 5.3 per 100,000 [16, 17] but as low as 0.02 per 100,000 person-years in a Russian study [18]. Dementia and neurobehavioral abnormalities were thought to be rare in CBD but are now accepted to be a common presenting problem depending on whether patients initially present to movement disorder, dementia, or psychiatry clinics. Whereas one study noted that at initial presentation, only 19% of 36 patients had "slight generalized cognitive impairment" [19], another study observed that among 13 pathologically confirmed cases, 69% had dementia at presentation [20]. The H1/H1 tau haplotype has been identified as heightening susceptibility to both CBD and PSP (with the H2 haplotype perhaps being protective) [21], but no clear genetic etiology has been identified.

Progressive Supranuclear Palsy

The population prevalence of PSP ranges from about 3 to 6 per 100,000 [22, 23], but these estimates may be conservative due to diagnostic inaccuracy. Annual incidence of PSP has been estimated between 0.14 [18] and 1.7 per 100,000 person-years [24]. In persons 50 years and older, incidence has been reported at 5 per 100,000 [25]. Neither incidence nor prevalence of PSP is strongly associated with any demographic or genetic risk factors, except older age [22]. No adequate epidemiologic studies of neuropsychological impairments in PSP have been conducted, and dementia prevalence estimates in PSP of

50–80% might be overestimates due to common visual disturbances and information processing speed abnormalities. A study with over 300 patients observed impairments on the Dementia Rating Scale in 57% of patients and on the Frontal Assessment Battery in 62% of cases [26].

Clinical and Neurological Presentation

Parkinson's Disease Dementia and Dementia with Lewy Bodies

Separate criteria have been proposed for PDD [27] and DLB [28] (see Tables 34.2 and 34.3). An essential feature differentiating PDD and DLB is the time of onset of dementia in relation to onset of motor signs. When neurobehavioral symptoms precede or occur within the first 12 months of the motor signs, then a diagnosis of DLB is made. By contrast, when cognitive symptoms have their onset more than 12 months after the onset of parkinsonism, then PDD is diagnosed.

Parkinson's disease dementia requires that a prior diagnosis of Parkinson's disease has been made. Several criteria for PD diagnosis have been proposed, but the most widely accepted are those of the UK Parkinson's Disease Society Brain Bank (or Queen Square) criteria [29]. Diagnosis of PD requires the presence of a parkinsonian syndrome evidenced by bradykinesia and at least one of muscular rigidity, 4–6 Hz resting tremor, and postural instability not related to proprioceptive, vestibular, visual, or cerebellar dysfunction. The diagnosis of definite PD requires at least three supportive features: unilateral onset, persistence of symptom asymmetry,

Table 34.2 Clinical diagnostic criteria for PDD (based on Emre et al. [27])

Core features: (both required for probable or possible PDD)
1. Diagnosis of Parkinson's disease per UK Parkinson's Disease Society Brain Bank criteria
2. Dementia of insidious onset and slow progression in the presence of PD, defined by:
(a) Impairment of more than one domain of cognition
(b) Impairment represents a decline from premorbid functioning
(c) Impairment in day-to-day functioning not ascribable to motor or autonomic dysfunction
Associated features: (typical cognitive profile as outlined below in at least two of the four domains and at least one of the behavioral symptoms required for diagnosis of probable PDD; atypical cognitive profile in one or more domains allows for diagnosis of possible PDD, in which behavioral disturbance may or may not be present)
1. Cognition
(a) Impaired attention which may fluctuate within or across days (b) Impaired executive functions, e.g., planning, conceptualization, initiation, rule finding, set maintenance or shifting, bradyphrenia (c) Preserved language, though word finding and complex sentence comprehension deficits may be present (d) Impaired memory, usually with benefit from cuing and better recognition than recall
2. Behavior
(a) Apathy (b) Changes in mood and personality, including features of depression and anxiety (c) Delusions, commonly of the paranoid type (d) Hallucinations, usually visual, complex, and well formed (e) Excessive daytime sleepiness/somnolence
Features making the diagnosis of PDD uncertain: (none of these features can be present when diagnosing probable PDD; one or both of these features can be present when diagnosing possible PDD)
1. Another abnormality capable of impairing cognition but judged not to be the cause of the dementia (e.g., vascular disease on neuroimaging) 2. Time interval between onset of motor and cognitive symptoms is unknown
Features suggesting another condition as causing the mental impairment: (if present, PDD cannot be diagnosed)
1. Cognitive and behavioral abnormality occurs solely in the context of other conditions, such as confusional state due to systemic disease or intoxication or major depressive disorder 2. Features consistent with probable vascular dementia per NINDS-AIREN criteria

Table 34.3 Revised clinical diagnostic criteria for DLB (based on McKeith et al. [28])

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social , occupational, or daily function activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability tend to be prominent and occur early
Core clinical features (The first three typically occur early and may persist throughout the course.)
Fluctuating cognition with pronounced variations in attention and alertness Recurrent visual hallucinations that are typically well formed and detailed REM sleep behavior disorder, which may precede cognitive decline One or more spontaneous cardinal features of parkinsonism, namely, bradykinesia (slowness or diminished amplitude of movement), rest tremor, and rigidity
Supportive clinical features
Severe sensitivity to antipsychotic agents, postural instability, repeated falls, syncope or other transient episodes of unresponsiveness, severe autonomic dysfunction (evidenced by, e.g., constipation, orthostatic hypotension, urinary incontinence), hypersomnia, hyposmia, hallucinations in other-than-visual modalities, systematized delusions, apathy, anxiety, and depression
Indicative biomarkers
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy Polysomnographic confirmation of REM sleep without atonia
Supportive biomarkers
Relative preservation of medial temporal lobe structures on CT/MRI scan Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity or the cingulate island sign on FDG-PET imaging Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range
Probable DLB can be diagnosed if:
(a) Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers
(b) One core clinical feature in the presence of one or more indicative biomarkers
Probable DLB should *not* be diagnosed on the basis of biomarkers alone
Possible DLB can be diagnosed in the presence of:
(a) One core clinical feature of DLB without indicative biomarker evidence
(b) One or more indicative biomarkers in the absence of core clinical features
DLB is less likely:
(a) In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation
(b) If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting, the term that is most appropriate to the clinical situation should be used, and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended

progression of symptoms, excellent response to levodopa, levodopa response sustained for 5 years, levodopa-induced dyskinesias, or a clinical course over 10 years. Exclusion of various conditions capable of producing parkinsonism is required. PD most often becomes symptomatic during the sixth decade of life, but juvenile and young-onset forms occur. The most common initial cognitive complaint in both patients with PDD and those with DLB may involve memory. One study reported that 67% of PDD and 94% of DLB patients initially complained of memory problems [30]. However, patients may also initially complain of word-finding problems, difficulty keeping up with conversations due to slowness of thought, inefficiency with work,

domestic chores and financial management, as well as problems with concentration, indecisiveness, and apathy [31]. In our experience, patients and/or their care partners may also report fairly early in PDD that the patient has problems with day-to-day and repair tasks with which they were previously facile (e.g., sequencing of recipes, trouble reassembling disassembled objects such as lawn mowers). In the case of DLB, cognitive changes are also likely to be accompanied by complaints of visual distortions and hallucinations and signs of possible rapid eye movement (REM) sleep behavior disorder (RBD) (e.g., acting out dreams while asleep).

Corticobasal Degeneration

Because the clinical features of CBD can be produced by conditions other than CBD, and pathologically confirmed CBD has heterogeneous clinical presentations, it has been proposed that *corticobasal syndrome* (CBS) be the preferred term for conditions characterized by the core motor and cortical features of CBD regardless of etiology. In contrast, CBD has been proposed to be reserved for neuropathologically distinct CBD regardless of clinical presentation [32]. Separate sets of diagnostic criteria have been developed to account for this symptom heterogeneity [33] (see Table 34.4). Probable CBD (cr-CBD) is based on stricter clinical research criteria offering greater diagnostic specificity, while possible CBD (p-CBD) is diagnosed on the basis of broader criteria and diverse presentation of symptoms, thereby allowing for greater diagnostic sensitivity. Both sets of criteria require insidious onset and gradual progression of the disorder with symptoms lasting greater than 1 year. However, age of onset for cr-CBD is 50 years or older, while p-CBD has no age cutoff. Additionally, tau genetic mutations are exclusion criteria under cr-CBD but not p-CBD, and phenotypes may include progressive supranuclear palsy syndrome (PSPS) only under p-CBD criteria.

Average age of onset for CBD is typically in the mid-1960s, and mean time to death from diagnosis is about 7 years [33]. CBD can present with either predominantly motor or cognitive dysfunction [34]. Typical initial complaints include clumsiness, stiffness, or jerkiness of an arm and less frequently, clumsiness of a leg (stubbing one's toes when walking). The most striking motor features of CBD include markedly asymmetric, progressive, akinetic-rigid parkinsonism of gradual onset that responds minimally to levodopa, associated with focal dystonia with or without contractures and hand, limb, gait, and speech apraxia. CBD is sometimes accompanied by focal stimulus-sensitive myoclonus, usually involving the most affected limb and jerky action-induced tremor. Common cortical signs in CBD include asymmetric ideational and ideomotor apraxia, cortical sensory deficits (e.g., astereog-

Table 34.4 Diagnostic criteria for corticobasal degeneration (based on Armstrong et al. [33])

	Clinical research criteria for probable sporadic CBD	Clinical criteria for possible CBD
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms (years)	1	1
Age at onset (years)	≥50	No minimum
Family history (two or more relatives)	Exclusion	Permitted
Permitted phenotypes	1. Probable CBS 2. Frontal behavioral-spatial syndrome, plus at least one CBS feature	1. Possible CBS 2. Frontal behavioral-spatial syndrome or nonfluent/agrammatic variant of primary progressive aphasia, plus at least one CBS feature
Genetic mutation affection τ (e.g., MAPT)	Exclusion	Permitted

nosis, agraphesthesia), and alien hand syndrome. The latter may involve a sense of lack of ownership in the absence of visual cues of the limb, involuntary purposeful movements, or frank interference of one limb with the other's execution of purposeful movement. Patients often complain of clumsiness with fine finger movements and abnormal reaching movements.

Progressive Supranuclear Palsy

PSP shares some pathological and clinical features with CBD and frontotemporal dementia (e.g., primary progressive aphasia). Average age at symptom onset is 65 years, and the disease course typically lasts 6–9 years [23, 35]. 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 [25]. Only about 5% of cases have symptom onset before age 50. At the present time, there are no effective pharmacological or neurosurgical treatments for PSP [36].

The most common phenotype of PSP, referred to as Richardson's syndrome (PSP-RS), accounts for an estimated 76% of PSP cases and presents with the classic vertical gaze palsy (slowing of vertical saccades, usually affecting downgaze before upgaze) and postural instability [38]. Additional phenotypes, however, vary considerably in phenomenology. Symptoms may include imbalance evident in falls, accompanied by greater axial than appendicular rigidity, impoverished postural reflexes, dysarthria (commonly a hypophonic monotone), sloppy eating habits due to poor eye-hand coordination, nonspecific visual difficulties, loss of eye contact, and slowness of thought [37]. Cognitive complaints, when present, early on may include visual, concentration, or executive problems. Parkinson's disease-like symptoms also observed in PSP (PSP-PD) may include resting tremor, unstable and wide-based gait, symmetric bradykinesia, and a masked face with a seemingly perpetually startled expression (raised brow). PSP-PD has been associated with a slower, less severe disease progression lasting about 12 years [39]. Recognizing different clinical subtypes is not only important when considering PSP in the differential diagnosis but also for patient counseling with regard to potential medication response and prognosis.

Research diagnostic criteria have been refined to aid in early detection and improve sensitivity and specificity of clinical diagnosis stratified by three levels of certainty: probable PSP, possible PSP, and suggestive of PSP [40]. Additionally, four core domains of PSP have been proposed: ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction (see Table 34.5).

Table 34.5 Core clinical features for PSP (based on Höglinger et al. [40])

	Functional Domain			
Levels of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	O1: Vertical supranuclear gaze palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	O2: Slow velocity of vertical saccades	P2: Tendency to fall on the pull test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	C2: Frontal cognitive/ behavioral presentation
Level 3	O3: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 34.4.

Mandatory inclusion criteria for all domains include presence of a sporadic, adult-onset, gradually progressive neurodegenerative disease, for which symptoms are not explained by a different diagnosis. Definite PSP confirmed postmortem offers the highest level of confidence in diagnostic accuracy while probable PSP diagnosis has high specificity. Possible PSP offers high sensitivity, and a clinical presentation meeting suggestive of PSP criteria offers the potential for early diagnosis.

Specific combinations of core features and supportive clinical and imaging features are used to identify clinical predominance types. These types include Richardson's syndrome (PSP-RS), ocular motor dysfunction (PSP-OM), postural instability (PSP-PI), Parkinsonism resembling idiopathic Parkinson's disease (PSP-P), frontal lobe cognitive or behavioral presentations (PSP-F), progressive gait freezing (PSP-PGF), corticobasal syndrome (PSP-CBS), primary lateral sclerosis (PSP-PLS), cerebellar ataxia (PSP-C), and speech/language disorders (PSP-SL; see Table 34.6).

Neuropathology

Parkinson's Disease Dementia and Dementia with Lewy Bodies

The pathological feature of PDD and DLB is the presence of aggregates of alpha-synuclein, in the form of Lewy bodies (LB; neuronal cytoplasmic inclusions) and Lewy neurites (LN; axonal and dendritic inclusions). Traditionally, PD has been defined by neuronal loss and LB in the substantia nigra. However, LB and LN are also found outside the substantia nigra. Braak et al. developed a 6-stage system [41] outlining the systematic progression of LB pathology from preclinical PD through advanced PD. In the first two stages (preclinical), olfactory and brain stem regions show LB and LN, and by the time of clinical diagnosis (usually at stage III or IV), the LB and LN extend to midbrain, including the substantia nigra, basal forebrain, transentorhinal cortex, and hippocampal CA2 cell field. In the final two stages (V and VI), LB and LN become evident in cortical association areas and eventually in much or all of the neocortex.

An instructive study evaluating the Braak staging system is the prospective Sydney Multicenter Study of PD [42]. These researchers found three phenotypes of patients: (1) a group with early, prominent dementia and akinetic-rigid PD (corresponding clinically to DLB), (2) a group of older PD patients (onset after 70 years) developing dementia in 3–10 years (corresponding clinically to PDD) who have widespread alpha-synuclein pathology, and (3) a younger PD group (onset before 70 years) in which dementia occurs late in the disease (after 10–15 years) and there is cell-loss dominant pathology with lesser alpha-synuclein deposition. Another study similarly found that PD patients developing dementia late in the disease had less cortical alpha-synuclein pathology but greater cholinergic abnormalities than those developing dementia early on, whose pathology resembles more strongly that of DLB [43]. Others have observed that alpha-synuclein in PD mimics prions and that PD may, in fact, be a prion disorder resulting from toxic buildup of alpha-synuclein [44]. Both alpha-synuclein and prion proteins have an α-helical-rich conformation that can aggregate to form β-sheet-rich structures. Moreover, transmission of alpha-synuclein has been shown to occur between affected nerve cells overexpressing the protein and healthy neighboring transplanted stem cells, similar to contamination of cells in prion disease [45].

A significant number of persons with DLB are also found to have amyloid plaques at autopsy. Amyloid pathology may be less likely implicated in PDD. One possibility for the somewhat divergent findings obtained from studies of cerebrospinal fluid (CSF) beta-amyloid markers and functional amyloid imaging in PDD is that CSF biomarker levels may reflect biologic processes other than amyloid deposition in the brain. Although PD is initially primarily associated with dopaminergic pathophysiology, other neurotransmitter systems become involved with disease progression, and both DLB and PDD involve significant dysfunction of the dopaminergic and cholinergic systems.

Table 34.6 Degrees of diagnostic certainty for PSP, obtained by combinations of clinical features and clinical clues (based on Höglinger et al. [40])

Diagnostic certainty	Definition	Combinations	Predominance type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	Def. PSP
Probable PSP	Highly specific but not very sensitive for PSP Suitable for therapeutic and biological studies	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	Prob. PSP-RS
		(O1 or O2) + A1	PSP with progressive gait freezing	Prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	Prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	Prob. PSP-F
Possible PSP	Substantially more sensitive but less specific for PSP Suitable for descriptive epidemiological studies and clinical care	O1	PSP with predominant ocular motor dysfunction	Poss. PSP-OM
		O2 + P3	PSP with Richardson's syndrome	Poss. PSP-RS
		A1	PSP with progressive gait freezing	Poss. PSP-PGF
		(O1 or O2) + C1	PSP with predominant speech/language disorder	Poss. PSP-SL
		(O1 or O2) + C3	PSP with predominant CBS	Poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP Suitable for early identification	O2 or O3	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		O3 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, or other specific clinical clues)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1 [highest], 2 [mid], 3 [lowest]), they contribute to the diagnosis of PSP (see Table 34.5)
s.o.: suggestive of

Corticobasal Degeneration

The pathological hallmarks of CBD include ballooned and achromatic neurons which are most numerous in frontoparietal cortex but are also seen in the anterior cingulate, amygdala, and insular cortex. Tau-containing neuronal inclusions are evident in cortex and striatum. The frontoparietal cortices typically show asymmetric atrophy. The pons, medulla, and dentate are also atrophied, and the caudate may appear flattened. The substantia nigra shows decreased pigmentation and cell loss. Neuronal loss and gliosis, in addition to being evident in frontoparietal cortex, are seen in basal ganglia, thalamus, subthalamic nucleus, dentate, and red nucleus.

Progressive Supranuclear Palsy

PSP, unlike PD, compromises the entire substantia nigra, and dopaminergic depletion is comparable in caudate and putamen. Neuronal loss and gliosis are evident in the globus pallidus, subthalamic nuclei, red nuclei, dentate, superior colliculi, and periaqueductal gray matter. Neurofibrillary tangles (different from those seen in AD), and neuropil threads, are observed in the basal ganglia, brain stem, dentate, and the nucleus basalis of Meynert, which is a major cortical cholinergic output structure.

Structural and Functional Neuroimaging Findings

Parkinson's Disease Dementia and Dementia with Lewy Bodies

Advances in structural and functional neuroimaging, in part using radioactive tracers, are beginning to confirm and clarify the role of various pathologies in the neurobehavioral features of PDD. Studies have shown an association between dementia in PD and neocortical, medial temporal, and amygdala atrophy [46]. DLB is marked by findings of greater temporal, parietal, and occipital atrophy, whereas PDD has been associated with predominately frontal atrophy ([47–49]. Consistent patterns of frontal dysfunction in PDD and posterior dysfunction in DLB have been observed across imaging modalities. On diffusion-weighted imaging, a purported indicator of white matter integrity, fractional anisotropy was more reduced in DLB in posterior temporal and occipital regions compared to PDD [51]. Functional connectivity, a measure of signal coherence between brain regions, was reduced among neighboring frontal regions in PDD and among neighboring posterior regions in DLB [49]. Some divergent findings have shown greater frontotemporal atrophy in DLB compared to PDD but may be confounded by group differences in duration or severity of dementia or parkinsonism [50].

[11C]PIB PET imaging provides an estimate of the brain's beta-amyloid load. Increased PIB uptake (greater amyloid deposition) has been reported commonly in DLB and less commonly in PDD [52–54]). PIB uptake in both DLB and PDD has been associated with higher ApoE4 prevalence, dementia severity, CSF Abeta 42 levels [55], and visuospatial impairment [53]. Cortical acetylcholinesterase (AChE) activity, imaged in vivo using [11C]methyl-4-piperidyl acetate (MP4A), showed reduced levels especially in posterior brain regions in PD and PDD [58, 59]. Decreased cholinergic binding in PDD has also been observed for the M1/M4 muscarinic receptors in the basal forebrain, temporal lobe, striatum, insula, and anterior cingulate; however, when trialed on cholinesterase inhibitor medication, improved performance on Mini-Mental State Exam (MMSE) was reported and associated with increased or preserved function of frontoparietal and default-mode network regions [60]. Decreased AChE activity has also been shown to impact working memory and executive deficits in PDD [57] while being associated with depression in PD/PDD [56]. Dopaminergic imaging using PET and SPECT reveals reduced dopamine transporter binding and fluorodopa uptake in the striatum in DLB and, more particularly, in PDD [61]. Posterior (especially occipital) cerebral blood flow and glucose metabolism are especially reduced in DLB and PDD [62–64]).

Corticobasal Degeneration

Structural MRI has revealed cortical atrophy occurring in frontoparietal (see Fig. 34.1), temporal, and occipital lobes, corpus callosum, and bilateral thalamus [65–67]). Specific biomarkers shown to distinguish CBD from other atypical parkinsonian disorders include gray matter loss in the premotor/supplementary motor cortices and the posterior midcingulate/frontomedian cortex [67]. White matter hypointensities have been reported in the putamen [65], and atypically increased average diffusion coefficients on diffusion-weighted imaging were reported in the motor thalamus, pre- and postcentral gyri, and supplementary motor area, thus suggesting reduced integrity of white matter tracts in these areas [68]. PET and SPECT findings are consistent with presynaptic dopaminergic abnormalities in CBD, thus revealing asymmetric decrease in fluorodopa uptake and dopamine transporter binding in caudate and putamen, with the side contralateral to the hemibody most affected showing the greater reduction [69]. Similarly, reductions in glucose metabolism in the hemisphere contralateral to the affected hemibody were found in frontal and parietal cortices, thalamus, and caudate nucleus [70]. Mild reductions in acetylcholinesterase activity have been observed with PET imaging, especially in the frontal, parietal, and occipital cortex [71].

Progressive Supranuclear Palsy

Structural MRI findings supportive of a diagnosis of PSP include midbrain atrophy correlated with oculomotor signs (see Fig. 34.2) and superior cerebellar peduncle atrophy, though putaminal atrophy which is also seen in other forms of parkinsonism may be evident [65]. The ratio of the midbrain to pontine diameter, in particular, is reduced in PSP and may offer a highly specific and noninvasive biomarker, at a value less than .52 [72]. Cortical (especially frontotemporal) atrophy also occurs, and frontal atrophy has been linked to scores on the Frontal Behavior Inventory [73] and executive dysfunction [74]. Reduced glucose metabolism on FDG PET has been reported, occurring most prominently in the midbrain and mesial frontal cortex [75]. Imaging of pre- and postsynaptic dopaminergic abnormalities does not differentiate PSP from other forms of parkinsonism such as multiple system atrophy, but imaging of postsynaptic dopaminergic abnormalities can be helpful in differentiating PSP from PD [69]. Cholinergic imaging has shown reduced acetylcholinesterase activity in paracentral and thalamic regions suggesting a loss of ascending fibers from the pedunculopontine and laterodorsal tegmental nuclei [71]. Recent development of tau-binding radiotracers has enabled imaging of tau deposits and shown an increased tau burden in subcortical areas,

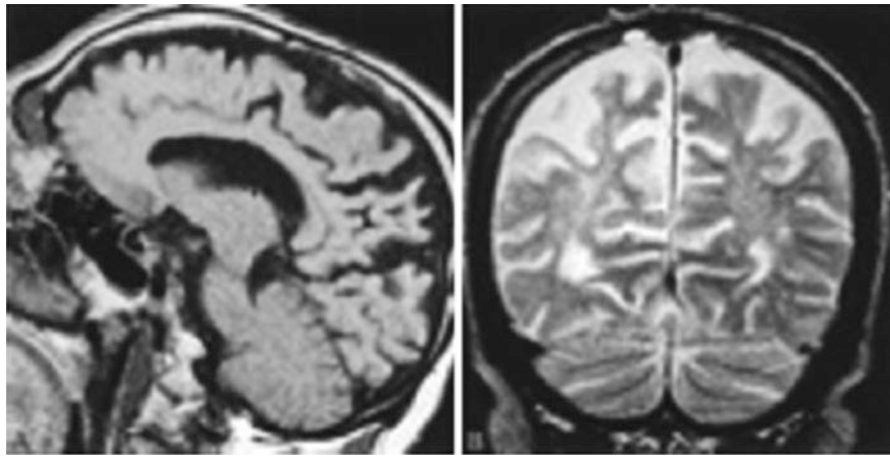

Fig. 34.1 MRI scan in corticobasal degeneration (note asymmetric atrophy, especially frontoparietal)

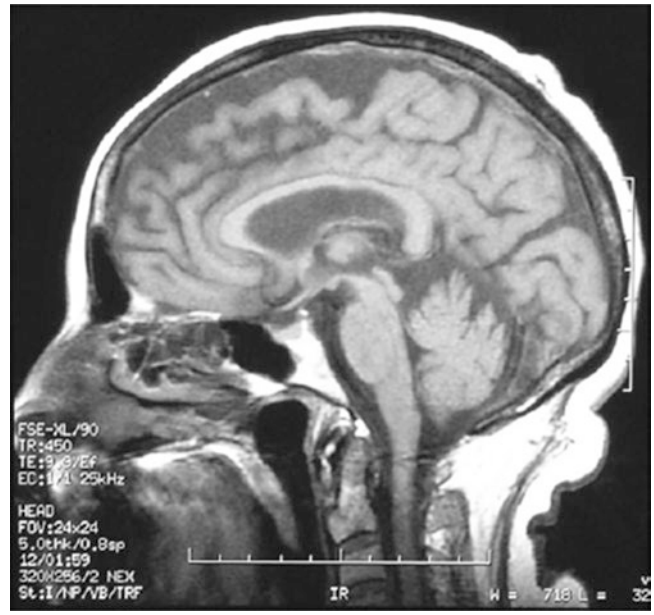

Fig. 34.2 Sagittal T1-weighted MRI in progressive supranuclear palsy: note thinning of the midbrain tegmentum and tectum and frontal atrophy

including the globus pallidus and midbrain [76] along with the putamen and subthalamic nucleus in PSP [77]. Tau imaging is a potentially promising research tool for differential diagnosis, measuring lesion load and disease prognosis [78].

Neuropsychological Hallmarks

Parkinson's Disease Dementia and Dementia with Lewy Bodies

Reviews comparing cognitive performance in PDD and DLB [1, 79] can be consulted for further detail and additional references.

Attention and Working Memory

Performance on simple attention tasks, such as span tasks, is preserved in PD, but as the disease progresses, impairments may be observed even on cued attention tasks. Working memory-demanding tasks reveal impairments early in PD [80], and these deficits progress in PDD. Complex (sustained, divided) attention tasks, such as Stroop and visual cancellation tasks, are more likely than simple tasks to elicit attention impairment in DLB or PDD [30]. In comparison to PDD, DLB may involve greater impairments on tasks such as WAIS-R Arithmetic, Stroop, and Trail Making tests [81] and WAIS-R Digit Span backwards [82].

Executive Functions

Executive deficits may have particular importance as harbingers of PDD. Planning, often assessed with tower tasks, can be slowed or inaccurate in PD or even stimulus bound in PDD [83]. Card sorting tests evaluating conceptualization and maintenance and switching of set may show patients with PD to (a) be slow to conceptualize, (b) have difficulty shifting set, and (c) lose set. Set-shifting deficits are more apparent in patients with declining mental status and evident especially when extra- rather than intra-dimensional shifts are required.

While poor executive function is a hallmark of both PDD and DLB, greater impairment has been observed in patients with DLB on a card sorting task [82] and on a screening measure of conceptualization [84, 85] compared to PDD. However, another conceptualization measure, the identities and oddities task, showed no differences between groups [30].

Language

Patients with PDD have more impaired verbal fluency than PD patients, but verbal fluency may be similarly impaired in PDD and DLB [30]. Visual confrontation naming is preserved in PD. While some found naming to be comparably impaired in PDD and DLB [30], the relative preservation of naming in DLB compared to AD may have diagnostic significance [86]. Occasionally observed mild impairments in sentence comprehension or repetition have been ascribed to attention/executive limitations in PD [87], but performance in PDD is typically not impaired on comprehension and repetition tasks.

Learning and Memory

The relative integrity of recognition relative to free recall has been interpreted as indicative of a retrieval deficit in PD. It must be emphasized that recognition is not necessarily intact in PD [88, 89]. Furthermore, memory profiles in PD are heterogeneous [90], and semantic encoding may be deficient [91, 92], perhaps reflecting executive deficits or problems in the use of self-initiated rather than externally imposed learning strategies. PDD and DLB memory impairments are similarly severe (but less severe than in AD) [30]. Nonetheless, qualitative aspects of memory impairment may clinically distinguish DLB and PDD [93]. Whereas DLB manifests poorer recall and more rapid rates of forgetting, PDD makes more perseverative errors during list learning [93]. Remote memory may be impaired in PDD, but the temporal gradient of the loss is equally severe across all past decades implicating a retrieval deficit [94, 95].

Visuoperceptual and Spatial Functions

Comparably severe deficits in PDD and DLB have been observed on numerous visuospatial and constructional tasks, including pentagon copying, BVRT stimulus matching, visual cancellation, visual discrimination, and space and object perception [30, 96, 97]. Profound difficulties with visuospatial and constructional tasks, e.g., drawing and copying of figures, are often evident even in mild to moderate DLB (see Fig. 34.3).

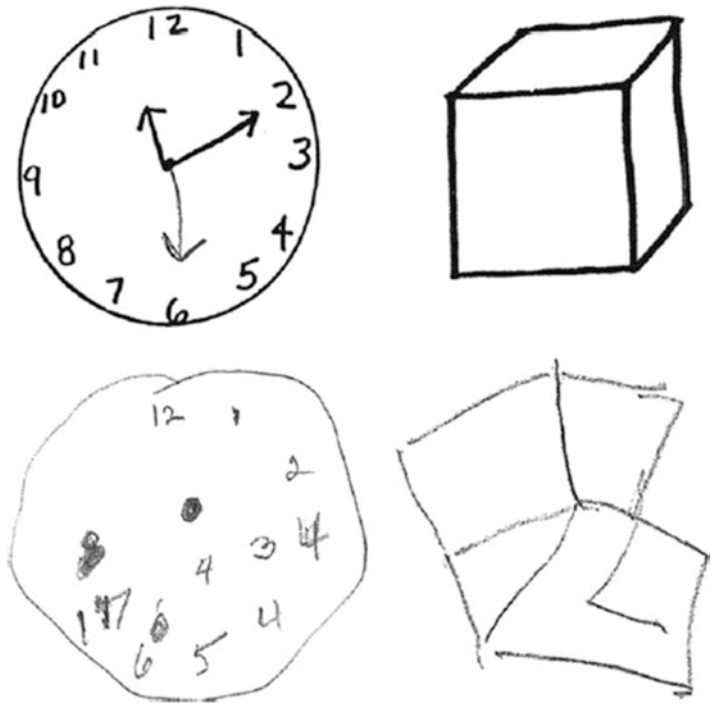

Fig. 34.3 Copies of a clock and cube by a 78-year-old patient with dementia with Lewy bodies (DLB) (Mattis Dementia Rating Scale Total Score 113/144)

Neuropsychiatric Features

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [98] contains separate categories and criteria for mood and anxiety disorders due to medical conditions (including PD). The PDD criteria [27], however, do not require a separate diagnosis of a mood disorder because the criteria recognize the common coexistence of neuropsychiatric symptoms. Nonetheless, the presence of any neuropsychiatric feature is probably best documented explicitly in the medical record and neuropsychological evaluation report so that adequate treatment is undertaken. That depression undertreated in PD is evidenced by the finding 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 range [99]. Similarly, it appears that anxiety and depression frequently go unrecognized by clinicians treating PD [100]. Screening for neuropsychiatric conditions is important, and recommendations for use of specific scales in various neuropsychiatric conditions by Movement Disorder Society task forces are provided in Table 34.7.

Depression is common in PD, occurring in about half of all patients, but reliable comparisons of depression prevalence estimates for PDD and DLB are not available. One study reported major depression to occur in about 13% of patients with PDD and in about 19% of patients with DLB (29% of PDD and 34% of DLB had less severe forms of depression) [101]. One meta-analysis reported a prevalence of 42% in PD studies using DSM criteria [102], but incidence and prevalence rates are higher in research than community samples (about 50% vs. 10%) [103].

About 50% of patients with PD have significant symptoms of anxiety, and as many as 75% of those patients with PD *and* depression may have a comorbid anxiety disorder [104]. However, the

Table 34.7 Recommended and suggested rating scales for the assessment of neuropsychiatric features in Parkinson's disease

Feature	Recommended scales (stronger evidence)	Suggested scales (weaker evidence)
Depression [194]	Screening (and recommended cutoff in PD): Hamilton Depression Rating Scale (HAM-D, 9/10), Beck Depression Inventory (BDI, 13/14), Hospital Anxiety and Depression Scale (HADS, 10/11), Montgomery-Åsberg Depression Rating Scale (MADRS,14/15), Geriatric Depression Scale (GDS-30, 9/10; GDS-15, 4/5)	For patients with dementia (though insufficient evidence): MADRS, GDS; Cornell Scale for Depression in Dementia (CSDD, 5/6)
Anxiety [195]	None	Beck Anxiety Inventory (BAI), HADS, Zung SAS, Zung ASI, STAI, HARS, Neuropsychiatric Inventory (NPI) anxiety section
Apathy and anhedonia [196]	Apathy Scale (Starkstein et al.), Unified Parkinson's Disease Rating Scale (UPDRS) item 4 (motivation/initiative)	Apathy Evaluation Scale (AES; Marin), Lille Apathy Rating Scale (LARS), Neuropsychiatric Inventory (NPI) item 7, Snaith-Hamilton Pleasure Scale (SHAPS)
Psychosis [197]	Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Schedule for Assessment of Positive Symptoms (SAPS)	Parkinson Psychosis Rating Scale (PPRS), Parkinson Psychosis Questionnaire (PPQ), Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Clinical Global Impression Scale (CGIS)
Sleep disturbances [198]	*Daytime sleepiness*: Epworth Sleepiness Scale (ESS) *Overall sleep impairment*: Parkinson's Disease Sleep Scale (PDSS), Pittsburgh Sleep Quality Index (PSQI), Scales for Outcomes in Parkinson's Disease (SCOPA-Sleep)	*Daytime sleepiness*: Inappropriate Sleep Composite Score (ISCS); Stanford Sleepiness Scale (SSS)

reported prevalence of actual anxiety disorders (vs. symptoms) in PD ranges from 5% to 40% [105]. Almost 20% of PD patients had generalized anxiety, 20% had a social phobia (with another 20% experiencing significant social anxiety) [106], and recurrent panic attacks may occur in up to 24% of levodopa-treated patients [107]. Although patients with PD rarely meet the full DSM criteria for obsessive-compulsive disorder (OCD), a considerable number have symptoms of OCD. Anxiety disorders occur with comparable prevalence in PDD and DLB [101], and one study reported that anxiety may occur in about two-thirds of patients with DLB [108].

Psychosis is common in PDD and DLB (but more common than in PD) [101]. Although occurring more often in DLB than PDD, hallucinations (76% of DLB, 54% of PDD) and delusions (57% of DLB, 29% of PDD) are of a similar quality in both patient groups, with paranoid and phantom boarder delusions and well-formed visual hallucinations being among the most prominent features [101]. Apathy is another behavioral syndrome that has been observed in both PDD and DLB. Finally, patients with PD may be predisposed to developing impulse control disorders (ICDs), which are marked by failure to resist an impulse, drive, or temptation to perform an act harmful to either the self or others [98]. ICDs have been linked to use of dopamine agonists in PD and were found to affect 13.6% of PD patients, with 3% experiencing two or more compulsive behaviors [109]. Compulsions most often manifested in gambling, sexual behavior, buying, and eating (the former two occur more often in men, while the latter two occur more often in women).

Corticobasal Degeneration

Attention and Working Memory

Impairments in digit span are not uniformly observed [110]. Autopsy-confirmed CBD patients have been shown to have mild impairments in digit span backward (but not forward span) at initial neuropsychological evaluation about 3 years after symptom onset and more marked impairments (on average, more than two standard deviations below normative means) by follow-up about 2 years later [111]. In the same sample, profound impairments were noted on the Stroop interference task at both evaluations.

Executive Functions

Executive dysfunction, as indicated by poor performance on tasks such as the WCST [112–115] and Trail Making Test [110, 116], is common in CBD. Performance on executive tasks such as "20 Questions" is more compromised in frontotemporal dementia (FTD) than in CBD and therefore may be especially helpful in differentiating FTD from CBD [117].

Language

Primary progressive aphasia can be a presentation of CBD [118]. The aphasia in CBD is most commonly nonfluent (about 56% of cases), followed in frequency by anomic aphasia (30%) [119]. Fluent and mixed cases were quite rare: each about 5–7% of cases. Performance on language tests in patients with the traditional CBD presentation is somewhat inconsistent, but a key feature of the language problems in CBD is phonologic [120]. Verbal fluency is impaired [112], probably in large part due to the executive demands of those tasks [121]. Performance on semantic memory tasks such as conceptual matching and visual confrontation naming [120] and expressive vocabulary is relatively preserved and impaired in only a minority of patients [110, 122]. When naming is impaired, disproportionate benefit is derived from cuing, suggesting a retrieval rather than semantic memory deficit [116, 122].

The apraxia in CBD is most often ideomotor, but ideational and limb kinetic apraxias do occur occasionally [112, 123–125]. Patients most often have difficulty demonstrating the use of tools or utensils.

Learning and Memory

Memory impairments in CBD involve both encoding and retrieval deficits [112, 122] but may be rarer and milder than the apraxia and impairments in executive functions [111].

Remote memory impairment has been interpreted to be related to retrieval deficits given poor recall, but intact recognition has been observed on remote memory tasks [116].

Visuoperceptual and Spatial Functions

Poor drawing (constructional apraxia) is commonly observed in CBD. Visuospatial impairments have also been observed [114, 119].

Neuropsychiatric Features

With respect to emotional and neuropsychiatric issues, the Neuropsychiatric Inventory (NPI) disclosed depression in 73% of CBD patients, but apathy (40%), irritability (20%), and agitation (20%) also occur at considerable rates [126]. In comparison to PSP patients, CBD patients have apathy less frequently, but depression and irritability are more frequently reported.

Progressive Supranuclear Palsy

Cognitive deficits are more likely to be evident in the classical version of PSP (Richardson's syndrome) than in the parkinsonian subtype [38, 127].

Attention and Working Memory

Verbal attention is often normal on elementary tests, but deficits in visual attention are common in PSP [128]. Bradyphrenia is very common and often severe in PSP [129] and should be considered when interpreting deficits in higher-level cognitive functions.

Executive Functions

Executive dysfunction occurs early in PSP and is hypothesized to arise from a differentiation of the basal ganglia and prefrontal cortex [130] though imaging also reveals correlations between frontal atrophy and executive deficits and frontal behaviors [73, 131]. The executive deficits are readily observed on brief bedside and cognitive screening measures, such as the Frontal Assessment Battery and the Mattis Dementia Rating Scale (especially on the initiation/perseveration subtest) [26]. Deficits observed in CBD include compromised planning, problem solving [132], and cognitive flexibility [133]. Progression of deficits in problem solving and cognitive flexibility may be especially rapid in PSP in comparison to other frontostriatal disorders [134]. 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 [135] and reliably differentiates PSP from PD and FTD [136].

Language

Speech problems like dysarthria and hypophonia occur earlier [39] and are more common in PSP as compared to other movement disorders [137]. Impairment in verbal fluency follows the classic "subcortical" pattern of letter fluency being more affected than category fluency [138], although the effects of PSP on action (verb) fluency [139] will be important to determine since PSP is associated with greater deficits in naming verbs than nouns [140]. When present, deficits in confrontation naming of nouns may be attributable to visual misperceptions, rather than semantic memory deficits [141]. Patients with PSP may also display ideomotor apraxia (associated with left posterior frontal and subcortical volume loss) [142], although it is less pronounced than in CBD [125]. Patients with PSP may present initially with primary progressive aphasia or nonfluent aphasia [143–145].

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 [84]. Tests of episodic memory reveal a mixed encoding/retrieval profile whereby free recall is impaired, but recognition discrimination is generally within normal limits [113]. Remote memory is largely unaffected [146], though a mild deficit in remote autobiographical memories (without a temporal gradient) has been observed and attributed to retrieval deficits [147]. Nondeclarative learning and memory deficits are observed on measures of procedural learning but not perceptual priming [129].

Visuoperceptual and Spatial Functions

Oculomotor deficits are a hallmark of PSP, with impairment in voluntary vertical eye movements considered a primary diagnostic feature. Other neuro-ophthalmologic abnormalities occasionally observed 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 [134], orienting [128], tracking, and attention, which may be correlated with more severe oculomotor deficits [148]. Even early in PSP, subtle abnormalities may be observed in clock drawing (see Fig. 34.4).

Neuropsychiatric Features

Apathy is the most common neuropsychiatric symptom in patients with PSP, perhaps reflecting pathology within medial pre-frontostriatal loops (see [149]). Apathy prevalence in PSP may be as high as about 90% [150] and is far more common and severe in PSP as compared to PD, which is more likely to present with depression, hallucinations, and delusions [151]. Although apathy is sometimes misdiagnosed as depression, the latter does not present as a prominent neuropsychiatric feature of PSP [150]. Persons with PSP also exhibit behavioral signs of disinhibition [151]. As many as three-quarters of patients with PSP may evidence changes in "personality" [135], which can include increased irritability [151]. Given patients' possibly limited insight into their cognitive and behavioral deficits [152], neuropsychiatric symptoms often exacerbate caregiver stress and burden.

A summary of the neurological, radiological, and neuropsychological features of PDD, DLB, CBD, and PSP is provided in Table 34.8.

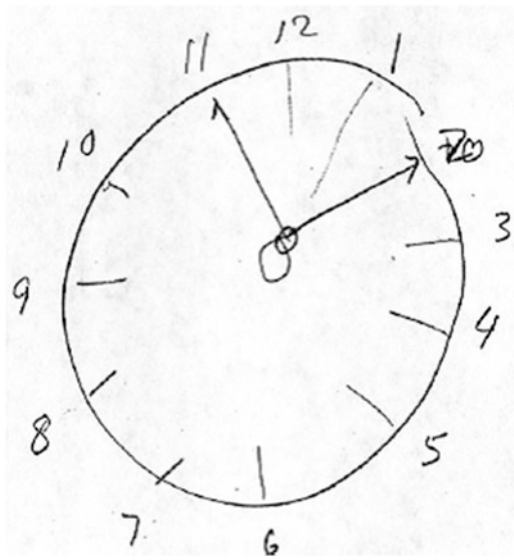

Fig. 34.4 Clock drawn to command by a patient with progressive supranuclear palsy. Note the similarly sized clock hands, indecisiveness in placing the hand origin, and double perseveration (of 1 and 2) at the number "2." The heart-shaped figure next to "2" appears to be a perseveration of the circles indicating the origin of the hands. Also, the numbers are placed outside the clockface. The difficulties seem most consistent with executive rather than visuospatial dysfunction

Other Movement Disorders with Dementia

Several other movement disorders are associated with dementia. Huntington's disease is an autosomal dominant disorder associated with choreiform movements, dementia, and neuropsychiatric disturbances. The disorder is not covered in detail here since patients are typically younger. The dementia, however, is considered a prototypical "subcortical" dementia. Similarly, Sydenham's chorea (St. Vitus' dance), associated with group A beta-hemolytic streptococcal infection, is not covered here as it usually presents in childhood.

A form of parkinsonism, multiple system atrophy (MSA), not responsive to levodopa treatment, is associated with cognitive impairments, but rarely dementia, and reviews of this condition's neuropsychology have been offered elsewhere [153]. Wilson's disease, a genetic disorder of copper metabolism, can be associated with dementia, but presentation is usually in childhood or young adulthood. It is of note that cerebrovascular disease can produce parkinsonism, but vascular parkinsonism accounts for a small fraction of cases with parkinsonism coming to autopsy [108]. Most cases are accounted for by Parkinson's disease, multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy. Vascular dementia and some

Table 34.8 Summary of neurological, radiological, and neuropsychological characteristics of Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP)

Feature	PDD	DLB	CBD	PSP
Clinical features	Asymmetric onset of rigidity, bradykinesia, or tremor; initially levodopa responsive but slow loss of levodopa responsiveness; dementia onset associated with postural instability and gait disturbance	Tremor less common than in PDD and more postural than at rest, signs less asymmetric than in PD/PDD	Markedly asymmetric rigidity; parkinsonism is minimally levodopa responsive. Other signs: apraxia, alien limb, dystonia, myoclonus, jerky tremor; cortical sensory deficits	Axial rigidity disproportionate to appendicular rigidity; "en bloc" movement; vertical gaze abnormality; a small subset of PSP patient's parkinsonism may be initially responsive to levodopa but mostly unresponsive to treatment
MRI scan atrophy	Little cortical atrophy, hippocampal atrophy variable	Little cortical atrophy, hippocampal atrophy variable	The posterior frontal and parietal cortex atrophy is pronounced	Frontal and midbrain atrophy
SPECT and PET hypoperfusion	Mostly frontoparietal and occipital	Posterior: occipital-parietal	Asymmetric frontoparietal and thalamic	Frontal-subcortical
Attention/ working memory/ processing speed	Moderate impairment	Moderate to severe impairment, evident early	Mild to moderate impairment	Mild to moderate impairment
Executive functions	Moderate to severe impairment	Mild to moderate impairment	Normal to moderate impairment	Moderate to severe impairment, evident early and typically rapidly progressive
Language	Normal to moderately impaired; fluency impairment seen early, but visual confrontation naming and repetition relatively intact until late in disease	Normal to moderately impaired; fluency impairment is most common, but some patients may have marked naming impairment like Alzheimer's	Apraxia disproportionate to expressive and receptive language impairment	Normal to moderately impaired, verbal fluency impairment seen early
Visuospatial/ perceptual and constructional	Mild to severe impairment	Moderate to severe impairment, typically seen early	Normal to moderate impairment	Mild to severe impairment, perhaps secondary to gaze abnormalities; executive dysfunction may impact
Learning and memory	Mild to severe; affects mainly encoding and retrieval, storage only later in disease; less pronounced than in Alzheimer's; remote memory impairment variable, but typically no temporal gradient and retrieval problems evident	Mild to severe, less pronounced than in Alzheimer's early on, storage (forgetting rates) variable, remote memory impairment variable but typically no temporal gradient	Mild to moderate; mainly retrieval deficits, some encoding problems; retrograde is not temporally graded	Normal to moderate, often secondary to executive deficits impacting encoding and/or retrieval strategies
Neuropsychiatric	Depression and anxiety prominent, hallucinations (esp. visual), paranoid (esp. Othello), and phantom boarder delusions	Depression and anxiety prominent, hallucinations (esp. visual), paranoid (esp. Othello), and phantom boarder delusions	Depression with lesser apathy	Frequent apathy, disinhibition and personality changes, depression less common

other conditions that can be associated with parkinsonian features (e.g., normal pressure hydrocephalus, Alzheimer's disease) are discussed in separate chapters in this volume.

Neuropsychological Assessment: Practical Issues and Pointers

Review of the Medical Record

Medical records should be reviewed as in any other neuropsychological evaluation. In the case of movement disorders, especially those presenting with dementias, this review is particularly important as it allows one to plan for an adequate examination and to anticipate factors that might interfere with standardized test administration. In addition to the usual information gleaned from medical records, record reviewing for patients with movement disorders should address the following:

- Age and age at onset of movement disorder symptoms.
- Age at onset of cognitive changes, since this information may facilitate determination of PDD vs. DLB, and estimation of the rate of cognitive decline (e.g., PSP is associated with especially rapid progression of executive deficits).
- Side of onset of movement disorder symptoms such as tremor, rigidity, and bradykinesia and perceived asymmetry (PD and CBD often have asymmetric profiles, whereas DLB and PSP have more symmetric presentations, especially axial motor symptoms).
- Nature of parkinsonian symptoms (e.g., tremor, rigidity, bradykinesia, postural instability, and gait disturbance) and presence of non-parkinsonian motor features (e.g., dystonia, myoclonus, which may suggest a tauopathy).
- Timing of antiparkinsonian and other medications and when the patient is likely to be in the best motor "ON" state.
- Presence of motor fluctuations and their timing. Knowledge of fluctuations (e.g., wearing off, freezing) and involuntary movements (e.g., dyskinesia or dystonia) allows for planning and timing of the evaluation.
- Existence of pathological daytime sleepiness or somnolence and time of occurrence (and REM sleep behavior disorder) and, if available, review of polysomnography studies. Such knowledge allows one to establish at what time of day the patient is likely best tested and how much testing might reasonably be undertaken in one appointment.
- Presence of marked tremor or apraxia that might interfere with tests with strong motor demands.
- Presence of visual problems (e.g., double vision) or gaze abnormalities (especially in PSP) that might interfere with standard test administration.
- Presence of marked attention fluctuations (especially in DLB) that might yield spurious patterns of strengths and weaknesses across cognitive tests.
- Existence of hallucinations (especially in DLB) or affective disturbance that might compromise patient effort on testing or ability to respond meaningfully.
- Comorbid medical conditions, especially endocrine conditions such as thyroid dysfunction or diabetes (patients may need snack breaks to maintain adequate blood sugar levels).
- Utilization of medications with anticholinergic effects that might impact concentration and memory (including not only agents used to treat tremor but also conditions such as urinary incontinence).
- History of prior neurosurgical intervention for movement disorder (e.g., pallidotomy, deep brain stimulation, fetal tissue transplantation). If stimulators are present, determine current setting and known side effects (e.g., dysarthria).

Interview

All information obtained from medical record review should be verified during interview along with the regularly obtained medical and

psychosocial information. In addition, it should be established whether there is a family history specifically of dementias or movement disorders.

A question that arises in interview is whether patients and care partners are accurate in reporting cognitive and other behavioral and functional changes. In the case of PD, accuracy of report may vary with respect to the function being reported upon. It has been found that patients are accurate reporters of disability, even in the presence of cognitive compromise and depression [154]. In contrast, in the case of memory impairment, whereas the patient and care partner's report is typically concordant and related to patient scores on objective cognitive measures, patient-care partner report discrepancies increase as a function of patient cognitive impairment and depression [155]. One study reported that care partners may focus on select aspects of cognitive deficit such as verbal recall [155], but another study found good concordance between caregiver report and patient's objective performance on a range of cognitive tasks, including those measuring memory, executive function, language, and psychomotor speed [156]. A useful observation to keep in mind is that patients, including those with PDD and DLB, may frequently complain of memory disorders initially [30], but what patients describe as memory disorders may actually represent other deficits. For example, reported trouble remembering names or words may refer to dysnomia, and a reported inability to recall how to operate equipment or machinery (e.g., sewing machines, lawn mowers) may refer to executive dysfunction.

During the interview, it is important to prepare the patient for evaluation. The patient's anxiety about evaluation should be allayed as far as possible, and patients should be informed that they will probably find some tasks easier than others and that variations in performance and skills are the norm rather than the exception. The patient should be encouraged to report when they feel the onset of dyskinesias or dystonias or fluctuations in motor functions. Even if it is not possible to discontinue or take a break in evaluation, the presence of these features should be noted to facilitate later interpretation of test results. Similarly, patients should be monitored for fatigue and especially in DLB, and some cases of PDD, the examiner should be alert to fluctuations in attention.

Screening Instruments

Frequently physicians and neuropsychologists need to screen for cognitive impairment in persons with movement disorders. While the use of screening instruments has been the subject of empirical investigation in PD and PDD, less attention has been paid to screening in PSP, CBD, and DLB. Thus, an important issue is how well screening instruments perform in detecting cognitive impairments in movement disorders.

In comparison to full neuropsychological evaluations, the advantages of cognitive screening instruments include their brevity, relatively simple administration and scoring, patient acceptability, and limited expense. Cognitive screening can be helpful in deciding whether a patient might require full neuropsychological evaluation. Possible disadvantages of screening instruments include the limited information obtained, the use of cutoff scores that may not be adequately corrected for demographics and base rates, and limited sensitivity and specificity for use across a broad range of disorders. Another issue is that relatively few screening instruments have been developed for movement disorders and the application of instruments primarily developed for Alzheimer's disease may have limited applicability given such instruments' emphasis on memory and relative neglect of executive functions and working memory. Recently, more emphasis has been placed on developing instruments specifically for use with PD and PDD (and presumably such instruments might have utility in other movement disorders), but no instruments have been developed specifically for PSP, CBD, and DLB. Recent studies of PSP and CBD have utilized generic screening instruments such as the Dementia Rating Scale (DRS), Addenbrooke Cognitive Examination (ACE), and Frontal Assessment Battery (FAB) for screening [26, 157].

Several overviews of screening instruments commonly used with or designed for PD have recently been published [158, 159]. It should also be borne in mind that recommendations made for cognitive assessment in PD by an American Academy of Neurology Committee [160] are based on a now outdated literature review and have limited relevance.

Three commonly used screening instruments not specifically designed for PDD and DLB are the Mini-Mental State Exam (MMSE) [161, 162], the Dementia Rating Scale (DRS and DRS-2) [163, 164], and the Montreal Cognitive Assessment (MoCA) [165]. Patients with PD and other dementias make qualitatively different errors on the MMSE [166]. These qualitative differences aside, the MMSE de-emphasizes working memory and executive functions and might lack sensitivity to cognitive changes associated with subcortical-frontal dysfunction. This suspicion was confirmed by a study comparing PD patients with and without mild cognitive impairment (defined by a neuropsychological test battery). The mean MMSE score of the mildly impaired group was only 1.5 points lower than that of the intact group and in the normal range (mean 28.0, standard deviation 2.1) [167]. The MMSE also appears to be less sensitive than the DRS to cognitive deficits in atypical parkinsonian syndromes [157] and the Montreal Cognitive Assessment (MoCA) [165] in PD [168]. Nonetheless, the MMSE probably has adequate sensitivity and specificity in detecting impairment among unequivocally demented patients with PD (in whom screening may not be needed). Using DSM-IV dementia criteria as the "gold standard," a study of 126 PD patients found a MMSE cutoff of 23(dementia)/24(no dementia) to have 98% sensitivity and 77% specificity [169]. Mean annual rate of change in the MMSE score is about 1 point for persons with PD without dementia but about 2–2.5 points for those with dementia [170].

The DRS's sensitivity and specificity in detecting cognitive impairment in PD and related disorders have not been adequately addressed, but several studies show different score profiles in PD, PDD, DLB, and AD. One study reported that, whereas an AD group earned lower Memory subtest scores than a PD group with comparable severity of cognitive impairment, the PD group attained lower Construction subtest scores. Discriminant function analyses using Memory, Initiation/Perseveration, and Construction subtest scores correctly classified 75% of the sample [171]. The Construction and Initiation/Perseveration subtest scores of the DRS are the most helpful in distinguishing PD patients from healthy controls [172]. Though PDD and DLB may differ minimally in their DRS profiles (with perhaps lower Conceptualization scores in DLB early on), Memory, Construction, and Initiation/Perseveration scores best distinguish between PDD/DLB and AD [84].

The MoCA has statistically validated psychometric properties for detecting cognitive dysfunction in PD [173, 174], DLB [175], and PSP [176] with sensitivity and specificity that exceed that of the MMSE for all patient groups. Its applicability in CBD, however, remains understudied. The MoCA assesses memory, language, and attention along with skills affected early on in PD, including executive and visuospatial functions that make it particularly well-suited for detecting mild dysfunction and documenting disease progression. One study reported a sensitivity of 81% and specificity of 95% in detecting PDD, making the MoCA's predictive diagnostic value comparable to a PD-focused screening instrument, the Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-Cog) [174]. In PSP, letter fluency on the MoCA differentiated PSP from PD with 86% specificity and 70% sensitivity [176], while DLB findings have similarly reported high sensitivity and specificity at 92% and 81%, respectively [175].

Another generic dementia screening instrument with potential utility in PD is the cognitive section of the Cambridge Examination for Mental Disorders (CAMCOG). Using a cutoff score of 80 points and below to identify dementia in PD, one study reported the instrument to show 95% sensitivity and 94% specificity [169]. Cognitively intact patients with PD (MMSE > 25) demonstrate an average annual rate of change of about four points on the revised version of the instrument (CAMCOG-R) [177].

Two screening batteries for persons with frontal and subcortical dysfunction have been published, including the Frontal/Subcortical Assessment Battery (FSAB) [178] and the Frontal Assessment Battery (FAB) [179]. The latter has been used in studies of PD, but its psychometric properties still require further exploration.

Several instruments specifically for use with PD have been developed, including the Mini-Mental Parkinson (MMP) [180], the Scales for Outcomes of Parkinson's disease-Cognition (SCOPA-Cog) [181], the Parkinson Neuropsychometric Dementia Assessment (PANDA) [182], the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [183], and the Parkinson's Disease-Cognitive Functional Rating Scale (PD-CFRS) [184]. These instruments show promise but remain to be validated in large, independent studies. No disease-specific cognitive screening instruments have been developed for use with DLB, PSP, or CBD, though instruments developed for PD should also have utility with other movement disorders that can present with mild cognitive compromise or dementia.

Selecting Neuropsychological Test Batteries for Movement Disorders and Possible Test Modifications

As is the case for any neuropsychological evaluation, test selection should consider the patient's condition or the differential diagnosis, the referral question(s), the patient and caregiver concerns, the normative and psychometric properties of the tests (e.g., availability of alternate forms, test-retest reliability, validity for use in movement disorders and dementia), and the patient's ability to tolerate and cooperate with the tests. When evaluating patients with movement disorders, awareness of the potential impact of various features of movement disorders (e.g., motor fluctuations, sleep disturbance and fatigability, choreiform and dystonic dyskinesias, gaze palsy, apraxia, dysarthria, and hypersalivation) on test performance needs to be considered (Table 34.9).

Standard test administration methods may need to be modified when working with patients with movement disorders. Downward gaze palsy, as seen in PSP, makes it difficult for patients to voluntarily look down at test forms. In such cases, stimuli may be held up for the patient to see at eye level, about 18" from the patient's face. When impediments such as slurred speech are evident, patients may be asked to repeat responses although this is frustrating to some patients, perhaps necessitating testing over multiple brief sessions. Hypophonia may be compensated for by an amplification device. Tests requiring pointing rather than oral responses may be more appropriate for patients with speech impairment.

A patient with tremor, dyskinesia, dystonia, or apraxia may require help from the examiner when completing tests or questionnaires requiring writing, circling of alternatives, or filling in of multiple choice blanks. Thus, such scales might be administered orally, with the examiner making the necessary written notation. On some tasks, such as card sorting or tower tests, the examiner may need to hold and move the cards or blocks/beads as instructed by the patient (standard timing cannot be used in such cases). In general, tests with significant motor demands are better avoided with patients who have movement disorders. Though non-motor tasks might be administered when patients have dyskinesias, the patient may still be distracted by these movements, and this needs to be considered in interpreting the test results.

In parkinsonian patients and patients with dementia who have sleepiness or somnolence, fatigue, severe motor "off" periods, or frequent fluctuations, breaks will need to be taken. Although there may occasionally be a need to compare performances "on" and "off" medications, it is recommended that patients be tested while on their antiparkinsonian medications (though anticholinergics are best discontinued and tapered prior to evaluation). In patients with advanced movement disorders, testing during the off state is unnecessarily challenging to patient and examiner, and the patient may also experience increased dysphoria and anxiety during off state, further complicating test interpretation.

Table 34.9 Neuropsychological tests commonly used in movement disorders with and without dementia

Cognitive domain	Test
Premorbid estimates	North American Adult Reading Test (NAART), Wechsler Test of Adult Reading (WTAR), Wide Range Achievement Test (WRAT), Advanced Clinical Solutions Test of Premorbid Functioning (TOPF)
Neuropsychological screening	Mattis Dementia Rating Scale (DRS), Mini-Mental Status Examination, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Montreal Cognitive Assessment (MoCA), Parkinson's Disease Cognitive Rating Scale (PD-CRS), Parkinson Neuropsychometric Dementia Assessment (PANDA), Scales for Outcomes of Parkinson's Disease-Cognition (SCOPA-Cog), Cambridge Examination for Mental Disorders (Cognitive section) (CAMCOG), Addenbrooke Cognitive Examination (ACE)
Intelligence	Raven's Progressive Matrices, Wechsler Abbreviated Scale of Intelligence (WASI), Wechsler Adult Intelligence Scale (WAIS) (recent editions)
Attention and working memory	Brief Test of Attention (BTA), Digit and Visual Span, Stroop Test[a], Digit Ordering Test, Letter Number Sequencing, Digit Symbol or Symbol Digit test
Executive function	Delis-Kaplan Executive Function Scale (DKEFS), Booklet Category Test, Trail Making Test (TMT)[a], Wisconsin Card Sorting Test (WCST), Tower of London (and various modifications), Cambridge Neuropsychological Test Automated Battery, Verbal fluency tests (phonemic, semantic, action)
Memory	Benton Visual Retention Test-recognition (BVRT-R), California Verbal Learning Test (CVLT/CVLT-II), Rey Auditory Verbal Learning Test (RAVLT), Selective Reminding Test, Rey Complex Figure Test (RCFT)[a], Wechsler Memory Scale (WMS) (recent editions)[a], Brief Visuospatial Memory Test (BVMT-R), Hopkins Verbal Learning Test (HVLT-R)
Language and praxis	Boston Naming Test (BNT), Controlled Oral Word Association Test (COWAT), sentence repetition, Token Test, Complex Ideational Material, Western Aphasia Battery subtests (including apraxia)
Visual and spatial perception and construction	Benton Facial Recognition Test, Benton Judgment of Line Orientation (JLO), Hooper Visual Organization Test (VOT), Clock Drawing
Motor/fine motor	Finger Tapping[a], Grooved Pegboard[a]
Mood state	Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Hamilton Depression Scale (HDS) or Hamilton Depression Inventory (HDI), the Parkinson Anxiety Scale (PAS), the Neuropsychiatric Inventory (NPI), Profile of Mood States (POMS), State-Trait Anxiety Inventory (STAI), Maudsley Obsessional-Compulsive Inventory, Yale-Brown Obsessive Compulsive Scale (YBOCS), Hospital Anxiety and Depression Scale (HADS), Montgomery-Åsberg Depression Rating Scale (MADRS), Cornell Scale for Depression in Dementia (CSDD)
Quality of life, coping, and stressors	Parkinson's Disease Questionnaire (PDQ), Medical Outcomes Study 36-item short form (SF-36), Sickness Impact Profile (SIP), Coping Responses Inventory (CRI), Ways of Coping Questionnaire, Life Stressors and Social Resources Inventory (LISRES)

[a]Note: Test may not be appropriate for patients with marked motor impairment

Assessment of Neuropsychiatric Symptoms

Given the frequency with which affective and other neuropsychiatric symptoms occur in movement disorders such as PDD, DLB, PSP, and CBD, information on these conditions should be obtained during medical record review and interview. In addition, it is often helpful to quantify the severity of symptomatology to document existence and severity of a condition, and consequently, completion of various observer rating

and self-report scales is recommended. The various scales recommended by the Movement Disorder Society (MDS) are listed in Table 34.7.

One particular issue in PD, PDD, and other movement disorders is that symptoms of depression and anxiety may overlap with those of the movement disorder. For example, sleep disturbance, psychomotor retardation, lack of energy, stooped posture, masked facial expression, dry mouth, and sexual dysfunction can be observed in PDD, DLB, PSP, and depression. Consequently, to improve diagnosis, it has been suggested that early morning awakening, anergia, and psychomotor slowing are not to be considered when diagnosing depression in PD. Due to symptom overlap, rating scales might overestimate depression in PD/PDD/DLB, and in the case of PDD, empirically derived alternate cutoffs have been provided for several depression scales [153].

Diagnosis of an anxiety disorder in PD is also hindered by symptom overlap. While the validity and reliability of anxiety rating scales have not been widely studied, recent development of a PD-specific anxiety scale has attempted to account for this overlap [184] and perhaps reduce the wide range of anxiety prevalence estimates in PD (6% to 55%) [185]. Elimination of anxiety inventory items reflecting autonomic and neurophysiologic dysfunction is not advised, as this might lead to underestimation of anxiety [186]. PSP often features apathy, and this should be assessed carefully. CBD, though also associated with a notable frequency of apathy, more often has depression. Although the questionnaires and scales recommended for PD neuropsychiatric evaluation have not been evaluated for the most part in other movement disorders, they seem reasonable choices in the absence of other evidence.

Assessment of Functional Status in PD

Comprehensive neuropsychological assessment encompasses functional domains which include orientation, attention, executive function, abstract reasoning, memory, language, basic and complex perception, visuospatial abilities, praxis, and motor skills [187]. Cognitive decline in more than one domain with concomitant loss of impairment in activities of daily living (ADLs) indicates the presence of a dementia, whereas mild cognitive impairment is limited to decline in less than two domains with preserved functional independence. Accurate detection of cognitive decline requires instruments with adequate psychometric properties and normative data representative of the population. An estimate of premorbid functioning, typically acquired through a reading test, is also integral in determining whether current cognitive status represents a relative decline. Taken together, these factors may aid in supporting differential diagnosis, assessing surgical risk, tracking cognitive decline or improvement, and predicting disease prognosis.

Competency in ADLs, while an essential distinguishing feature of MCI vs. dementia, has proven challenging to assess. Methods typically rely on unstructured interviews with patients and caregivers, cognitive testing, and self- or caregiver report on functional scales. However, these methods risk underestimating level of impairment or neglecting important aspects of the disease in which frontal and executive deficits are prominent. PD-specific questionnaires are needed to disentangle motor from cognitive impact on ADLs. Recently developed, the PD-Cognitive Function Rating Scale (PD-CFRS) has been shown to adequately capture cognitive impairment in PD with a cutoff score of ≥ 3 indicating functional impairment and an increase of two points being linked with significant worsening [184, 188]. Early validation studies also suggest the Penn Daily Activities Questionnaire (PDAQ), which assesses patient competency in common daily tasks, is a good measure of ADL functioning [189].

A Case of Possible Corticobasal Degeneration (Corticobasal Syndrome)

The case described was selected because it illustrates the difficulty one may have in clinically differentiating CBD and PSP, both tauopathies.

A 66-year-old, right-handed, white man with 16 years of education was seen in consultation at the request of a neurologist to facilitate differential diagnosis and treatment decisionmaking. The patient had initially been diagnosed as having Parkinson's disease by a neurologist at an outside facility, based on left-sided cogwheel rigidity and the presence of a very slight tremor.

The patient stated at evaluation that he had experienced some cognitive changes initially about 4–5 years prior to evaluation, more specifically noticing slowness of thought and difficulty speaking at work (he had had a management position overseeing data processing). Though the patient had initiated a change in his own job duties about 1.5 years prior to the evaluation, by the time of evaluation, he had retired due to his cognitive problems. His wife had only noticed some cognitive changes in her husband for the past year or so. He seemed to be reluctant to make decisions (although the quality of his decisions seemed adequate to the wife), and she had noticed that her husband had become avoidant of chores and had begun to have difficulty with certain chores. For example, when looking at tools to fix something, or at the lawn mower, he seemed uncertain what to do with the implements and machines. He occasionally had trouble buttering his toast but otherwise was able to cut food and use utensils.

In addition, the patient about a year before evaluation had become more hesitant to drive, had struck a mailbox, and consequently stopped driving. At evaluation, he reported that he had ceased driving due to what he described as difficulties with distance judgment and perspective.

The patient had been treated for depression with SSRIs for 6 months by his primary care physician about 2 years prior to this evaluation. His wife observed that her husband had been more easily frustrated and irritable than in the past, but the patient perceived that his depression had been a reaction to perceived cognitive and motor changes and the loss of a close friend. Recent mood was euthymic.

Regarding motor signs, the patient had a mild, non-bothersome tremor for 12–15 years prior to evaluation (and there was a family history of this), but in the year before, evaluation developed balance problems that he sometimes referred to as "dizziness." He had had four or five falls without head injury.

At the neurological evaluation, his score on the MoCA was 17/30, and declines were noticed in memory, verbal fluency, and executive and visuospatial functions. On his movement disorders exam, resting tremor was absent, though mild postural tremor was observed in the right arm. On finger to nose, he had mild intention tremor on the right compared to the left. Mild rigidity in the neck and mild-to-moderate rigidity in both upper and lower extremities were noted, greater on the left. Dysdiadochokinesis and mild bradykinesia were evident bilaterally, more so on the left, and the patient had difficulty with reciprocal hand movements. Ideomotor apraxia was greater on the left. He had no difficulty arising from a chair with his hands folded across his chest. Posture was slightly stooped. Observation of gait revealed good stride length but slightly reduced arm swing. On the retropulsion test, he recovered unaided after a few steps. Strength was 5/5 throughout. His cranial nerve exam was largely unremarkable. His extraocular movements were intact, but he had mild difficulty with smooth pursuits. Facial sensation and strength were intact and symmetric. His sensory exam was intact to light touch, temperature, and vibration in all four extremities. Reflexes were 2+ and symmetric throughout. Toes were down going bilaterally.

The patient had had limited benefit from antiparkinsonian medications (rasagiline and ropinirole) in the year before his evaluation. A CT scan of the head done at an outside institution about 2 years prior to this evaluation was interpreted as revealing of mild cerebral atrophy given age. An MRI done about 10 months prior to evaluation was interpreted as revealing of diffuse atrophy, greater on the right than left, and especially prominent in the frontal-parietal lobes.

Neuropsychological test results are presented in Table 34.10. Particularly evident were difficulties with memory (recognition appeared relatively preserved in comparison to free recall), fine visual motor coordination, dexterity and

Table 34.10 Neuropsychological test scores of a 66-year-old man with suspected corticobasal degeneration

Test	Raw score	Standard score (index (I) or T-score) or percentile*
Intelligence estimate Wechsler Test of Adult Reading (WTAR): Full-Scale IQ estimate	48	121 (I)
Cognitive screening Mattis Dementia Rating Scale (DRS-2): Total score (/144)	110	23
Attention/working memory/processing speed		
Wechsler Adult Intelligence Scale (WAIS-IV): Working Memory Index		83 (I)
Wechsler Adult Intelligence Scale (WAIS-IV): Processing Speed Index		50 (I)
Digit Span maxima	5 forward, 3 backward	
Spatial Span maxima	3 forward, 3 backward	
Trail Making Parts A and B (sec)	209, 300+	15, 13
Stroop (SNST) Color and Color/Word (/112)	69, 29	<2*
Executive function		
Wisconsin Card Sorting Test (WCST-64): Categories	1	6–10*
(WCST-64): Trials to First Category	12	>16*
(WCST-64): Perseverative Errors	12	41
Language Letter Fluency (FAS) (words/180 s)	10	19
Category Fluency (animals) (words/60 s)	4	7
MAE Sentence Repetition (/14)	9	7*
MAE Token Test (/44)	43	67*
Motor speed/dexterity Finger Tapping (dominant/nondominant hand) (average taps/10 s)	48.1, 34.7	46, 30
Grooved Pegboard (dominant/nondominant hand) (sec)	243 (all pegs placed), 300+ (only 21 pegs placed)	18, 19
Apraxia WAB Apraxia Exam (/60)	41	
Visuospatial/perceptual		
Benton Facial Recognition (/54)	32 (severe impairment)	
Judgment of Line Orientation (/30)	23	40*
Clock Drawing	2/3	
Verbal learning/memory		
Hopkins Verbal Learning Test-Revised (HVLT-R): Total Immediate Recall (/36)	14	22
Hopkins Verbal Learning Test-Revised (HVLT-R): Delayed (/12)	6	32
Hopkins Verbal Learning Test-Revised (HVLT-R): Recognition Discrimination Index (recognition hits—false positives) (0–12)	11–0	47
Brief Visuospatial Memory Test-Revised (BVMT-R): Total Immediate recall (/36)	10	29
Brief Visuospatial Memory Test-Revised (BVMT-R): Delayed (/12)	4	31
Brief Visuospatial Memory Test-Revised (BVMT-R): Recognition Discrimination Index (recognition hits—false positives) (0–6)	4–1	3–5*
Brief Visuospatial Memory Test-Revised (BVMT-R): Copy (/12)	12	
Mood state		
Profile of Mood States (POMS): tension-anxiety		50
Profile of Mood States (POMS): depression		64
Profile of Mood States (POMS): anger-hostility		43
Profile of Mood States (POMS): vigor-activity		<30
Profile of Mood States (POMS): fatigue-inertia		39
Profile of Mood States (POMS): confusion-bewilderment		66

*percentile

speed, verbal fluency, apraxia, processing speed, and to lesser extent working memory. Oral language comprehension was relatively intact, and executive dysfunction was mild. Significant affective distress was denied, and the patient only reported mild symptoms of depression. Overall, the neuropsychological profile of strengths and weaknesses in the context of progressive parkinsonism fairly unresponsive to medication suggested a likely tauopathy (note that CBD was more strongly suggested than PSP but the patient developed a gaze abnormality less than 1 year after evaluation). He also began to complain of clumsiness of the legs and stubbing his toes especially when climbing a curb.

Interested readers are referred to a recently published neuropsychology casebook for detailed case descriptions of other movement disorders with dementia, including PSP [190], CBD [191], and DLB [192].

Clinical Pearls

- When attempting to differentiate movement disorders with dementia, consider carefully not only test scores but also qualitative features of test performance as well as the onset, evolution, and nature of motor symptoms. Also, keep in mind the base rate of disorders, their epidemiology, and typical age at onset and duration. Be familiar with the most typical neuroimaging findings.
- Bear in mind that patient terminology may not correspond to reality when making complaints of cognitive deficit. Thus, patients may complain of memory problems but in fact refer to aphasia or anomia (trouble recalling or producing words) or executive dysfunction (an inability to recall how to operate equipment and machinery such as stoves, sewing machines, and mowers).
- The best way to ensure a smooth and efficient evaluation is to be prepared for patient fatigue, fluctuations in attention and motor function, and medication effects. These should be explored carefully in the medical record or when calling the patient to schedule an appointment.
- Patients often complain of trouble recalling people's names, regardless of condition. We recommend that patients use a cellular telephone or computer to append photos of acquaintances to contact information in the computer or telephone. This information, including picture name, can be reviewed prior to social encounters. Many of our patients have found this very helpful. Alternatively, they might review photo albums, although in our experience these contain too much information and may include too few of the persons commonly encountered.
- Patients with movement disorders, with or without dementia, often have bradyphrenia and trouble keeping up with social discourse. We encourage them to engage in conversation in small groups. One way to control the speed of the flow of conversation is by questioning. Regular questioning, without being annoying to other participants in the conversation, allows processing of information, relevant responses, and pauses that allow better encoding of information.
- In patients with movement disorders, it is critical to enquire about vision. Abnormalities of gaze and eye movements may be present, and patients may have double vision and difficulty focusing or seeing test materials.

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Neuropsychological Considerations for Parkinson's Disease Patients Being Considered for Surgical Intervention with Deep Brain Stimulation

Paul J. Mattis, Chaya B. Fridman, and Erica Meltzer

Introduction to Parkinson's Disease

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by motor symptoms, including resting tremor, bradykinesia, muscle rigidity, and postural instability. Cognitive and behavioral disturbances are also common to this disease and contribute to its functional disability [1–3]. Onset is typically around age 65 years, although approximately 8% of individuals develop the illness "early," between 21 and 40 years of age [3].

The relationship between the development of PD and the gradual death of dopamine neurons, specifically in the substantia nigra pars compacta (SNc), has been recognized since the 1950s [4–6]. It is now known that symptoms of PD manifest once a significant portion (approximately 60–70%) [7] of SNc dopaminergic cells die, resulting in increased activity within the motor circuitry (see [8] for a review). Specifically, the diminished dopamine level in the SNc reduces the inhibitory influence on the subthalamic nucleus (STN), which then exerts excessive excitatory influence on the globus pallidus pars interna (GPi). This, in turn, contributes to increased inhibition of thalamocortical neurons, which are responsible, in part, for the rhythmic tremors at rest, inability to initiate/complete voluntary movements, and cogwheel rigidity associated with PD [9].

Given the neural circuitry that has been implicated in PD, it is not surprising that patients often exhibit a subcortical pattern of cognitive impairment. The neuropsychological profile of patients with PD tends to reveal mild deficits in aspects of executive functioning, memory, and visuospatial functioning. Additionally, symptoms of depression are frequently reported [10]. Language abilities generally remain intact, although language deficits are occasionally reported and, in these instances, are largely secondary to executive dysfunction or motor impairment. The reader is referred to Chap. 34 for a more comprehensive discussion of the neurocognitive impairment associated with PD.

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Treatment for PD

Overview

Treatments for PD attempt to restore the motor circuit's delicate balance, either through introducing dopaminergic medications that increase the output of the substantia nigra or through surgical techniques that reduce the activity of the STN or GPi [11–13]. Levodopa, a dopamine supplement, is currently the gold standard of treatment for PD [14]. Levodopa replaces dopamine in the forebrain that is lost due to the illness, consistently reversing many of the key motor symptoms: akinesia, bradykinesia, and rigidity. However, it does not prevent the progression of the disease, and for most patients, the efficacy of the medication declines after 5 years of daily treatment [14]. Long-term use of levodopa is also hampered by treatment-induced motor complications, such as dyskinesias and motor fluctuations [15]. Furthermore, nondopaminergic symptoms (e.g., choking, drooling, sleep disturbances, mood disorders, dementia) ultimately start to emerge, contributing to the disability of late-stage PD [16]. As such, alternate treatments have been sought, including new surgical interventions.

History of Surgical Treatments for PD

The use of surgical treatment to obtain symptom relief in PD dates back over a century (for detailed review see [11, 17]). In the early 1900s, Victor Horsley and Henry Clarke introduced basic stereotactic neurosurgery techniques. After creating small openings in the skull, the researchers were able to target specific brain structures that they had previously identified using a three-dimensional Cartesian coordinate system. In 1909, Horsley began to use ablative surgery through lesioning certain areas of the sensorimotor cortex [11]. Although this technique successfully reduced the severity of resting tremors, additional impairment was evident in the performance of voluntary movements. The use of ablative surgery was further popularized in 1939 when Bucy and colleagues implemented the technique to lesion the corticospinal tracts. Also in 1939, Russell Meyers was the first to operate on the basal ganglia through an open craniotomy procedure. Although effective in alleviating some of the motor symptoms, there was a high mortality rate associated with the procedure, prompting explorations for safer treatments [11]. In the late 1940s, Spiegel and colleagues and Leksell furthered the use of stereotaxic techniques, resulting in the implementation of relatively less invasive approaches (for review, see [17]).

In 1952, while conducting a pedunculotomy of a patient with PD, Irving Cooper accidentally interrupted the flow in the anterior choroidal artery. To his surprise, the patient's tremor and rigidity vastly improved postoperatively [18]. This accidental finding prompted Cooper to deliberately use this procedure over the next several years to alleviate PD motor symptoms [17].

Throughout the 1950s and 1960s, spurred by advancements in the understanding of PD neuropathology, ablative surgeries were also widely used. Destructive agents, such as alcohol, heat, or cold, were introduced to a specified location to lesion the site [11]. Targeting specific areas of the basal ganglia proved to be a relatively effective and safe approach, leading to positive outcomes and reduction of certain motor symptoms.

Levodopa was first introduced for the treatment of PD in 1968. The outcome was so promising that the use of surgical techniques decreased dramatically over the next several years [11, 17–19]; however, in the late 1970s, it became evident that some patients became refractory to levodopa treatment over time. In other patients, treatment-induced motor complications and dyskinesias were observed. These findings, in conjunction with advancements in neuroimaging techniques and neurophysiological brain mapping, resulted in the reemergence of surgical intervention [11, 20].

Ablative techniques targeting the GPi and ventral intermediate nucleus of the thalamus (Vim) were frequently employed. Then, in the early 1990s, deep brain stimulation (DBS) became an accepted and effective method of treatment [18]. Like ablative techniques, DBS

treatment was aimed at the abovementioned targets (i.e., GPi, Vim) as well as the STN. Rather than destroying the targeted tissue through lesioning [17], DBS introduced a reversible electrical impulse to the surrounding neuronal tissues near the target [18]. This technique will be discussed in detail below.

Fetal Transplantation

More recently, researchers began implanting fetal stage neurons into the caudate-putamen or substantia nigra of PD patients. It was hypothesized that the transplanted neurons would grow, connect, and release DA, and thus, transplantation would enable the maintenance of a relatively steady supply of dopamine to remain in the synaptic clefts [21, 22]. However, double-blind clinical trials produced mixed results [23], and several transplantations resulted in the development of unforeseen, severe, off-medication dyskinesias that warranted DBS intervention [24]. Nevertheless, clinical improvement was noted for patients who were 60 years of age or younger [23], and the grafts were later found to remain viable 4 years postsurgery [25]. Further, there were no indications of cognitive decline following fetal tissue implantation [26]. In 2009, a large-scale, multicenter clinical trial was undertaken in Europe using human fetal ventral mesencephalic (fVM) tissue in patients with PD; grafting first commenced in 2015 [27]. Simultaneously, a global initiative, referred to as GForce-PD [28], was established so that there could be an exchange of information between the various investigators conducting research on the use of stem cells in treating PD. Therefore, at the time of this chapter, the use of fetal nigral tissue transplantation for the alleviation of PD symptoms remains exclusively an experimental treatment.

Gene Therapy

Gene therapy has become the focus of a few PD treatment studies in recent years. Using modified viruses (vectors), genetic material is introduced into the neurons within the motor circuit in the hopes of reestablishing normal brain activity. Recently, researchers have demonstrated that an AAV vector can be used safely to deliver the glutamic acid decarboxylase (GAD) gene directly into STN neurons [29]. There was no evidence of cognitive decline in these patients [30]. Given that reduced GABAergic input from the GP increases the activity of the STN in PD patients [31–33], Kaplitt and colleagues [29] hypothesized that the introduction of GAD, which catalyzes the synthesis of GABA, would restore the delicate balance of neurotransmitters within the motor circuit. Indeed, prior studies conducted in animals indicated that AAV-GAD improved brain function and PD-like symptoms without causing toxic side effects [34–37]. Although this single study was not designed to assess the effectiveness of the intervention, clinical outcomes were encouraging. Substantial improvements in both the "off" and "on" states were observed, beginning at 3 months after surgery and continuing until the end of the trial (i.e., 1-year postsurgery). However, results of a phase II randomized sham-controlled trial revealed only a small effect, as there was only a 23% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) 6 months after surgery [38], which is below the standard of effectiveness that is derived based on STN-DBS [39, 40]. Nevertheless, this mode of treatment, in a different format, may prove to be the intervention of choice in the future, as it does not require indwelling hardware or frequent readjustments and may restore the motor network function to baseline through activity-dependent release of GABA [29].

Additionally, a couple of phase I studies have recently investigated the use of gene therapy in reconstructing DA synthesis within the striatum. This is accomplished through stimulating striatal medium spiny neurons to create their own DA instead of receiving DA from the SN. The results have generated cautious optimism, as the interventions were tolerated for a few years, but only a small number of participants were treated [40–42]. More robust research is therefore needed to ascertain whether the treatments are effective and whether negative side effects ensue.

Deep Brain Stimulation (DBS)

DBS involves the application of high-frequency electrical stimulation directly into the neurons of the motor circuit. A burr hole is performed under local anesthesia. Then, using stereotactic guidance, stimulating quadripolar electrodes are implanted using both direct MRI and CT targeting, as well as "indirect targeting" based on the known locations of these targets relative to fixed midline structures (anterior and posterior commissure). Ventriculography, involving injection of contrast into the ventricular system, was routinely used prior to the CT and MRI era and is now used by only a few centers given the invasiveness of the procedure [43]. Thin wire electrodes are aimed at the target, and intraoperative stimulation is used to predict the effects of chronic stimulation, which assists in determining the final site of electrode implantation [44]. Once the signal strength and final contact position have been verified, which typically occurs 1–2 days after surgery, one or two internal pulse generators are implanted under the skin in the subclavicular region near the collar bone [1]. Traditionally, these generators create an open-loop system in which electrical stimulation is delivered on a set, constant, preprogrammed schedule. Finally, three-dimensional computer tomography or MRI scans are performed a few days later to confirm the position of the electrodes [9].

Risks associated with DBS surgery include air embolus, stroke, seizures, hemorrhage, hydrocephalus, infections, and lead fractures [45]. Nevertheless, the infrequent occurrence of such complications, coupled with the fact that the benefits of the surgery greatly outweigh the costs, ultimately led the FDA to approve DBS for the treatment of medically intractable symptoms of movement disorders in 2002 [9]. Since that time, thousands of patients have undergone the procedure [44].

Investigators are still not entirely certain how the treatment works at the cellular level (for review of the functional mechanism, see [46]). Microlesions from the procedure itself do produce motor network changes [47], but these changes dissipate over time. It is also clear that the changes in motor circuitry with STN-DBS and those with levodopa administration have much in common but are not identical [48]. It has been suggested that STN-DBS affects neuronal membrane potentials and voltage-dependent calcium channels surrounding the pathologic circuitry [9]. In doing so, DBS may be altering the firing pattern of STN neurons to immediately produce a therapeutic effect at the electrode's tip [49, 50]. It is also possible that the stimulation is not affecting the cell bodies; rather, the axons carrying signals into the STN from other areas may be the target of the stimulation's effects [9]. Support for this notion has been generated through studies of animal models of PD, in which optically stimulated cortical neurons, whose axons reach down to the STN, also diminish PD-like signs [51]. Recent work in patients with PD suggests that modulation of white matter tracts connected to the superior frontal gyrus and thalamus may contribute to the therapeutic benefits of DBS [52].

The most common targets for DBS include the STN and the GPi [53] and the Vim of the thalamus [57]. There have been several studies comparing the benefits of selecting one target over another, and STN-DBS and STN-GPi have generally been found to be equally effective in improving motor functioning [54, 55], though they may have their respective benefits/strengths. STN-DBS helps to alleviate some of the motor impairments during the "off" state [18], and postsurgically, patients are often able to reduce their medication doses [56], which is advantageous given that medication often has negative side effects (e.g., dyskinesias and hallucinations). However, the Veterans Affairs Cooperative Study showed that STN stimulation was associated with slightly greater risk of declines in processing speed and mood to some extent [54]. Furthermore, GPi DBS greatly reduces dyskinesias during the "on" state and may have a particulary positive effect on gait disturbance. DBS targeting the Vim of the thalamus [57] is generally utilized to treat only the contralateral tremor, without having an impact on rigidity or bradykinesia [18]. As such, the Vim is

not targeted as often as the other structures during DBS procedures. In addition, in some cases, PPN-DBS is done in combination with STN- or GPi-DBS. Further, DBS placement in the pedunculopontine nucleus has been shown to be effective in reducing freezing of gait [58] and postural symptoms [59]. Other studied targets include the substantia nigra pars reticulata [60] and the caudal zona incerta [61].

As the scientific community learns more about the subcortical pathophysiology of PD, target selection can be based more on the patient's most disabling symptoms, medication response (including side effects), and therapy goals [44].

Importantly, significant technological advances are currently underway to enhance the benefits derived from DBS, irrespective of the target. As recently reviewed by Fang and Tolleson [62], programmers are currently developing new technologies to provide clinicians with finer control of the stimulated areas, through increasing the number of contacts of DBS electrodes. Additionally, modifications are underway to allow clinicians to better direct the electrical current, thereby reducing potential negative side effects. A new technology known as optogenetics is promising in this regard. Optogenetics uses light-activated proteins and genetic approaches to precisely stimulate and modulate neural circuits and thus is being used to understand how to optimize DBS treatment [63].

Another major recent advancement in DBS technology is the development of a closed loop system, in which a DBS system detects and interprets a patient's brain activity and modifies stimulation parameters accordingly to maximize the clinical benefit obtained. To elaborate, there is evidence that increased oscillatory synchronization in the beta frequency band (13–35 Hz) correlates with motor impairment in Parkinson's disease and can be used as a feedback signal in a closed-loop DBS system [64–67]. Further, the use of a closed system will ideally lead to more tailored treatment, reduce the side effects that would otherwise be experienced with continuous stimulation, and be more energy effective [66].

Neuropsychological Outcome in Patients Undergoing DBS

The improvement in motor functioning following DBS has been well documented [68]. In contrast, studies focusing on the effects of DBS on cognition, mood, and behavior have yielded mixed findings. It is possible that the variation in findings is due to differences in the treatment protocols used at various centers. Other differences may include the comparison groups used and the characteristics of the patient populations, as well as small sample sizes and variable amounts of time that elapsed until follow-up. An overview of these findings is presented below.

Motor Outcome

STN-DBS and GPi DBS have both been reported to improve the cardinal motor features of PD, including tremor, bradykinesia, rigidity, akinesia, gait speed, stride length, lower limb joint movements, postural instability, and levodopa-induced dyskinesia [44, 68, 69]. Studies have generally shown no significant difference between STN-DBS and GPi-DBS in terms of their effects on motor symptoms [54, 55], though some research work suggests that each has their respective strengths/benefits for particular patients/symptom presentations, as discussed above. Further, DBS can reduce levodopa-induced motor complications, such as prolonged "off" periods and dyskinesias [70]. Although the long-term implications of these treatments are not fully appreciated, multiple studies of patients who are approximately 5 years posttreatment have suggested sustained efficacy [71, 72].

Cognitive Changes

Findings regarding the cognitive changes associated with DBS vary widely (for review, see [44]), with some studies reporting cognitive improvement, others revealing cognitive decline, and still others showing no alterations in neurocognitive functioning. However, the most consistent finding

is a mild decline in verbal fluency, both phonemic and semantic [73, 78]. While it was generally thought that this decline in verbal fluency cannot be accounted for by changes in psychomotor speed since performance on psychomotor tasks tends to remain stable or to improve [74], a recent study by Houvenaghel and colleagues [75] suggested that a decline in phonemic fluency following STN-DBS was related to a decline in cognitive speed postoperatively but not to general executive dysfunction. Several other explanations have been posited to explain this post-DBS cognitive weakness. Based on the activation of the left inferior frontal gyrus that was observed during neuroimaging studies of patients who underwent STN-DBS, Saint-Cyr and colleagues [76] hypothesized that stimulating the STN may impact the striato-thalamo-cortical circuit. This would then affect word generation, an ability that has been localized to the left inferior frontal gyrus. Alternatively, it is plausible that the current used to stimulate the STN may spread to adjacent cognitive circuits [74, 77], thereby disrupting the pathway associated with verbal fluency. Another current hypothesis is that the observed reduction in verbal fluency is a result of lesions produced when DBS electrodes are implanted [78, 79].

Decline in learning and memory has also been a consistent finding in DBS outcome studies; however, the clinical significance of these findings is questionable because the degree of decline may be limited [1]. Additionally, there is evidence to suggest that these abilities return to their pre-DBS state as time elapses [70, 80, 81]. It is possible, therefore, that the reported declines in learning and memory are due to secondary factors (e.g., edema, stimulator setting) and are not indicative of true impairment in these cognitive abilities.

There is also evidence in the research literature to suggest that a side effect of STN-DBS is reduced cognitive/executive control of action [82]. Specifically, STN-DBS may cause patients to have increased difficulty producing appropriate responses when overlearned inappropriate responses are viable alternatives. In daily living, this may manifest as problems with impulsivity and reward processing. Interestingly, Houvenaghel and colleagues [82] further suggest that patients with less severe PD may be at greatest risk for developing impulsivity postoperatively. That said, the functional consequences of these psychometric changes remain unclear.

Results of studies assessing the cognitive effects of STN-DBS in PD patients seem to suggest that the likelihood of decline is more frequently observed in older patients, who have a greater tendency to have presurgical cognitive impairments than younger patients [83]. However, Perriol and colleagues [84] found that neither age at time of surgery, disease duration, nor performance on a cognitive screen (Dementia Rating Scale (DRS) total score) prior to surgery impacted outcome. Overall, preoperative cognitive deficits, confusion, and history of psychosis (induced by dopaminergic medication) were the factors that predicted cognitive outcome 12 months after surgery [68, 85–87].

Psychosocial Changes and Quality of Life

The findings regarding psychiatric changes following surgery have also been mixed. Reductions in symptoms of depression and anxiety are commonly described by patients [1]; however, investigations that have focused on behavioral outcome have reported either no change in mood symptoms [68, 83, 84] or significant psychological disturbances and behavioral changes following DBS. Reported increases in mood symptoms were generally associated with dysthymia or emotional lability [84, 88]. Yet, there are preliminary reports documenting that patients have experienced periods of mania/hypomania [89, 90], mirthful laughter [91], and visual hallucinations [92] after undergoing DBS surgery. York and colleagues [83] reported that patients experienced slightly elevated levels of anxiety after undergoing DBS surgery, and this was observed to be highly correlated with disease duration [83]. All other investigations conducted to date have found that anxiety symptoms remain stable [93] or improve after the surgery is performed [94, 95]. Mild improvements in obsessive-compulsive symptoms and paranoid thoughts

have also been documented [93]. The National Institutes of Health's COMPARE study found that STN-DBS and GPi-DBS largely similarly impacted mood, although STN-DBS, but not GPi-DBS, was associated with somewhat increased anger [78].

The factors associated with poor emotional outcome are believed to be mediated by psychiatric state prior to the surgery. It has been reported that symptoms of depression that were present 1 year postsurgery were associated with preexisting psychiatric disorders [84]. Additionally, advanced age seems to be associated with increased risk for postoperative mood disturbance [84]. York and colleagues [83] point out that such findings may not be truly representative of the entire sample, as the individuals who experience psychological distress may also be those who refuse to return for their follow-up evaluations.

Just as postsurgical depression appears to be associated with the presence of depressive symptoms prior to surgery, patients who present with a long-standing history of impulsivity (i.e., gambling behaviors) may be poor surgical candidates, as there has been some evidence to suggest that these individuals are at increased risk for postoperative suicide attempts [96]. In contrast, symptoms of impulsivity that have been induced by dopaminergic medications can be mitigated with STN-DBS [97].

With respect to other psychiatric symptoms, treatment with dopaminergic agents is a primary cause of hallucinations in PD [98]. Since treatment with DBS may lead to a decrease in pharmacologic treatment, a reduction in these psychiatric symptoms can occur as a result. Interestingly, the existence of hallucinations presurgically does not appear to be a risk factor for the presence of these psychotic symptoms posttreatment [99, 100].

Improvements in quality of life have been reported for patients who underwent treatment with DBS [101] as well as for their families [102]. Although reduced reliance on medications has been cited as the most common reason for these improvements [103], advances in the ability to perform activities of daily living (ADLs) have also been reported [84, 94]. Further, improvement in ADLs may be present even 5 years posttreatment [103]. Nevertheless, the recovery of such abilities may not affect change in social adjustment. In fact, increased difficulty in interpersonal relationships has been reported in some patients postoperatively [72]. In addition, age may be a mediating variable in the relationship between STN-DBS and quality of life, as Derost and colleagues [104] found that STN-DBS improves motor complications equally in young (<65 years) and older (>65 years) PD patients but only improves postoperative quality of life in young patients. There is thus support for early DBS intervention to significantly impact quality of life.

Several studies have demonstrated improvements in health status following DBS [105–107]. Improvement has reportedly been noted in sleep architecture, sleep efficiency, and nocturnal mobility; total sleep time and a reduction of sleep fragmentation and wakefulness after onset have also been demonstrated [108, 109]. Another non-motor symptom that may improve with DBS is pain [110], and this may be related to improvements in rigidity and depressive symptoms with DBS treatment [111]. As discussed by Wang and colleagues [111], other medical factors that may improve with DBS and lead to some degree of improvement in quality of life are temperature sensation and sweating [112, 113], urinary symptoms [114, 115], and gastrointestinal problems [116].

A recent meta-analysis by Tan and colleagues [117] investigated STN- versus GPi-targeted DBS in terms of their respective effects on depression and quality of life and suggested that GPi was more favorable in this regard, although acknowledged that this remains a question open for discussion.

Published Recommendations for Neuropsychologists

Given the varying cognitive, affective, and behavioral profiles of people diagnosed with PD, as well as the neurocognitive changes that have been reported in patients who have undergone DBS surgery, neuropsychological assessments

have become an essential component of pre-DBS screening protocols at many medical centers [118]. The goal of such an evaluation is to aid in excluding patients who have Parkinson's plus syndromes (e.g., multiple systems atrophy, progressive supranuclear palsy, corticobasal degeneration) and are therefore not expected to benefit from surgery [119], as well as patients with preexisting cognitive deterioration or behavioral disorders that place them at increased risk for the exacerbation of their cognitive difficulties if they were to undergo DBS surgery [20, 76]. Additionally, neuropsychologists have historically played a role in the evaluation of cognitive outcome postsurgery [45].

In an effort to design a short (90 min) battery that could be used to exclude atypical PD candidates from undergoing DBS, Pillon [118] suggested that neuropsychologists administer the Mattis Dementia Rating Scale [120] as an estimate of global cognitive functioning; the Grober and Buschke test [121] to investigate verbal memory; the Boston Naming Test (BNT; [122]), an apraxia examination [123]; and the Rey-Osterrieth Complex Figure Copying (RCFT; [124]) to assess "instrumental functions." The author also recommends conducting a neuropsychiatric interview and administering the Montgomery and Asberg Depression Rating Scale (MADRS; [125]); the latter was specifically selected because it is sensitive to changes in depressive symptoms over time [118].

Others investigators have argued that the pre-DBS battery must be more comprehensive. For example, Okun and colleagues [45] report that in addition to the Dementia Rating Scale-Second Edition (DRS-II; [126]) and the Mini-Mental State Exam (MMSE; [127]), neuropsychologists should use the Wechsler Abbreviated Scales of Intelligence (WASI; [128]) to obtain an estimate of premorbid functioning. Okun's treatment team also recommends administering a Digit Span subtest, as well as the Paced Auditory Serial Addition Test (PASAT; [129]), emphasizing the need to more directly assess basic attention, working memory, and auditory information processing speed, respectively. Although their battery includes the Hopkins Verbal Learning Test-Revised (HVLT-R; [130]), Okun and colleagues [45] reportedly observed that many PD patients perform poorly on such word list learning tasks. As such, they also recommend administering the Logical Memory and Faces subtests from the Wechsler Memory Scale-Third Edition (WMS-III; [131]) to glean a better understanding of whether or not the patient is amnesic. The group further states that measures of language should include the Boston Naming Test [122], Controlled Oral Word Association Test (COWAT; [132]), and a measure of category fluency. Benton's Judgment of Line Orientation (JLO) and Facial Recognition [133] are suggested as appropriate visuospatial tasks, and the Stroop is used as a measure of executive functioning [134].

The Team and Their Roles

PD patients who are considering DBS surgery at our center, undergo a comprehensive evaluation consisting of consultations with a neurologist who specializes in movement disorders, a neurosurgeon who specializes in stereotactic surgery, and a neuropsychologist. The goal is to ensure that other treatments have been exhausted and to identify candidates who will benefit from the treatment and are physically, cognitively, and emotionally able to tolerate all aspects of surgery and postoperative care.

In general, candidates are first seen by the program's neurologist, and appointments with the neurosurgeon and neuropsychologist follow soon thereafter; however, this sequence often varies. For example, a neurologist outside of the movement disorder specialty may refer directly to neurosurgery since this is the discipline through which they would like their patients to receive treatment. In addition, sometimes movement disorder specialists refer directly to neuropsychology because they would like to understand the patient's risk for cognitive decline and the patient's capacity to understand and tolerate the psychologically demanding procedure and follow-up, prior to referring the patient to the DBS program.

During the preoperative evaluation, a patient's levodopa response is carefully assessed using the levodopa challenge test. Although DBS has been shown to improve the motor complications of levodopa (e.g., reduce the amount of off-period time, improve dyskinesias), levodopa-resistant features tend to persist despite treatment with DBS. Therefore, a levodopa challenge test provides information regarding the potential benefits that the patient may obtain from DBS surgery. Those who respond well to the levodopa challenge are predicted to have a better prognosis (e.g., fewer levodopa-resistant features) postsurgery than those who respond poorly.

Assessment Measures Utilized

Prior to the evaluation, the neuropsychologist reviews the patient's medical record, including the neurologist and neurosurgeon's consult notes and the relevant brain scans when available (i.e., CT, MRI, FDG-PET). Patients also complete a form prior to the assessment that documents details of their developmental, educational, vocational, medical, and psychiatric history. At the outset of each neuropsychological assessment, the patient and an informant (e.g., significant other, adult child) participate in a comprehensive clinical interview lasting approximately 30 min, conducted to gather background information, gain a thorough understanding of current symptomatology, and collect additional information that may assist in making a differential diagnosis. During the course of the interview, the neuropsychologist discusses the patient's reasons for considering DBS at this time, understanding of the surgical procedure, and risks associated with the treatment and expected outcome of the surgery. Information regarding any potential social stressors that may impact the patient's postoperative outcome is also discussed in detail. Conveying an understanding of treatment expectations is a key element of the neuropsychological evaluation because unreasonable expectations can result in a negative emotional response, regardless of the degree of motor improvement. Although all patients are informed about the likelihood of improvement and the types of symptoms that do and do not respond to treatment, some patients continue to believe that the surgery is a panacea. Therefore, although such patients may indeed experience an improvement in movement symptoms, their inability to fulfill an unreasonable belief (e.g., return to tennis) increases the risk that they will have a "catastrophic reaction." When there is an incongruity between patient and doctor expectations, additional patient education is required so that the discrepancies can be addressed directly.

A comprehensive neuropsychological battery is then administered in a single, extended session. Given that one of the main reasons for conducting a neuropsychological evaluation is to rule out the presence of a primary progressive dementia, it is imperative that the assessment battery adequately evaluates a range of cognitive domains including general cognition, attention/executive functioning, learning, memory, language, visuospatial functioning, sensorimotor, and mood/personality. The Dementia Rating Scale-Second Edition [126] is used to assist in distinguishing patients with dementia from those without. Because it includes measures of attention and executive functioning, it is more sensitive than the Mini-Mental State Exam [127] in assessing various subcortical degenerative diseases [118]. Additionally, the WAIS-III [131] Block Design and Similarities subtests are administered to measure current conceptual reasoning abilities.

Other subtests used to assess attention and executive functioning include the Repeating Numbers subtest from the Randt Memory Test (RMT; [135]) as a measure of basic attention and working memory, the Symbol Digit Modalities Test (SDMT; written and oral; [136]) as a measure of processing speed, and the Wisconsin Card Sorting Test-64 (WCST-64; [137]) as a measure of feedback utilization and perseveration. Motor disinhibition is assessed using a motor go/no-go task; bimanual and unimanual tasks of motor sequencing [138] are also administered. In addition, both the patient and a family member complete the respective Frontal Systems Behavior Scale (FrSBe; [139]) to provide greater insight

into the executive dysfunction that the patient is displaying in his or her everyday life.

Learning and memory are assessed for both verbal and visual information. Immediate verbal recall, learning over repeated presentations, and recall over a brief and extended delay period are assessed using the California Verbal Learning Test-Second Edition (CVLT-II; [140]). The Brief Visuospatial Memory Test-Revised (BVMT-R; [141]) is used to provide comparable information regarding the patient's visual learning and memory abilities.

For the assessment of language skills, naming is evaluated using the BNT [122], and phonemic and semantic fluencies are appraised through the COWAT (FAS; [133]) and animal naming, respectively. Auditory comprehension is assessed using the Commands subtest of the Boston Diagnostic Aphasia Examination (BDAE; [142]).

An understanding of the patient's visual perception/construction abilities is assessed using the Hooper Visual Organization Test (HVOT; [143]), Judgment of Line Orientation, and Facial Recognition [133]. Because praxis is only mildly impaired in the non-demented PD patient, the addition of an apraxia examination to the battery assists in making a differential diagnosis [118]. Finally, the severity of affective symptoms must be assessed because the presence of depressive symptoms has been shown to negatively impact recovery after DBS surgery [84]. In our center, the Beck Depression Inventory-Second Edition (BDI-II; [144]) and the Beck Anxiety Inventory (BAI; [145]) are both administered. A list of the measures administered at our center is summarized in Table 35.1.

Table 35.1 Measures used for pre-DBS assessment

Domain	Measures administered
General cognition	Dementia Rating Scale-2 (DRS-2) National Adult Reading Test (NART) WAIS-III Block Design WAIS-III Similarities
Attention/executive functioning	Repeating Numbers (Randt Memory Test) Symbol Digit Modality Test Trail Making Test Golden Stroop Wisconsin Card Sorting Test (WCST-64) Luria Motor Sequencing Tasks Motor go/no-go Frontal Systems Behavior Scale (FrSBe; self and family rating)
Learning/memory	California Verbal Learning Test-2 (CVLT-II) Brief Visuospatial Memory Test-Revised (BVMT-R)
Language	Boston Naming Test (BNT) Verbal fluency Boston Diagnostic Aphasia Examination (BDAE)-Commands
Visual perception/ construction	Benton Judgment of Line Orientation Benton Facial Recognition Hooper Visual Organization Test
Sensorimotor	Praxis
Mood/personality	Beck Depression Inventory-II (BDI-II) Beck Anxiety Inventory (BAI)

Case Examples

Case A: Brief Presenting Information

Case A is a 71-year-old woman who was first diagnosed with Parkinson's disease approximately 10 years prior to the pre-DBS assessment. She is interested in undergoing DBS surgery as she believes it may help make her ON/OFF cycles more predictable, which will help improve her quality of life by making it possible for her to participate in enjoyable activities more often and by enabling her to decrease some of her medications. Case A feels her medication is no longer as effective as it used to be because her ON states occur less frequently and are weaker than they were several years ago. She reports physical symptoms, including balance difficulties leading to falls (none have been serious to this point), tremor, and dystonia/dyskinesias, as well as increased difficulty performing her activities of daily living independently.

Case A reports that she is having occasional difficulty with her short-term memory, mainly recalling the temporal details of events, and some word-finding difficulty. She explained that she feels "sharp" at times and "dull" at other times. According to her husband, Case A may take longer to recall details; however, he does not feel that she ever forgets information completely. Medical history is otherwise significant for hypertension, cardiac arrhythmias, and arthritis. Case A reports experiencing some depression and anxiety symptoms over the past few years, but on exam, she endorsed only mild symptoms that were not considered to be clinically significant. Case A's performance on the neuropsychological assessment battery is presented in Table 35.2.

Case B: Brief Presenting Information

Case B is a 50-year-old man diagnosed with Parkinson's disease approximately 3 years prior to the pre-DBS assessment, who mainly experiences a unilateral hand tremor that causes him distress and prevents him from performing tasks, such as driving and working in construction. In response to questions about the surgical procedure, Case B is unable to clearly state how the treatment will help him or articulate the possible risks associated with the surgery. Further, his expectations appear to be unrealistic, indicating that he will be "back to normal" and able to work and drive again. With respect to neuropsychological symptoms, he denies any cognitive difficulties but indicates a history of depressive and anxious symptoms, with recent anxiety regarding his health and inability to work. He is divorced and currently lives alone. Case B has a long history of heavy alcohol abuse; he reports drinking as many as 24 beers per night and notes that he has at least one blackout per week. He indicates that he has not had alcohol in 2 months as part of his preparation for surgery but reports a desire to resume his regular consumption of alcohol after undergoing DBS surgery. Table 35.2 details the results of Case B's neuropsychological assessment.

Case C: Brief Presenting Information

Case C is a 57-year-old man diagnosed with Parkinson's disease approximately 8 years prior to the pre-DBS assessment, whose presenting physical symptoms include excessive dyskinesias, "very brief" ON time, poor posture, and balance difficulties. Case C was previously considered for DBS surgery 4 years prior; however, it was determined that his psychiatric risk was too great, and his physical symptoms (just posture and balance complaints at that time) are not considered to be universally improved with the procedure. It was determined that Case C had an adverse medication response to Mirapex, and he was depressed, hypersexual, engaging in excessive gambling, performing self-mutilation, and had passive suicidal ideation. When the medication was discontinued, he responded well, and the psychiatric symptoms subsided. In response to questions about the surgical procedure, Case C is hoping to increase his ON time and decrease the severity of his dyskinesias. He was able to appropriately articulate the possible risks associated with the surgery, and he seemingly has realistic expectations regarding treatment outcome.

With respect to neuropsychological symptoms, Case C reported that he has experienced a cognitive decline over the past 5–10 years, with a more significant drop over the past 6 months. Symptoms include word-finding difficulty and confusion during his OFF state, including comprehension and memory problems. While he denied any changes in mood, he reported that he has always been an anxious person, with some depression since his divorce several years ago. Although he is not receiving psychotherapy or psychopharmacologic treatment at the present time, he has had in the past. Case C currently lives in residential housing, due to his psychiatric history, and he works part time in security. Table 35.2 outlines the results of Case C's neuropsychological assessment.

Case A: Summary and Conclusions

Case A has identified a realistic treatment outcome that matches her neurological state and has

Table 35.2 Examination results for Case A, Case B, and Case C

DBS candidate	Case A		Case B		Case C	
	Approved for DBS		Failed prescreening		Approved for DBS	
Domain	Raw score	Percentile	Raw score	Percentile	Raw score	Percentile
General cognition						
DRS-2 total	139	41–59	122	3–5	134	19–28
Attention	36	60–71	33	11–18	35	41–59
Initiation/perseveration	37	60–71	31	6–10	36	41–59
Construction	6	41–59	6	41–59	6	41–59
Conceptualization	35	29–40	31	6–10	33	11–18
Memory	23	82–89	21	6–10	24	41–59
NART	FSIQ = 126		FSIQ = 112		FSIQ = 122	
WAIS-III						
Block design	28	50	29	25	29	37
Similarities	24	75	22	37	24	63
Attention/executive functioning						
Randt Memory Test—LSF; LSB	8; 7	91; 99	6; 4	34; 30	7; 5	37; 37
SDMT—Written; oral	39; 50	53; 63	31; 38	3; 4	35; 44	21; 30
Trail Making Test—A and B	33; 83	73; 68	46; 199	16; 4	73; 126	<1; 2
Golden Stroop						
Word	109	50	78	7	98	30
Color	79	50	42	1	57	7
Color/word	58	91	23	1	25	3
Interference	12	88	−4.3	34	−11.04	14
WCST-64						
Categories	4	>16	3	>16	2	11–16
Perseverative errors	4	>99	12	25	19	8
Failure to maintain set	1	–	0	–	1	–
Luria motor sequencing tasks	Within normal limits		Within normal limits		Within normal limits	
Motor Go/No-Go	Within normal limits		Within normal limits		Within normal limits	
FrSBe	Raw score	T = score	Raw score	T = score	Raw score	T = score
Self—total (before; after)	97; 142	124; 146	113; 136	87; 111	65	41
Apathy	22; 53	99; >160	33; 52	74; 120	16	37
Disinhibition	34; 39	146; >160	28; 27	56; 54	16	30
Executive dysfunction	41; 50	128: 152	52; 57	100; 111	33	55
Family—total (before; after)	73; 86	114; 130			81	52
Apathy	24; 38	112; 156			27	54
Disinhibition	15; 16	84; 88			20	40
Executive dysfunction	34; 32	124; 120			34	57
Learning/memory	Raw score	Percentile	Raw score	Percentile	Raw score	Percentile
CVLT-II total	41 (3, 7, 8, 11, 12)	46	29 (3, 4, 6, 8, 8)	7	29 (4,6,5,7,7)	7
List B	6	70	3	7	4	30
Immediate recall (cued)	8 (9)	50 (30)	8 (7)	30 (16)	5 (5)	16 (2)
Delayed recall (cued)	7 (8)	30 (16)	8 (7)	30 (16)	6 (7)	16 (16)
Hits (false positives)	13 (5)	16 (3)	14 (10)	50 (2)	12 (2)	16 (50)
Forced choice	16/16	–	16/16	–	16/16	–
BVMT-R total	14 (3,5,6)	12	20 (6,7,7,)	21	15 (3,5,7,)	5
Learning	3	34	1	7	4	58

(continued)

Table 35.2 (continued)

DBS candidate	Case A		Case B		Case C	
	Approved for DBS		Failed prescreening		Approved for DBS	
Domain	Raw score	Percentile	Raw score	Percentile	Raw score	Percentile
Delayed recall	7	34	7	14	5	4
Percent retention	117%	>16	100%	>16	71%	3–5
Hits (false positives)	5 (0)	>16 (>16)	5 (0)	11–16 (>16)	6 (0)	>16 (>16)
Recognition discrimination	5	>16	5	11–16	6	>16
Copy	12/12	–	11/12	–	11/12	–
Language						
BNT—correct (phonemic cues)	60 (N/A)	84	51 (3 of 9)	18	53 (5 of 7)	24
Verbal fluency—phonemic; semantic	54; 29	98; 25	47; 17	84; 1	32; 20	14; 34
BDAE Commands	15	58	14	1	15	58
Visual perception/construction						
Judgment of line orientation	30	>86	21	22	21	22
Facial recognition	49	72–85	52	88–97	41	16–21
Hooper	20	12	25.5	53	21	16
Motor						
Apraxia exam	Within normal limits		Within normal limits		Within normal limits	
Mood/personality						
BDI-II	5	Minimal	17	Mild	22	Moderate
BAI	2	Normal	17	Moderate	17	Moderate

associated this outcome with a plausible change in her life circumstances. There is little concern regarding Case A's cognitive functioning. Attention, executive, learning, memory, and visuospatial functions are all generally intact. Her performance does reveal a mild weakness in initial encoding, and she reports difficulties with executive functions. However, she does not exhibit rapid forgetting, and there is no evidence of a significant anomia. This pattern is typical of cognition in Parkinson's disease.

In sum, the patient is entering into the process fully informed and fully aware of the surgical procedure, as well as its risks and possible benefits. Her cognitive difficulties are relatively mild and in a pattern typical of Parkinson's disease. Therefore, there is no evidence of a secondary neurodegenerative disorder, and she is not at risk for greater than typical cognitive side effects. Finally, although she exhibits some mood issues, she does not have a clinically significant psychiatric disorder that would interfere with postsurgical quality of life or put her at risk for greater mood difficulties. In such a case, participation in a series of psychotherapy sessions before and after surgical intervention could be considered.

Case B: Summary and Conclusions

Case B is experiencing significant difficulties across multiple cognitive domains, with his greatest impairment in complex attention and memory functions. This pattern of dysfunction is consistent with the frontosubcortical dysfunction associated with Parkinson's disease; however, the degree of impairment is somewhat greater than expected in an individual his age, especially considering that the time since diagnosis is only 3 years. It is very likely that his difficulties are compounded by more diffuse brain dysfunction associated with long-term alcohol abuse. Further, Case B exhibits mild to moderate mood difficulties, with greater anxiety than depressive symptoms.

Several issues should be considered in reference to his possible participation in surgical intervention. First, Case B does not appear to fully understand the procedure itself and the associated risk, but more importantly, his expectation for the treatment appears to be unrealistic. Second, he exhibits significant cognitive and mood difficulties. Finally, and most concerning, is his history of alcohol abuse. Given the patient's history and report during the exam, the prognosis for successful cessation is poor. If he is to be further considered for surgical treatment, enrollment in a formal substance abuse treatment program would be recommended, with the period of abstinence set by the surgical risk.

Case C: Summary and Conclusions

Case C is experiencing some difficulties across multiple cognitive domains, with the area of greatest concern being executive functioning. He is experiencing slowed processing speed, cognitive inflexibility, and perseveration. More mild difficulties are apparent in memory and visuospatial functioning, but performance in these domains is in part implicated by his executive dysfunction. His memory difficulties are characterized by poor learning and retrieval, but he has intact retention over time for information previously encoded. He has intact basic perceptual and construction abilities, with difficulties in spatial processing and integration. Language functions are largely intact with some retrieval difficulties apparent. In addition, Case C is endorsing significant emotional symptoms.

Overall, Case C's pattern of cognitive difficulties is fully consistent with what is seen in Parkinson's disease. Despite the severity of deficits, there is no indication of a secondary neurological illness that would put him at risk for greater than typical cognitive side effects from the DBS procedure. He exhibits realistic expectations for the procedure, has a strong support network, including living in a supported environment, and has close relationships with his siblings who live locally and see him regularly. Case C is reporting significant, albeit mitigated, symptoms of depression and anxiety that are currently not being treated directly and present some concern for the procedure. Therefore, it is strongly recommended that Case C participates in individual psychotherapy, as well as have a psychopharmacological consultation, prior to moving forward with the DBS procedure. These treatments will not only help address his long-standing affective symptoms but will also provide him with an additional support system while he engages in the process of considering the procedure, undergoing the surgery, and recovering thereafter. Although Case C is experiencing significant cognitive deficits and emotional symptoms, it was determined that he would be considered a viable surgical candidate with appropriate supports in place to monitor his psychiatric state. His medical risk for surgery is low, given his age and health, and a clinical judgment was made in this case that the potential benefit to his quality of life postoperatively is greater than his risk factors, considering that his symptoms are fully consistent with the disease.

Other Patient Populations Treated with DBS and Clinical Considerations

DBS has proven to be an effective method of treatment for several other disorders, as well. In fact, the FDA approved of this surgery for the amelioration of symptoms associated with essential tremor (ET) 5 years before it was approved for use in PD patients. Since that time, DBS surgery has been used to mitigate the symptoms of numerous movement and affective disorders. Neuropsychologists continue to be an integral part of the treatment team for these surgical indications; however, there is less evidence on which to base clinical practice. In general, the role of the neuropsychologist remains the same, assessing the patients' understanding of the procedure and quantifying the patients' cognitive, behavioral, and emotional status to aid in the prediction of

outcome. However, the focus of course is different, especially in psychiatric indications.

DBS and Essential Tremor

ET is a slowly progressive disease that is usually characterized by postural tremor; intention tremor is seen in approximately half of ET patients, as well [146, 147]. These patients also have a disorder of tandem gait, which is usually mild. Propranolol and primidone tend to be the first-line treatments, and in most cases, the symptoms of ET can be treated solely with one or both of these medications [148]. As the illness progresses, the frequency of the tremors tend to decrease; however, their amplitude increases, exacerbating the resultant disability and significantly impacting daily activities and quality of life. When the disease progression has reached such a point, or when symptoms are not properly managed with pharmacotherapy, DBS of the ventralis intermedius nucleus (Vim) of the thalamus is often considered [44]. Outcome studies have revealed that it is very likely that the pure postural tremor of the upper extremities will improve after DBS of the ventralis intermedius/zona incerta (for review, see [148]). The success rate is slightly decreased if the patient presents with an intention tremor or a more proximal tremor predominates. In fact, only 50% of patients with intention tremors experience long-term improvement [149]. Results of outcome studies further suggest that bilateral DBS may be considered if head, voice, or trunk tremors are the main reason for surgery [150], yet bilateral thalamotomy is associated with high risks of complications and should not be conducted [151].

Tourette's Syndrome

According to the DSM-V [152], Tourette's syndrome (TS) is a chronic, neurobehavioral disorder that is characterized by motor and phonic tics, which may wax and wane but that persist for a minimum of 1 year. Patients who have been diagnosed with TS and who experience functional impairment in their ability to socialize are usually treated with neuroleptics, adrenergic agonists, and dopamine agonists [153]. Pharmacotherapy is often accompanied with behavioral treatment in which techniques such as habit reversal training are implemented. Because symptoms are often refractory to these various treatments and are frequently reported to cause significant distress, various neurosurgical procedures have been attempted to mitigate both motor and phonic tics [155]. Among these procedures, DBS is considered to be an appropriate technique to use when TS symptoms are refractory to medications [153] although studies demonstrate a significant risk for postsurgical complications (medical, psychiatric, and cognitive) [154]. Part of the intralaminar nucleus of the thalamus, known as the centromedian-parafascicular complex (CM-PF), is considered to be the preferred target for DBS treatment of TS symptoms [156], as stimulation in this area has effectively allayed tics and improved the behavioral aspects of TS [157]. However, it has been suggested that stimulating the GPi or the anterior limb of the internal capsule may prove to be even more advantageous than DBS of the CM-PF for other behavioral features of the disorder [153, 154]. Future studies remain necessary to ascertain which site should be targeted for which patients.

Recommendations for the use of DBS in Tourette's Syndrome were published in 2015. It was suggested that potential patients are screened by a multidisciplinary team at a DBS center. Given the potential for post-DBS complications, it was recommended that, for cases of "urgent indications" and for any individual younger than 18 years, a local ethics committee or institutional review board should be consulted prior to surgery [154].

Major Depressive Disorder

More recently, DBS has been used to treat endogenous depression [49]. Like PD, major depressive disorder (MDD) was initially treated

using ablative surgeries until monoamine oxidase inhibitors and tricyclic antidepressants were found to effectively improve depressive symptoms [158]. Nevertheless, a large number of patients diagnosed with depression remain refractory to these classes of medications and to the selective serotonin reuptake inhibitors (SSRIs). Although electroconvulsive therapy (ECT) can be used to treat medically resistant depression, many patients are hesitant to undergo such a procedure due to the stigma associated with it [159] or because they are apprehensive that the ECT may result in long-standing neurocognitive side effects [158]. This has spurred investigations into the effectiveness of other nonpharmacologic therapies, including vagus nerve stimulation, transcranial magnetic stimulation, ketamine infusion therapy, and DBS (for review, see [158, 160–162], respectively). Investigators who have studied the safety and efficacy of DBS for the treatment of MDD symptoms have targeted a wide array of areas, including the orbitofrontal cortex, anterior cingulate gyrus, corpus striatum, GP, subgenual cingulate, ventral capsule/ventral striatum, ventral capsule/ventral commissure, nucleus accumbens, and inferior thalamic peduncle [162]. The various outcome studies that have been conducted to date have been fairly compelling [163–168]. Across investigations, treatment resulted in sustained effects in most patients, and thus far, only minor complications from the surgery have been reported [158].

Obsessive-Compulsive Disorder

DBS has also been used in the treatment of symptoms associated with obsessive-compulsive disorder (OCD). An estimated 30–40% of patients diagnosed with OCD do not respond to medications, which frequently prompts off-label use of alternative treatments [169], including DBS. To date, the thalamic/capsular area seems to be the target of choice in the preliminary studies that have been conducted. Over a decade ago, Nuttin and colleagues [170] used DBS to treat six patients with severe OCD through implanting quadripolar electrodes into the anterior limb of the internal capsule. Of the 4 people who continued in the study, 3 were reportedly "much improved," and 1 remained "unchanged"; a follow-up study conducted 21 months postsurgery indicated that individuals who had improved did not remit [171]. Further, the stimulation resulted in changes in regional activity, particularly in the pons, as measured by fMRI, and lower frontal metabolism as seen on PET imaging, 3 months after surgery [172]. Other investigators who implanted the same location also reported that most patients were improved post-DBS [173, 174]. The right nucleus accumbens has also been the target of DBS surgery for the treatment of OCD [175]; stimulation resulted in complete symptom remission 24–30 months after surgery in 3 of the 4 patients. Single-case studies have suggested that stimulation of the caudate [176] or the inferior thalamic peduncle [177] can also be effective in reducing or eliminating OCD symptoms.

Conclusion

Over the past decade, DBS has proven to be an effective treatment for several medically refractory movement disorders and appears to have promising palliative effects for a variety of psychiatric disorders. Although a number of investigators have studied the neuropsychological implications of DBS surgery in an effort to identify inclusionary and exclusionary criteria for the procedure, no consensus has been reached regarding the degree of neurocognitive or psychiatric dysfunction that would render a patient to be an inappropriate candidate [45]. Therefore, neuropsychologists must keep abreast of the ever-increasing literature on this topic and create and explicitly state the criterion to be used within their program.

Clinical Pearls

- Take the time to learn about PD, parkinsonian disorders, and the disorders that can interfere with treatment success. Without a clear understanding of the natural history of cognitive and emotional symptoms in PD and other movement disorders, it is difficult to interpret the exam findings.
- Antiparkinson medication may need to be withheld for the purposes of other assessments, and this can potentially confound the neuropsychological evaluation. Try to coordinate the neuropsychological exam at a time when patients have taken their medications, and they will be in the "ON" state.
- Do not restrict your differential diagnosis to those disorders common to PD. PD is a disorder of mid- to late-adulthood, and each individual has many risk factors that are related to his or her genetic, environmental, emotional, and medical status, which are not necessarily a result of the patient's PD or common concerns such as Alzheimer's disease.
- Remember that the role of the neuropsychologist includes being a psychologist. Depression and anxiety are symptoms of PD, not just a reaction to a disabling disease, and these difficulties affect quality of life.
- Although mood symptoms can potentially be treated with DBS in other brain regions, they are not treated by DBS in the STN, GPi, or Vim. Mood symptoms can persist even after successful DBS for motor aspects of PD, resulting in threats to quality of life.
- Expectations are everything. Just as mood disturbances limit treatment success, so do unrealistic expectations. The neuropsychologist plays a key role in assessing the patient's understanding of the anticipated postsurgical outcome. Presurgical counseling and additional education about treatment expectations may be needed.
- Although the treatment team will take the patient's level of motoric disability into account in their final decision, care must be taken to not let this factor bias your interpretation of the neuropsychological data.
- There are no pathognomonic signs for exclusion and risk. However, the following are often considered as negative findings:
- Generalized cognitive decline at a level that is suggestive of dementia, for example, a Dementia Rating Scale less than 123.
- Pattern of cognitive deficits associated with focal cortical dysfunction.
- Memory performance suggesting greater deficits in the retention of learned information than in learning and retrieval.
- Language difficulties out of proportion to executive deficits.
- History of impulsive/obsessive behaviors associated with disease onset and treatment, such as pathological gambling.
- History of suicidal ideation/attempts.
- Major depressive disorder, or other Axis I psychiatric disorder, that has gone unrecognized or intractable to treatment.
- Specific phobias related to medical procedures.
- A hyperfocus on a single outcome specific to their environment. For example, a patient may have a restriction in a hobby in which he or she needs to use a particular tool.
- Expectations that include environmental changes, such as having better access to job opportunities.

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Idiopathic Normal Pressure Hydrocephalus

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Lisa D. Ravdin, Melanie Lucas, and Heather L. Katzen

Clinical Presentation

The clinical symptom triad of cognitive impairment, gait disorder, and incontinence is considered the classic presentation of iNPH, hence the well-known mnemonic "wacky, wobbly, and wet." However, contrary to clinical lore, it is now widely recognized that all three symptoms are not required for diagnosis. Most commonly, disturbed gait is the presenting symptom which brings the individual to medical attention, followed in frequency by cognitive impairment and urinary symptoms [1, 2]. In rare instances, cognitive dysfunction can predate the onset of gait abnormalities in iNPH [3]. Nevertheless, variations in symptom presentation, with cognitive symptoms greater in severity than the disturbance in gait, should also raise the suspicion of comorbid disease (e.g., diagnosis of both Alzheimer's disease and iNPH).

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Gait

As described above, gait abnormalities are typically the first symptoms to become apparent and are the most readily recognized feature of iNPH. The gait dysfunction in iNPH has been described as "magnetic," "glue-footed," "short-stepped," or "shuffling." While the term "gait apraxia" has also been used, this may not be accurate given the observation that many patients can execute correct walking movements in a recumbent or supine position [4]. This clinical observation has been qualitatively described in the literature and may differentiate iNPH from other movement disorders, yet it has never been carefully studied. iNPH patients typically present with complaints of fatigue brought on by walking, difficulty with chair and bed transfers, halting ambulation down a sloping surface, and inability to walk at an expected pace [5]. Abnormal turning ("en bloc" turning) is also a characteristic feature of the gait abnormality, with multiple steps being needed to turn in place.

Whenever possible, gait assessment should be visually recorded. The use of an objective scale to evaluate specific gait features is recommended so that changes can be assessed following

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diagnostic testing and posttreatment. The most commonly used standard measure of gait in iNPH is the Gait Scale [1]. This measure assesses eight features of gait including tandem walking, turning, trunk balance, stride width, stride length, foot-floor clearance, start hesitation, and foot corrections during a 10-meter timed walk [1]. A number of steps and time to completion are also recorded and total scores range from 2 to 40. Other gait scales commonly used in hydrocephalus include the Tinetti Balance and Gait Assessment [6] and the Timed "Up and Go" test (TUG) [7].

It is notable that some standardized gait scales employ a cutoff of greater than two steps to indicate abnormal turning; however, we have found that many healthy older adults tend to take multiple steps to make a 180° turn on command. In our experience, up to four steps is within the normal range and should not be considered an indication of en bloc turning. iNPH patients often require 5 or 6 steps and in some cases as many as 10–12 steps. In severe cases, patients with iNPH may be unable to turn at all without someone to hold their hands and guide them around. It is important to note that in the very early stages of the disease, individuals may present with relatively normal turning but may go on to develop worsening gait and en bloc turning if left untreated. In general, assessment of gait should be conducted without assistive device when deemed safe to do so, safeguarding the patient by maintaining a close distance (side-by-side). The assessment should aim to cautiously tax the patient at short distances to provide the most accurate gauge of functioning prior to intervention.

Urinary Symptoms

Urinary incontinence has not been well characterized in iNPH and is the least common symptom to be reported at the time of diagnosis. While frank incontinence is present in about half the cases, particularly in advanced stages, increased frequency and urinary urgency are far more common in the early stages of the disease. This is very important to note, as questions about urinary symptoms need to extend beyond asking about the presence or absence of frank incontinence. Specific follow-up questions regarding frequency of urination and a sense of urgency should be included and may reveal subtle bladder symptoms that would otherwise go unreported. The etiology underlying these early symptoms in iNPH is detrusor overactivity [8], which is characterized by involuntary contractions of the smooth muscle surrounding the bladder during the filling phase, thus prompting urination.

The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) [9] is a well-validated and reliable instrument to assess frequency and severity of urinary leakage and the impact incontinence has on everyday life. Similarly, the Overactive Bladder Questionnaire-Short Form (OAB-q SF) captures symptom bother and health-related quality of life [10, 11]. It is also not uncommon in iNPH for patients to develop a "functional incontinence," where the gait disturbance may interfere with successful toileting. Since occasional episodes of incontinence may be attributed to inability to walk fast enough to get to the bathroom, patients may not report these as bladder symptoms unless specifically asked. It is important to note that in iNPH, patients are usually aware of urinary urge or accidents; loss of awareness is not a characteristic of iNPH. Bowel incontinence can also occur in the late stages of iNPH.

Cognitive Dysfunction

Cognitive deficits in iNPH range from subtle cognitive dysfunction to a frank dementia [12]. It is estimated that hydrocephalus may be a contributing factor in up to 6% of dementia cases [13], yet that figure is likely an underestimate given the challenge of parceling out iNPH in the context of other dementing disorders. Early cognitive symptoms can readily go undetected or can falsely be attributed to normal aging and cerebrovascular risk factors. In our experience, many high-functioning patients do not report subjective cognitive changes early in the disease course and perform well on global measures that are typically

employed in neurology and neurosurgery clinics (e.g., Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], Modified Mini-Mental State [3MS]). However, detailed neuropsychological assessment frequently reveals more subtle executive deficits and psychomotor slowing, even when cognitive symptoms are denied by the patient.

In its purest form, the cognitive profile associated with iNPH reflects fronto-subcortical systems dysfunction and can include reduced psychomotor and information processing speed, executive deficits, as well as compromised complex attention and memory [12, 14–17]. Deficits in memory are characterized predominantly by difficulty acquiring new information and retrieval. This is typically secondary to deficits in the organization and efficient processing of information. Delayed recall is impaired but can often be prompted by cueing. The disproportionate impairment in delayed free recall versus recognition observed in iNPH is indicative of a frontally mediated memory issue relative to memory functions subserved by the temporal cortex that are commonly affected in Alzheimer's disease (AD). There is also evidence of visuoperceptual and visuospatial impairments implicating posterior cortical areas [18, 19]. Early cognitive compromise attributable to iNPH presents as mild frontal systems dysfunction. If unrecognized and left untreated, cognitive symptoms may progress to a more severe frontal dysexecutive syndrome. Lack of treatment for a prolonged period may lead to the development of profile that appears to be consistent with a more generalized dementia. As true with other progressive dementing disorders, advanced untreated cases result in cognitive compromise indistinguishable from other forms of dementia. The presence of cortical deficits such as aphasia, agnosia, and alexia can be seen in the more advanced stages of iNPH but likely signal comorbid disease or alternate diagnoses if present early on. As always, onset and duration of symptoms are critical factors to be considered in the differential diagnosis.

With regard to the cognitive profile, there are many occasions in which the neuropsychological test results suggest involvement of not only frontal systems but a more widespread cognitive decline that may indicate comorbid AD, vascular cognitive impairment, or another neurodegenerative process. However, the presence of another disorder does not negate the fact that iNPH may contribute to the presentation and, even more importantly, is not necessarily a contraindication for treatment. In our experience, many patients with comorbid neurodegenerative conditions have been successfully treated for iNPH. While the cognitive symptoms typically do not show substantial improvements post-shunt in patients with significant comorbid disease, improvements in gait can be associated with increased independence in activities of daily living and can significantly improve the patient's quality of life as well as make physical management easier for the caregiver.

Behavioral/Psychiatric Symptoms

The most common neuropsychiatric symptom reported with iNPH is apathy, followed by anxiety and aggression [20–22]. Several case reports of psychiatric disturbances in association with iNPH have appeared in the literature, including depression [20, 23], bipolar mania [24], psychosis [25, 26], and obsessive-compulsive disorder [27]. Although atypical, psychiatric symptoms can emerge as a presenting feature and may complicate the diagnostic process [26]. The pathogenesis of psychiatric presentations in iNPH is not well understood. Symptoms may develop due to neurochemical changes associated with the underlying brain disorder. In some cases, behavioral symptoms, such as depression, may be "reactive" or arise secondary to the physical and mental disability. Nevertheless, it is important to recognize the behavioral disturbances associated with iNPH since they may be refractory to conventional pharmacological treatment and may, in some cases, be responsive to shunt placement. Research has demonstrated significant improvements in a range of neuropsychiatric symptoms with shunt placement, including delusions, agitation, depression, and disinhibition, and these improvements have been

associated with cognitive improvements as assessed by the Frontal Assessment Battery [28].

Demographics

Symptoms of iNPH typically develop with an insidious onset in the sixth and seventh decade of life [1, 29]. It has been estimated that approximately one half of a percent of the population over 65 suffers from NPH-related symptoms; however, few definitive incidence or prevalence studies of iNPH have been conducted [30, 31]. A review of five population-based studies from three countries revealed estimates ranging from 0.4% to 3.0%, concluding that approximately 1% of the population will develop iNPH by the age of 80 [32]. Many hydrocephalus experts feel that this is an underestimate of the true prevalence of this condition. A recent epidemiologic survey study conducted in Japan estimated the crude prevalence of iNPH to be 10.2 per 100,000 persons [33], while review of statutory health insurance records in Germany suggests an annual incidence rate of 1.08 per 100,000 [34].

Although no large-scale epidemiological studies have been conducted, there does not appear to be a gender or racial predilection [35]. The vast majority of iNPH cases are sporadic, yet detailed linkage studies have not been performed. In an ongoing effort to understand variability in the diagnosis, progression, and treatment responsiveness of iNPH, the Adult Hydrocephalus Clinical Research Network (AHCRN) has developed a core data project. The AHCRN is collecting information on demographic characteristics, diagnosis, etiology, and treatment outcomes across multiple centers within the USA and Canada. To date, information from over 500 individuals with hydrocephalus has been collected. Important etiologic differences in adult hydrocephalus subtypes are emerging, including disproportionate number of comorbidities in iNPH relative to other hydrocephalus subtypes, which include hypertension, diabetes, coronary artery disease, spinal stenosis, obesity, and sleep apnea [36]. The goal is to coordinate research efforts to overcome issues related to small sample sizes and lack of uniform procedures that has plagued adult hydrocephalus research for many years.

Pathophysiology

The cause of ventricular enlargement in iNPH is poorly understood. A CSF absorption deficit or an imbalance between CSF production and absorption has been postulated; the exact pathophysiologic mechanism and specific neuroanatomic substrates underlying the symptoms in iNPH remain unknown. Ventricular dilatation may cause disruption of descending periventricular fibers from the supplementary motor areas or compression of deeper subcortical circuits involving the globus pallidus. It has been proposed that ventricular enlargement may lead to increased vascular stretching, thereby decreasing compliance and decreasing capacitance of the system [37, 38]. It has also been suggested that infarction in the deep white matter fibers leading to decreased periventricular tensile strength could be a mechanism underlying iNPH [39, 40].

Differential Diagnosis

The differential diagnosis of iNPH often includes primary neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD).

Like PD, iNPH presents with gait changes, motor slowing, and a profile of frontal systems dysfunction on cognitive testing. In particularly challenging cases when it is difficult to differentiate the two conditions, the treating physician may sometimes consider a trial of levodopa (L-dopa) to see if there is a clinical response. While there are some reports of iNPH showing brief or partial response to L-dopa, this is atypical and may be indicative of comorbid disease (i.e., PD). L-Dopa treatment failures would rule out idiopathic PD, and these cases may then be directed to a tap test to prognosticate about shunt responsiveness.

Other Parkinsonian syndromes may also be nonresponsive to L-dopa and tap test.

iNPH patients can also be misdiagnosed with AD. Historically, gait disorder is more prominent and noted to be the initial presenting feature in the majority of iNPH cases, whereas cognitive decline is the predominant presenting feature in AD. However, this notion may be in part due to the fact that objective cognitive testing was not historically part of the diagnostic workup of iNPH. Rather, basic mental status screening instruments such as the MMSE were most frequently used. The MMSE is not sensitive to frontal subcortical dysfunction, the pattern of impairment most associated with iNPH. The MoCA [41], also a brief screening measure, includes tasks such as clock drawing and trail making and is more sensitive to declines in frontally mediated cognitive functions as compared to the MMSE. While the MoCA may be preferable for cognitive screening in iNPH given the sensitivity to frontal dysfunction, more extensive neuropsychological examination should be conducted whenever possible. Especially in the early stages of iNPH, screening measures may not be sensitive to the subtle cognitive changes that can be observed. Therefore, it is important to note that reports of normal mental status based on screening measures do not necessarily negate the presence of cognitive deficits that may be detected by more extensive neuropsychological assessment.

Neuroimaging can be helpful in terms of the differential diagnosis of AD versus iNPH. The degree and pattern of ventricular enlargement are key, but the differences are often subtle and are not always interpreted accurately to an untrained eye. Scans revealing ventriculomegaly with cerebral atrophy greater than expected for age are typically interpreted as consistent with AD. In these cases, the ventricular changes are attributed to a secondary consequence of cerebral atrophy. When close inspection of the pattern of ventricular enlargement reveals rounded frontal horns and marked enlargement of the temporal horns and third ventricle, this would suggest the changes are not simply a consequence of atrophy but rather they are consistent with iNPH. In these cases, the degree of ventricular enlargement is out of proportion to the cerebral atrophy. The term *hydrocephalus ex vacuo* is sometimes used to describe ventricular enlargement in association with brain atrophy and can be differentiated from iNPH. Periventricular hyperintensities and elevation of the corpus callosum may also increase suspicion of iNPH on imaging. Neuroimaging will often be repeated over time to aid in diagnosis and to track disease progression or response to treatment; however, the presence or absence of ventricular changes does not always directly correspond to changes in clinical symptoms or deficits on formal testing. Axial MRI images of an iNPH and AD brain are shown in Fig. 36.1.

There are several other conditions with varying etiologies that are common in aging populations that can produce gait changes, bladder symptoms, and cognitive dysfunction. Gait signs and symptoms can be associated with joint disorders such as hip, groin, or knee pain and other conditions (peripheral neuropathy and spinal stenosis), as well as slowing and other gait changes that can be attributable to normal aging. There are a host of etiologies underlying cognitive disorders in the elderly. A frontal systems disturbance can be observed secondary to other neurologic disorders (FTD and vascular disease), psychiatric disorders (depression, bipolar), and a multitude of other causes. Urinary symptoms are also common in older adults and can present with urinary tract infections, diabetes, a variety of bladder conditions, prostate problems in men, and gynecological abnormalities in women. Table 36.1 shows a list of conditions that are often considered in the differential diagnosis of iNPH.

Evidence-Based Diagnostic Criteria

In 2005, a set of evidence-based international guidelines were published to aid in the diagnosis and management of iNPH [42] and were followed

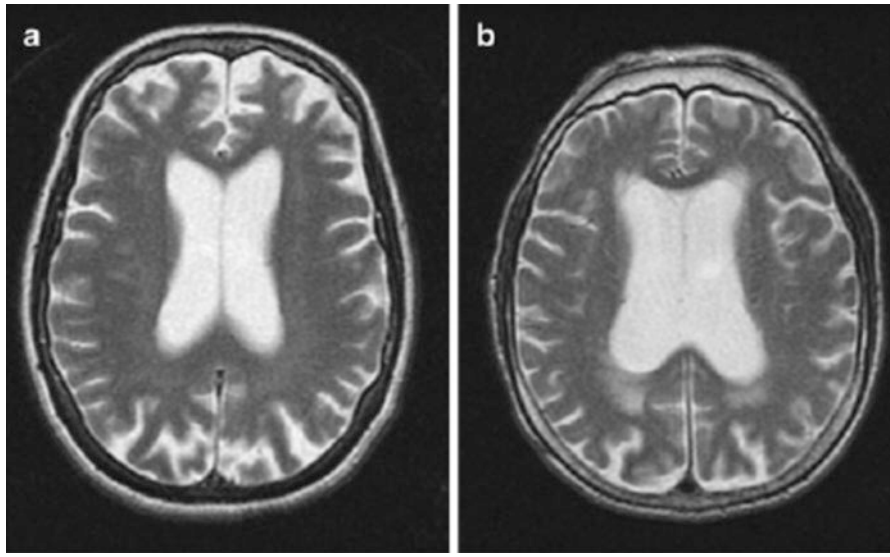


Fig. 36.1 Imaging characteristics in iNPH versus AD. Comparison of AD and iNPH on brain MRI. Axial images show (**a**) ventriculomegaly with significant cortical atrophy in AD and (**b**) ventriculomegaly without significant cortical atrophy in iNPH

Table 36.1 iNPH differential diagnosis

Neurodegenerative disorders	Other conditions
Alzheimer's disease	Spinal stenosis
Parkinson's disease	Noncommunicating hydrocephalus
Vascular dementia	HIV
Dementia with Lewy bodies	Lyme disease
Frontotemporal dementia	B_{12} deficiency
Spongiform encephalopathy	Collagen vascular disorders
Corticobasal degeneration	Neurosyphilis
Multisystem atrophy	Bladder spasticity
Progressive supranuclear palsy	Osteoarthritis

by Japanese guidelines, which were updated in 2012 [43].

The international guidelines recommend the classification of iNPH into "probable," "possible," and "unlikely" cases based on data gathered from clinical history, neuroimaging, physical exam, and physiological criteria (see Table 36.2).

Probable iNPH

A diagnosis of "probable" iNPH requires a history of gait disturbance and at least one of the other symptoms in the classic triad (cognitive or urinary). Also required is an insidious onset after the age of 40 years, a suggestion of progression over time, a minimum duration of 3–6 months, no antecedent event, and no evidence of another medical, neurologic, or psychiatric condition that could fully explain the symptoms. Of note, the Japanese guidelines require onset after age 60 and do not stipulate that gait disturbance must be present for diagnosis of iNPH, but rather, that more than one of the symptoms in the clinical triad is present.

There must also be brain imaging (CT or MRI) performed after the onset of symptoms that indicates ventricular enlargement not entirely explained by cerebral atrophy or congenital enlargement. This can be quantified by an Evan's index of 0.3 or greater [44, 45] or some other equivalent measurement of the ratio of ventricular size to cranial diameter. No evidence of macroscopic obstruction to CSF

Table 36.2 Idiopathic normal pressure hydrocephalus classification: probable, possible, and unlikely categories

Probable iNPH	Possible iNPH	Unlikely iNPH
I. *Clinical findings must include*:	I. *Clinical findings include*:	
a. Gait/balance disturbance consistent with NPH b. Symptoms in at least one other domain (cognition, control of urination) c. Insidious onset (versus acute) after 40 years of age d. Minimum symptom duration of 3–6 months e. Evidence suggesting progression of symptoms over time f. No antecedent neurologic, psychiatric, or general medical conditions sufficient to explain in the presentation	a. Symptoms of either: 1. Incontinence and/or cognitive impairment in the absence of an observable gait/balance disturbance 2. Gait disturbance or dementia alone b. Reported symptoms may: 1. Have subacute or indeterminate mode of onset 2. Be nonprogressive or not clearly progressive 3. Begin at any age after childhood 4. Have <3 months or unknown duration 5. Follow *remote* events that in the judgment of the clinician are not likely to be causally related (e.g., mild head trauma, history of intracerebral hemorrhage, childhood/adolescent meningitis, or other conditions) 6. Coexist with other neurologic, psychiatric, or general medical disorders but in the judgment of the clinician not entirely explained by these conditions	a. No evidence of ventriculomegaly b. Signs of increased intracranial pressure such as papilledema c. No component of the clinical triad of iNPH is present d. Symptoms fully explained by other causes (e.g., spinal stenosis)
II. *Brain imaging* (*CT or MRI*) *must show*:	II. *Brain imaging* (*CT or MRI*) must show ventricular enlargement consistent with hydrocephalus but can be associated with:	
a. Enlargement of the ventricular system not entirely attributable to cerebral atrophy or congenital enlargement b. No macroscopic obstruction to CSF flow c. At least one of the following supportive features: 1. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampal atrophy 2. Callosal angle >40° 3. Evidence of altered brain water content, including periventricular signal changes (CT/MRI) not attributable to microvascular ischemic changes or demyelination 4. An aqueductal or fourth ventricular flow void on MRI	a. Evidence of cerebral atrophy sufficient to potentially explain ventricular size b. Structural lesions that may influence ventricular size	
III. *Physiological*: CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H_2O)	III. *Physiological*: Opening pressure measurement not available or pressure outside range required for probable iNPH	

Details regarding specific gait, cognitive, and urinary symptoms necessary for diagnosis are reviewed elsewhere [36]
iNPH idiopathic normal pressure hydrocephalus, *CT* computed tomography, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *SPECT* single-photon emission computed tomography

flow should be observed. In addition, either enlargement of the temporal horns of the lateral ventricles not fully accounted for by hippocampal atrophy, callosal angle of 40° or more, evidence of altered brain water content not attributable to microvascular ischemia or demyelination, or an aqueductal or fourth ventricular flow void on MRI must be observable

on brain imaging. The Japanese guidelines also include an unusually enlarged Sylvian fissure and basal cistern and narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) as neuroimaging features suggestive of iNPH.

The clinical examination must confirm the history criteria above including the presence of gait/balance disturbance as well as impairment in either cognition or urinary function. Gait and balance disturbance requires the presence of at least two of nine possible characteristics, including (1) decreased step height, (2) decreased step length, (3) decreased walking speed, (4) increased trunk sway during walking, (5) widened standing base, (6) toes turned outward on walking, (7) retropulsion, (8) turning requiring three or more steps for 180°, and (9) impaired walking balance. If cognitive symptoms are present, they must not be attributed to another condition. The criteria specifically state that there must be a documented impairment in performance on a cognitive screening instrument or evidence of deficits in at least two cognitive domains (e.g., psychomotor functioning, fine motor speed, fine motor accuracy, attention, memory, executive functions, or behavioral/personality). To document symptoms in the domain of urinary continence, patients must have either (1) episodic or persistent urinary incontinence not attributable to primary urological disorders, (2) persistent urinary incontinence or urinary and fecal incontinence, or (3) two of the following: urinary urgency (frequent perception of a pressing need to void), urinary frequency (more than six voiding episodes in an average 12-h period despite normal fluid intake), or nocturia (the need to urinate more than two times in an average night).

In addition to the above requirements, a diagnosis of "probable" iNPH requires a CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H_2O) as determined by a lumbar puncture or a comparable procedure. Pressures that are significantly higher or lower than this range are not consistent with a "probable" iNPH diagnosis. In comparison, the Japanese guidelines specify CSF of ≤200 mm H_2O and normal CSF content as suggestive of iNPH.

Possible iNPH

The criteria required for a diagnosis of "possible" iNPH are somewhat less rigorous. The history may indicate a subacute or indeterminate mode of onset, symptoms may be nonprogressive, duration may be less than 3 months, and symptoms may begin at any age after childhood. Also, as long as an antecedent event is not judged by the clinician to be causally related to the onset, mild head trauma, remote history of intracerebral hemorrhage, childhood and adolescent meningitis, or other condition may be present. Further, a comorbid neurologic, psychiatric, or medical condition does not prohibit the iNPH "possible" diagnosis, as long as it is not thought to entirely explain the presentation. The brain imaging must demonstrate ventricular enlargement consistent with hydrocephalus but can show evidence of cerebral atrophy or structural lesions that may influence ventricular size. Clinical findings may include gait disturbance or dementia alone or incontinence and cognitive impairment without gait disturbance. CSF opening pressure may be unavailable or can be outside the defined range (5–18 mm Hg or 70–245 mm H_2O).

Unlikely iNPH

An improbable or "unlikely" iNPH diagnosis is simply defined by a presentation in which there is (1) no evidence of ventriculomegaly, (2) no signs of increased intracranial pressure such as papilledema, (3) no component of the clinical triad, and (4) symptoms explained by other causes (e.g., spinal stenosis).

Clinical Evaluation

Routine clinical evaluation for iNPH includes clinical history and neurologic examination, bedside assessment of mental status, gait evaluation, and structural brain imaging. Without additional procedures, research indicates a 46–61% response rate to surgical treatment [46]. Consensus guidelines [42] also recommend lumbar puncture, CSF

drainage, and outflow resistance studies, as well as neuropsychological testing. While functional brain imaging, urodynamic studies, video or computerized gait evaluation, and other laboratory investigations may provide additional information in some case, these were deemed as lacking sufficient evidence to include as part of the iNPH consensus criteria [42].

CSF tap test is not required according to the consensus criteria but is recommended as a diagnostic tool by both the international and Japanese guidelines. In fact, CSF drainage remains the most widely used test to prognosticate shunt responsiveness. The procedure, also called a large volume lumbar puncture, involves removal of approximately 50 cc of CSF. Measuring gait and cognitive function 24 h after CSF tap test in those with suspicion of iNPH, one group recently found a significant increase in gait speed and improved performance on cognitive tests measuring attention, executive functioning, and callosal transfer (Color Trails Test Index, Digit-Symbol Coding, Backward Digit Span, Stroop, and a verbal dichotic listening task) [47]. Improvement in clinical symptoms following a tap test is associated with an increased likelihood of a positive surgical outcome; however, this technique has also been found to have a high false-negative rate [48–50]. While the standard of care has typically been for the clinician to make subjective observations of the patient's gait and mental function following tap test, these methods have inherent bias. More objective detailed clinical assessment should be performed both before tap test and about 2–4 h after CSF removal to evaluate change. The pre- and posttap assessment should include standardized gait and cognitive assessment. In the event of equivocal results, a repeat test or referral for another type of CSF drainage procedure may be helpful. Given the high false-negative rate, lack of tap test response does not completely rule out a diagnosis of iNPH nor does it preclude shunt responsiveness [42]. In our experience, conducting pre- and posttap assessment on the same day increases the high false-negative rates, as patients are exceptionally fatigued by the time the post-procedure test is conducted. We recommend doing the pretap cognitive exam on another day in close proximity to the scheduled tap test.

External lumbar drainage (ELD) is a more prolonged CSF drainage procedure in which larger volumes of fluid are removed, typically over several days. CSF is typically drained at a rate of 10 cc/h through a catheter placed temporarily in the lumbar region. ELD has been shown to have good prognostic value with a sensitivity of 50–100%, specificity of 60–100%, and positive predictive value of 80–100% [46]. If there is a strong suspicion of iNPH and the tap test is negative or equivocal, the ELD procedure may be considered. Until recently, ELD had only been performed at a limited number of sites in the USA, yet a growing number of clinical research settings have implemented it as part of the standard presurgical workup. It is important to note that this procedure requires hospitalization and can be associated with complications such as infection or nerve root irritation, and the clinical decision of whether or not to conduct ELD should be considered on case-by-case basis. As with a tap test, detailed assessment of gait, cognition, and urinary symptoms should be performed to objectively assess response. The postdrainage neuropsychological evaluation and standardized gait assessment are key factors in determining response. The neuropsychologist plays an integral role in these evaluations by providing objective data regarding changes in performance.

Treatment Response

Response following shunt placement for iNPH varies dramatically, with reported improvement rates ranging from 30% to 96% [51]. While treatment response rates for iNPH are traditionally thought to be lower than in secondary forms of hydrocephalus, a recent study found that this can be explained primarily by the fact that iNPH patients frequently have comorbid disease. With favorable preconditions (e.g., low comorbidity), iNPH patients were shown to have an approximately 80% chance of good outcome, even among patients with advanced age [52].

While the insertion of a shunt is a relatively minor neurosurgical procedure, morbidity rates have been reported to be approximately 30% [53]. Major complications have been reported to occur in about 10%, and minor complications occur in approximately 14% of patients [54]. Common complications include intracerebral hemorrhage, subdural effusions, subdural hematomas, infection, shunt malfunction, over drainage, and hypotensive headaches.

Although all three symptoms in the clinical triad can show dramatic improvement following treatment, a substantial number of patients show incomplete resolution of one or more of the symptoms. In general, gait is reported to be the earliest and most frequent symptom to improve. Research has suggested that both a greater severity and duration of symptoms prior to intervention and the existence of comorbid disease are factors associated with poorer outcome [55]. Also, there is agreement that if left untreated or inadequately managed, iNPH often progresses to a severe state of impairment and dependency, resulting in markedly compromised mobility as well as a full-blown dementia. While all three symptoms in the clinical triad are not required for a diagnosis, several studies have shown that the presence of the complete triad is associated with better outcome following treatment [56, 57].

There has been great variability in the literature regarding recovery of cognitive functions. Some studies report no change in mental status, while others suggest improvement in up to 90% of patients. Conflicting findings may be explained by variations in the depth of cognitive examination and the way in which cognitive improvement is defined, as well as the length of study follow-up intervals. Several studies have documented improvement in overall mental status using screening measures, but there is less agreement about whether specific cognitive deficits may respond differentially to treatment [1, 12, 58]. It has been shown that patients with overt dementia exhibit clear gains in mental status following surgery, whereas patients with more subtle impairment in executive skills tend to show less striking improvement [12, 17]. Others have suggested that the more severe impairments, particularly those patients who exhibit verbal memory and visuoconstructive impairments, may be more likely to be refractory to treatment. One study found patients who showed pre-shunt impairment in immediate verbal recall and copy of a complex figure were six times less likely to exhibit overall cognitive improvement after shunt placement relative to those less impaired prior to shunting [59]. In our experience, even patients with subtle cognitive compromise show objective improvement in cognitive functioning and report an overall sense of improved cognitive efficiency. In severely impaired patients that are basically untestable before surgery, there are sometimes changes in affect and in the ability to participate in basic aspects of the evaluation that provide qualitative evidence of improvement.

Another methodological issue that contributes to our limited understanding about the recovery of specific cognitive functions in iNPH is that most investigations lack a control group, making it difficult to disentangle practice effects from a true treatment effect. One recent study used comparison data from two age- and education-matched control samples (one disease control sample diagnosed with probable AD and another consisting of healthy controls) and found 1-year post-shunt improvement on the Trail Making Test A and the Frontal Assessment Battery, which is a brief battery of six tasks designed to assess executive function; however, effects of prior exposure to test material could not be examined since the controls were only tested at one time point [60]. We recently evaluated 12 iNPH patients and 9 controls with comprehensive neuropsychological testing at baseline and at 6-month follow-up [61]. The iNPH group showed greater improvement than controls on a timed test of mental tracking and sequencing (Trail Making Test B). iNPH caregivers also reported improved activities of daily living (ADLs) and reduced caregiver distress, suggesting functional and quality of life improvements for both the shunt responder and their caregiver. Similarly, others have found health-related quality of life improvements 6-month post-shunt surgery to the level of age-matched controls [62].

Neuropsychological Assessment

A neuropsychologist may encounter iNPH in the context of a diagnostic evaluation, follow-up assessment to track changes over time, an examination to help establish response to intervention (tap test, ELD, shunt), or for research purposes. Detailed cognitive testing is recommended, particularly in patients with more subtle abnormalities, since screening measures and bedside testing may not pick up mild deficits. Mental status screening tests have poor sensitivity to the subcortical pattern of cognitive dysfunction typically observed in iNPH [63]. Repeat neuropsychological assessment is useful in monitoring disease progression and response to treatment or may be used to help identify shunt malfunction. Fatigue, both physical and mental, can contribute to reduced performance, and we have found that obtaining the patient's best performance is most readily accomplished when conducting the exam in two sessions.

Taking the Clinical History

Cognitive difficulties, including deficits in insight and/or memory, may interfere with a patient's ability to provide a complete and accurate history. It is therefore critical for the clinician to gather history and background information from a collateral source. A well-informed caregiver or third party who is knowledgeable about the patient's premorbid and current level of functioning should be interviewed.

In order to understand the disease presentation and course, one should ascertain whether the onset of symptoms was acute or insidious and whether the symptoms have been static or progressive and the severity of deficits and degree with which they impact everyday functioning. Since iNPH does not have a known antecedent cause by definition, inquiries regarding potential precipitating factors should be made to rule out SNPH. Although familial occurrence of iNPH is rare, other heritable conditions should be ruled out. Family history questions should focus on neurodegenerative disorders such as PD, AD, Huntington's disease, and other neurologic conditions that are often considered in the differential diagnosis. Falls are common, and questions about gait changes should also inquire about head injuries or loss of consciousness that may have occurred during those events. Detailed questions about subtle bladder symptoms need to be addressed with particular attention to frequency and urgency as well as frank incontinence. Personal and family psychiatric histories should also be reviewed since behavioral symptoms can sometimes appear or be exacerbated in iNPH. As always, a standard review of past medical and surgical history is also an important part of the evaluation.

Selection of Neuropsychological Measures

Recent updates to National Institute of Health research priorities included the need for development of valid and reliable neuropsychological assessments and adaptive behavior assessments for hydrocephalus that are appropriate for patients with various cultural backgrounds [64]. As always, selection of tests will vary based on the nature of the referral and the patient's presentation. Most initial referrals are for diagnostic purposes or for characterization of the extent of cognitive impairment. In these cases, a relatively comprehensive battery should be employed that mirrors that of a typical memory disorders evaluation, especially since comorbid conditions may need to be ruled out. When more specific referral questions, such as assessing potential response to intervention (tap test, ELD, shunt), are at hand, a more selective battery can be implemented. A sample neuropsychological battery for use in NPH is listed in Table 36.3. This is a core group of tests that we have found to be sensitive to changes in NPH and that we use in our NPH research program.

Not surprisingly, many of the traditional neuropsychological measures of higher cortical functions are unchanged in the posttap session or immediately following surgery, but measures of processing and motor speed often show

improvements. We have found that measures of upper extremity motor speed can be helpful in determining response to tap test [74], particularly since there are many cases where lower extremity motor functioning is severely compromised and cannot be formally assessed with standard gait scales (i.e., the patient is unable to ambulate without assistance). The recommended battery for assessing change pre- to post-CSF drainage (tap test or ELD) is heavily weighted toward motor and psychomotor tests in order to maximize the ability to realize small gains over the short term. Many of these tests are standardized measures that are regularly used in neuropsychological clinics. Two less well-known measures that we have incorporated into our battery that have not been well standardized, but provide excellent qualitative data, are the Line Tracing Test and the Serial Dotting Test [75]. Relative to healthy controls, we have found those with iNPH require more time to complete the Serial Dotting Test and are more prone to make errors on this test than the Line Tracing Test [76]. These two psychomotor speed and precision tests shown in Fig. 36.2 have also been demonstrated to be sensitive to change in NPH [77].

Table 36.3 Core battery for repeat assessment in iNPH

Global cognitive measures (i.e., MoCA [41], Dementia Rating Scale [65], or 3MS [66])
Boston Naming Test [67]
Controlled Oral Word Association [68]
Hopkins Verbal Learning Test—Revised [69]
Wechsler Adult Intelligence Scale IV [70] (Digit Span)
Trail Making Test A and B [71]
Symbol Digit Modalities Test [72]
Grooved Pegboard Test [71]
Finger Tapping Test [71]
Line Tracing Test [73]
Serial Dotting Test [73]
Gait Scale [1] (videotaping of gait is helpful)
ICIQ-Urinary Incontinence-Short Form (ICIQ-UI-SF) [9]
Overactive Bladder Questionnaire-Short Form (OAB-q SF) [10]

We have found that to minimize fatigue and to optimize performance, the pretap evaluation should be done on a day prior to the day of the spinal tap, preferably 1 or 2 days before and always within 1 week if possible. The posttap assessment should always be done on the same day as the spinal tap. Although there is limited

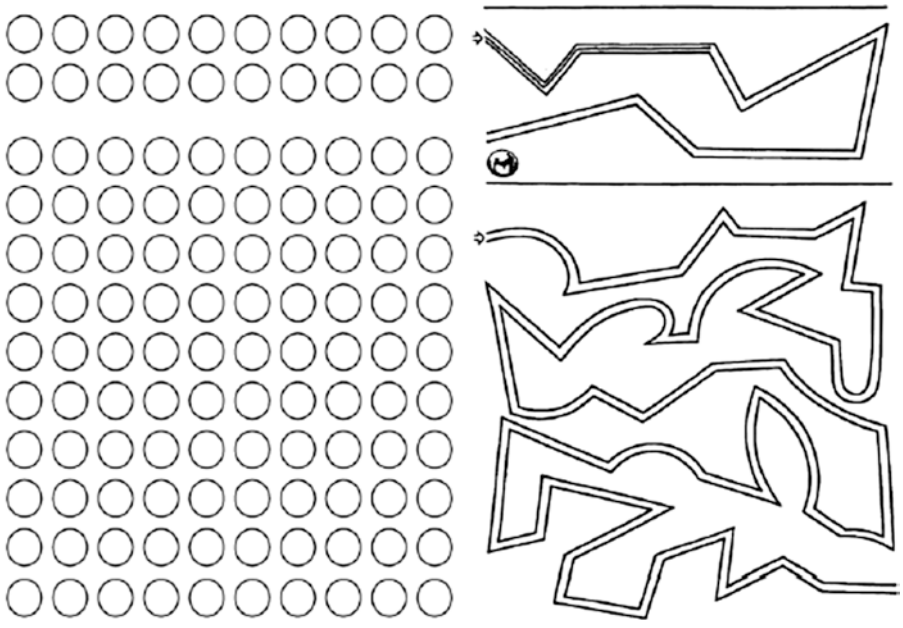


Fig. 36.2 Line tracing and serial dotting

data regarding the optimal time for measuring posttap performance, and there are likely great individual differences in the response peak, the majority of experts suggest conducting the post-tap assessment between 2 and 4 h after the removal of spinal fluid [77]. Not uncommonly, family members report improved gait and sometimes improved attentiveness within 24 h after the tap test. We recommend routinely contacting patients the day after the tap to obtain this type of qualitative data. Post-shunt evaluations can also be useful to evaluate response to treatment and in some cases help determine whether there may be a shunt malfunction. For example, if a patient that initially demonstrated a clear response post-shunt developed a reemergence of symptoms, neuropsychological assessment may be helpful in documenting the nature and severity of the change to provide evidence of a possible shunt obstruction or other type of shunt malfunction. Repeated assessments post-shunt can be useful in documenting recovery of function, as illustrated in the case example provided below.

Management of iNPH is accomplished with a multidisciplinary approach to patient care. The neuropsychologist is a key member of the team and can play an important role in the diagnostic process, prognosticating about candidacy for treatment and monitoring recovery of function. A case example that demonstrates neuropsychological assessment of recovery of function post-shunt is presented below.

Case Example: Recovery of Function Following Shunt

A brief summary is provided for Mr. X, an 82-year-old right-handed gentleman who underwent a series of neuropsychological assessments before and after shunt placement (baseline and follow-up post-shunt exams at 2, 5, and 8 months). The patient initially presented with severe gait disturbance, moderate cognitive decline, and mild urinary symptoms of approximately 1-year duration with a reportedly progressive course. Neuroimaging reportedly revealed prominent ventriculomegaly out of proportion to cerebral atrophy. The patient was diagnosed with iNPH and underwent shunt placement.

At the time of diagnosis, Mr. X enrolled in a clinical research protocol, which included baseline and post-shunt neuropsychological and gait evaluations. A brief summary of his performance on select measures administered as part of the research protocol is provided below.

Baseline Results

The pattern of baseline cognitive test scores reflected significant decline from premorbid functioning, which was estimated to be in the high average range. Mr. X demonstrated borderline to impaired performance on two global cognitive screening measures (3MS = 82/100; DRS total = 118/144). Detailed neuropsychological testing revealed impairments in memory, semantic fluency, executive functions, visuospatial abilities, processing speed, and motor skills (dominant > nondominant). Attention, confrontation naming, and phonemic fluency were intact. Overall, the observed pattern of performance revealed moderate frontal subcortical dysfunction, and this was interpreted as consistent with iNPH.

Follow-Up Results

Comparison of baseline and post-shunt evaluations suggested considerable improvement in cognition as evidenced by significant gains on a global scale of cognitive functioning (see Fig. 36.3). Several measures of motor speed and dexterity, rapid motor processing, and mental tracking demonstrated moderate improvement over time (see Fig. 36.4). Moderate improvement was also observed on verbal fluency and memory by the 8-month follow-up exam (see Fig. 36.5). Dramatic improvement in gait was observed clinically as well as documented on a standardized gait scale (see Fig. 36.6). At baseline, Mr. X walked 10 m in 20.5 s and 23 steps. At the final

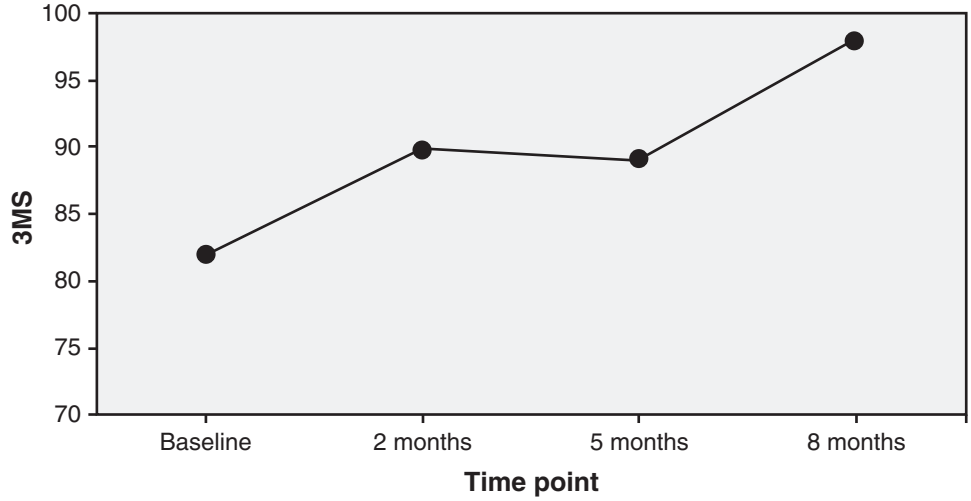
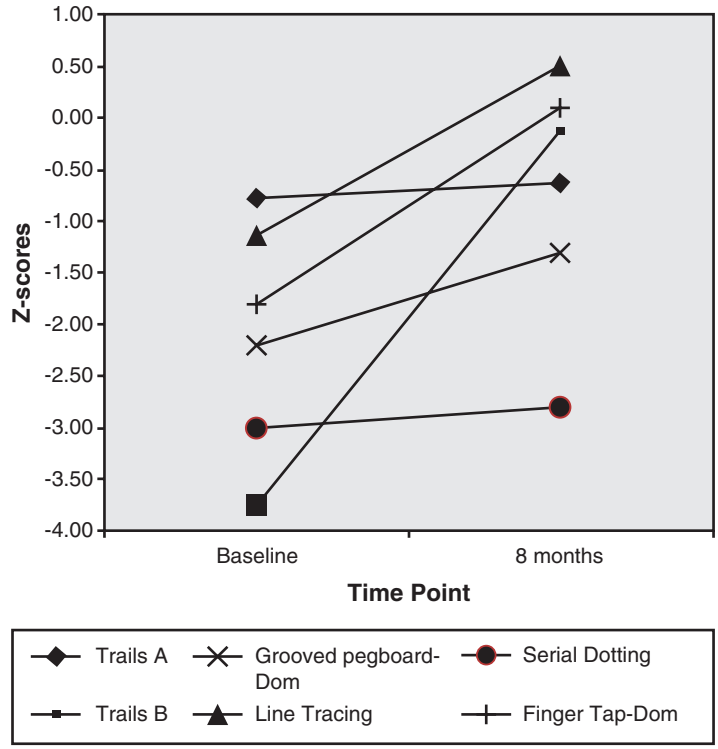


Fig. 36.3 Case example of post-shunt change in Modified Mini-Mental Exam (3MS)

Fig. 36.4 Case example of post-shunt change in motor and psychomotor tests



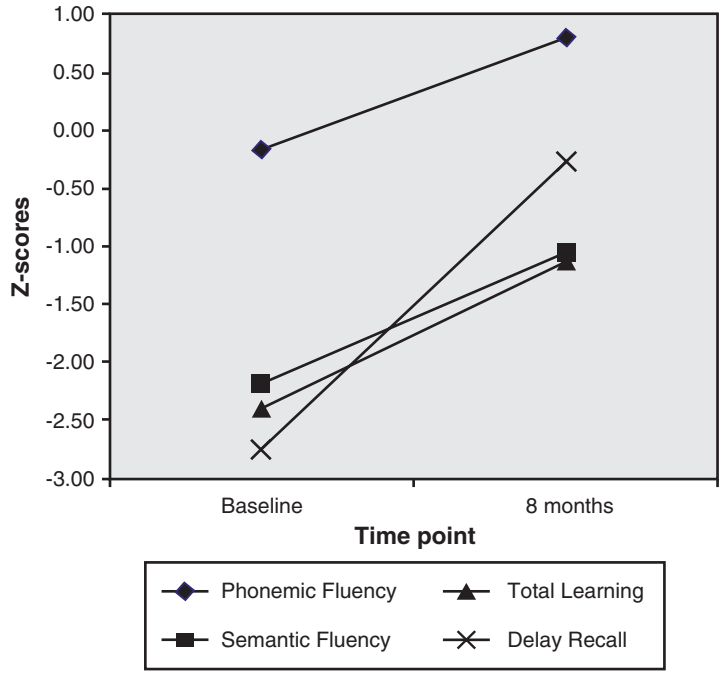


Fig. 36.5 Case example of post-shunt change in fluency and memory tests

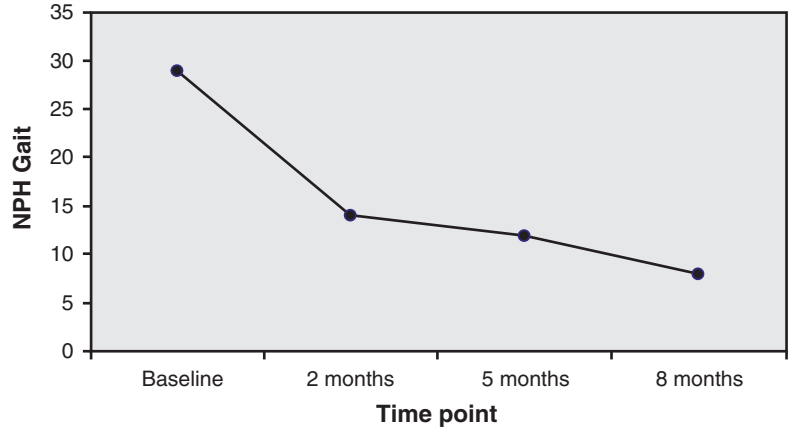


Fig. 36.6 Case example of post-shunt change in NPH Gait Scale. *Note*: Higher scores indicate greater impairment

follow-up visit 8 months postsurgery, Mr. X walked 10 m in 10 s and 9 steps, a clinically significant improvement. Not all cognitive measures reflected improvement; deficits persisted on some tasks of psychomotor speed, and relative weaknesses (low average performance) were evident on measures of motor dexterity, semantic fluency, and learning. Consistent with anecdotal reports and information from the literature, the earliest and most prominent gains post-shunt were changes in gait, with improvements in cognition evolving over the extended recovery period.

Clinical Pearls

- Comorbidity is common in iNPH but does not preclude shunt candidacy or response.
- Post-shunt improvements in gait can lead to increased independence in activities of daily

living as well as improved quality of life, even if cognition remains compromised. Increased mobility reduces the burden of physical management for the caregiver.

- Many iNPH patients can execute correct walking movements in a recumbent or supine position, potentially differentiating the gait dysfunction of iNPH from other movement disorders.
- When inquiring about urinary symptoms, ask about urgency and frequency, since not all patients have frank incontinence.
- Despite reports of intact cognition as assessed by bedside mental status testing, many patients with iNPH exhibit frontal systems dysfunction on detailed neuropsychological testing.
- The gold standard for gait assessment in iNPH is typically a neurologist's subjective assessment of gait; the neuropsychologist can bring a unique set of skills that provide objective measures of response.
- In cases where gait is severely compromised or postdrainage changes are subtle, tests which rely on the integrity of upper extremity motor functioning can provide additional data to inform management.
- Consistent with the literature demonstrating a high false-negative rate for tap tests, we have seen iNPH patients with negative tap test respond to shunt.
- ELD can be superior to tap test for prognosticating about shunt responsiveness, but it may not be appropriate for all patients, and it is only performed at specialty centers.

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Episodic and Semantic Memory Disorders

37

Russell M. Bauer, Leslie Gaynor, Charles Moreno, and Taylor Kuhn

It has been nearly five decades since the famous patient H.M., who represents a paradigmatic case of the human amnesic syndrome, was first described in the literature. In its most pure form, the human amnesic syndrome involves a disabling impairment in new learning accompanied by some degree of impairment in aspects of remote memory in the context of relatively normal intellectual ability, language, and attention span. The hallmark feature, *anterograde amnesia*, involves "recent" memory; the essential feature of the deficit is that the patient is impaired in the conscious, deliberate recall of information initially learned after illness onset. In cases where remote memory is impaired (*retrograde amnesia*), the deficit is often temporally graded or time-limited and is generally worse for memories acquired in recent time periods than it is for memories acquired in the very remote past.

Neuropsychological research has clearly shown that lesions within the brain's extended memory system (medial temporal lobe, diencephalon, and basal forebrain) produce anterograde amnesia while leaving other aspects of memory (retrieval of general knowledge, vocabulary, names) relatively intact. This chapter focuses on one way of characterizing this difference, the distinction between "episodic" and "semantic" memory, and discusses the clinical features and assessment of disordered function in each of these two domains. A list of disorders producing primary impairments in episodic or semantic memory is provided in Table 37.1.

The Episodic–Semantic Distinction

The episodic–semantic distinction has historical roots dating back to William James [1]. Hebb's [2] proposed distinction between short-term and long-term memory, along with ubiquitous evidence from neuropsychological investigations of brain-damaged patients, gave rise to a variety of two-component models of memory, each attempting to characterize spared versus impaired memory function in amnesia. In 1972, Tulving [3] first distinguished between two memory systems ("episodic" and "semantic" memory). Although these two systems differ in content (episodic memory has come to be synonymous with memory for specific events and their context, while semantic memory involves general knowledge), the core difference involves the subjective experience of remembering associated with each system. Episodic memories are accompanied by

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Table 37.1 Diseases and problems producing disorders of episodic and semantic memory

Disorders of episodic memory	Disorders of semantic memory
Alzheimer's disease (early)	Alzheimer's disease (mid/late)
Amnesic mild cognitive impairment	Semantic dementia
Stroke (PCA, thalamic perforators)	Herpes simplex encephalitis
Aneurysm rupture/repair (ACoA)	Neurosyphilis
Cerebral anoxia	Stroke (MCA, PCA, cortical)
Wernicke–Korsakoff syndrome	Focal retrograde amnesia
Herpes simplex and HSV-6 encephalitis	Dissociative (psychogenic) amnesia
Autoimmune limbic encephalitis	
Traumatic brain injury	
Transient global amnesia (TGA)	
Electroconvulsive therapy (ECT)	
Dissociative (psychogenic) amnesia	

an experience of autobiographical remembering (in Tulving's terms, self-knowing or "autonoetic"), while semantic memories lack this quality and are accompanied by a feeling of "knowing" rather than "remembering." However, some semantic information, although retrieved without autonoetic experience, may refer to autobiographic content, as in personal semantic information that has been extracted from one's life experiences (e.g., "I like football," or "I'm a bicycle enthusiast"), suggesting that episodic and semantic memory can interact in forming higher-order concepts about the self [4]. Over time, the episodic–semantic distinction has been useful in explaining key characteristics of the human amnesic syndrome.

Spared Function in Amnesia

Many authors have argued that selective impairment of episodic, but not semantic, memory accounts for the finding that amnesic patients retain substantial intellectual, linguistic, and social skill despite profound impairments in the ability to recall specific information encountered in prior learning episodes [5–7].

Retrograde Amnesia

The episodic–semantic distinction may explain temporally graded retrograde amnesia [5]. Cermak suggested that as biographical material ages, it becomes progressively more semantic. Through retelling, it becomes less tied to specific recollective episodes and increasingly incorporated into one's personal/family history or "folklore." More recent memories are less likely to have been retold or elaborated beyond their original form and thus may retain more of a distinct episodic quality. If amnesia reflects a selective impairment in episodic memory, then memories from more remote time periods would be relatively more semantic and relatively spared as a result of this process.

Anatomy of Memory

The episodic–semantic distinction is broadly consistent with anatomic facts. Lesions to the brain's extended memory system (hippocampus/medial temporal lobe, diencephalon, and basal forebrain) predominantly produce episodic memory impairment, while cortical lesions to anterior temporal and parietal cortices tend to produce semantic memory impairments [8]. This distinction is further elucidated within a contemporary clinico-anatomic model of human memory called "multiple trace theory" (MTT; [9]) that is reminiscent of Cermak's [5] ideas. MTT posits that as long as memories retain their episodic quality (e.g., autobiographical mode of recollection, context dependency, sensory–perceptual vividness), they remain hippocampus dependent. Each time an episodic memory is retrieved, it is contextually re-encoded within the hippocampus and by dynamic networks of activation involving the hippocampus and cortical processing areas. Activation of these networks leads to formation

of multiple traces in a network that becomes increasingly distributed with each recollective episode. As a result, older episodic memories (i.e., those that have been retrieved numerous times in different contexts) are more widely distributed within the MTL than are recent ones, and different structures/regions within the MTL come to make their own contribution. Moreover, as the distributed network widens via multiple encodings, it eventually can become independent of the hippocampus and supported solely by neocortex. These memories lose their context dependency or autobiographic quality over time to the extent to which they have been retrieved in multiple contexts. By this process, some episodic memory can gradually become "semantic" in quality. Thus, semantic memory results at least in part from gradual transfer of memory from hippocampus-dependent networks to cortical ones.

Although it is tempting to regard anterograde amnesia as "episodic" and retrograde amnesia/remote memory disturbance as "semantic," evidence supports the view that both episodic and semantic memories can exist within each of these compartments. With respect to amnesia, MTT predicts that MTL damage will result in impairment of both recent and remote episodic memories, with more extensive damage leading to more extensive impairment. Although early studies with amnesic patients such as H.M. reportedly found largely intact remote memory, recent reevaluations support the existence of more extensive retrograde amnesia than previously thought [10].

Double Dissociation Between Episodic and Semantic Memory

If the episodic–semantic distinction reflects a general principle of brain organization, then these domains of memory should show double dissociation in cases of focal brain disease. While data described above provide ample evidence that episodic memory can be impaired in the absence of a deficit in semantic memory [3], what about the opposite? There have been several case reports demonstrating impaired semantic retrieval in the absence of a deficit in episodic/autobiographical retrieval [11–13]. Several well-described cases of focal retrograde amnesia (i.e., disproportionately impaired retrograde memory with relatively spared anterograde memory) have also contributed to our understanding of the relationship between episodic and semantic memory [14–20]. In some cases [19], a distinction within remote memory has been found in which the patient is impaired in retrieval of general knowledge but unimpaired in retrieval of remote autobiographical events. Damage to the anterior temporal cortex is involved in most cases of focal retrograde amnesia, and damage to limbic–diencephalic structures contributes to impairment in remote "autobiographical" memory. However, not all cases of focal retrograde amnesia are clearly suggestive of an episodic–semantic distinction, since careful analysis of the memory loss in some cases reveals equivalent impairments in remote autobiographical memory and factual knowledge [21]. Finally, there is also ample evidence that a developmental impairment in episodic memory does not preclude the acquisition of factual knowledge or language competence during development [22]. The acquisition of semantic knowledge is largely independent from episodic memory processes and takes place through spared cortical regions subjacent to the hippocampi [22].

Although dissociations have been reported, amnesics can have both episodic and semantic impairments [23–27]. For example, Cermak et al. [24] found that Korsakoff patients had difficulty generating words from "conceptual" semantic memory ("name a fruit that is red"). Butters and colleagues [23] similarly found Korsakoff amnesics to be deficient on a verbal fluency task.

A fundamental problem is that episodic and semantic memories are not easily dissociable behaviorally [25] and may in some circumstances involve activation of the same or similar structures in functional imaging studies [28]. One confound is that they interact in complex ways (e.g., episodic learning can have a stimulating effect on semantic search rate [29]).

As indicated earlier, multiple trace theory provides a contemporary reformulation of the

episodic–semantic memory distinction within a functional–anatomic account of the activity of the medial temporal lobe memory system. From the perspective of multiple memory systems accounts of spared and impaired function, MTT offers a promising way to conceptualize episodic and semantic memory as points on a processing continuum. Of equal importance, it provides a neurobiologically realistic model of memory dissociations that accounts for a large amount of clinical and research data.

Disorders of Episodic Memory

Clinical Features

The primary clinical features of episodic memory disorders have already been described and involve impairment in new learning (anterograde amnesia) and at least some degree of remote memory loss (retrograde amnesia). Depending upon etiology, remote memory loss can be worse for more recent time periods, confined to a specific time period or nonspecific [8]. As mentioned earlier, the classic amnesic syndrome is most commonly accompanied by relative sparing of intellectual and attentional ability, language, and other performance domains that rely on established knowledge. Memory function that is not dependent on conscious, explicit recollection (i.e., implicit memory) is also relatively spared.

Etiology

Serious episodic memory loss is a common problem in clinical neuropsychological evaluations and has considerable localizing significance. It is also a helpful diagnostic finding since it is a distinguishing feature of several neurological disorders. Episodic memory disorders impair functional capacity along a spectrum of severity, with only the most severe types qualifying as "amnesic." Below, we review some of the more important disorders.

Mild Cognitive Impairment

The concept of *mild cognitive impairment* (MCI) was introduced to describe a syndrome in older adults with memory complaints in the context of mild memory deficits that do not compromise everyday function, who have relatively normal (compensated) instrumental activities of daily living (ADLs), and no dementia [30, 31]. Subtypes of MCI are widely recognized, including amnestic (primarily involving memory) and nonamnestic (primarily involving a non-memory cognitive area) forms, each of which can involve one (single domain) or more than one (multidomain) area of impairment [30]. The primary importance of the MCI concept relates to its role as a possible prodromal stage of dementia. Longitudinal studies indicate that approximately 10–15% of patients with MCI convert to Alzheimer's disease each year, compared to overall conversion rates of 1–2% in cognitively normal elders [32]. Behavioral markers and concurrent presence of entorhinal and hippocampal atrophy appear to most strongly predict eventual conversion [33]. It is important to note that MCI encompasses both objective evidence and subjective report of age-related memory impairment that often relies on the report of a person familiar with the patient's functioning. Many objectively normal adults may complain of memory loss, particularly if they are in intellectually demanding positions. The isolated presence of a memory complaint without objective evidence may indicate the presence of depression or adjustment difficulties that are themselves worthy of independent clinical attention. By the same token, depression, anxiety, and other neuropsychiatric symptoms that may give rise to a subjective memory complaint are quite common in MCI [34]. However, it is also possible that early memory complaints seen as "subjective" may be indicative of the early presence of Alzheimer's disease pathology in the trans-entorhinal cortex, which is the first site of cortical neurofibrillary tangle aggregation in the early stages of Alzheimer's disease [35, 36]. This early pathology may result in a clinical syndrome known as

pre-MCI, which results in a significantly higher rate of progression to MCI or dementia than cognitively normal older adults [37].

Degenerative Disorders

Many degenerative dementias such as Pick's, Huntington's, and Parkinson's disease eventually affect memory, but Alzheimer's disease (AD) manifests with an episodic memory impairment in the initial stages [38]. Nearly all of the neural systems thought to be important in memory are affected by AD, including the medial temporal lobe [39–41], basal forebrain [42], thalamus [43], and neocortex. Recent evidence suggests that dysfunction in temporal/limbic–frontal connectivity via the uncinated fasciculus is strongly associated with the appearance of episodic memory dysfunction in prodromal AD [44]. Although Alzheimer's disease primarily affects episodic memory first, it may also affect some aspects of semantic memory such as verbal fluency [45]. Eventually, semantic memory is more severely affected, as are other cognitive domains including language, visuoperceptual ability, and executive function. While the memory deficit seen in AD and other cortical dementias primarily involves episodic memory, significant loss of semantic memory can be seen in a variant of frontotemporal dementia, so-called semantic dementia [46, 47]. Thus, the memory loss found in AD and frontotemporal dementia is not as "pure" as in other forms of amnesia and takes place in the context of broader cognitive decline. Semantic dementia is discussed more fully below.

Effects of Anticholinergic Medication

Many commonly used medications have significant central anticholinergic actions, including antihistamines commonly used in nonprescription sleep and allergy medications, some antidepressants, and medications used to manage urinary frequency and incontinence. These drugs are often used in cognitively healthy older adults and may result in impairments in episodic memory performance and an increased risk of progression to dementia [48]. Anticholinergic drugs can impair memory [49], and withdrawal of these medications in patients with memory deficits may result in dramatic improvement in memory [50].

Vascular Disease

Stroke can produce amnesia when critical areas are infarcted. Strokes affecting the posterior cerebral artery territory (posterior medial temporal lobe and retrosplenial cortex) [51]) and the thalamic penetrating arteries [52] have been implicated, as has basal forebrain amnesia from anterior communicating artery aneurysm hemorrhage or surgery [53]. Infarction of the fornix with or without basal forebrain lesions can also present with isolated amnesia [54, 55]. In vascular cases, the onset of amnesia is abrupt. Improvement is variable, and patients may be left with serious permanent deficits, even following small infarctions.

Cerebral Anoxia

Depending upon the degree and duration of ischemia or hypoxia, neuronal loss may be widespread or very focal. Neurons in specific regions of the hippocampus, such as CA1 and CA4, are sensitive to oxygen loss and thus are more likely to experience neuronal damage following a hypoxic event [56]. Hippocampal neuronal death is often followed by memory impairment. Amnesia has been reported following cardiac arrest in which the only pathological feature identified was loss of neurons in field CA1 of the hippocampus [57]. Significant impairment in episodic memory has been reported in samples of children who experienced extreme hypoxic or anoxic events and subsequent reduced hippocampal volume due to transposition of the great arteries [58], acute respiratory failure [59], and sickle-cell disease [60]. Problems and issues in characterizing the extent of damage from anoxic or ischemic insults have received some attention [61].

Wernicke–Korsakoff Syndrome

Alcoholic Korsakoff syndrome most frequently develops after years of alcohol abuse and nutritional deficiency [62–64] but can also result from chronic avitaminosis secondary to malabsorption syndromes [65] or in patients who refuse to eat in the context of a psychiatric disorder [66]. Patients first undergo an acute stage of the illness, Wernicke's encephalopathy, in which symptoms of confusion, disorientation, oculomotor dysfunction, and ataxia are present. After this resolves, amnesia can persist as a permanent symptom. Severe anterograde amnesia and an extensive, temporally graded retrograde amnesia are characteristic features. Neuropathological damage affects the thalamus (mediodorsal and anterior nuclei) and the mammillary bodies [67]. Since these structures are part of larger limbic circuits, it is not surprising that the anterograde amnesia in Wernicke–Korsakoff syndrome may also result from white matter damage that results in disconnection of the diencephalon and medial temporal lobe [68]. Substantial deficits in memory encoding, coupled with signs of frontal executive and visuospatial dysfunction, are common.

Herpes Simplex and HSV-6 Encephalitis

Herpes simplex causes inflammation and necrosis, particularly in the orbitofrontal and inferior temporal regions. It thus involves limbic structures, including the hippocampus, parahippocampal gyrus, amygdala and overlying cortex, polar limbic cortex, cingulate gyrus, and orbitofrontal cortex [38]. Patients may present with personality change, confusion, headache, fever, and seizures and are often amnesic. Prompt treatment with antiviral agents can control the illness, and full recovery is possible. However, damage to the aforementioned structures often leaves the patient with severe anterograde and retrograde amnesia. The amnesic syndromes in patient D.R.B. (also known as Boswell; [69]) and patient S.S [70, 71]. have been particularly well characterized. Herpes simplex infection can occasionally lead to a syndrome of focal retrograde amnesia that is described more completely below [14, 72, 73]. Human herpes virus-6 (HHV-6) also can target the limbic system and present with amnesic syndromes, confusion, sleep disorders, and seizures [74]. Hokkanen and Launes [75] review other infectious agents that can leave residual neuropsychological sequelae, including memory loss.

Autoimmune Limbic Encephalitis

This condition usually presents with personality change, agitation, and amnesic symptoms. It was first described as a paraneoplastic syndrome [76–79], but it can also occur in patients without neoplasm [80]. Over the past decade, several autoantibodies have been associated with different forms of limbic encephalitis (see [81, 82]). Neuronal antibodies (Hu, Ma2, CV2/CRMP5, amphiphysin, and atypical intracellular antibodies) in patients with various neoplasms (small cell and non-small cell lung cancer, testicular tumors, thymomas, and others) have been associated with an inflammatory disorder affecting neurons throughout the neuraxis but often with particular intensity in limbic structures including the hippocampus. Although the pathogenesis is autoimmune, response to immunotherapy is usually poor. However, patients with Ma-2 antibodies in association with testicular cancers often improve after surgery. Patients with antibodies to voltage-gated potassium channels (VGKC), sometimes associated with thymoma or small cell lung cancer, but more often without known neoplasm, can have a more selective limbic encephalitis that often responds to immunotherapy with steroids, IVIG, or plasma exchange [80]. A syndrome of amnesia, psychosis, seizures, and central hypoventilation progressing to coma has been attributed to antibodies that react with NMDA receptors [83], and this syndrome may respond dramatically to immunotherapy.

Although first described in association with neoplasms, only 60% of a large series had cancer [84], and the same syndrome has now been reported in children, many without neoplasms [85]. Similar autoantibodies have been identified in patients with epilepsy and systemic lupus [86].

Trauma

Following closed head injury, patients may have an acute anterograde and retrograde amnesia, the duration of which correlates with the severity of the injury as measured by the Glasgow Coma Scale or the duration of unconsciousness [87]. The duration of posttraumatic amnesia (memory for ongoing events after trauma) is a good predictor of long-term functional outcome [88–90]. The retrograde amnesia typically improves along with improvement in anterograde amnesia, providing evidence that a retrieval deficit is responsible for the portion of the retrograde memory loss that recovers. Residual memory impairment is usually a feature of broader cognitive and attentional impairment, but it can be prominent with severe injuries [91, 92]. Pathological changes are variable and widespread. Memory dysfunction may be caused by anterior temporal lobe contusions, temporal lobe white matter necrosis, or diffuse axonal disruption [87, 93]. Cases of focal retrograde amnesia in the relative absence of a new learning defect have been reported after closed head trauma [16, 17]. Episodic memory impairment and other cognitive and neuropsychiatric changes are also reportedly typical to the clinical presentation of a subset of individuals with chronic traumatic encephalopathy, otherwise known as CTE [94], though no prospective neuropsychological studies of pathologically verified CTE cases during life have been reported. CTE is a tauopathy that seems to be associated with activities carrying a high risk of repetitive head impacts/injury, such as American football, soccer, boxing, ice hockey, and wrestling [95]. The prevalence of CTE in athletes is still unknown, and there are significant gaps in our understanding of neuropsychological features of CTE [96].

Transient Global Amnesia

This distinctive form of amnesia begins suddenly and usually resolves within a day [97–100]. A severe impairment in new learning and patchy loss of information learned prior to onset is seen. The patient often asks repetitive questions and may be aware of the memory deficit. After resolution, neuropsychological testing is usually normal except for amnesia for the episode [100]. Although the etiology of transient global amnesia (TGA) is unclear, epilepsy [101, 102], emotional stress [103], occlusive cerebrovascular disease [104, 105], migrainous vasospasm [106–108], head trauma [109], vertebrobasilar dyscontrol [97], and venous insufficiency [110] have all been mentioned as possibilities. There are many reports of small diffusion-weighted imaging (DWI) abnormalities in CA1 of the hippocampus in patients with TGA within the first 48 h [111–114]; these lesions typically are transient [115, 116] and are more likely to be evident after 24–48 h of symptom onset (and hence, after symptomatic resolution in the majority of patients). The striking predilection of these punctate lesions for the lateral hippocampus leaves little doubt as to their relevance to the clinical findings; however, their pathogenesis remains enigmatic. Disrupted functional connectivity between the hippocampus and other medial temporal lobe structures has been identified in the hyperacute phase of the amnesia and may also contribute to episodic memory impairment [117]. Although the DWI characteristics are suggestive of ischemia, patients with TGA do not appear to be at greater risk for cerebrovascular disease than controls [98, 118]. Epileptic TGA [119–121] usually has a shorter duration, is more likely to recur, and may be associated with EEG abnormalities.

Electroconvulsive Therapy

Used for relief of depression, electroconvulsive therapy (ECT) can produce rapidly recovering anterograde and temporally limited retrograde amnesia [122–124]. More severe impairment is

seen after bilateral versus unilateral application. The anterograde defect is related in severity to the number of treatments and is characterized by rapid forgetting and poor delayed recall [125]. Substantial, often complete, recovery takes place in the few months after treatment ends [123, 126–129]. The retrograde amnesia appears to be temporally limited, involving only the few years prior to treatment onset. It, too, recovers almost completely in the months after treatment. Though the data is by no means clear, some authors have suggested that ECT-induced memory loss models bilateral temporal lobe disease [125]. New studies also suggest that ECT can be used to purposefully induce memory loss for reactivated emotional episodic memories in patients with depression [130].

Dissociative (Psychogenic) Amnesias

Psychologically induced loss of memory may be normal, as in amnesia for events of childhood [131–133] or for events during sleep [134]. Alternatively, they may be pathological, as in the amnesias associated with dissociative states, with multiple personality, or with simulated amnesia [135–137]. A striking loss of personal autobiographical memory is a hallmark of functional amnesia, and amnesia for one's own name (in the absence of aphasia or severe cognitive dysfunction in other spheres) is seen exclusively in this form of memory loss. Retrograde loss is often disproportionate to anterograde amnesia, and some patients will demonstrate loss of skills or other procedural memories typically retained by organic amnesic patients. Some studies have reported disproportionate loss of "personal" as opposed to "public" information in the retrograde compartment [138], a fact that is discussed in terms of the episodic–semantic distinction by Reinhold and Markowitsch [139]. Good general reviews are provided by Kihlstrom and Schacter [140] and Stanilou and Markowitsch [141].

Disorders of Semantic Memory

Clinical Features

In contrast to the patient with episodic memory impairment, the patient with semantic memory loss finds it difficult to retrieve and use previously stored factual, linguistic, or perceptual knowledge. The impairment may affect the comprehension or production of words, concepts, facts, semantic relationships, and general knowledge. Episodic memory, though not entirely normal, is relatively spared, and the patient typically has no great disability in learning and retrieving knowledge of ongoing day-to-day events. A closer look at the pattern of disruption over time reveals that the loss of semantic knowledge initially affects the ability to retrieve specific exemplars within broad categories and the patient may be capable eventually of identifying only typical items that show high family resemblance of their parent category. The disorder affects naming, language comprehension, expressive and receptive vocabulary, and fact retrieval. Behavioral changes coincident with semantic loss may occur and may include withdrawal, a reduction in interests, or the development of new preferences for food or activity [142], but these are not typically predominant features or reasons for referral.

Although disorders of semantic memory are typically nonspecific (i.e., do not differentially affect specific semantic categories), several well-described cases of category-specific semantic deficits have left little doubt that selective loss of semantic memory exists. Warrington and Shallice [143] reported four cases of category-specific semantic loss for living versus nonliving things after partial recovery from herpes simplex encephalitis. Since Warrington and Shallice's initial demonstration, a large literature has accumulated showing that *selective impairment of living things* is most common [144]. Substantial literature has examined the implications of category specificity for understanding the organization of semantic memory. While these cases are most consistent

with a categorical, meaning-based organization of the memory store, other data either indicate that category specificity can be accommodated within a modality-specific semantic network affecting visually based category distinctions [145] or which outright favor a more interactive, modality-specific view [146]. Category specificity is relatively rare (fewer than 150 reported cases exist) and is most common after herpes simplex encephalitis. It is not commonly seen in degenerative conditions that produce semantic memory impairments, including Alzheimer's disease [147] and semantic dementia [148].

Etiology

Semantic memory impairments are seen in a variety of disease states, with the most common causes being degenerative disease (semantic dementia variant of frontotemporal dementia, mid-stage Alzheimer's disease) or a post-acute outcome of CNS infection (herpes simplex encephalitis; HSVE). These diseases affect semantic memory differently, and each presents with a unique neuropsychological profile and associated comorbidities. However, all of these diseases are associated with relatively intact somatosensory and motor abilities, procedural memory, verbal abilities, and visuospatial skills. As such, knowledge of the disease course, outcome, neurologic and neuropsychological profile, and treatment are all necessary in order to successfully complete a differential diagnosis and provide effective medical care to affected patients. All three of these diseases affect the neural substrates that mediate semantic memory, primarily the temporal cortex. Both lateral and medial structures of the temporal lobe that are involved in the encoding, consolidation, and retrieval of semantic information can be affected. The semantic memory impairment seen in these conditions is briefly reviewed below.

Structural pathology in semantic memory impairments varies depending on the neurodegenerative disorder. For example, the clinical syndrome of frontotemporal dementia (FTD), a heterogeneous neurodegenerative disorder, is useful in elucidating the patterns of atrophy that correspond with the behavioral and language disturbances associated with the syndromes. Although neuroimaging studies suggest frontal and temporal lobe atrophy as a key feature in patients with FTD, other cortical areas such as the insula and cingulate, as well as subcortical structures such as the basal ganglia and thalamus, are associated [149]. In semantic dementia (SD), the anterior and inferior regions of the temporal lobe are consistently affected [150, 151].

Semantic Dementia

Semantic dementia (SD) is one of the three prominent subtypes of FTD (progressive nonfluent aphasia and behavioral variant are the others), which results from frontotemporal lobar degeneration. Patients with SD may present with word-finding difficulties, aphasia, anomia, visual associative agnosia, or impaired understanding of semantic words and images. Pathologically, most patients have ubiquitin-positive, tau-negative inclusion bodies, though some may have pathology consistent with Pick's disease or Alzheimer's disease [142, 152].

The most prominent early feature in semantic dementia is the reduction of expressive vocabulary, commonly described as a "loss of memory for words" [153, 154]. Episodic memory problems may also be present but are typically mild in comparison [155]. Receptive vocabulary also deteriorates, though changes may be subtle initially. As the disease progresses, spontaneous speech becomes increasingly anomic, with word-finding pauses and substitution of more generic words (e.g., "thing") for specific lexical items [142]. Many patients with SD also have defective *person knowledge*, manifested in impairments in naming people, generating information about them from their names or faces, and, in severe cases, recognizing the identity of faces or determining whether they are familiar. SD is associated with other cognitive deficits including drawing from memory, object decision, lexical decision, verb morphology, and surface dysgraphia and dyslexia [121, 156].

Alzheimer's Disease (Later Stages)

AD begins focally in the trans-entorhinal cortex of the temporal lobe, affecting the hippocampus early in the disease. As the disease progresses, pathological features move in a posterior and lateral fashion to affect the lateral temporal lobe, basal forebrain, thalamus, and neocortex of the parietal and frontal lobes, ultimately affecting virtually all areas thought to be important for memory. Because of increasing cortical involvement later in the disease, a broad spectrum of neuropsychological deficits may eventually emerge. In the later stages of the disease, executive function, language, and even postural stability and gait may be affected.

Semantic memory impairment in AD may be reflected in reduced receptive vocabulary and reduced ability to retrieve and understand words [157]. The impairment is greater for more recently acquired words than for words learned earlier in life [158], which has been postulated to result from the richer semantic embeddedness of earlier-acquired words [159, 160]. A recent study suggested that this effect was related to the degree of involvement in the left anterior temporal neocortex as measured by voxel-based morphometry [161].

How does the semantic impairment in AD compare to that of SD? A recent longitudinal study by Xie et al. [162] showed that while SD and AD patients were not different early in the disease, the semantic impairment in SD eventually outstripped that seen in AD later on. In this study, the SD patients performed more poorly than AD on semantic memory at all time points, whereas measures of episodic memory, initially worse in AD, eventually converged as the diseases progressed. A recent study suggested that SD patients performed more poorly than AD patients on word sorting and naming tests from the Cambridge Semantic Memory Test (CMST), though the overall test was not able to differentiate the groups [45]. Particularly, in early stages of the disease, substantial overlap in deficits might exist. However, it is reasonable to postulate that episodic memory impairments typically exceed semantic memory impairments in early AD, while the reverse is true of SD. Tests of other functions (e.g., visuospatial function) differentially affected in AD versus SD might prove useful in differential diagnosis. The Adlam et al. [45] study suggests that despite some semantic memory impairment in AD [163, 164] and episodic memory difficulties in SD [165], the two groups can be differentiated when measures of the two types of memory are combined with measures of visuospatial ability.

Herpes Simplex Encephalitis (HSE)

HSE is an acute inflammation and necrosis of the brain resulting from a herpes simplex virus-1 strain infection of the limbic structures, including the hippocampus, parahippocampal gyrus amygdala and overlying cortex, polar limbic cortex, cingulate gyrus, and orbitofrontal cortex. HSE often presents acutely with fever, personality changes, confusion, seizures, hemiparesis, and headaches. In the post-acute period, HSE is associated with a range of neuropsychological impairments owing to the typically bilateral, though sometimes asymmetrical, medial, and lateral temporal lobe involvement. Remote memory is typically impaired with a "flat" temporal gradient [166]. Episodic and semantic memory can both be profoundly impaired, including the ability to retrieve remote autobiographical information [73]. Classic amnesic syndromes after HSE have been reported by McCarthy and Warrington [167] and Cermak [70, 71].

Some HSE cases suffer a more restricted impairment of semantic memory, often in the form of a category-specific deficit. Most commonly reported are patients who have selective impairment in accessing information pertaining to "living things" [168], though the opposite has been found and methodological issues in defining "category specificity" may be useful for the clinician to consider [169]. The fact that category specificity is seen more commonly after HSE (which predominantly affects anteromedial temporal cortex) than it is in SD (which involves more anterolateral temporal cortex) is intriguing. Noppeney et al. [170] suggest that the medial

temporal cortex may represent semantic categories that are more interrelated (in their words, "tightly packed") in semantic space, while the lateral temporal cortex might play a more general semantic role.

Transient Epileptic Amnesia

TEA is a type of temporal lobe epilepsy that is associated with remote memory impairment [171, 172]. Remote memory is defined as memories encoded over 1 year in the past that has episodic and semantic components [21]. Focal retrograde amnesia is defined as the inability to recall memories in the past (retrograde amnesia), while the ability to learn and retain new information is spared (anterograde amnesia), in other words, retrograde amnesia without anterograde amnesia [173]. Although the performance on standard tests of anterograde memory was normal in some patients with TEA, they were impaired in memory for autobiographical events across the lifespan providing evidence for focal retrograde amnesia [174]. However, the structural pathology is unclear. While hippocampal volume was not associated with indices of autobiographical memory in group of patients with TEA, a single-case study revealed neuronal loss and gliosis in the right and the left hippocampus and was more evident in anterior than posterior hippocampus [175].

Other Etiologies

Other forms of brain disease can produce semantic memory deficits (e.g., neurosyphilis, stroke), usually in the context of other impairments that correlate with the site of damage. Capitani et al. [176] found that 12 of 18 patients with left posterior cerebral artery stroke involving the fusiform gyrus displayed semantically based naming deficits and 5 showed distinct category specificity. Half of the left PCA patients showed additional deficits in verbal semantic knowledge. Unlike the majority of HSE cases, who showed differential impairments for animals, some of the left PCA patients showed distinct impairments in naming plants, with relative sparing of animals. Other cases are the result of trauma affecting orbitofrontal and anterolateral temporal regions or reflect comorbid symptoms of serious neurologic disturbances (e.g., brain tumor). In general, the clinician should be aware of the fact that most patients with significant semantic memory impairments have (typically bilateral) damage to the lateral anterior temporal lobe or temporoparietal association cortex and should clinically evaluate semantic memory with appropriate tests in any patient who has damage within these regions.

Clinical Examination

Preexamination interview of the patient suspected of having semantic memory impairment is critical and offers insight into the broad cognitive domain in which impairment is suspected. Critical data include age, mode of onset (acute vs. insidious), progression of cognitive decline, duration, and degree of impairment in activities of daily living. The onset of the impairment should be clearly determined along with its course (remitting, stable, or progressive). An insidious onset suggests a dementia such as AD or SD–FTD. An acute onset suggests an infectious, vascular, or traumatic origin. HSE can occur at any time point across the adult lifespan, whereas dementia typically begins primarily after the age of 40. Within the degenerative disorders, a younger age of onset has been associated with SD which has a mean age of onset of 59 or FTD which has a mean age of onset of 63 [177]. Although there are exceptions, AD tends to onset later. The mean age of onset of AD is 68, with early onset defined as that which begins prior to the age of 60 and late onset that which begins after 65 years of age [178]. Acute onset of febrile illness followed by more chronic semantic memory impairment should suggest an infectious process such as HSE. Conversely, gradual, progressive impairment of semantic memory most likely signals a neurodegenerative process. HSE can remit and often does so in a pattern of alternative remission and relapse. HSE can be

effectively treated, and when treated, survival is assured in the significant majority of cases. However, survivors can be left with a range of impairments from complete recovery to mild impairment from restricted impairment of language or memory to severe dementia [179]. In terms of independent activities of daily living (IADLs), patients with AD will be initially impaired by episodic memory failure, while those with SD or HSE may lose the ability to follow customary routines or to understand key concepts such as finances. The pattern of loss should be ascertained during the clinical interview and should inform test selection during the neuropsychological examination.

While a fixed battery of tests is attractive due to broad applicability to research databases and to ease of comparison with existing norms and already evaluated patient populations, it is not common to include comprehensive tests of semantic memory in standard neuropsychological batteries. In the patient suspected of semantic memory impairment, a well-validated battery of tests, the Cambridge Semantic Memory Test (CSMT) Battery, can be used to parse semantic from autobiographical memory impairment and can determine whether the impairment is modality or category specific. Good normative data exists. However, while the CSMT is useful for evaluation of the type and nature of semantic memory deficits, it is not sufficiently sensitive to differentiate advanced AD from SD [45]. Additionally, research has shown that the Four Mountains Test, a compilation of a topographical perception task with a topographical short-term memory task and a nonspatial perception and related short-term memory task, is a sensitive measure than can be used to distinguish AD from FTD [180]. These authors showed that patients with AD and amnesic MCI were impaired on the topographical short-term memory task but not on perception when compared to the FTD participants. While the non-topographical task revealed no group differences, this data suggests that short-term memory for topographical information can be impaired in AD, regardless of stage of disease, and is therefore a sensitive diagnostic measure.

The neuropsychologist should be aware that differential diagnosis depends critically on the relative patterning of semantic memory deficits compared to other aspects of the performance profile. SD will tend to exhibit semantic language impairments and executive dysfunction early in the disease in the context of intact visuospatial skills and relatively intact episodic memory. By the time AD patients exhibit disabling semantic memory impairments, their episodic memory problems will be quite significant, but they may show relatively preserved language and visuospatial skills and varying executive function that declines as a function of disease progression. HSE-related semantic memory deficits more commonly are category specific, such that selection of standard neuropsychological tests may be insufficient to disclose their deficit. Standardized tests of semantic memory are critical in evaluating these patients. HSE affects executive functioning while leaving language and visuospatial skills primarily intact.

Regardless of the preferred type of battery, special considerations and techniques should be employed when assessing potential semantic memory deficits. “Testing the limits” should be employed when working with patients who do not perform the tasks in the allotted time but who are capable of completing the tasks given enough time. Since speed of memory retrieval is often a sign of a degraded semantic memory system, relaxing time constraints allows the clinician to investigate the boundaries of a patient’s capability. Although many other factors are involved, improvement with relaxation of time constraints suggests some deficit in semantic access, while lack of improvement may indicate a loss of semantic representations.

SD is the primary cause of semantic language impairment in FTD. Language should be fully assessed to rule out other forms of FTD (e.g., behavioral variant, progressive nonfluent aphasia). The concomitant, equal impairment of production *and* comprehension may distinguish SD from progressive nonfluent aphasia. Standardized aphasia batteries (Western Aphasia Battery, Boston Diagnostic Aphasia Examination) provide

an overview of performance that can be supplemented by individual tests of naming (Boston Naming Test), auditory comprehension (Token Test), semantic processing (Pyramids and Palm Trees, a subtest of the Cambridge Semantic Memory Test), grammar and syntax (Test for Recognition of Grammar), repetition (Western Aphasia Battery), fluency (Controlled Oral Word Association, DKEFS Fluency), and tests of writing and reading. SD patients have been shown to exhibit more significant impairment on the Boston Naming Test than either FTD or AD patients [181]. The COWA is particularly useful, as research suggests that temporal lobe-damaged patients and AD patients perform worse on semantic fluency measures (e.g., fruits/vegetables) than on letter fluency (e.g., S). Patients with frontal lobe disease tend to perform worse on letter fluency than on semantic fluency, due to the increased demand on strategic retrieval processes [182]. However, this discrepancy was observed only when fruits and the letter S were used. No group differences were observed when animals and the letter F were compared. This finding illustrates the necessity of a broad assessment of language so that such potential confounds may be more fully understood.

In cases where remote memory/knowledge is affected, the assessment should be sufficiently thorough to enable an understanding of the type of memory impaired (autobiographical vs. semantic), time of memory impaired (remote vs. retrograde vs. anterograde amnesia), and whether or not the memory deficit is context specific. First, it must be established that the memory impairment is one of semantic memory rather than autobiographical memory. This can be achieved by using such batteries as the Wechsler Memory Scale (WMS-IV) that are composed of measures designed to assess the full range of memory domains. Additional standardized measures of episodic memory include the Hopkins Verbal Learning Test, the California Verbal Learning Test-II, the Rey Complex Figure, the Continuous Visual Memory Test, and the Brief Visual Memory Test-Revised. Focused measures which assess either autobiographical or semantic memory are available as well. For remote autobiographical memory, the Crovitz task ("describe an event from your past that involved a 'flag'"), the Autobiographical Memory Interview [183], or Squire's TV Test [184] may be useful, though clinicians are cautioned about the lack of precise normative data. General tests of vocabulary (WAIS-IV) are useful, as are tests of factual event knowledge that require patients to identify famous faces (Famous Faces Task; Presidents Test) or to show knowledge of well-known public events from different decades that were not part of their personal life experience (Boston Remote Memory Battery). By assessing the patient's ability to recognize and recall information that is not bound to their own life-event memory, these tasks measure deficits in semantic memory. While semantic memory can be impaired in AD and SD, episodic, autobiographical knowledge is an early sign of AD. Both episodic and semantic memories can be impaired in varying extents in HSE. Semantic memory impairments that are not language bound in terms of either perception or production and are also not context specific are more likely the result of AD. Both FTD and AD have been shown to be impaired on verbal memory tasks; AD may be more likely to display visual memory deficits [181]. HSE and focal stroke are the most likely disorders to produce a category-specific semantic memory impairment, and the clinician should, if necessary, develop in-house tests to informally assess for this possibility if more extensive, standardized tests of semantic memory are unavailable.

Assessing executive function can be useful for further differentiating SD–FTD from AD. Common measures include the Wisconsin Card Sort Test (WCST), the Delis–Kaplan Executive Function System, the Category Test, the Stroop Color Word Test, and measures of motor organization and inhibition (Luria's contrasting programs, Go-No-Go, recursive figures and serial hand sequences). Ideally, executive functioning should be assessed as part of any neuropsychological evaluation and is important in the investigation of semantic memory impairment. As executive function is primarily mediated by

frontal lobe structures, and SD is a subset of frontal lobar degeneration, executive dysfunction is common in SD patients. However, this does not necessarily distinguish SD from AD or HSE, since some executive dysfunction should be expected in association with all etiologies we have discussed, particularly in later disease stages. HSE often presents with comorbid personality changes and alterations in consciousness, and later-stage AD frequently involves personality changes, disinhibition, emotional lability, and apathy.

Other Neurodiagnostic Considerations

In most cases, neuropsychologists who are asked to evaluate patients with episodic and semantic memory disorders will function within an interdisciplinary team that includes specialty physicians (neurologists, psychiatrists, neurosurgeons). It is obvious that the neurobehavioral workup of these patients should supplement available neurodiagnostic information from the neurologic and physical exam, laboratory studies, and neuroradiologic investigations. Neuroimaging data suggest that both SD and HSE involve pathological changes in similar, though not identical, regions. HSE often results in bilateral anterior temporal damage extending into the amygdala and may include gray matter atrophy in the medial structures of the anterior temporal lobe and the insula. These medial structures are relatively spared in SD; atrophy is more commonly observed in the lateral temporal cortex, either unilaterally or bilaterally. The hallmark of early onset AD is focal hippocampal atrophy that is often readily apparent on MRI. Finally, genetic testing can add informative but not definitive data to a diagnostic profile. Carriers of the apolipoprotein E ε4 allele (*APOE* ε4) have been found to be at increased risk for developing AD; the *APOE* ε2 allele has been suggested to serve a protective effect against the development of AD. Simply having an *APOE* ε4 allele does not denote future development of AD, but this information can be added to a preponderance of evidence during a dementia consensus debate. Parallel developments in the genetics and neurohistochemistry of frontotemporal dementia are beginning to elucidate specific genetic and immunohistochemical markers that might be useful in the differential diagnosis of SD and other FTD variants [185].

As has been demonstrated, there are numerous etiologies of acquired and degenerative semantic memory impairment, each with a unique disease onset, course, and neuropsychological profile, and numerous tools to measure and evaluate these deficits. Thorough understanding and implementation of appropriate measures, as well as educated and concise interaction between health-care providers, are essential for the proper evaluation, diagnosis, and treatment of amnesic syndromes.

Clinical Pearls

- Evaluation of patients with suspected episodic or semantic memory disorders should always include the participation of a collateral informant who can verify the patient's report, which may appear accurate to the naïve examiner.
- Examination of the patient with episodic memory impairment should be capable of separating encoding, retention, and retrieval processes through the use of multiple tests.
- Virtually any neurologic disorder above the cervical vertebrae can affect episodic memory function; diagnosis typically relies on interdisciplinary evaluation.
- Although the commonly used neuropsychological tests are capable of screening for aspects of semantic memory dysfunction (e.g., vocabulary, fluency measures), systematic evaluation of semantic memory disorders will typically require the use of instruments specifically designed for this purpose (see text).
- Episodic memory is most affected by disease processes affecting the medial temporal lobe, diencephalon, and basal forebrain, while semantic memory is most affected by cortical dysfunction.

Table 37.2 Evaluation of episodic and semantic memory disorders

Domain	Test	Norms	AFP[a]?	Reference
Episodic/recent memory				
Verbal memory	WMS-IV Logical Memory	√	√	Wechsler et al. [186]
	Hopkins Verbal Learning Test-Revised	√	√	Benedict et al. [187]
	California Verbal Learning Test-II	√	√	Delis et al. [188]
	Rey Auditory Verbal Learning Test	√	√	Schmidt [189]
Nonverbal memory	WMS-IV Visual Reproduction	√	√	Wechsler et al. [186]
	Rey Complex Figure	√	√	Meyers and Meyers [190]
	Brief Visual Memory Test	√	√	Benedict [191]
	Continuous Visual Memory Test	√	√	Trahan and Larrabee [192]
Prospective memory	Cambridge Test of Prospective Memory	√	√	Wilson et al. [193]
Episodic/remote memory	Crovitz Paradigm			Crovitz and Schiffman [194]
	Autobiographical Memory Interview	+/−	√	Kopelman et al. [183]
	TV Test, Remote events test			Squire and Slater [184]
Semantic memory	Cambridge Semantic Memory Test	√	PPT[b]	Adlam et al. [45]
	WAIS-IV Vocabulary, Information	√	√	Wechsler et al. [195]
Language/semantic processing	Western Aphasia Battery-Revised	√	√	Kertesz [196]
	Boston Diagnostic Aphasia Examination	√	√	Goodglass et al. [197]
	Boston Naming Test	√	√	Kaplan et al. [198]
	Controlled Oral Word Association	√	√	Benton et al. [199]
	DKEFS Fluency	√	√	Delis et al. [200]
	Test for Reception of Grammar	√	√	Bishop [201]
	Reading and Writing Tests			Various available
Executive functioning	Wisconsin Card Sorting Test	√	√	Grant and Berg [202]
	Booklet Category Test	√	√	DeFilippis and McCampbell [203]
	Delis–Kaplan Executive Function System	√	√	Delis et al. [200]
	Stroop Test	√	√	Stroop [204]
	Luria Motor Programming			Luria [205]

[a]Denotes whether test is available for purchase on the commercial market
[b]The Pyramid and Palm Trees Test (a subtest of the CSMT) is commercially available

- Episodic and semantic memories are distinguished primarily as different modes of retrieval; episodic memory has an autobiographical character, while semantic memory does not.
- The clinician should keep in mind that the episodic–semantic memory distinction is not the same as the recent–remote memory distinction. Episodic memories can be quite old and retrieved from the remote compartment, just as new semantic memories are acquired all of the time (Table 37.2).

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Evaluation of Comorbid Epilepsy and Dementia

38

Kelly Coulehan and H. Allison Bender

Introduction

Epilepsy and dementia are both commonly occurring neurological disorders. In fact, these disorders fall in the top four most common neurological illnesses, along with migraine and stroke [1]. Alzheimer's disease (AD) is estimated to occur in over five million people across the USA [2] and epilepsy in just under three million individuals [1]. Overall prevalence rates for dementia more broadly are approximately 1–2% at age 65 years and as high as 30% by age 85 [3]. For example, in individuals over 65 years of age, dementias account for up to 17% of epilepsies seen in the elderly [4]. Similarly, the highest incidence of newly diagnosed epilepsy cases occurs over the age of 65 years [5]. The factors playing into their heightened co-occurrence in this age group are not well known. However, it is known that epilepsy in the elderly often presents differently than epilepsy in younger adults, and that symptoms of dementia can be exacerbated by seizures. Due to the high prevalence rates of epilepsy and dementia, it is important for neuropsychologists to understand the bidirectional relationship between dementia and epilepsy.

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Definition of Epilepsy and Seizures

Seizures can be defined as a strong surge of abnormal electrical activity causing an excessive discharge of neurons. This electrical abnormality results in a variety of clinical semiologies that are also accompanied by changes in electroencephalography (EEG). Common seizure semiologies include motor abnormalities (e.g., automatisms, tonic-clonic movements, head deviation, eye deviation), behavioral arrest, reduced cognitive functions, and/or sensory perceptions (e.g., gastric rising, tingling, ringing, changes in vision, taste, and smell). The underlying neuronal abnormality that causes seizures is not fully understood. However, seizures are most likely the results of 1) abnormal cellular membranes resulting in lowered firing thresholds and/or 2) an imbalance between excitatory and inhibitory neurotransmitters.

Epilepsy is broadly defined as a disorder of the brain characterized by a persistent predisposition to epileptic seizures [6]. More specifically, epilepsy is diagnosed when at least two unprovoked seizures occur more than 24 h apart. An unprovoked seizure is one that has no clear antecedent cause. An epilepsy diagnosis can be given following one unprovoked seizure if the probability of further seizures is similar to the general recurrence risk after two unprovoked seizures (at least 60%) [6].

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Seizures can be characterized in a number of ways. Recently, the International League Against Epilepsy (ILAE) revamped the clinical definitions of seizures. Based on 2017 ILAE criteria [6, 7], there are three broad categories of seizures, which include generalized onset, focal onset, and unknown onset. Generalized onset seizures involve the whole brain at the outset of the seizure and can be further characterized by motor or nonmotor (i.e., absence) features. Focal onset seizures begin in a localized area of the brain and are further subcategorized as focal aware or focal impaired awareness seizures. Both aware and impaired awareness focal seizures can be categorized with a motor onset or a nonmotor onset. Additionally, focal onset seizures can generalize to involve the whole brain; these seizures are referred to as focal to bilateral tonic-clonic seizures. Patients can present with multiple seizure types and seizure types can vary throughout the course of an individual's epilepsy. Epilepsy type is categorized into four groups including focal, generalized, combined generalized and focal, and unknown. The term "pharmacoresponsive," which suggests that seizures are controlled by antiepileptic drugs (AEDs), is now to be used when appropriate.

Epilepsy in Patients with Dementia

Cerebrovascular disease accounts for about one-third of newly diagnosed cases of epilepsy in older adults [8]. Other common etiologies for new-onset epilepsy in elderly populations include: toxic and metabolic causes, dementia, and tumors [4] and, less likely, head injury, neurological infection, or drug interactions [9–11]. That being said, approximately 12% of new-onset seizures in elderly patients are attributed to degenerative disorders [8, 12, 13]. Seizures are most common in the advanced stages of AD [14], but early stage onset is also associated with increased risk of seizures [15–17]. Regardless of when in the disease process seizures occur, patients with dementia, particularly AD, have a five- to ten fold increase in risk of seizures [12]. It is estimated that between 10 and 22% of patients with AD will experience at least one seizure [8, 16, 18, 19]. In individuals with dementia, characteristics associated with the disorder may interact with known etiologies of epilepsy. For example, preexisting dementia increases the risk of poststroke epilepsy, [20] and the use of acetylcholinesterase inhibitors for treatment of AD has the potential to elicit increased neuronal hyperactivity [21, 22].

Individuals with epilepsy are at an increased risk for developing dementia as an older adult. One potential reason for this increased risk is that individuals with chronic epilepsy exhibit medical factors that increase the risk of developing dementia at a higher rate, including cardiovascular disease and increased inflammatory markers [23–25]. Inflammation in epilepsy is commonly attributed to the adverse effects of both seizures and antiepilepsy drugs (AEDs) [26]. In AD, inflammation is thought to contribute to disease progression and severity [27]. As such, the onset of seizures in patients with AD has been associated with a faster progression of disease symptomology and functional impairment [28, 29]. Specifically, epilepsy can result in a worsening of cognitive performance (particularly in language), a reduction in autonomy, a greater risk of injury, and a higher mortality rate among those with dementia [4, 28]. Volicer et al. (1995) found that 82% of dementia patients who suffered an initial seizure showed a sudden worsening of symptoms resulting in long-term care admission within 6 months of the seizure onset. However, such declines can be curbed with prompt, effective AED therapy and increased seizure control [30, 31].

Age is a clear risk factor for the development of both epilepsy and dementia. The incidence and prevalence of epilepsy increase with age throughout adulthood and are highest, approximately 25%, in patients over 65 years [13, 32, 33]. Considering that 5% of people over the age of 65 will develop dementia with incidence rates doubling approximately every 4–5 years [2], there is a very large population of people comorbidly affected by epilepsy and dementia. Comorbidity may be due to the fact that hippocampal sclerosis (i.e., severe neuronal cell loss and gliosis) is common in both disorders [34]. Structural and neurochemical brain changes resulting from chronic epilepsy may negatively impact cognitive function over time, making the brain of a

patient with epilepsy more susceptible to the development of dementia.

Shared Neurobiological Substrates of Seizures and Dementia

The neuropathological processes underlying both seizures and dementia are likely to play a role in the increased comorbidity rates of these disorders. However, the abnormal neurological mechanisms involved in each of these disorders are not fully understood. There is evidence to suggest that neuronal hyperexcitability, amyloid beta protein, and tau are contributing factors to the comorbidity of epilepsy and dementia.

Neuronal hyperexcitability is the primary process underlying seizure occurrence. In dementias, neuronal death that occurs in the context of degenerative disorders may offset the balance of inhibitory and excitatory neuronal functioning through selective loss of inhibitory neurons [35]. This imbalance ultimately leads to hyperexcitability and seizure occurrence. However, mouse models of AD have demonstrated both a decrease *and* an increase of neuronal activity. Interestingly, the increased neuronal activity, or "hyperactive" neurons, was found exclusively near beta-amyloid plaques [36, 37]. In fact, mouse models of AD revealed that high levels of amyloid beta protein are sufficient to elicit epileptiform activity even in early stages of AD and in the absence of overt neuronal loss [38]. Based on these models, there would appear to be an association between seizures and beta-amyloid plaques, a defining feature of dementia. In fact, amyloid beta protein was found to be elevated in surgically resected human temporal lobe tissue from patients with intractable epilepsy [39]. While amyloid beta appears to be a key factor in epilepsy and dementia, the cause for increased levels of amyloid beta remains unknown.

Increased levels of unstable tau protein are also characteristic of dementia and lead to the development of neurofibrillary tangles. Aggregates of tau are also found in patients with epilepsy and in experimental models of epilepsy [40]. Research has demonstrated that tau plays a role in the regulation of network synchronization, i.e., the balance of inhibitory and excitatory neurons. Mouse models have shown that when levels of tau are experimentally decreased, neuronal hyperactivity is decreased, which normalizes the balance between excitatory and inhibitory neuronal activity [41]. A normalization of this balance effectively increased the seizure threshold. However, in AD, where aggregations of tau are increased, a lowered seizure threshold would be expected. Consistent with this hypothesis, it is known that seizures are more common in patients with AD than in the general elderly population [16].

Although amyloid beta and tau appear to be likely contributors to susceptibility of seizures in those with AD, it is probable that there are multiple factors at play. In particular, comorbid vascular lesions, the apolipoprotein E (APOE) ε4 allele, and excessive neuronal cell loss in hippocampal and parietal cortices may also be factors involved in increased seizure occurrence in AD [8, 35, 42]. However, understanding the associations between amyloid beta, tau, and neuronal hyperexcitability lays the groundwork for the development of interventions aimed at these areas of the disease process and provides insight into the comorbidity of epilepsy and dementia.

Diagnostic Decision–Making in Patients with Seizures and Dementia

Epilepsy and dementia share common characteristics of cognitive decline and altered mental status which can mask the presence of the other disorder and lead to misdiagnoses; hence, the incidence of epilepsy in older patients may be two to three times higher than reported throughout the extant literature [5]. In particular, the absence of specific symptoms characteristic of seizures in younger adults may undermine an epilepsy diagnosis [5]. For at least half of all older adult patients who present with a symptom that ultimately was classified as a seizure, epilepsy was not initially considered as a primary differential diagnosis [5]. Rather, older adults with new-onset seizures often present with vague clinical symptoms, which increase the likelihood of misdiagnosis [43]. To illustrate, McBride, Shih, and Hirsch (2002) found that a dif-

ferential diagnosis of epilepsy was not considered in 73% of elderly patients who ultimately were diagnosed with epilepsy. Common initial misdiagnoses include altered mental status, confusion, "blackout spells," memory disturbance, syncope, dizziness, dementia, transient ischemic attack (TIA), depression, metabolic disorders, and/or psychiatric disorders [43–45]. As a result, patients treated with dementia drugs on initial diagnosis may show lack of symptom improvement due to untreated seizures [46]. In addition to the nonspecific presentation of seizure semiology in the elderly, a diagnosis of epilepsy is further complicated among older adults by potential coexisting cognitive impairment, which may lead to an incomplete history, under-reporting of events, a failure to recognize transitory confusional states, and absence of witnesses if patient lives alone [5, 47–49].

The vague clinical presentation of epilepsy in the elderly is quite different than what is typically observed in younger adults. For example, auras are less common and are often nonspecific (e.g., dizziness) and automatisms are less frequent [43]. Postictal states are frequently more prolonged in older adults, particularly if there is underlying brain dysfunction [50]. Postictal confusion may last as long as 1–2 weeks in an elderly patient, as opposed to minutes in younger individuals. This prolonged postictal confusion can be confused for dementia or delirium [5, 15, 47, 51]. Similarly, comorbid dementia can obscure the recognition of seizures. While the incidence of both focal and generalized epilepsy increases in older adults, the most dramatic increase is in focal epilepsy, and this is true of AD [16, 52]. In the elderly, focal onset seizures with alteration of consciousness are the most frequent seizure type [10, 53]. Secondary generalization of seizures is less common occurring in only 26% of elderly patients, as opposed to 65% of younger adults [45]. In older patients with chronic, rather than new-onset epilepsy, seizures may become briefer, and generalized tonic-clonic seizures may become less frequent or even disappear [54]. Additionally, while focal seizures most often arise from the temporal lobe in the general population, events of this type often originate from extratemporal or frontal regions in older patients, as these areas are often preferentially affected by stroke [5, 10, 52].

Status epilepticus (SE), a medical emergency associated with increased morbidity and mortality, is more common in older patients than younger adults. SE is a prolonged seizure lasting more than 30 min or a cluster of intermittent seizures lasting for more than 30 min, during which time the patient does not regain consciousness. In one hospital-based study, SE was the mode of presentation for first seizure in 25% of older individuals [55]. Stroke, either acute or remote, is the most frequent underlying etiology (in about one-third of patients) of convulsive SE [56]. The morbidity and mortality of SE are not only significantly greater in older adults [45], but rates increase with both seizure duration as well as number of comorbid medical conditions [57]. Mortality related to seizures can also occur through sudden unexpected death in epilepsy (SUDEP). SUDEP is an unexplained death of individuals with epilepsy, with no anatomical or toxicological cause found at postmortem examination. SUDEP is more common in younger adults, particularly those between the ages of 20 and 40 years, than in the elderly [58]. This is primarily due to the fact that older adults often have multiple comorbidities, in particular, cerebrovascular or cardiovascular disease. As such, distinguishing cause of death in an older adult with epilepsy as SUDEP versus cause of death related to a comorbid medical condition can be quite challenging, confounding estimates of the incidence of SUDEP in the aged population.

Common Differential Diagnoses

There are a number of diagnoses that can mimic seizures or dementia. It is of utmost importance to assess for the presence of these differential diagnoses to avoid unnecessary or inappropriate treatments and interventions, as well as to facilitate swift, aggressive treatment, when necessary. Medications for both epilepsy and dementia can have significant side effects, as well as drug-to-drug contraindications. Accurate diagnosis and treatment is particularly critical in older adults who are more susceptible to iatrogenic factors and to symptom exaggeration with inappropriate pharmacological interventions following a misdi-

Table 38.1 Common differential diagnoses

Disorder	Symptoms	Likely epilepsy if…	Likely dementia if…
Delirium	1. Disturbance in attention, awareness, and cognition 2. Develops over a couple hours to a few days 3. Fluctuates in severity over the course of the day	1. Relatively quick return to baseline cognition 2. Stereotyped motor movements or automatisms are present 3. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Transient ischemic attack	1. Typically begins with paresis 2. Typically non-stereotyped 3. Duration is approximately an hour	1. Paresis after event can occur 2. Isolated, complete, and brief speech arrest 3. Recurrent stereotypes events 4. Duration is typically less than 2 min 5. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Transient global amnesia	1. Striking, acute onset, amnesia 2. Usually last several hours 3. Patient can respond during episode	1. Acutely impaired cognition resolves relatively quickly 2. Lethargy following return to baseline cognition 3. Patient likely to be unresponsive or abnormally responsive during episode 4. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover
Syncope	1. Temporary partial or complete loss of consciousness with interruption of awareness followed by prompt return to baseline 2. Possible incontinence in elderly 3. No decline in cognitive functioning	1. Duration is typically less than 2 min 2. Lethargy following return to baseline cognition 3. Stereotyped motor movements or automatisms are present 4. EEG correlate	1. Loss of consciousness is uncommon 2. Cognitive symptoms with a gradual onset and progressive decline
REM sleep disorder	1. Vivid dreams that are acted out 2. No atonia	1. Vivid dreams are not acted out 2. Atonia during sleep 3. Stereotyped motor movements or automatisms are present 4. EEG correlate	1. Vivid dreams are not acted out 2. Atonia during sleep 3. Cognitive symptoms with a gradual onset and progressive decline
Psychogenic non-epileptic seizures (PNES)	Common features: 1. Likely history of traumatic event 2. Duration more than 2 min is common 3. Gradual onset 4. Fluctuating course of severity 5. Eyes closed 6. Side-to-side head movements	1. Duration typically less than 2 min 2. Stereotyped motor movements or automatisms are present 3. Incontinence (does not occur in PNES) 4. EEG correlate	1. Cognitive symptoms with a gradual onset and progressive decline 2. Cognitive functioning does not recover

agnosis. Table 38.1 shows common differential diagnoses for older adults with symptoms that may be associated with epilepsy or dementia. Getting a clear description of the event and history of symptoms, particularly from a reliable collateral source, is key to accurate diagnosis. Common differential diagnoses for seizures and dementia include delirium, transient ischemic

attack, transient global amnesia, syncope, REM sleep disorder, and psychogenic non-epileptic seizures (PNES). Below is a brief overview of these differential diagnoses. For a more detailed discussion of differential diagnoses common in the elderly with dementia or epilepsy, please refer to the following references [9, 59–63].

Delirium

Delirium may be difficult to distinguish from focal seizures with impairment of awareness, particularly in a patient with baseline neurologic impairment [64]. However, tremor, asterixis, and myoclonus are not uncommon in delirium. Hallucinations may be a feature of either condition. Duration of delirium is much longer than a seizure and can last up to a day. Severity of symptoms in delirium tend to fluctuate over the course of the event [3], whereas ictal and postictal cognitive changes show a steady improvement back to baseline.

Transient Ischemic Attacks (TIAs)

Transient ischemic attacks are commonly mistaken for seizures; however, they may also induce seizures. Brain ischemia produces reduced neural activity and produces symptoms, such as hemiparesis or hemisensory loss [60]. In contrast, seizures usually cause "positive" symptoms from neuronal hyperactivity. However, "limb-shaking TIAs" may represent a source of diagnostic confusion in this regard. The presence of limb shaking is a well-established sign of hemisphere hypoperfusion, due to severe carotid or middle cerebral artery disease [60]. Although a TIA is commonly considered as a cause for confusional episodes, confusion is rarely a manifestation of TIA, and chronic, recurrent stereotyped events are much more likely to be seizures than TIAs [60].

Transient Global Amnesia

Transient global amnesia (TGA) is a syndrome of abrupt and temporary (<24 h) disruption of anterograde memory. Features that distinguish TGA from seizures include: no clouding of consciousness, no focal neurological signs, full recovery of cognitive functions except for memories during the event itself, and rare recurrent episodes [65]. Among patients with TGA, repetition of the same statements or questions is commonly reported [65]. Compared to TGA, episodes of transient epileptic amnesia (TEA) are typically briefer (<1 h), commonly occur upon waking, have a high recurrence rate, and may be accompanied by other features suggestive of epilepsy such as automatisms or olfactory hallucinations [65].

Syncope

Syncope is characterized by a sudden loss of consciousness and muscular tone followed by spontaneous recovery of full cognitive functions. Classically, syncope occurs when the patient has been upright and is more likely when they are also hot and dehydrated [63]. Warning symptoms of syncope characteristically consist of feeling hot, sweaty, and lightheaded and experiencing visual changes (e.g., seeing stars, vision going white, black, grey, becoming blurred, closing in) and auditory symptoms (e.g., sounds seeming distant, muffled, distorted) [66]. Syncope is not associated with confusion or amnesia following the episode [67]. Syncope can be associated with orthostatic hypotension, hypoglycemia, and hyperglycemia.

Rapid Eye Movement Sleep Behavior Disorder

Rapid eye movement (REM) sleep behavior disorder is characterized by vivid dreams in REM sleep without the usual accompanying muscle atonia. This results in individuals "acting out" their dreams, especially when they are vivid or frightening [68]. Motor movements associated with the acted out dreams, such as kicking, running, and screaming, are common [69]. As such, these behaviors may resemble clinical features of

seizures. Patients are usually able to describe the dream, a feature that is helpful in distinguishing this from seizures [70]. REM sleep behavior disorder in older adults is most commonly associated with alpha-synuclein neurodegenerative disorders including dementia with Lewy bodies and Parkinson disease [69].

Psychogenic Non-epileptic Seizures

Psychogenic non-epileptic seizures (PNES) are episodes that resemble an epileptic seizure, but have no electrographic correlate. Psychiatric disorders, such as anxiety and depression, often underlie PNES. As such, assessment of emotional and behavioral distress, coping style, and personality factors play a key role in revealing the determinant of PNES. It is possible for PNES to have a late onset in older adulthood, and it appears to be about as common in the elderly as it is in younger adults [43, 71]. Although the clinical manifestations of PNES are fairly consistent across age groups, late-onset PNES episodes are distinct from those occurring in younger patients with respect to antecedent psychological trauma. In older patients, health-related traumatic events are more likely (e.g., falls, stroke, myocardial infarction), while in younger patients, antecedent sexual abuse is common [72].

Imaging and Mapping Diagnostic Tools for Seizures and Dementia

Diagnostic tests for epilepsy include both noninvasive and invasive diagnostic techniques. Noninvasive measures include EEG and brain imaging. Invasive measures can include subdural grid and strip electrodes, as well as intracranial depth electrodes. Both invasive and noninvasive measures are aimed at identifying seizure onset zone. For a discussion of these diagnostic techniques in the elderly with seizures, please refer to [73].

In 2012, the FDA approved the use of Amyvid PET scans as a diagnostic screening tool for AD. While increased specificity of this tool is likely to improve over time, Amyvid PET scans are currently best used to rule out a diagnosis of AD. The Amyvid PET scan utilizes a radioactive tracer with affinity for beta-amyloid. If an individual's beta-amyloid deposits on this scan are significantly higher than expected for same-aged, healthy, non-dementing individuals, that patient is considered to have an increased likelihood of dementia. Amyvid PET is a useful tool to clarify potential diagnoses, prevent inappropriate interventions, and guide treatment decisions [74].

Antiepileptic Drugs and Dementia

Appropriate selection of antiepileptic drugs (AEDs) for any epilepsy patient of any age is based on seizure type, patient characteristics, and side effects of the medication. However, older adults are at an increased risk to the vulnerability of side effects, toxicity of AEDs, and failing medications (i.e., poor adherence) due to adverse side effects [75]. Furthermore, higher rates of cognitive difficulties among the elderly increase risk of medication failure due to poor medication management (e.g., forgetting to take medications, taking the incorrect dose). Given these increased vulnerabilities, careful selection of AED treatment regimens that will have the highest success rate in older adults is critical to successful management of seizures. For example, slower, more gradual titration, monotherapy, and lower dosage are recommended for older adults [45, 76]. In fact, older adults are more likely than younger patients to become seizure free with low AED doses [45]. Additionally, the coexistence of comorbid medical, neurological, or psychiatric conditions is higher in older adults and may be a factor in choosing a particular AED considering side effects and interactions with other drugs. Combination therapy of AEDs with other medications may amplify adverse side effects common to both drugs [76, 77].

The most common side effects across all AEDs include sedation, slurred speech, unsteadiness, clumsiness, dizziness, nausea, and adverse cognitive and behavioral effects [78]. AEDs are typically classified as "old"

(developed before the late 1990s) or "new" (developed after the late 1990s). The new AEDs have better tolerability for all age groups and are likely to produce less adverse effects, particularly in elderly patients. This is important considering that older adults are often more susceptible to AED-induced cognitive side effects, ataxia, and dizziness, with a secondary increased tendency toward confusion and falls [73]. It is also worth noting that older adults are more susceptible to the sedative effects of benzodiazepines [79]. Therefore, AEDs such as clobazam should be avoided or managed carefully by experienced epileptologists. Detailed overview of AED risks and benefits in older adults are provided elsewhere [5, 10, 15]. While the extant literature on AED use in elderly patients is quite limited, the few available studies support the effectiveness and tolerability of lamotrigine (LTG) and gabapentin (GBP) in elderly patients [52]. As such, it is recommended that LTG and GBP be considered as initial therapy for older patients with newly diagnosed seizures [80].

Within younger adults, AED intervention is typically not implemented until a patient has experienced two or more unprovoked seizures. In older adults, it has been recommended that treatment be initiated after a single unprovoked seizure. Immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first two years [81]. This is particularly true in the context of a prior stroke due to the high risk of subsequent seizures and their potential serious consequences, including falls or fractures [56, 82].

Surgical Interventions

In patients who have failed adequate trials of two tolerated and appropriate AED schedules, there is increased likelihood that their seizures are drug resistant. Regardless of timing of treatment initiation, seizures remain drug resistant in approximately 20% of elderly patients [83]. For younger adults with drug resistant, or intractable epilepsy, surgery is often a consideration. That said, offering surgical treatment to elderly patients is a controversial topic [84–86] due to concerns related to exacerbation of cognitive decline [85, 86]. However, there have been studies finding that cognitive outcomes following temporal lobectomy for epilepsy are similar across younger and older adults [85, 86], unless there is evidence of a presurgical memory impairment [87]. The decision to proceed with surgery in older adults should be considered on a case-by-case basis taking into account patient characteristics, support level, functional capabilities, and cognitive skill. The goal of surgery for any patient is reduced seizure burden and improvement in overall quality of life.

As alternatives to surgery, epilepsy treatments for drug-resistant seizures include vagal nerve stimulation (VNS) and responsive neurostimulation (RNS). VNS is a procedure in which a device is placed under the skin on the chest that sends electoral pulses to the brain via the vagus nerve. It is believed that these pulses disrupt the rhythmic pattern associated with seizures. There is limited research on VNS in the elderly; however, Sirven et al. (2000) showed that VNS in adults aged 50 years or older is well tolerated and efficacious.

RNS involves the placement of a device under the skull, which monitors brain wave activity. The device is attached to electrodes placed within the suspected seizure onset zone. When abnormal electrical activity is detected, the device signals an electrical pulse to the area of abnormal activity to stop seizure onset. There are currently no studies to date on RNS in the elderly. Research into the efficacy, tolerability, and safety of this procedure in older adults is warranted. Finally, laser interstitial thermal therapy (LITT) is a relatively new surgical intervention for drug-resistant epilepsy. This procedure uses heat to target and ablate tissue of suspected seizure onset zone. Research across all age groups receiving this intervention is needed to determine efficacy, tolerability, and safety.

Clinical Assessment

Neuropsychologists play a key role in the treatment of both epilepsy and dementia patients by quantitatively defining an individual's neurocognitive strengths and weaknesses and recommending appropriate interventions to improve overall quality of life. More specific functions of the neuropsychological evaluation within these populations include assessing cognitive and behavioral functioning to guide medication management, to assess the impact of seizures on cognition, to guide preoperative surgical planning, and to obtain a baseline of cognitive functioning by which to measure any changes in the future. Given the frequent fluctuations in symptomology across these disorders, particularly when occurring comorbidly, there are a number of considerations to be mindful of throughout the interview, assessment, and when making recommendations.

Clinical Interview

In addition to the standard information obtained during an interview, such as relevant background related to the presenting complaint, medical history, psychiatric history, developmental history, social history, and educational/occupational history, there are a number of additional considerations specific to dementia evaluations in individuals with seizures. Since there is a great deal of overlap between symptoms of dementia and epilepsy, careful history taking and evaluation of all areas of neurocognitive difficulties, behavioral changes, and mood symptoms are critical features of the examination in order to determine whether seizures are a potential etiology that deserve further neurological investigation [52]. A focus on a detailed understanding of onset and progression of symptoms and how these overlap with any changes in seizures, AEDs, other medications, medical comorbidities, and other relevant life events (e.g., retirement, death of a spouse) is key.

A current and accurate medical history is important in determining potential etiology of seizures. New seizure onset in older adults is commonly associated with cerebrovascular disease, stroke, metabolic disturbance, head trauma, infectious disease, tumor, and drug interactions, so it is important to get a clear medical history. Similarly, cognitive difficulties can be due to a number of etiologies, and particular attention should be paid to the presence of other medical conditions, symptoms of altered mental status, sleep problems, and psychological distress. In particular, depression and lower social support are common in older adults and can potentially negatively impact cognitive functioning [88, 89].

Obtaining collateral information is of utmost importance for older adults with epilepsy or dementia due to potential lack of insight into or awareness of cognitive difficulties as well as difficulty describing one's own seizures. It is also particularly important to assess level of independence with activities of daily living, since this is helpful in differential diagnosis and forming recommendations. Checklists or questionnaires assessing activities of daily living, such as the Bristol Activities of Daily Living Scale [90], may be particularly useful in this regard.

Test Selection and Assessment Process

Prior to selecting tests for use with older adults with epilepsy, careful consideration of the testing environment, ease of accessibility, and possible limitations is needed. Ideally, the testing environment should be a welcoming environment that may put an otherwise anxious patient at ease. This is particularly important with older adults, as they may have an increased sensitivity to the effects of cortisol (i.e., stress) on memory performance [91]. For example, if possible, the following are recommended: 1) conducting an initial interview separate from testing to allow the patient to acclimate to the environment prior to returning for testing, 2) having an evaluator sensitive to the needs of older individuals, 3) decreasing the emphasis on the memory component of tasks when providing instructions, and 4) conducting the assessment in the morning or the time

that reports suggest the patient is in their best mental state [92]. Accessibility of the testing environment may also ease anxiety in the elderly. Clearly navigated spaces for walkers and wheelchairs, as well as comfortable and sufficient chairs to accommodate accompanying family members can be helpful. Increased frequency of motor and sensory deficits (e.g., poor vision and hearing) in this population requires understanding any limitations of the patient and adapting tests appropriately.

Test selection should take into careful account the robustness of the norms available for older adults. The Mayo's Older Americans Normative Studies (MOANS) provide normative data for individuals between the ages of 56 and 95 [93, 94]. As in any neuropsychological evaluation, test selection should take into account the specific referral question. In the epilepsy population, measures to help localize and lateralize dysfunction should be included. The National Institute of Neurological Disorders and Stroke (NINDS) has put forth recommended tests to use for the assessment of patients with epilepsy. These measures were chosen by experts in the field of epilepsy for their validity within the epilepsy population. While these assessment recommendations are not an exhaustive list of potential measures appropriate for use with epilepsy patients, these "Common Data Elements" (CDE) were developed to increase the efficiency and effectiveness of clinical research and clinical treatment. Table 38.2 outlines the core suggested measures to use with an epilepsy population aged 16 years and above.

Given that these measures are not specific to older adults, additional consideration of measures appropriate for the use in an elderly population that may be presenting with symptoms of dementia is important. In particular, further attention should be paid to the domains of memory, language, and motor skills, which are areas commonly affected by primary neurodegenerative disorders. Furthermore, more global assessments are useful in assessing older adults who may not be capable of completing a lengthy neuropsychological evaluation. Elderly patients may become fatigued more quickly during testing, and a shorter battery is often necessary. In such situations, batteries such as the Dementia Rating Scale – Second Edition (DRS-2) [106] or the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [107] may prove particularly useful.

Table 38.2 NINDS common data elements for epilepsy

Domain	Recommended measures
Premorbid estimation	American National Adult Reading Test (AMNART) [95]
Intellectual functioning	Wechsler Adult Intelligence Test-Fourth Edition (WAIS-IV) [96], Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) [97]
Learning and memory	Rey Auditory Verbal Learning Test (RAVLT) [98], Brief Visual Memory Test (BVMT) [99], Rey-Osterrieth Complex Figure [100], Wechsler Memory Scale: Visual Reproduction [101], Nonverbal Selective Reminding Test
Language	Boston Naming Test (BNT) [102], Controlled Oral Word Association Test (COWAT) [103], Animal Fluency
Visuospatial	WAIS-IV or WASI-II Block Design, WAIS-IV Perceptual Reasoning Index
Executive functioning	Trail Making Test [103], Digit Span subtest from the WAIS-IV, Wisconsin Card Sorting Test (64 card version) [104]
Processing and motor speed	WAIS-IV Coding and Symbol Search, Grooved Pegboard [105]

Depression is a common psychiatric comorbidity in individuals with seizure disorders; people living with epilepsy tend to report more depressive symptoms than individuals without seizure disorders [108]. In addition, older adults with epilepsy have been found to report higher levels of depressive symptoms when compared to both healthy age-matched older adults [109, 110] and older adults with mild cognitive impairment [111]. Depressive symptoms have been shown to negatively impact performance on neuropsychological tests in adults with temporal lobe epilepsy [112]. In particular, adults who exhibited depressed mood (as assessed by a semi-structured psychiatric interview) performed worse on measures of overall intelligence, visuoperceptual ability,

language, visual memory, and executive functioning, as compared to non-depressed adults with temporal lobe epilepsy [112]. Similarly, increased rate of depression in older adults with epilepsy (as measured by self-report questionnaires) is associated with diminished performance on measures of global cognitive functioning, memory, executive functioning, and verbal fluency, as compared to both healthy age-matched older adults [110] and older adults with milder impairments [111]. The use of mood measures specific to the aged population (e.g., Geriatric Depression Scale, Geriatric Anxiety Inventory) [113, 114] is recommended. Furthermore, given that poor insight is common among individuals with dementia, collateral report or clinician ratings of mood symptoms may be valuable. For example, the Hamilton Anxiety Rating Scale (HAM-A) [115] evaluates anxiety related symptomology evident during clinical interview.

Sleep problems may be of particular importance in older adults with epilepsy, as older age (i.e., 65 years and older) is associated with a shorter, lighter, and more disturbed sleep [116]. Perhaps more importantly, sleep problems in older non-demented adults are associated with diminished cognitive functioning [117, 118]. Specifically, Schmutte et al. (2007) reported that self-reported sleep complaints (i.e., delayed sleep onset and prolonged sleep duration) among older, community-dwelling, adults aged 75–85 were associated with significantly worse performance on measures of word knowledge, memory, visuospatial functioning, and fund of information. This relationship remained significant even after controlling for potential moderating factors such as: depression, sleep medications, age, education, and physical ailments. In contrast, only a small number of studies have investigated the role of sleep problems on cognition in elderly epilepsy populations; therefore, it is not yet possible to draw any conclusions on the impact of sleep on neuropsychological functioning in this group of individuals. However, given the known negative impacts of poor sleep on cognitive functioning, assessment of sleep in elderly individuals with epilepsy through instruments such as the Pittsburgh Sleep Quality Index (PSQI) [119] is recommended.

Assessment of Health-Related Quality of Life

The current research on health-related quality of life specific to older adults with epilepsy is extremely limited [120]. Despite the paucity of studies, elderly epilepsy populations are at increased risk for factors associated with diminished health-related quality of life, including depression [121], adverse side effects of AEDs [122], and comorbid medical illnesses [120]. The 31-item Quality of Life in Epilepsy (QOLIE-31) [123] is likely to be a useful tool in assessing health-related quality of life among elderly patients with epilepsy. This measure focuses more on the specific concerns of epilepsy patients and less on general health-related quality of life domains, such as pain and physical function. The QOLIE-31 is a self-report measure that consists of 31 questions assessing seven domains of seizure worry (7 items), overall QOL (2 items), emotional well-being (5 items), energy-fatigue (4 items), cognitive functioning (6 items), medication effects (3 items), social functioning (5 items), and an overall score.

Formulation of Findings

Consistent with standard practice in neuropsychology, outlining and describing the patient's cognitive profile in terms of their strengths and weaknesses is an important first step in conceptualizing neuropsychological functioning. Emotional, behavioral, and activities of daily living data should also be reviewed and integrated into the conceptualization of the case. If there is significant impairment, clearly describe the areas and severity of cognitive weakness. The profile of cognitive impairment should be contextualized in concert with relevant background information, medical history, psychological functioning, collateral information, behavioral observations, and imaging/lab tests.

All of this information should be reported within the context of the diagnoses being offered, if any. If possible, the extent to which these data are lateralizing or localizing should be discussed.

As noted above, AEDs carry risk for cognitive side effects. Determining the extent of AED impact on neuropsychological testing is an important consideration, particularly in the elderly who are at increased susceptibility to AED side effects. As such, noting cognitive complaints that coincide with changes in medications, dosage changes, and experiences of medication side effects should be documented in the report. Overlooking the possibility that medications are responsible for some cognitive inefficiencies potentially precludes the effective treatment of those symptoms by modifying the medication regimen [124].

Recommendations

Recommendations should always be tailored to the patient's particular strengths and weaknesses in the context of their individual needs. A list of common recommendations for patients with epilepsy and dementia is provided below for reference. Recommendations are divided into those addressing cognitive, medical, behavioral, and psychological issues.

Cognitive

- Interventions aimed at remediating deficits in particular areas of cognitive weakness need to be tailored to the patient's neuropsychological profile of strengths.
- Serial evaluation within 12 months, or sooner if clinically indicated, is often necessary to track changes in cognitive functioning over time; this is particularly important for patients with suspected dementia.
- Cognitive training or rehabilitation may be helpful within this population. Cognitive therapy often involves "brain games" that work to strengthen the connections in one's brain needed to complete tasks. Additionally, cognitive rehabilitation is helpful in developing compensatory strategies to "work around" areas of cognitive weakness.
- It is likely helpful to point to activities and lifestyle changes that can aid in cognitive improvement, such as 1) frequent and varied cognitively stimulating activities, such as reading, crossword puzzles, Sudoku, chess, etc., 2) moderate and regular exercise, 3) healthy eating habits, and 4) socialization.
- Individuals with poor functional independence in activities of daily living may benefit from more structure embedded into their daily lives and routine. For example, use of pill boxes, to-do lists, calendars, alarms, breaking things down into simple steps, and written copies of instructions are a few possible simple suggestions that may go a long way in increasing feelings of independence and self-efficacy.

Medical

- A recommendation to the patient's physician to review pharmacotherapy may be warranted if it is suspected that AEDs or other medications may be causing adverse cognitive or behavioral side effects.
- For both epilepsy patients and dementia patients, it is important to recommend that medications be closely monitored by their prescribing physician due to an increase risk of medication non-compliance in these populations.
- Medical decision-making abilities should be considered, such as assigning a healthcare proxy.
- Additional tests, including brain imaging and additional lab work, may be appropriate.
- If seizure activity is suspected, referral to an epileptologist for comprehensive evaluation is recommended.
- Given that cerebrovascular disease is a common etiology of both epilepsy and dementia, recommendations to reduce relevant vascular related risk factors that may be

impeding cognitive functioning are important.

Behavioral

- Safety interventions to address frequent difficulties with medication management, forgetting to turn off the stove, managing finances, and wandering or getting lost.
- Results of the neuropsychological evaluation may suggest that a formal driving evaluation is warranted.
- An assessment by an occupational therapist may be helpful to determine the patient's functional capabilities and whether or not modifications in activities are required.

Psychological

- Given the negative impact of anxiety/depression on cognitive functioning, it may be recommended that these concerns be addressed with formal psychotherapy or pharmacotherapy.
- Psychoeducation may be helpful to both the patient and caregivers regarding dementia and epilepsy in older age.
- Psychoeducation regarding effects of mood on cognition may be needed.
- Caregivers may experience high levels of stress, which, in turn, can impact care for the patient. Social support groups for caregivers are valuable to patient care.

In addition to the recommendations outlined, providing patients with resources to websites, support groups, help groups, and psychoeducation are important, tangible recommendations. Education regarding basic facts about epilepsy and its cognitive and mood implications can be empowering. There are several online resources for education and online forums for epilepsy in general as well as ones specific to seniors with epilepsy:

- Through the Epilepsy Foundation, patients can find information on seniors with epilepsy in their section, "Epilepsy and the Senior Community." More information can be found at http://www.epilepsy.com/learn/age-groups/epilepsy-and-senior-community.
- American Epilepsy Society: https://www.aesnet.org/for_patients.
- National Institute for Neurological Disorders and Stroke: https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page.
- Center for Disease Control and Prevention: https://www.cdc.gov/epilepsy/index.html.
- Many states and cities have local epilepsy groups that can be helpful for locating services for the individual patient.

Case Report

Background An 81-year-old, right-handed, Caucasian woman with 12 years of education was referred for neuropsychological evaluation due to recent, new-onset seizures. Per family report, the patient experienced a recent fall and subsequently woke up on the floor without memory for prior events. She was hospitalized for 6 days with no further medical complications. Six months later, the patient experienced two episodes that were suspicious for seizures, which involved loss of consciousness and nausea. Three months later, the patient experienced an odd sensation on the top of her head and a feeling of profound exhaustion, followed by speech arrest and an alteration of consciousness. Subsequent to this event, she was taken via ambulance and experienced a generalized tonic-clonic seizure *en route* to the hospital. Brain MRI showed "prominent frontal and parietal convexity of subarachnoid spaces." Video EEG showed "left temporal slowing suggesting left temporal cerebral dysfunction."

From a cognitive perspective, the patient reported a diminution of abilities since these suspicious episodes, including increased forgetfulness, frequent episodes of anomia that included paraphasias, slowed thinking, and poorer balance and gait. That being said, she continued to manage her activities of daily living (ADLs) independently.

Table 38.3 Case study neuropsychological assessment results

ACS-TOPF	2011(%ile)	2013(%ile)	Direction of change
Total	86	79	–
DRS-2			
Attention	37	9	↓
Initiation/Perseveration	2	75	↑
Construction	16	9	–
Conceptualization	63	75	–
Memory	25	9	–
Total	9	37	↑
WASI-II			
FSIQ	25	21	–
Block Design	8	7	–
Vocabulary	62	63	–
Similarities	58	37	–
Matrix Reasoning	12	16	–
WAIS-IV			
Digit Span	37	63	–
Coding	75	84	–
Symbol Search	68	95	↑
CVLT-II/RAVLT			
Trial 1	7	3	–
Trial 5	7	<1	↓
Total Recall	16	<1	↓
List B	16	27	–
Immediate Recall	16	<1	↓
Delayed Recall	32	<1	↓
Recognition Hits	1	4	–
WMS-IV			
Logical Memory I	50	37	–
Logical Memory II	50	63	–
Grooved Pegboard			
Right (dominant)	<1	<1	–
Left	<1	<1	–
Trail Making Test			
Part A	27	7	–
Part B	<1	47	↑
Verbal Fluency			
FAS	75	87	–
Animals	–	13	NA
BNT			
Total + stimulus cue	–	55	NA
Stroop			
Word	25	–	NA
Color	3	–	NA
Color-Word	<1	–	NA
WCST			
Categories	–	47	NA
Total Errors	–	55	NA

(continued)

Table 38.3 (continued)

RCFT			
Copy	<1	–	NA
Immediate Recall	<1	–	NA
Delayed Recall	18	–	NA
BVMT-R			
Total Recall	–	<1	NA
Delayed Recall	–	<1	NA
Discrimination Index	–	3	NA
Mood			
BAI	7	14	↑
BDI-II	18	17	–

Note: *ACS* Advanced Clinical Solutions, *BAI* Beck Anxiety Inventory. *BDI-II* Beck Depression Inventory Second Edition, *BNT* Boston Naming Test, *BVMT-R* Brief Visuospatial Memory Test – Revised, *CVLT-II* California Verbal Learning Test Second Edition, *DRS-2* Dementia Rating Scale Second Edition, *FSIQ* Full Scale Intelligence Quotient, *RCFT* Rey-Osterrieth Complex Figure Test, *RAVLT* Rey Auditory Verbal Learning Test, *TOPF* Test of Premorbid Functioning, *WAIS-IV* Wechsler Adult Intelligence Scale Fourth Edition, *WASI-II* Wechsler Abbreviated Scale of Intelligence Second Edition, *WCST* Wisconsin Card Sorting Test, *WMS-IV* Wechsler Memory Scale Fourth Edition

In addition to presenting concerns, the patient's medical history was significant for hypothyroidism, hyperlipidemia, and peripheral neuropathy. Surgical history was significant for partial thyroidectomy, hip surgery following a car accident (no head injury), cataract repair, and gynecological surgery. At the time of the assessment, the patient was prescribed the following medications: lamotrigine, metoprolol, simvastatin, raloxidene, Caltrate, and levothyroxine. The patient's mother reportedly had an undiagnosed memory-related disorder. Family history was also significant for heart disease, stroke, and cancer.

The patient graduated from high school and held employment in clerical work. She was retired at the time of the assessment. The patient endorsed affective distress, including feelings of anxiety and fear, due to recent seizure episodes, and memory difficulties. Additionally, she reported that she often wakes up early and cannot fall back to sleep. As such, she often experienced fatigue throughout the day and has started taking a daily 1-h nap.

Clinical Assessment The patient was alert and oriented to person, place, and time throughout the assessment. Receptive and expressive language skills appeared intact during casual conversation, with no evidence of paraphasias. Her thought process was logical and goal oriented. However, the patient was observed to be distracted and talkative throughout the assessment, which often required redirection to the task at hand. Perseverative responding was also observed. Initial neuropsychological evaluation was conducted 10 months after first suspected seizure event, and a follow-up neuropsychological evaluation was administered two years later (Table 38.3).

For the purposes of this case presentation, a change in performance more than one standard deviation is indicated. It is worth noting that in clinical practice, reliable change indices (RCI) should be calculated to determine significant change in functioning over time [125]. From 2011 to 2013, the patient showed both improvements and declines in areas of cognitive functioning. Declines were observed in areas of memory and attention. Improvements were noted in areas of processing speed, aspects of executive functioning, oral motor skills on DRS-2, and manual motor skills on DRS-2. Although it is difficult to determine the factors involved in her cognitive improvement, it could be speculated that adequate seizure control is playing a role. The improvements observed in selected areas of functioning argue against the presence of a

neurodegenerative disorder. Furthermore, specific declines in verbal memory are consistent with seizure semiology of left temporal origin. Across both assessment points, variable attention was noted which impacted the patient's ability to learn new information. Finally, depressive symptoms remained consistent between the two assessments; however, anxiety levels reportedly increased. Even within the context of increased psychological distress, the patient was able to demonstrate improvement in performance. Given the patient's neurocognitive profile in 2013, as well as denied decline in activities of daily living, she would not meet the criteria for a primary neurodegenerative disorder. However, this is a patient that should be carefully monitored over time for a developing dementing process given her age and seizure disorder with associated cognitive changes.

Clinical Pearls

- It is important to clarify the referral issue before evaluation, as well as describe the purpose and structure of the evaluation.
- Always obtain collateral information when possible. Patients with both epilepsy and dementia may have difficulty reporting their own symptoms due to cognitive difficulties or limited insight.
- Level of independence in completing activities of daily living is important to assess for an accurate diagnosis of neurocognitive disorder (mild vs. major). Both basic and instrumental tasks of daily living should be assessed.
- In general, there is a high rate of medical and psychological comorbidity among individuals with epilepsy and dementia. It is important to obtain a comprehensive medical and psychiatric history and be aware of the effects of additional conditions on cognitive functioning.
- Common initial misdiagnoses include altered mental status, confusion, "blackout spells," memory disturbance, syncope, dizziness, dementia, transient ischemic attack (TIA), depression, metabolic disorders, and/or psychiatric disorders.
- Postictal confusion may last as long as 1–2 weeks in an elderly patient, as opposed to minutes in younger individuals. This prolonged postictal confusion can be confused for dementia or delirium
- Poor sleep is well known to negatively affect cognitive functioning, and poor sleep is a common comorbidity in both epilepsy and dementia. It is important to thoroughly assess sleep quality and sleep hygiene (e.g., how many hours do you sleep? Do you wake up during the night? Do you have trouble falling asleep/staying asleep? Do you feel rested in the morning? Is your sleep restful? Do you have vivid dreams/nightmares?)
- The assessment battery should be appropriate for both epilepsy and dementia patients with particular focus being paid to: keeping it short due to fatigue and a focus on language, memory, and motor skills.
- Assessing for depression and the impact of mood on neuropsychological results is key to deciphering diagnoses.
- It is important to use robust normative data available for older adults (such as the MOANS norms).
- Older adults often have a polypharmacy medication regimen. Understanding the cognitive impact of these drugs, alone and in combination with each other, is important when conceptualizing cognitive findings.
- Cognitive remediation therapy, individual or group, may help facilitate improvement of symptoms or reduce the rate of decline of cognitive functions.

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39 Evaluating Cognition in Patients with Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a chronic condition characterized by persistent airflow limitation that is not fully reversible. COPD is associated with an enhanced chronic inflammatory response in the lungs to inhale noxious particles. A mixture of small airway disease (narrowing or abnormalities of the small airways), emphysema (destruction of gas-exchange surfaces called alveoli), and changes in the pulmonary vasculature occur to varying degrees across patients. Bronchitis, which refers to chronic cough and sputum production, is common but not present in all patients. Key clinical manifestations of COPD include shortness of breath, exercise intolerance, acute respiratory events (exacerbations), and comorbidities such as cardiovascular complications, depression, and anxiety. COPD is the third leading cause of combined morbidity, disability, and mortality in the United States [1]. The prevalence and impact of COPD are predicted to increase in the coming decades due to continued exposure to COPD risk factors and the shifting age of the population [2].

Although cigarette smoke is clearly the most common risk factor for COPD, other factors contribute via gene environment interactions. The fact that less than half of heavy smokers develop COPD and some non-smokers develop COPD illustrates the complexity of disease development [3, 4]. The best documented genetic risk factor for COPD is an inherited deficiency in alpha-1 antitrypsin, a serine protease inhibitor [2]. Identifying and understanding genes that confer an increased risk for airflow limitation is currently a major focus of ongoing research [5]. Occupational exposures (i.e., farming or work in dusty occupations), environmental air pollution (increased particulates), and indoor air exposure (smoke from use of biomass fuels) also contribute to accelerated loss of lung function. Other factors that influence disease development include early life events such as maternal smoking, low birth weight, asthma, and severe childhood respiratory infections. Male gender predominance in COPD has been reported, which may be related to higher exposure to cigarettes and other toxins. The idea that women are more susceptible to the effects of cigarette smoke than men has been suggested and is also an ongoing area of research [6, 7].

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Classification of Severity of COPD

In 2001 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) released its first report titled "Global Strategy for the Diagnosis, Management, and Prevention of COPD," which summarized the current state of scientific knowledge on COPD and presented disease management and prevention strategies. The GOLD statement has been updated several times since its original release, most recently in 2017. The use of spirometry results obtained after administration of an inhaled bronchodilator, such as albuterol, to classify severity of airflow limitation has been the core of the GOLD definition of COPD since 2001 (see Table 39.1). Spirometry measures the amount and rate of air a patient breathes in and out over a period of time. Testing before and after a bronchodilator minimizes variability in how the test is administered and provides some information about the potential responsiveness of the airways to medication. As can been seen in Table 39.1, decreasing FEV_1, which reflects the volume of air that can be forced out in the 1 s after taking a deep breath, is the key measure with regard to severity of airflow limitation. A ratio of FEV_1/forced vital capacity of <0.70 is required for diagnosis based on GOLD criteria.

The impact of COPD on any individual patient is due not only to degree of airflow limitation but also to symptom severity, exacerbation history and future risk, and the presence of comorbidities. The current GOLD approach to assessing COPD severity incorporates all of these factors into a "combined COPD assessment tool" using post-bronchodilator spirometry measures, the patient's history of hospital admission for exacerbations, and symptom severity assessed via one of two common questionnaire measures (i.e., the Modified Medical Research Council (mMRC) dyspnea scale [8] or the COPD Assessment Tool [9], which are described below). This combined assessment groups patients into A–D to provide information about symptom burden and exacerbation risk [2]. While it is certainly helpful for a neuropsychologist working with patients to understand the GOLD diagnostic scheme and symptom severity rating, it is also important to recognize that individuals may experience and seek medical help for chronic respiratory symptoms and show evidence of structural changes in their lung in the context of normal spirometry [10]. Treatment goals focus on reducing the impact of chronic respiratory symptoms on patients' daily lives, reducing the risk of future acute exacerbations of symptoms, and treating medical comorbidities [2].

Table 39.1 COPD GOLD [2] severity of airflow limitation

	Spirometric classification based on post-bronchodilator FEV_1
GOLD 1 mild	$FEV_1/FVC < 0.7$ $FEV_1 \geq 80\%$ predicted
GOLD 2 moderate	$FEV_1/FVC < 0.7$ 50–79 FEV_1% predicted
GOLD 3 severe	$FEV_1/FVC < 0.7$ 30–49 FEV_1% predicted
GOLD 4 very severe	$FEV_1/FVC < 0.7$ $FEV_1 < 30\%$ predicted

FEV 1 forced expiratory volume in 1 s, *FVC* forced vital capacity

Common Medical Diagnostic Tests

Diagnosis of COPD by a physician involves a thorough medical history, physical examination, and pre- and post-bronchodilatory spirometry, with a chest CT or additional measures ordered depending upon the clinical situation. In the following section, brief information about common medical tests a neuropsychologist may encounter when reviewing the medical record of a patient with COPD will be reviewed.

Spirometry

As mentioned above, post-bronchodilator spirometry is needed to make a certain diagnosis of COPD. The test measures the volume of air exhaled during a maximal forced expiratory maneuver (i.e., blowing out as hard and fast as possible until the lungs feel absolutely empty). The patient must take a deep breath and blow into

a mouthpiece attached to a spirometer. A computerized sensor within the spirometer calculates and graphs the results, typically presented as volume vs. time. Of particular importance for COPD diagnosis and monitoring is the volume forced out within the first second (forced expiratory volume in 1 s, FEV1) and total volume of air forced out of the lungs (forced vital capacity, FVC).

Alpha–1 Antitrypsin Screening

Alpha-1 antitrypsin deficiency (α-1) is a genetic condition that increases risk of liver disease and emphysema [11, 12]. α-1 antitrypsin is a protein primarily produced in the liver and released into the bloodstream that protects the lungs against damage from things like infections and smoke. In addition to treatments that may be used in COPD in general (e.g., bronchodilators, corticosteroids), some individuals with α-1 antitrypsin deficiency may be candidates for α-1 augmentation therapy [13].

Exercise Capacity

Exercise capacity is an important component of the evaluation of COPD patients, given that limitations in exercise capacity have a significant impact on day-to-day functioning. Several different exercise measures are available including treadmill or cycle testing, the 6-min walk test, or shuttle walk testing. Assessment of exercise capacity is most often conducted in the context of pulmonary rehabilitation or physical therapy evaluation.

Dyspnea

A commonly used measure of breathlessness in COPD is the Modified Medical Research Council (mMRC) dyspnea scale [8]. The scale is a five-item questionnaire on which patients rate their own disability from dyspnea, with grade 1 indicating the least impact from breathlessness (i.e., only breathless with strenuous exercise) and grade 5 indicating the most severe impact (i.e., too breathless to leave the house or breathless when dressing/undressing).

Chronic Respiratory Symptom Severity

The COPD Assessment Test (CAT) [9] is an eight-item questionnaire measure of health status impairment that focuses on the impact of common symptoms of COPD. Eight symptoms (e.g., cough, mucus production, breathlessness, chest tightness, confidence leaving home, sleep, and energy) are rated on a 0–5 scale. Scores range from 0 to 40 with higher scores indicating more severe symptom impact.

Additional tests that are often ordered for patients with COPD include arterial blood gases, sleep study, cardiology evaluation, occupational medicine consultation, and health and behavior assessment with a psychologist or psychiatrist.

Common Medical Comorbidities of COPD

COPD has traditionally been understood as a disease of the lungs characterized by chronic airflow obstruction; however, the importance of extrapulmonary effects of COPD has been increasingly recognized [14–16]. COPD has systemic effects that can have an important impact on the patient's health including cachexia, skeletal muscle wasting, osteoporosis, anemia, cardiovascular disease, and depression. The consequences of systemic inflammation on other organ systems have been one major area of focus in understanding extrapulmonary changes in COPD [17].

Cardiovascular disease is one of the most prevalent comorbidities in COPD [18–21]. COPD is associated with a two- to threefold increase in the risk of ischemic heart disease, stroke, and sudden death [21]. Although smoking is a risk factor for both COPD and cardiovascular disease, the association between airflow obstruction (e.g., FEV_1) and cardiovascular disease

exists even after adjusting for risk factors that are common to both conditions including age, sex, smoking history, cholesterol, and socioeconomic class, suggesting that there is a direct underlying relationship [20]. Additional medical comorbidities of COPD typically include anemia and osteoporosis [22].

COPD is associated with an increased rate of psychological symptoms, particularly anxiety and depression. In a comprehensive review of 81 studies, Hynninen and colleagues [23] reported that the prevalence of psychiatric disorders ranged from 30% to 58%. Depression and anxiety appear to be the most commonly observed psychological problems in COPD [23–27]. The prevalence of depression has been estimated between 10% and 79.1% [23, 28–30]. Some of the discrepancies in estimates may relate to the method of assessing depression. For example, prior studies with higher levels of depression have tended to use self-report questionnaires rather than a clinically derived diagnosis of major depression [31, 32]. Eiser and colleagues [33] screened a large group of COPD patients with moderate to severe COPD using screening questionnaires followed with a psychiatric interview. They report prevalence rates of depression of 35% using the questionnaire and 21% by clinical interview. This is consistent with another study that diagnosed depression in COPD utilizing a structured psychiatric clinical interview and reported that 23% of the COPD patients had major depression [34]. The prevalence of depression in older adults in the general population has been estimated between 8% and 20%; thus, studies to date clearly indicate higher depression rates in patients with COPD [34].

The symptoms of anxiety, depression, and dyspnea are not mutually exclusive. Whereas dyspnea is a characteristic feature of panic attacks, feelings of panic and anxiety are also a frequent manifestation of pulmonary disease. In COPD, approximately one third of patients meet clinical criteria for an anxiety disorder, with panic disorder being the most common. Approximately one fourth of patients meet criteria for panic disorder, which is ten times the rate in the general population [25]. Symptoms of depression and anxiety are important to consider as they may contribute to cognitive impairment in COPD, in addition to their impact on quality of life and clinical outcomes like acute exacerbations.

Neuropsychological Studies in COPD

Cognitive impairment is common in patients with COPD, with estimates ranging from approximately 40 to 60% depending upon characteristics of the specific sample (e.g., in- vs. outpatient) and definition of cognitive impairment (e.g., reduction in a single domain relative to age-matched peers vs. global impairment [35–37]). A recent systematic review and meta-analysis of mild cognitive impairment (MCI) in previously published observational studies of patients with COPD included a total of 14 studies that largely used global measures of cognition (most commonly the MMSE) and strict threshold for MCI [38]. This systematic review concluded that the pooled prevalence of MCI in COPD was 25% documenting the high prevalence of MCI in COPD relative to the general population.

Multiple studies using longer standardized neuropsychological test batteries have also identified deficits in patients with COPD and examined some measures of clinical severity in relation to cognition [39–45]. Much of the focus has been on the impact of pulmonary dysfunction on cognition. The association between airflow limitation measured using spirometry and cognitive performance has been relatively inconsistent with some positive [39, 45–48] and some negative studies [45, 49, 50]. In COPD patients with moderate to severe hypoxemia, deficits have been reported in simple motor movement and overall strength, perceptual-motor integration, abstract reasoning, attention to auditory stimuli, learning and memory, and language skills [31, 33–35, 37–39]. Grant and colleagues [40] combined data from a number of sites of a multicenter NIH trial and reported that mildly hypoxemic COPD

patients (mean age = 61.6, mean PaO_2 = 67.8) performed significantly lower than controls on a global index of cognitive functioning. Twenty-seven percent of COPD patients with mild hypoxemia showed global deficits as compared to 61% of patients with severe hypoxemia. The mildly hypoxemic group performed significantly below matched controls on measures of associate learning, immediate recall of verbal and nonverbal material, logical analysis and reasoning, sustained visual attention, and fine motor coordination. Liesker and colleagues [51] also reported that COPD patients (N = 30) with mild hypoxemia showed decline in visuomotor speed and attention compared to healthy controls. In a large review of COPD studies with and without hypoxemia, the correlations between cognitive functions and degree of hypoxemia were less impressive and thought to be inconsistent [22]. Airflow limitation is a downstream effect of underlying physiology, and ultimately hypoxemia measured by arterial blood gases (ABG) has been most consistently associated with cognitive impairment in COPD [35, 36, 52–56], although relatively few studies have included blood gases in their analysis. There is some evidence that cardiovascular fitness is associated with cognition. Etnier and colleagues [48] found that exercise capacity (6 min walk test distance) was associated with cognitive performance. COPD treatment studies have generally observed improvement in cognition with physical rehabilitation [57], but those cognitive improvements have not been associated with a corresponding change in hypoxemia [58]. Improvement in cognition following cardiac rehabilitation has been shown to be associated with improved cardiovascular fitness, suggesting that cardiovascular factors may be important in cognitive improvement following pulmonary rehabilitation as well [48]. The need to develop and test alternative pathways linking the lung and brain in COPD has been highlighted in several review articles calling for additional research modeling the impact of COPD on the brain including inflammatory and cardiovascular mechanisms [59–61].

Due to the age of the COPD population, the potential for other central nervous system (CNS) disorders, including a progressive neurodegenerative disorder such as Alzheimer's disease (AD), should be considered in differential diagnosis. We compared 32 mildly hypoxic COPD patients to 32 subjects with mild Alzheimer's disease (AD) and 32 healthy controls matched on age, education, and gender [62]. Results indicated that the mild AD group performed worse than the COPD group on all measures except verbal fluency. In contrast to AD or another neurodegenerative process, there may be some improvement in cognition in patients with COPD, particularly memory gains following oxygen or multidisciplinary rehabilitation. Therefore, repeat neuropsychological assessment 6–12 months following treatment, as well as consultation from neurology and neuroradiology, may be useful in a complete workup in COPD patients with severe memory disorders.

Neuroimaging Studies of Patients with COPD

To date studies examining brain structure and function in COPD show, as may be expected, that brain changes are generally associated with more advanced COPD and hypoxemia [39, 47, 63, 64]. Of the studies that have used brain MRI in COPD [59, 63, 65–69], just a few have also included measures of multiple domains of cognitive functioning beyond the global MMSE [63, 66, 68]. There is some evidence of cerebral gray matter volume loss in advanced COPD [63, 65, 70]; however, there is increasing data suggesting that alterations in cerebral white matter may be one of the earliest brain changes in COPD [66, 71]. Van Dijk and colleagues [67] observed that a population-based sample of individuals using inhaler medication, and thus assumed to include patients with COPD, had higher ratings of periventricular white matter lesions than other participants [67]. Lower blood oxygen concentration (SaO_2 from pulse oximetry) was associated with a

higher periventricular white matter lesion rating in that sample. Dodd and colleagues [66] compared DWI and resting fMRI between 25 non-hypoxemic patients with COPD and 25 healthy controls and found differences in white matter integrity (i.e., lower fractional anisotropy on DTI in those with COPD) after adjusting for stroke risk and smoking history. One recently published brain MRI study [72] sought to investigate the relationship between structural brain MRI evidence of small vessel disease (using qualitative visual rating scales), hippocampal volume (considered as a "marker of neurodegeneration"), and cognitive performance in 25 cognitively high- and low-performing participants of the COgnitive-PD study. The study did not identify evidence for a relationship among these measures but concluded additional studies are needed. Overall, to date studies examining brain structure and function in COPD show that while brain changes are generally associated with worsening airflow limitation and hypoxemia, much of the variance in brain outcomes remains unexplained.

Interdisciplinary Treatment of COPD

Comprehensive rehabilitation programs for treatment of COPD include a wide range of assessment procedures and educational programs, instruction on respiration, psychosocial support, and exercise training with the goal of restoring patients to the highest level of independent function [73]. There is evidence that suggests that comprehensive multidisciplinary rehabilitation programs can also improve cognitive functioning and psychological status in emphysema/COPD patients [31, 73–75]. Studies from our group have suggested improved verbal memory and visuomotor sequencing in patients with lung volume reduction surgery compared to rehabilitation at a 6-month follow-up using a comprehensive battery [58]. In a later study with a much larger sample, there were no differences between the two groups on a visuomotor sequencing task over a 3-year period [76]. Notably, the first study utilized a comprehensive battery, and the second study included only the measure of visuomotor sequencing.

Role of Neuropsychologist

At hospitals such as ours (National Jewish Health (NJH) in Denver, CO), the role of the neuropsychologist in the pulmonary assessment and rehabilitation process is well established and integral to the program. Physicians board-certified in pulmonology are directly responsible for assessment, diagnosis, treatment, and evaluation. In addition, board-certified physicians in cardiology, allergy and immunology, otolaryngology, orthopedics, and other medical specialties are available to evaluate a variety of comorbid medical disorders in the COPD patients. Physical therapists and exercise physiologists formulate the plan to help individuals reach their maximal physical function, and occupational therapists teach efficient coordinated activities for daily living skills specifically designed to limit breathlessness. The team also includes a respiratory therapist to assist in diagnostic procedures, a patient education coordinator to develop and maintain educational materials, a pharmacist to assist staff and patients with medication issues, and a dietitian to provide assessment and recommendations for nutritional care. A behavioral health clinician (including clinical psychologists and social workers) is available for all patients for consultation and intervention to address adjustment to illness, adherence concerns, other behavioral factors impacting illness, and mental health issues impacting medical management. In addition, there is access to a smoking cessation counselor to assist with behavioral and pharmacological interventions of tobacco cessation and a psychiatrist for patients who need medical and or pharmacological intervention to treat possible psychiatric comorbid conditions.

The neuropsychologists on the team evaluate patients who are experiencing cognitive difficulties, such as deficits in memory or attention, and work closely with the team to recognize deficits and help adapt treatment plans to the specific patient's cognitive strengths and weaknesses. In contrast to the behavioral health clinician specifically evaluating health behaviors, coping styles, depression, and emotional factors, the neuropsy-

chologist's role in our clinic is specifically devoted to cognitive functioning and to any continued consultation for neurology, neuroradiology, etc. Specific referral questions will be reviewed below.

Common Neuropsychological Referral Questions

The referrals for neuropsychological assessment in our facility are typically initiated by the pulmonologist or the behavioral health clinician after their initial appointment with a patient. Intake documents also track patient/family concerns regarding memory and mental abilities, and some COPD patients are flagged prior to their visit for brief cognitive evaluations. All referrals essentially request information regarding (1) the presence, degree, and domains of cognitive impairment (2), etiological factors (i.e., is cognitive dysfunction related primarily to COPD or other factors such as other CNS changes such as a progressive dementia) (3), what is the role of depression and anxiety in the cognitive dysfunction (4), what impact do the cognitive skills have on the day-to-day life of the patient (i.e., patients ability to live independently given cognitive impairment), and (5) is the patient able to understand and carry out medical treatment regimens.

The neuropsychologist might address potential problems with medication adherence (i.e., whether the patient has adequate compensatory strategies), difficulties related to use of inhaler or use of oxygen, and the patient's capacity to care for themselves following surgery/major medical intervention.

Clinical Interview

When conducting a clinical neuropsychological interview with patients with COPD, there are several unique issues to consider in addition to gathering the typical background/medical history information that would be obtained during any neuropsychological evaluation. First, for patients on oxygen, it is helpful to discuss at the beginning of the appointment how much oxygen they require to last through the assessment. It is far better to determine ahead of time that more oxygen is required than to run out midway through testing. Acute drops in oxygen saturation and associated symptoms like fatigue might impact test results causing them to poorly reflect the patient's typical status. If oximetry is available in your clinical setting, it can be helpful to obtain a resting measure of SaO_2 to determine if the patient is hypoxemic on the day of testing. Asking about perceived shortness of breath and level of fatigue on the day of testing is also helpful to understand if the day is typical for the patient.

Depending upon one's clinical setting, it may be helpful to provide additional explanation of the multidisciplinary model of care, specifically the role of neuropsychology in treating patients with COPD (e.g., some common roles are described in the referral question section above). Patients with COPD may be referred by pulmonary or primary care physicians who are concerned about the patient's cognition, while the patient is primarily focused on respiratory symptoms like shortness of breath and has not raised his or her own concerns about cognition. Explaining the neuropsychological evaluation in the context of improving quality of life and daily functioning and understanding cognitive strengths and weaknesses to assist the medical team in working with the patient can be helpful in alleviating hesitance a patient may feel about seeing a neuropsychologist.

During the interview, it is helpful to ask if patients and their family members have noticed fluctuations in the patient's perceived cognitive function in association with changes in respiratory status. Patients might experience fluctuations in cognitive status depending upon their physical activity level, symptoms of COPD, on or off oxygen, or after taking medications. Many patients with COPD experience exacerbations of their symptoms that require outpatient treatment with steroids or hospitalization. Anecdotally, patients with COPD and their families often describe worsening cognition following hospitalization, as can be the case with any ICU or hospital stay, although the reasons for this in COPD specifically have not been explored in the

research literature. Understanding potential fluctuations in cognitive symptoms can help with determining the degree to which cognitive symptoms are attributable to pulmonary disease and making recommendations about how patients can plan the timing of engaging in demanding cognitive tasks.

Due to the impact that physical symptoms of COPD have on activities of daily living, it is necessary to spend some time clarifying with the patient how their cognitive symptoms impact daily tasks. Patients tend to report about activities that they can and cannot do and are less likely to think about *what* aspect of the task is difficult for them. The distinction between limitations in daily tasks due to physical vs. cognitive symptoms is clearly important for diagnosing cognitive impairment and may require some additional prompting in this population.

As a part of any neuropsychological interview, information about past history that may impact brain function is obtained. In COPD, patients are more likely than the general population to have had past environmental exposure to toxins/chemicals, as this is one risk factor for subsequently developing COPD. Furthermore, since smoking is the top risk factor for COPD and nicotine use and use of other substances are common, it is important to ask about potential substance use. There is surprisingly little information regarding actual rates of substance abuse in COPD, as the few articles published to date on alcohol use in COPD have primarily examined the impact of alcohol use on pulmonary symptoms [77]. Nonetheless, in our clinic, we have observed that concerns about alcohol use are common enough in patients referred for neuropsychological testing to have incorporated expanded substance use questions as an area of focus in the interview.

Neuropsychological Testing

The neuropsychological test battery used in our COPD population emphasizes assessment of the domains of processing speed and attention, learning and memory for verbal and nonverbal material, executive functions, and visuoconstructive and visuomotor skills. Intellectual testing or estimated IQ testing is also frequently assessed. Various language skills and academic abilities (i.e., math, spelling, reading comprehension) might also be considered in relation to the referral question and concerns about comprehension of oral and written information and role in day-to-day activities (i.e., understanding written instructions and forms, paying their own bills, etc.). As with most evaluations, considerations for test selection include the age and education of the patient, the overall health and expected stamina of the patient, and the referral question. We also recommend that patient's with prescribed oxygen have sufficient oxygen available in their tanks upon the start of the appointment. In our facility, backup oxygen is available if necessary but may require special arrangements in some outpatient facilities.

In our clinic, there may also be differences in testing based on the availability of the patient. In-state patients with complex referral question (i.e., COPD vs. progressive dementia vs. depression) are typically scheduled for more in-depth evaluations whereas out-of-state patients scheduled to be in our clinic for 1–2 weeks are more likely to get a brief neuropsychological battery designed specifically for our COPD clinic (see case example below). Interpretation of tests utilizing normative data adjusting for age, education, gender, and ethnicity is always considered. In our clinical setting, the neuropsychological test results for the COPD clinic are available within 24 h and presented at the weekly team meeting in order to incorporate findings into day-to-day care and provide specific recommendations (i.e., neurology, neuroradiology) for patients who require additional evaluation of the CNS.

Case Example of Neuropsychological Screening in COPD

As an example, we will review a neuropsychological evaluation performed on a female patient participating in the COPD assessment and rehabilitation program at National Jewish Health in Denver, CO. Ms. Jones was a 64-year-old Caucasian, right-handed female who was referred

by her pulmonologist for our brief out-of-state neuropsychological battery due to concerns regarding cognitive dysfunction that were noted by the patient and her family on her intake forms and subsequently by the pulmonologist during her on-site intake. Ms. Jones reported having significant difficulty with memory, thinking of the names of things, communicating, and concentrating. Her husband, who was present during the interview, indicated that she was easily distracted and would regularly forget things that had been told to her 5 min before. During the interview Ms. Jones reported that she has been having some memory problems for approximately 10 years, with a notable decline in the year before her evaluation. Medical records indicated that she had a history of tobacco abuse, COPD GOLD stage II, obesity, shortness of breath, oxygen dependence, mild pulmonary hypertension, and symptoms of depression. She reported that she smoked an average of one pack of cigarettes from age 18 to 56. The patient had no history of head injury, other neurological illness, learning disability, substance abuse, mental health treatment, or previously identified hearing or visual problems. Ms. Jones graduated from high school with above average grades and later completed course work in general studies but did not complete 1 full year of college credit. The patient had been retired for 12 years and prior to that was a realtor. Her medications included Advair 5/500, Incruse Ellipta 62 mcg per day, Lipitor 20 mgs per day, sertraline 50 mgs per day, benazepril 10 mgs per day, Ventolin 40 mgs per day, Relpax 40 mgs as needed, and oxygen 2.5 L as needed.

No unusual behaviors were noted during the evaluation, and the patient was fully ambulatory on supplemental oxygen. Her SaO_2 level at the beginning of the neuropsychological testing session was 91. She did not appear to have any difficulty understanding test instructions. However, the examiner did have to repeat instructions at times and she appeared to have some mild hearing problems throughout the background interview and testing. Her effort appeared within normal limits. She completed the brief measure of psychological functioning (Hospital Anxiety and Depression Scale [78]), and she endorsed mild symptoms of depression.

Impairment levels for the patient's neuropsychological test scores (based on normative data adjusting for age, education, and when possible gender and ethnicity) are shown in Table 39.2. Overall, her neuropsychological test results indicated mild cognitive dysfunction. Based on her educational and work history, as well as her estimated premorbid IQ, these scores likely represented a decline from average premorbid functioning. As noted in Table 39.2, Ms. Jones was mildly impaired on a measure of auditory attention. She was mildly impaired in her learning and mildly to moderately impaired in her brief delayed for verbal information. She was below average but not significantly impaired in her learning and brief delayed recall for visually presented material. Her recognition for verbal and visual information following a delay was intact. She performed normally in her drawing of a clock to command and copy. She was mildly impaired on a test that required efficiency in following new sequential material. Her basic verbal and nonverbal reasoning was intact. She had no difficulty naming items, but her verbal fluency was mildly impaired. She was normal in most aspects of visuomotor speed and visuoconstruction.

The etiology of Mrs. Jones' mild cognitive deficits was deemed to be most likely related to her history of COPD and other pulmonary issues including episodes of hypoxemia. In addition, there was some evidence of a minor mood disturbance that may have reduced her overall cognitive efficiency. Finally, some minor difficulty with her hearing was noted, and this may have impacted her performance on some tests such as auditory attention.

The recommendations that were provided to the patient, her family, and the rehabilitation team first addressed her poor verbal learning and memory for verbal material and the importance of using compensation techniques. Given their concerns regarding medication use, it was recommended that she use a carefully constructed checklist or a pill box for medication types and dosages by the hour. Use of a schedule or appointment book was also recommended for day-to-day activities. Given her relative strength in visual learning, she was likely to learn new techniques

Table 39.2 Brief neuropsychological battery for COPD assessment: case example

Function	Measure	Performance range
Intellectual functioning		
Oral reading/estimated premorbid IQ	WTAR[a]	Average
Attention and processing speed		
Attention to numeric sequences	WAIS-IV[b] digit span	Mildly impaired
Visual scanning and tracking speed	Trail making Test[c] form A	Average
Nonverbal attention and learning	WAIS-IV coding	Average
Executive functioning and problem solving		
Sequencing efficiency	Trail making test form B	Mildly impaired
Verbal abstract reasoning	WAIS-IV similarities	Average
Nonverbal reasoning	WAIS-IV matrix reasoning	Average
Learning and memory		
Verbal list acquisition	HVLT-R[d] total trials 1–3	Mildly impaired
Verbal list free recall	HVLT-R delayed recall	Mildly to moderately impaired
Verbal list recognition	HVLT-R recognition	Average
Nonverbal acquisition	BVMT-R[e] total trials 1–3	Below average
Nonverbal recall	BVMT-R delayed recall	Below average
Nonverbal recognition	BVMT-R recognition	Average
Language functioning		
Naming to confrontation	BNT—Short form[f]	Average
Verbal fluency	COWAT[g]	Mildly impaired
Semantic fluency	Animal naming	Mildly impaired
Visuospatial functioning		
Visuoconstruction	WAIS-IV block design	Average
Drawing to command	Clock[h] drawing	Average
Drawing to copy	Clock copy	Average

[a]*WTAR* Wechsler test of adult reading [79]
[b]*WAIS-IV* Wechsler adult intelligence scale—fourth edition [79]
[c]Trail making test [80]
[d]*HVLT-R* Hopkins verbal learning test—revised [81]
[e]*BVMT-R* brief visuospatial memory test—revised [82]
[f]*BNT* Boston naming test—short form [83]
[g]*COWAT* controlled oral word association test [84]
[h]Clock drawing test [32, 85]

better by watching or using visual cues. For example, instead of describing a new activity, such as getting on a treadmill to exercise, it was recommended that medical providers demonstrate the activity and have her practice several times. In addition, keeping written notes and printing out any available material for new procedures were suggested. As noted by her family, she was a little slow to generate words, which was likely related to her COPD, as this is a common finding in the literature. Although her minor difficulty with verbal expression was deemed unlikely to dramatically interfere with her day-to-day life, recommendations included providing additional time for the patient to express herself to make interaction more comfortable for the patient. As part of the rehabilitation team, the patient met with a behavioral health clinician and continued her routine medical treatment back in her home state. Given concerns regarding her hearing, an audiological evaluation was recommended. Repeat cognitive testing following any substantial medical or multidisciplinary treatment was recommended to identify significant changes (improvement or decline) over time.

Clinical Pearls

- Patients with COPD demonstrate cognitive impairment that worsens with severity of COPD and the presence of hypoxemia.
- Cognitive areas that are most commonly impaired include aspects of verbal learning

and memory, visuomotor speed, and verbal fluency.

- Cognitive dysfunction in COPD patients may be mediated by a number of comorbidities, including cardiovascular disease, depression, and anxiety.
- Determine at the onset of the appointment if the patient is prescribed oxygen therapy and whether sufficient oxygen is available to last throughout the exam.
- Query about exposure to environmental toxins as well as smoking and substance use/history.
- It is common for patients with COPD and their families to describe worsening cognition following hospitalization, as can be the case with any ICU or hospital stay, yet this has not been systematically studied.
- Moderate to severe neuropsychological deficits may suggest the need for additional neurologic workup (i.e., neurologic exam, neuroimaging) to assess other CNS comorbidities.
- Repeat neuropsychological testing following medical therapy (i.e., oxygen or medication changes) or comprehensive rehabilitation may be useful in documenting change over time and to assess any potential for other CNS disorders.
- Identification of cognitive strengths and weaknesses in COPD patients can be utilized to propose compensation techniques for day-to-day activities and for a rehabilitation team to work effectively with the patient.

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40 Neuropsychological Assessment of Adults Being Considered for Mechanical Circulatory Support

Chris E. Morrison and Danny M. Tam

Overview of Heart Failure

Heart failure (HF) is a complex clinical syndrome characterized by impaired myocardial performance and neurohormonal abnormalities that lead to circulatory insufficiency and congestion [1]. In practice, the determination of HF is a clinical diagnosis based on the patient's history and physical examination, as no single test alone is diagnostic [2]. While the presentation of patients with HF can range from asymptomatic to critically decompensated, the cardinal features are commonly fatigue, dyspnea (shortness of breath), and peripheral edema [3]. Ischemic cardiomyopathy is the most common etiology of HF in the industrialized countries followed by hypertensive, dilated, and metabolic (i.e., diabetes mellitus, hypothyroidism) cardiomyopathies. While heart failure can result from disorders of the myocardium, pericardium, and endocardium, the majority of HF patients have symptoms related to left ventricular dysfunction [2].

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Epidemiology

Heart failure has been described as a growing pandemic and serious public health issue, contributing to an estimated $39 million in costs in the United States [4]. Approximately 5 million individuals in the United States have HF, with 550,000 newly diagnosed patients annually [5]. It is estimated that by 2030, over 8 million Americans will be living with HF [6]. In the United States, African-Americans have the highest risk for developing HF, followed by Hispanic, Caucasian, and Chinese Americans [7]. At 40 years of age, both men and women have a similar one in five lifetime risk of developing HF [7]. Epidemiological research indicates that HF is primarily a condition of the elderly [8], with an incidence approaching 10:1000 after the age of 65 [2]. Consequently, approximately 80% of patients hospitalized for HF are over 65 years old [9], and HF represents the most common discharge diagnosis for patients on Medicare and cause for readmission within 60 days [7].

Neurocognitive Impact of HF in Adults

Although the prevalence of cognitive impairment in patients with HF varies depending on sample and disease characteristics, rates have generally been reported to range from 25% to 75%. Because

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HF can ultimately result in low systolic blood pressure, poor cerebral perfusion, and impairment in cerebral neurohormonal autoregulation [10–13], there can be a range of secondary effects on neuronal functioning. This secondary impact of HF on the brain can be followed by neuropathology, decline in cognitive functioning, and reduced ability for independent management of daily activities. Such functional losses can all contribute to lower quality of life.

In patients with HF, reduced cardiac output and associated ischemic brain damage have been proposed as being the primary contributors to some of the structural abnormalities found on neuroimaging [12]. The most apparent findings include more severe white matter hyperintensities relative to healthy individuals, along with the presence of small vessel disease [14]. Mesial temporal regions, which are particularly sensitive to hypoxia, also show neuronal loss [15]. Grey and white matter changes have been described in the frontal insula, as well as in subcortical structures (e.g., mammillary bodies, putamen) [16–18].

Chronic HF has been associated with global cognitive deterioration as assessed by brief screening measures [19, 20], although a more focal profile of impairment in aspects of attention, executive functioning, processing speed, and memory has also been reported when more extensive neuropsychological batteries were utilized [19, 21].

Depression is also a common comorbidity. Approximately 55% of patients with HF have depression, with 20% at clinically significant levels [22, 23]. Depression has been found to be a risk factor for poorer cognitive performance in patients with HF, particularly when there is also memory impairment [24], and may in fact play an interactive role. It has been suggested that depression in some HF patients may reflect underlying structural changes in the brain [25]. This may be consistent with proposals of a vascular depression associated with deep white matter hyperintensities [26].

Patients with HF have also been found to have higher rates of self-reported impairment in managing instrumental activities of daily living (IADLs), with cognitive impairment as an independent predictor of level of IADL functioning, including driving and medication management [27]. Heart failure patients diagnosed with mild cognitive impairment (MCI) via screening measures were found to have adequate knowledge regarding HF but significantly poorer scores on a HF self-care scale [28]. The consistent deficits observed in attention, processing speed, and executive functioning in this population likely interfere with a patient's ability to manage medication regimens, respond to changes in symptoms, and seek treatment [29, 30]. These types of difficulties are likely to be magnified when patients with HF are required to manage a life-saving medical device.

The Left Ventricular Assist Device (LVAD)

In patients with refractory HF, a heart transplant is generally considered the best option for treatment, with high rates of 1-year survival and up to 60% survival over 10 years [31, 32]. However, the viability of this option is limited by organ availability. Furthermore, some patients may not be suitable transplant candidates, or their risk profile may increase (due to health decompensation) while on waiting lists. This has led to the use of methods for mechanical circulatory support (MCS) to increase patient survival, improve quality of life, and reduce morbidities.

While there are many methods for MCS, the left ventricular assist device (LVAD) is one of the most commonly used. The LVAD is an implantable pump designed to provide support to the left ventricle in order to maintain adequate blood flow. It was first approved by the Food and Drug Administration (FDA) in 1994 with the initial indication of serving as a bridge to transplantation in patients with advanced HF who were not expected to survive until a transplant option became available. While this continues to represent a large majority (up to 80%) of LVAD cases [33], there has been a rise in patients implanted

with an LVAD as a destination therapy (DT) in those deemed ineligible for a transplant, either due to comorbidities or other risk factors. This change in treatment indication to include DT has changed some of the prior age-related limitations for surgical eligibility. The mean age of patients undergoing DT increased from 52.7 to 61.7 years [34, 35].

Modifications in LVAD treatment indications have occurred with changes to the technology. The first generation of LVAD devices were larger, contained more moving parts, and were more prone to postsurgical complications than current models. They operated using a pulsatile flow technology, which was designed to mimic the natural conditions of human hemodynamics. Newer generation LVAD devices have the advantage of being smaller and quieter, with fewer moving parts and increased durability, and operate via continuous flow [35]. Surgery involves implantation of an internal pump through a sternotomy, with a lead connecting via a driveline to an externally worn control unit requiring a constant power source (e.g., battery).

Risks and Outcomes

Although outcomes are better than with medical therapy alone for select patients [36], the risk/benefit profile for this method of MCS is complex. Apart from advances in technology and surgical technique, LVAD outcomes are based in large part on the appropriate screening and selection of candidates [37, 38]. The cardiac team considers the severity of HF, as well as a number of other cardiac and noncardiac factors. Although a comprehensive review of all the medical considerations reviewed by the cardiac team is beyond the scope of this chapter, in brief, cardiac and anatomical risk factors that are associated with postoperative complications or mortality include right ventricular dysfunction [39], extremes in body weight [40], and arrhythmias [41]. Noncardiac factors that impact patient selection due to their association with negative outcomes include advanced age [34], systemic illnesses with short predicted survival [42], irreversible or progressive neurological conditions (e.g., stroke with severe impairment, dementia), psychiatric comorbidities [38], and poor social support.

The greatest mortality risk associated with LVAD surgery occurs during the immediate postoperative period prior to discharge [43]. Acute complications can involve organ failure, right ventricular failure, infection, or embolic events [44, 45]. More long-term post-implant risks include stroke, renal dysfunction, gastrointestinal bleeding, infection, and device malfunction/failure [33]. The 1-year survival rate with the newer continuous-flow devices is 74% [34, 46].

While some studies have examined neuropsychological outcomes in LVAD recipients, few have included a presurgical baseline assessment to provide a basis for comparison. Additionally, the contribution of cognition and mood has tended to be examined separately [47] making a distinction between etiologies challenging. Comparisons of preimplantation baseline data to postsurgical evaluations conducted at ~2 to ~15 months post LVAD placement indicate significant improvement in verbal memory with stability in other cognitive domains [47]. While most patients do appear to exhibit improvement in cognition after implantation, cognitive decline has also been reported to occur in approximately 25% of patients 1 year postsurgery, with older age and destination therapy as predictors of change [48].

In terms of mood, studies have generally found either no significant adverse mood outcomes or even some improvement in symptoms of depression and anxiety [47, 49]. While LVAD patients typically report improved health status and fewer mood symptoms than other HF patients who receive medical management alone, this improvement is typically not to the same degree as that seen in heart transplant recipients. This difference may be partially due to patients having frequent reminders that they are living with an LVAD device (e.g., needing to clean and maintain parts of the device), necessitating some adjustment and reconceptualization of their "normal" routine and lifestyle [50, 51].

The LVAD Team

In order to best identify the range of patient characteristics that are associated with optimal outcome and/or best management of risk for morbidity/mortality, a multidisciplinary team is needed. Current standards call for such a team to include, at a minimum, a heart failure physician, a dietician, and a pharmacist [52]. Recently published guidelines and consensus statements also emphasize the importance of evaluating neurological, neurocognitive, psychological, and psychosocial functioning when considering an individual's candidacy for LVAD placement [53, 54]. For example, understanding the patient's neurological status (e.g., presence of severe neurological disorder), whether patients have the fundamental neurocognitive ability to manage the LVAD equipment, and whether they have achieved psychological and behavioral readiness to live with MCS are all important factors in the risk/benefit assessment of patients being considered for LVAD placement.

Patients with HF who may be candidates for LVAD implantation generally undergo a staged evaluation process by the team. The cardiologist will review the medical history, as well as complete a physical exam, cardiopulmonary testing, blood panel, and other tests (e.g., electrophysiology and imaging) as appropriate to determine if the patient is a medically suitable LVAD candidate. Once this first criterion is met, other disciplines, such as social work, palliative care, psychiatry, and neuropsychology, are asked to perform assessments of the patient. Some of the overarching goals of these later evaluations are to identify, and manage if possible, risk factors for a poor outcome, as well as better understand a patient's ability to care for themselves following surgery. The social worker tends to focus on psychosocial factors that could potentially impact living with an LVAD, including financial concerns and lifestyle adjustments. Consultation with a psychiatrist is undertaken to evaluate for psychological processes (e.g., significant mood disorder) and/or active substance abuse that may be a barrier to the patient's commitment to the complexities of living with an LVAD. Finally, the neuropsychological evaluation aids in helping the team determine whether the patient has a progressive neurodegenerative process (dementia being a rule out for eligibility) or cognitive impairment that could affect their ability to manage postsurgical care.

Presentation and Settings

Although the presentation of HF patients can vary widely, common symptoms that prompt acute medical intervention can include increasing fatigue, shortness of breath, and difficulty with exertion. When LVAD placement is being considered in these HF patients, the neuropsychologist may be asked to perform an evaluation when patients are in acute medical crisis, medically stabilized but still in an inpatient setting, or in the outpatient clinic following some level of adequate medical management of cardiac decompensation.

In the more acute scenarios, it is not unusual for patients to have medically decompensated over the previous weeks or months. The neuropsychologist may encounter these patients in the cardiac intensive care unit, perhaps still intubated or having just been extubated. When receiving such a referral, part of the initial assessment will involve determining whether the patient has sufficient arousal and stamina to engage adequately with the evaluation process. Communication with the cardiac team may be sufficient for this purpose. However, these patients may have a waxing and waning status that requires the neuropsychologist to directly determine if an assessment with the patient is possible. Ultimately, because of the patient's compromised medical condition, neuropsychological assessment in this setting may be quite limited, as will conclusions from the exam. Nevertheless, any screening that is performed can be used to track the patient's changing cognitive status as they become more medically stabilized. Although objective data may be limited in these exams, at the very least, the neuropsy-

chologist's interview with the family will help contribute to an understanding of cognitive symptoms that may have been present prior to the most recent cardiac decompensation.

Probably the most common setting for performing a pre-LVAD neuropsychological evaluation is the inpatient cardiac care unit. In this setting, patients may be encountered in bed sitting up or even sitting up in a chair. A more typical inpatient neuropsychological exam can then be conducted. However, it is important to keep in mind that patients will often have low energy, thereby limiting their ability to participate in sustained periods of cognitive testing. Furthermore, as can be surmised from the list above, many different specialists will be seeking time with the patient, who may be moved on and off the unit as various medical tests are performed. These interruptions will require the neuropsychologist to be strategic with how the battery is developed and the testing completed.

On rare occasions, it may be possible to schedule patients for outpatient neuropsychological assessment should the patient be stabilized sufficiently for discharge while the pre-LVAD surgical planning is completed. However, to accommodate the timeline that is often needed in this situation, the neuropsychologist must be able to integrate these patients into their outpatient schedule within a few days of the hospital discharge. Even in this outpatient situation, the patients are frequently easily fatigued, necessitating a somewhat limited testing session.

In order to optimize timing and access to these patients, good communication with the cardiac team is critical. For the neuropsychologist who is just beginning work with a multidisciplinary LVAD team, it can be extremely helpful to meet with the cardiac team coordinators (often a nurse practitioner) to educate them on the necessary requirements for completing a neuropsychological exam. Although it may be self-evident to readers of this chapter, the requirement for uninterrupted periods of time and a patient who is awake and communicative may not be initially appreciated by our cardiology colleagues and their support staff (Table. 40.1).

Table 40.1 Common etiologies of cognitive impairment in LVAD candidates

Acute compromise of cardiac functioning (e.g., low ejection fraction)
Delirium
Mild cognitive impairment due to vascular disease
Vascular dementia (e.g., due to strategic infarct, Binswanger's disease)
Alzheimer's disease (AD)
Mixed (AD/vascular) dementia
Depression

History and Interview

This patient population typically has a litany of cardiac and other health conditions, many of which pose risk for cerebrovascular disease and associated cognitive impairment. At the time of the LVAD work-up, patients are frequently low in energy, cognitively compromised due to their medical status (e.g., ejection fractions are often <20%), and generally not feeling well. In this context, it is rare that a patient can tolerate several hours of interaction with the neuropsychologist. Furthermore, when evaluations are performed on an inpatient basis, there are many other specialists who need access to the patient and other presurgical tests that need to be performed. Therefore, the neuropsychologist must be strategic in how their time is spent with the patient in terms of clinical interview and testing.

By the time the neuropsychologist becomes involved, the cardiologist has already critically reviewed the complex medical history and entered it into the electronic medical record (EMR). Thus, after reviewing available EMR information, the neuropsychologist's time with the patient is likely better spent on developing the timeline and progression of any cognitive symptoms or functional decline, as well as the details of any neurological history (e.g., cardiology notes may document "CVA" though there may be little information on cognitive sequelae) that can impact interpretation of the test scores and estimations of prognosis for cognitive change following LVAD placement. For example, a patient who describes intact occupational and daily functioning followed by acute health and cognitive

decline in the weeks or month leading up to hospitalization may have a very different trajectory of cognitive recovery or cognitive risk following an LVAD implantation compared to a patient who has experienced progressive cognitive decline over a longer time period. As in all settings where cognition may be significantly compromised, obtaining collateral information from a family member or close friend can be critical to this process.

Review of psychiatric history and current mental health presentation is also a component of the patient selection criteria for establishing their ability to be compliant with the medical care associated with LVAD placement [38, 55]. Although a separate psychiatric consult may be part of the pre-LVAD screening process, psychiatry services may not be available in every setting. Thus, the neuropsychologist could be called upon to perform a psychiatric screening and assessment as part of their neuropsychological evaluation. Significant psychiatric or substance abuse history, past compliance with and response to mental health treatment, as well as current psychiatric/substance use status can have a significant impact on a patient's eligibility for LVAD placement. In addition, the patient's overall interest in extending their life must be ascertained as this is also a critical factor in determining the appropriateness of life-extending surgery. For example, in patients who report ambivalence or express apathy regarding the prospect of surgery, there is concern about their commitment and willingness to be active participants in their postsurgical care. In more extreme circumstances, such as when patients are suffering from major depression (particularly with suicidal ideation), the risk of misusing the LVAD equipment in a suicide gesture/attempt is higher. Finally, one could imagine that other forms of medically refractory severe psychiatric symptoms (e.g., thought disorder, delusions, hallucinations) can prohibit a patient's ability to operate the LVAD equipment. In these and related circumstances, putting a patient through the process of LVAD placement and all the associated postoperative life changes would not be consistent with the medical edict of "do no harm."

A significant psychiatric or substance abuse history would not necessarily preclude a patient from consideration for LVAD placement if their symptoms are currently well managed (i.e., regular follow-up with a psychiatrist/psychologist, medication adherence). Evaluating for this, as well as whether symptoms have ever previously adversely impacted their self-care, is important. There must typically be some indication that the patient can follow medical and mental health treatment plans and, if relevant, contract to abstinence of any substances of abuse and undergo counseling/rehabilitation.

Another important component of the pre-LVAD screening assessment process involves gaining an understanding of the patient's psychosocial context. In the initial postsurgical period following discharge, patients are often largely (if not completely) dependent on caregivers to implement and adhere to the home care regimen [56–58]. Therefore, it is important to discuss with the patient (and any collateral sources) exactly who would be available to assist with follow-through on medical recommendations and appointments and be available in case of device malfunction [55]. In addition to asking who would comprise the patient's support network, it can also be important to determine what the patient's own perception of their support system is, as it has been found that even perceived social support in patients with HF has been associated with better self-care behaviors (e.g., diet and medication adherence) [59] and confidence in one's own self-care abilities [28]. As many cardiac teams will have a social worker who performs much of this aspect of the pre-LVAD screening process, the neuropsychologist may be able to access this information from the EMR and not need to duplicate efforts in this area.

Through the course of the interaction with the patient, it can be extremely enlightening to elicit their understanding of the procedure, their knowledge of how life will change following implantation of the LVAD equipment, and their postsurgical hopes and expectations. The downstream consequences of a mismatch between what has been communicated to the patient and what the patient's understanding is can be quite

detrimental to quality of life. Asking patients to briefly describe their understanding of the treatment regimen can be useful for this purpose. For the reader's edification, instructions and responsibilities that are typically communicated to the patient and caregiver include general information on operating the device and interpreting the digital display indicators, care requirements for the LVAD and its components, maintenance of daily records (e.g., temperature, weight, LVAD readings), medication adherence, compliance with infection precautions, and avoidance of any high-impact activities that can cause damage or trauma to the LVAD and driveline. It can also be informative to determine what the patient's specific goals are should they receive the LVAD and experience an improvement in their functioning. Some patients may respond in a way that indicates they have expectations for outcome that are not feasible (e.g., expressing a desire to engage in water or contact sports) or are otherwise unrealistic. When a discrepancy between patient and physician expectations is discovered, the neuropsychologist can provide feedback to the cardiac team so that additional patient education can be given.

Approach to Neuropsychological Assessment

As described earlier, the prevalence of cognitive impairment in patients with HF has been reported to range from 25% to 75%. However, the cognitive profile in HF patients who are specifically candidates for mechanical assistive devices has not been as well characterized. One study found that 67% of LVAD candidates met criteria for mild cognitive impairment when assessed using a brief screening measure [60]. When a cross section of patients with advanced HF was examined and grouped by disease severity, the results indicated generalized cognitive decline, with the worst performance noted in patients being considered for a mechanical assistive device [61]. These authors found that the earliest abnormalities detected in the outpatient group with less severe HF were in motor speed and grip strength. With progression of cardiac disease, specific deficits were observed in verbal recall, nonverbal memory, and processing speed [61]. Another study using a smaller sample set but with more comprehensive tests revealed that 89.5% of pre-implant patients had impairment in executive functioning, with approximately half of patients performing below expectations on specific measures of rapid set-shifting and letter fluency [47].

There are both transient and static factors that contribute to neuropathology and associated cognitive dysfunction in this population, and, as a result, the goals of the neuropsychological evaluation in the pre-LVAD screening process are twofold. First, it is critical to rule out frank dementia as such a condition renders a patient ineligible for LVAD placement. Second, based on the literature, it is clear that various manifestations of MCI are quite common in this population. It is important for the neuropsychologist to characterize the nature and extent of any cognitive impairment in order to help the team understand how any cognitive deficits might impact the patient's ability to learn to operate and maintain the LVAD equipment. Given these parameters and the multitude of variables that must be considered when developing an assessment approach (e.g., age, educational background, premorbid ability, linguistic and cultural background), prescribing a fixed battery of tests for the purposes of "evaluating LVAD candidacy" is a nearly impossible task. However, the following guidelines for how to focus the assessment approach and suggestions for tools that may be useful are offered.

When considering an approach to evaluating this population of patients, there are a few factors that must be weighed heavily. First, as indicated, the evaluation must be brief. The low energy these patients often present with and the limited access the neuropsychologist may have in terms competing with other consult services and procedures for the patient's time can be significantly rate limiting. Focusing the evaluation on key domains of functioning will help with truncating length. Specifically, attention, memory, and executive functioning are all fundamental to determining if the patient has the cognitive capability for learning how to use the LVAD device,

completing the responsibilities of care and maintenance, and using judgment when critical decision-making is required (e.g., understanding warning lights on the digital display and ascertaining appropriate lifesaving next steps that may need to be completed in a very short amount of time).

Some domains of cognitive ability may not be a critical focus of the test battery. For example, while assessment of processing speed is relevant in many clinical settings, virtually every patient assessed in this population is likely to demonstrate psychomotor slowing due to their medical circumstance. Thus, specific efforts to evaluate processing speed are likely to yield the same outcome (impairment) in nearly every patient and therefore offer very little in new and helpful diagnostic information.

When considering specific test selection, for the reasons stated, there should be emphasis on brief repeatable measures. The availability of multiple alternate forms is helpful as patients may require follow-up assessment during the course of their hospitalization or following their surgery. Screening measures for a brief characterization of global cognitive ability are often a useful place to start. Tools such as the Dementia Rating Scale-2 (DRS-2) [62] that have an alternate form and touch on several different cognitive domains are helpful in this regard. In patients who are younger or where there is less of a concern for dementia, the DRS-2 may be omitted or placed lower on the priority of tests to administer.

Assessment of memory for the purposes of ruling out dementia and determining the presence and type of MCI is a necessary element in any battery of tests in this referral context. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [63] is particularly helpful in this population as it not only includes three memory subtests but also integrates a selection of other tasks that screen attention, visuomotor processing speed, language, and visuospatial/visuoconstruction ability. The availability of up to four alternate forms provides additional advantages and flexibility. The RBANS has been shown to produce different profiles of impairment across index scores depending on etiology [64, 65], which can be helpful in detecting the subcortical profile of deficits that can emerge in the context of cerebrovascular cognitive impairment. Additionally, the RBANS has shown a relationship to functional impairment based on informant report [66], particularly with performance on the Immediate Memory and Total Scale indices [67].

As the RBANS does not include tests of executive functioning, supplementing the battery with measures of set-shifting and problem solving is important. Researchers have utilized the Trail Making Test, part B [68], in some studies as the sole criterion of cognitive decline, citing the range of frontal functions requisite in completing this measure and the availability of multiple forms, as well as the extensive support in the literature for this task as being sensitive to cardiac and vascular neurological impairments [69–72]. That said, it may not sufficiently assess problem solving skills of the type needed for triaging action points related to the LVAD digital displays and care/maintenance of the LVAD equipment. Addition of a higher-order executive function tasks such as the Wisconsin Card Sorting Test-64 (WCST-64; [73]) can be helpful in understanding how a patient manages novel situations, whether there are concerning difficulties with perseveration, and even how they tolerate frustration in a challenging situation.

As mentioned previously, it is extremely important to assess mood in these patients. Whether the neuropsychologist is the sole mental health provider on the team or whether there is also a psychiatrist performing a separate diagnostic interview, it is often helpful to supplement the psychiatric interview with brief, self-report inventories of mood symptoms. Although the Beck inventories (Beck Depression Inventory-II, [74]; Beck Anxiety Inventory, [75]) are certainly useful, HF patients generally have multiple health comorbidities that can drive endorsement of somatic symptoms on such measures. Therefore, questionnaires that minimize physiological symptoms, such as the Geriatric Depression Scale (GDS; [76]), may be more useful, regardless of the patient's age.

Table 40.2 LVAD assessment at NYU Langone Medical Center

Dementia Rating Scale-2 (DRS-2)
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Trail Making Test A and B
Wisconsin Card Sorting Test-64 (WCST-64)
Other common supplemental measures
Digit span
Verbal fluency
Beck Depression Inventory-II (BDI-II) or Geriatric Depression Scale (GDS)
Beck Anxiety Inventory (BAI)

A list of the typical measures administered at NYULMC is summarized in Table 40.2.

Feedback to the Treatment Team

The results of the neuropsychological evaluation performed for the purposes of understanding LVAD eligibility are generally needed by the treatment team within 24–36 h of when the testing was completed. In addition to accommodating the requirement of rapid report turnaround, there are other features of working with this type of treatment team that influence how the neuropsychologist may approach report writing in this setting. Unlike other referral sources (e.g., behavioral neurologists, psychiatrists) who may be somewhat more interested in the details of the patient's background or the neuropsychological test data, the cardiology treatment team is often primarily interested in the "bottom line" (e.g., answers to the referral questions described above) with less concern for how the neuropsychologist reached their conclusions. Furthermore, as stated, the team is less likely to need the neuropsychologist to recapitulate the complex medical history that has already been carefully laid out in the EMR by the cardiac team leader. Thus, a brief 1–1.5-page report is often sufficient to meet the needs of the care team.

Writing a very short and focused communication can be more challenging than writing the more traditional neuropsychological consultation report. The example report appended at the end of this chapter is provided to facilitate a better understanding of what is most likely to be needed in this treatment context. Within the narrative, it is important to mention any environmental (e.g., interruptions, noise) or patient-specific (e.g., extreme fatigue limiting the scope of the exam) factors that may have compromised the data. As in any clinical evaluation, the history of cognitive impairment and functional decline (as supported by a collateral report) is also important to include. This information facilitates drawing preliminary conclusions about whether any identified (or suspected) cognitive impairment represents a dementia or whether the patient might be expected to improve in terms of neurocognitive function once heart functioning is improved with MCS. The clinician's best hypotheses on these issues should be plainly stated, and the method for follow-up clearly delineated in the Conclusions section of the report.

Case Example: Model Report

Referral Mr. Doe is a 69-year-old, right-handed Caucasian man referred for neuropsychological testing as part of a presurgical work-up for LVAD placement.

Past Medical History Cardiomyopathy, CHF, Afib, ICD implantation (2010), CVA (2010–? embolic etiology with full recovery), COPD, NIDDM, and BPH. *Psychiatric History:* No past psychiatric contact or report of mood disorder. Situational anxiety in the context of his recent health decline and the proposed surgery. *Social History:* Married, 2 adult children. Completed HS; no history of LD or academic difficulties. Worked in auto repair for most of his life; in the last 3 years, he has worked part-time sorting mail. When feeling well, he likes to go on walks, visit friends and casinos, and go on cruises. He denied any cognitive difficulties; his wife feels he is more forgetful, particularly in the last 3 months. Both agree that the only changes in his ability to perform IADLs are related to his health problems.

Tests Administered Test of Premorbid Functioning (TOPF); Wechsler Abbreviated Scale of Intelligence-II (WASI-II) two-subtest; Dementia Rating Scale-2 (DRS-2); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) – Form A; Trail Making Test (TMT); Wisconsin Card Sorting Test-64 item (WCST-64); Beck Depression Inventory (BDI-II); Beck Anxiety Inventory (BAI).

Behavioral Observations Testing was conducted at bedside within the CCC unit. Speech output was normal; thought content was coherent and goal directed. He was cooperative and engaged with the examiner but easily fatigued; testing was split into two segments. Mobility was slightly limited owing to the various IVs and medical monitoring devices.

Test Results Premorbid general intellectual functioning is estimated to be in the average range. Performance was within normal limits on an extended mental status exam (138/144). His global performance on a neuropsychological screening measure was generally at expectations; however, his ability was somewhat uneven across domains.

When test performance is taken together with observations, the fundamentals of expressive and receptive language functioning were considered to be within normal limits. Immediate span of auditory attention was adequate; however, verbal working memory was impaired. In terms of verbal memory, although his rate of learning was mildly diminished, he demonstrated the capacity for encoding and retention when given sufficient learning opportunities.

On visually mediated tasks, he struggled with visuospatial processing and visual reasoning. On some measures he was slow to visually scan a page for target identification. Memory for visual information was poor. Overall slow processing speed (likely related to fatigue) clearly affected his performances on timed measures. Due to diplopia (and his associated efforts to compensate by closing one eye), interpretation of these low scores on visual scanning, visuospatial construction, and nonverbal memory tasks is limited.

Aspects of executive functioning were impaired. Specifically, marked difficulty on untimed and timed measures of cognitive flexibility, novel problem solving, and hypothesis testing was noted.

On self-report questionnaires, he denied significant mood-related symptoms (BDI-II = 2; BAI = 6). Though he is very frustrated with the limitations his health condition has imposed on his very busy daily life, he is in good spirits and future oriented.

Impression Overall, this screening revealed a pattern of neurocognitive strengths and weaknesses that meet criteria for at least MCI. Given the history of recent onset cognitive decline in the context of normal adaptive functioning (from a cognitive perspective), it is likely that many of the cognitive weaknesses seen in this exam are related to his currently declining cardiac status. Some of the low scores seen in this exam could be secondary to peripheral factors (e.g., double vision) and will therefore not be integrated into the formulation at this time.

It is reassuring that Mr. Doe's verbal memory is intact, suggesting adequate ability to learn the procedures associated with LVAD use. His difficulty with cognitive flexibility and problem solving is more concerning. To compensate for these difficulties and to optimize his surgical outcome, it will be important for the cardiac team to train him on the device hardware in a distraction-free environment and working on one thing at a time. He does not easily switch between tasks or subjects (he becomes rather confused when faced with multiple choices and the need to apply different rules/procedures for different situations). In addition, because of the observed difficulty with efficient problem solving, it may be helpful to have him demonstrate with the LVAD hardware how he would go about handling various scenarios with regard to the alarms and readouts requiring an action from the patient. This will help the team understand his ability to

grasp basic concepts and if additional training is needed.

Finally, there are no indications of current mood disorder and the patient is future oriented. He is anxious to proceed with LVAD placement so that he may resume many activities that contribute to his quality of life. He was able to acknowledge that LVAD placement would lead to some restrictions in his daily life.

Clinical Pearls

- It is critical to provide the cardiac team with education regarding how a neuropsychological evaluation can be performed validly.
- Get educated on the procedure and device the patient is being evaluated for. Our clinical battery changed after they provided us with an in-service and we became more familiar with all the cognitive elements needed to operate the device and manage the equipment.
- Obtaining a collateral interview is key for ascertaining whether cognitive impairment occurred exclusively in the context of acute cardiac decompensation.
- Be short and be creative with your approach to cognitive assessment.
- Be brief and to the point in consultation reports. Do not provide pages of history and test descriptions.

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Hepatic Encephalopathy

41

Heidi Musgrave and Robin C. Hilsabeck

Hepatic encephalopathy (HE), also referred to as portosystemic encephalopathy (PSE), is a metabolically induced, usually reversible neuropsychiatric syndrome resulting from failure of the liver to perform its detoxifying function. HE is usually associated with acute or chronic liver dysfunction but can also be due to portosystemic shunts that divert portal blood into circulation before removal of toxins by the liver. In its mildest form, HE manifests as subtle cognitive or motor difficulties that may not be detectable upon clinical exam alone. HE is one of the most serious complications of liver dysfunction and is a feature of fulminant hepatic failure. In its most severe form, HE results in coma and death. Between one-third and one-half of hospitalizations of patients with *cirrhosis* are due to HE, and the frequency of hospitalization for HE has doubled over the past decade, with average hospital stays between 5 and 7 days [1, 2]. HE is a marker of poor prognosis [3], resulting in death in over 75% of patients within 3 years of their first episode [4]. In patients with acute liver failure, prognosis is even grimmer, with only about half surviving hospitalization [5]. Although rare, acute liver failure is the most frequent indication for emergency liver transplantation in most countries [6].

Classification and Grading of HE

In an attempt to provide consistency within the literature, scientific study, and treatment of HE, the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) convened in 2014 to create a standardized Practice Guideline [7]. This classification system is based on etiology, severity of symptoms, time course, and whether the episode is precipitated by known or unknown factors. Each area should be addressed and rated at each encounter.

Underlying Etiology

The type of HE is based on underlying liver dysfunction. Type A is associated with *a*cute liver dysfunction, type B with portosystemic *b*ypass in

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Table 41.1 Etiologies of hepatic encephalopathy (HE)

Type	Etiology
Type A	Resulting from acute liver failure
Type B	Resulting predominantly from portosystemic bypass or shunting
Type C	Associated with cirrhosis

the absence of liver disease, and type C with liver cirrhosis, which is the most common (see Table 41.1).

Continuum of Severity

Severity of HE is graded on a scale from minimal to 4, where minimal represents a normal clinical examination and 4 is coma. Minimal and grade 1 are also known as "covert" HE, and grades 2–4 are considered "overt" HE. The most widely used method of grading HE is the West Haven criteria (WHC) [8, 9], which is determined by clinical examination and based on the subjective evaluation of the clinician (see Table 41.2). This method has been criticized for lack of sensitivity to detect subtle brain dysfunction [10]. For this reason, neuropsychological or neurophysiological measures are recommended to identify covert HE [11, 12]. Identifying covert HE is essential so that symptoms can be monitored and treatment be initiated given that covert or minimal hepatic encephalopathy has a negative effect on quality of life and ability to maintain functioning [13–20]. In general, basic activities of daily living are preserved, while activities that involve divided attention, visuospatial abilities, and motors skills, such as driving, are often impaired [21].

It is important to remember that although specific criteria have been determined to be characteristic of each grade, clear distinctions between grades sometimes cannot be made, and patients may fluctuate from grade to grade within minutes or hours, further clouding the clinical picture. According to Bajaj and colleagues, once the patient exhibits disorientation to time and asterixis, the patient is considered to have moved down the continuum from covert to overt HE [22].

Table 41.2 West Haven criteria (WHC) and International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) categorization for grading hepatic encephalopathy (HE)

International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)		Characteristics
Unimpaired		No history of HE/no encephalopathy
Minimal	Covert	No evidence on clinical exam/positive findings on neuropsychological testing
Grade 1		Oriented to time, decrease in attention span, dyscalculia, change in sleep cycle
Grade 2	Overt	Disorientation for time, personality change, asterixis, fatigue, inappropriate behavior, lethargy, or apathy
Grade 3		Confused, gross disorientation, odd behavior, somnolence or semi-stupor, disoriented to space
Grade 4		Coma

Adapted from Vilstrup et al. [7], Table 2. Copyright © 2014 by the American Association for the Study of Liver Disease

Time Course

Elucidating the clinical course of HE can facilitate identification of the underlying etiology so that correction of the precipitating event can be accomplished as quickly as possible. A firm grasp of the history and timing of episodes of HE allows the clinician to develop an effective treatment plan and set appropriate expectations for family members and caregivers. Table 41.3 displays the possible time courses of HE and

Table 41.3 Differentiating HE based on time course

	Time course	Common underlying factors
Episodic HE	Episodes that occur more than 6 months apart	Infections, GI bleeding, diuretic overdose, electrolyte disorder, constipation, unknown
Recurrent HE	Episodes of HE that occur within 6 months of each other	Electrolyte disorder, infections, unknown, constipation diuretic overdose, GI bleeding
Persistent HE	Symptoms or behavioral changes that are always present with recurrent episodes of overt HE	

Strauss and da Costa [23]

the most common underlying factors associated with each [23].

Precipitating or Spontaneous Factors

Quick evaluation and confirmation of precipitating factors that contribute to the onset of HE will hasten treatment and improve the possibility of reversal. If there are no significant precipitating factors found, the possibility of progression of the underlying liver disease must be considered. The most common precipitating factors of HE are presented in Table 41.4.

Table 41.4 Common precipitating factors of hepatic encephalopathy (HE)

Electrolyte imbalance
Hyponatremia—abnormally low levels of sodium in the blood
Hypokalemia—abnormally low levels of potassium in the blood
Metabolic alkalosis—pH or acidity of tissue is elevated above normal levels
Increased nitrogen load
Gastrointestinal bleeding
Excess dietary protein
Azotemia—abnormally high levels of nitrogen-containing compounds in the blood
Constipation
Central nervous system-acting drugs (especially narcotics, tranquilizers, and sedatives)
Infection (particularly bacterial peritonitis, urinary tract, skin, or pulmonary)
Surgery
Dehydration
Urinary obstruction
Renal failure
Transjugular intrahepatic portosystemic shunt (TIPS), particularly in patients aged 60 and older
Superimposed liver injury from acute hepatitis, drug-induced liver injury, etc.
Hepatocellular carcinoma
Terminal liver disease

Epidemiology

Unfortunately, an accurate incidence of HE in the population is difficult to ascertain. Estimations of the occurrence of HE are based on the incidence of cirrhosis. Cirrhosis is a result of damage to the liver causing scar tissue and interfering with the liver's ability to function properly. Cirrhosis can be caused by alcohol use, chronic viral hepatitis, and steatohepatitis, also known as nonalcoholic fatty liver disease (NAFLD). NAFLD is related to obesity and metabolic syndrome and is estimated to become the single most common indication for liver transplantation [24].

According to the National Health and Nutrition Examination Survey (NHANES), 0.27% of the US population is estimated to have cirrhosis. 26.4% of this population has a 2-year mortality rate [25]. It is believed that minimal HE occurs in up to 80% of cirrhotic patients at some point in time in their disease process [15]. Overt HE is estimated to have an incidence rate of up to 45% of cirrhotic patients. For patients who have undergone a TIPS (transjugular intrahepatic portosystemic shunt), up to 50% are at risk for overt HE [2]. Complications of cirrhosis such as minimal HE, infections, variceal bleeding, and ascites increase the likelihood of overt HE in the first 5 years of diagnosis [26]. There is suspicion that diabetes and hepatitis C virus infection may also contribute to this risk [27–31]. Persons who have an episode of overt HE are likely to have another episode of HE within the following year;

Table 41.5 MELD score and associated mortality probability

MELD score	Mortality probability
9 or less	1.9% mortality
10–19	6.0% mortality
20–29	19.6% mortality
30–39	52.6% mortality
40	71.3% mortality

individuals with recurrent overt HE have a 40% cumulative risk of developing HE in the next 6 months [32].

For patients who have undergone a TIPS, up to 50% are at risk for overt HE and death [2]. In 2002 the Model for End-Stage Liver Disease (MELD) score replaced the Child-Pugh score for assessing transplantation need. This formula, which was updated in 2016 [33], is currently used to prioritize patients for liver transplantation by the United Network for Organ Sharing and Eurotransplant. Scores range from 6 to 40, with higher scores conferring a higher mortality risk (see Table 41.5). There are easily accessible apps and online calculators to obtain a patient's MELD score.

Pathogenesis

The exact mechanisms underlying HE are complex and still largely unknown, but ammonia neurotoxicity plays a major role [34–37]. A primary reason ammonia may build up in the blood stream is disruption of the urea cycle. Urea is a nitrogen-containing waste product of protein metabolism. When protein is metabolized, deamination (breakdown) of amino acids produces ammonia. In addition to protein metabolism, intestinal bacteria produce ammonia that is then absorbed into the portal system, the major source of blood flow to the liver. A healthy liver would quickly convert ammonia into urea, which would then be excreted primarily by the kidneys. In the presence of liver dysfunction, ammonia is synthesized more slowly into urea or not at all, allowing ammonia to accumulate in the blood stream. Healthy muscle tissue metabolizes ammonia in this manner, but individuals with cirrhosis are impaired due to muscle wasting, physician recommendations for low-protein "liver failure" diets, and an increased catabolic state (i.e., when the body is breaking down tissue). Certain medications (e.g., benzodiazepines) sensitize the central nervous system (CNS) to ammonia, even at normal levels. Natural benzodiazepines may also be important since a benzodiazepine antagonist (e.g., flumazenil) briefly improves the clinical course of some patients who were not administered pharmaceutical doses of benzodiazepines [38].

When pathologic ammonia is allowed to reach the brain, astrocytes provide the primary means to eliminate it through the synthesis of glutamine [37]. Glutamine is produced by adding one molecule of ammonia to glutamate, an amino acid present in over 90% of neurons, where it acts as an excitatory neurotransmitter. As glutamine accumulates, its osmotic effect causes the astrocyte to take in water, resulting in brain edema and increased intracranial pressure (ICP). Thus, HE is hypothesized to occur when astrocytes are unable to maintain osmotic equilibrium in response to the ammonia-induced increase in glutamine. On autopsy, astrocytes of patients with chronic liver disease show morphologic features characteristic of Alzheimer type II astrocytosis (e.g., pale, enlarged, and frequently paired nuclei, prominent nucleole, proliferation of cytoplasmic organelles) [37].

Another by-product of the ammonia-induced increase in glutamine that may contribute to the pathogenesis of HE is oxidative stress [39–41], which results when reactive oxygen species (ROS) such as free radicals and peroxides cannot be removed efficiently, causing significant damage to cell structures and even cell death. Ammonia has been shown to generate ROS when added to astrocyte cultures [42, 43], and glutamine increases free radical production [44]. Ammonia also induces oxidative and nitrosative stress in mitochondria after being carried in and released by glutamine [45–47].

Other neurotransmitter systems also are affected by ammonia both directly and indirectly through alteration of transmitter synthesis and recirculation [37, 48]. Altered serotonergic and dopaminergic transmission has been described [49–51], as has activation of glutamatergic NMDA receptors and modulation of

γ-aminobutyric acid (GABA) receptors by elevated levels of neurosteroids and endogenous benzodiazepines [45, 52]. Overstimulation of excitatory NMDA receptors by ammonia has been shown to induce neuromodulation, neurodegeneration, and neuronal apoptosis [53].

Inflammatory mediators, such as pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6, whether produced in the brain as a result of edema and/or ICP or in the periphery in response to infection also have been implicated in the pathogenesis of HE [40, 41, 54]. This hypothesis is supported by a more rapid progression to severe HE in the presence of infection in patients with acute liver failure [55, 56], as well as astrocyte swelling induced by cytokine exposure in cell cultures [57].

Clinical Presentation

Cognitive, behavioral, and motor dysfunction are the characteristic features of HE, although the pattern and severity differ among grades. Patients with overt HE display changes in mental status over the course of hours or days consistent with the diagnostic criteria for delirium detailed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [58]. Overt HE can develop spontaneously but is often precipitated by electrolyte imbalances, increased nitrogen load, medications, infection, or a host of other factors (see Table 41.3). Once HE and any precipitating factors are identified and treated, patients usually return to baseline functioning within a few days (i.e., episodic HE). In cases of persistent HE, which is less common, the patient's mental status continues to fluctuate for more than 4 weeks without returning to baseline, and this is an indication for liver transplantation [59].

The most severe grade of HE, grade 4, is the easiest to recognize, as patients are usually in a coma. Although patients may respond to pain, there often is no response to voice or gentle physical prodding and no spontaneous speech. Patients may open their eyes, but this is not done on command or in conjunction with any purposeful behavior. Decerebrate or decorticate posturing may be seen, even without sternal pressure [60], and may be a sign of raised ICP. Increased ICP is associated with poor outcome, including high rates of mortality, if not controlled [61].

Hallmarks of grade 3 are somnolence and confusion, including disorientation to place [62]. Patients in grade 3 are difficult to rouse and keep awake and may not orient to the clinician. Once awakened, they have trouble paying attention and participating in conversation. They may act strangely and laugh inappropriately, display paranoia, or become easily agitated. Motor findings may include clonus (i.e., rapid involuntary muscle contraction and relaxation after forced extension or stretching), Babinski's sign (i.e., toes splay out instead of curve inward when sole of foot is rubbed with a blunt instrument), or nystagmus (i.e., rapid involuntary eye movements that are usually side to side but can be up and down).

In grade 2, patients are often lethargic but easy to arouse and engage in conversation. Their movements and thinking are slow. Their speech tends to be slow and monotonous and also may be soft and dysarthric. They typically are aware of their location (i.e., setting and city) but usually are not oriented to time (i.e., month or day of the week). Although most can obey simple commands and recognize common objects, they typically cannot perform simple addition and subtraction and have trouble remembering recent events. Cranial nerves are usually intact, but patients in grade 2 may display either decreased or increased tone or deep tendon reflexes, reduced speed or clumsiness of rapid alternating movements, ataxia, tremor, or asterixis (i.e., "flapping" of the wrist when arms are held straight out with wrists flexed and fingers outstretched and widely separated). Patients too lethargic to lift their arms can be instructed to grasp the examiner's hands or extend the tongue since sustained movement in patients with asterixis oscillates between tense and relaxed (i.e., never constant) [63]. They may have fetor hepaticus, a uniquely pungent, sweet odor of the breath.

Patients in grade 1 HE are usually alert and typically oriented to place and generally to time. They may sometimes appear lethargic, but they more often report that they are tired, and their

sleep–wake cycle is off. They may be sleeping more than usual or have reversal in their sleep–wake cycle, so they sleep more during the day and need medication to sleep at night. These patients often can perform simple arithmetic but have trouble with multiplication or division. Handwriting may be small and difficult to read. Similar to patients in grade 2, memory for recent events is impaired. Motor abnormalities are similar to those displayed by patients in grade 2, as well, although dysarthria, tremor, and hyperreflexia are the most common in grade 1 [62, 64]. It is important to remember, however, that motor abnormalities in overt HE can be transient and do not always align with a particular grade of HE. The possible exception to this is asterixis, which, when present, is usually an indicator of grade 2 [59].

As noted above, patients with minimal HE usually display no obvious abnormalities on clinical exam. However, they sometimes exhibit subtle motor dysfunction, with motor akinesia (i.e., difficulty initiating motor movements), tremor, and rigidity being most common [65]. They or their family members may complain of cognitive problems; disturbances in sleep, appetite, and sexuality; and reduced efficiency in performing work and home activities. The ability to perform basic activities of daily living, such as bathing and dressing, is often not affected. Cognitive testing displays a frontal–subcortical pattern of deficits, with impairments most often seen in psychomotor speed, attention/concentration, visuospatial/constructional skills, and executive functions [66–68]. Poor performances on measures of learning and memory may be found but usually are secondary to attentional and visuospatial/perceptual difficulties rather than deficits in memory per se [69, 70]. Intellectual functioning and language abilities typically are preserved.

Differential Diagnosis

Because the symptoms of HE are not specific, it should be considered only in patients with known or suspected liver disease or other portosystemic shunts. The clinician must additionally rule out other causes of mental status change with neurological symptoms, including intracranial bleeding, metabolic abnormalities, ischemic brain disease, CNS infection or neoplasm, Wilson's disease, substance-induced delirium, and postictal state (see Table 41.6). Seizures and focal neurological signs, such as hemiparesis and hemiplegia, are uncommon [71] and may suggest another etiology. If HE does not resolve within 72 h of treatment, another cause of encephalopathy or unresolved precipitating factor should be considered.

Table 41.6 Hepatic encephalopathy differential diagnosis

Intracranial bleeding
Subdural hematoma
Intracranial hemorrhage
Metabolic encephalopathies caused by
Uremia
Sepsis
Hypoglycemia
Hypoxia
Ketoacidosis
Hypercapnia
Thyroid dysfunction
Cerebral edema
Ischemic brain disease
Ischemic stroke
Transient ischemic attack
Central nervous system abscess, encephalitis, or meningitis
Central nervous system neoplasm
Wilson's disease
Substance-induced intoxication or withdrawal
Postictal state

Treatment

The 2014 EASL/AASLD Practice Guidelines for treatment of overt HE, type C, recommend a four-pronged approach. The first step is to identify the person with altered consciousness and begin supportive therapies. The second step involves ruling out other neurological diseases that may account for the altered mental status. Identifying any known precipitating factors that were found on the diagnostic work-up is the third step. The fourth step is to start known treatments for the precipitating event.

Given the primary role of ammonia neurotoxicity in the pathogenesis of HE, management strategies focus on reduction or elimination of ammonia, in addition to treatment of precipitating factors, when identified [72, 73]. The most commonly administered treatment for HE is lactulose, which is a nonabsorbable disaccharide that remains undigested until it reaches the colon. It reduces plasma ammonia levels by inhibiting ammonia production of bacteria and increasing fecal nitrogen excretion. It is usually administered orally, but in the more severe grades of HE or in patients with ascites (i.e., fluid retention in the abdominal cavity) or peritonitis (i.e., inflammation of visceral or abdominal lining), administration via retention enema is preferred [59, 63].

In spite of its long-standing and widespread use, the efficacy of lactulose has been questioned [74], and patients are often noncompliant due to unpleasant side effects, such as increased intestinal gas, abdominal distention and cramping, and diarrhea [59, 75]. On the other hand, Sharma and colleagues report that there is not enough evidence to not recommend nonabsorbable disaccharides for the treatment of HE despite inconsistent study outcomes [75]. Nonresponse to lactulose has been shown to be predicted by high MELD scores, high white cell count, low blood sodium, low mean arterial pressure, and hepatocellular carcinoma [76].

Therefore, alternative treatments for HE are a topic of intense study [77]. Nonabsorbable antibiotics, such as neomycin, vancomycin, and rifaximin, have been suggested with the goal of reducing bacteria-producing ammonia in the gut. While the efficacy of neomycin and vancomycin has not been well established, rifaximin has been found to be equivalent or superior to placebo, other antibiotics, and nonabsorbable disaccharides for both lowering ammonia and improving cognitive functioning [78]. The combination of rifaximin and lactulose has been found to reduce mortality when compared to lactulose and placebo [79].

L-ornithine L-aspartate (LOLA) is the salt of two natural amino acids (i.e., ornithine and aspartate) and is another treatment option occasionally used outside of the United States. LOLA is believed to reduce ammonia levels by converting ammonia to urea and glutamine [80]. LOLA delivered via IV has shown to lower plasma ammonia rates and improve performance on psychometric testing [81].

Due to the lack of effective treatments for HE, prevention is the goal [12, 63], particularly given evidence of increased severity of cognitive impairment with each additional episode of overt HE [63]. Along with diligent management of underlying liver disease and its complications, close monitoring of dietary protein intake is recommended in patients with a history of HE, as large amounts of protein can increase plasma ammonia levels and possibly precipitate HE, while too little protein correlates with mortality and development of complications [82, 83]. Up to 75% of patients with HE are found to be malnourished due to lack of protein [84]. Adequate protein intake is essential to improve nutrition to avoid loss of muscle mass and lower the risk of accelerated fasting metabolism. Malnutrition itself is a risk factor for HE in cirrhotic patients [85]. Patients with cirrhosis should be assessed for sarcopenia and nutritional status (AASLD Practice Guideline).

Probiotics are currently being studied for those recovering from HE and in prevention of recurrence of HE. It is hypothesized that gut dysbiosis may contribute to inflammatory processes that potentiate brain edema and neuroinflammation associated with HE [86]. While there is some evidence that probiotics reduce plasma ammonia levels and are comparable to lactulose for secondary prophylaxis of [87], other studies show no effect on mortality, recovery from HE, or quality of life [88]. Due to mixed evidence and wide variability in the content of probiotics, they are not currently recommended for treatment of HE [89].

Findings on dietary supplementation with branched-chain amino acids have been mixed, with some studies showing positive effects on cognitive functioning [90, 91], particularly in patients with persistent HE [92], and prolonged event-free survival [85], and others showing no effect at all [93]. Gluud, Borre, Cordoba, Marchesini, et al. (2013) performed a meta-analysis on eight studies that evaluated treatments of HE comparing lactulose, rifaximin, and BCAAs [94, 95]. They concluded that BCAAs improve presentation of symptoms of

both minimal and overt HE but have no effect on survival per se.

Liver transplantation is indicated for patients with recurrent episodic or persisting HE due to increased mortality rates [35], with extracorporeal albumin dialysis serving as a potential bridge to liver transplantation [96, 97].

Clinical Evaluation

Although the core manifestations of HE have been recognized and agreed upon for years, a "gold standard" for the diagnosis of HE remains elusive. Definition and classification of even the basic behavioral and motor alterations need further refinement to distinguish among grades of HE, particularly the less severe grades. Therefore, diagnosis must be based on multiple approaches, including clinical examination, laboratory findings, neuroimaging, neurophysiological measures, and neuropsychological assessment.

Clinical Examination

The clinical interview and physical and neurological exams are the mainstays for assessing HE. The clinician must ensure a history of known or suspected liver disease or the presence of a portosystemic shunt and exclude other potential causes of encephalopathy. Early identification of HE is crucial as delays in diagnosis may result in death. A thorough review of possible precipitating factors also is critical so that appropriate treatment can be initiated promptly. For inpatients with HE, examination of mental status should be performed at least 2–3 times a day [98].

In determining grade of HE, the WHC (Table 41.2) can be employed quickly and easily and provides a useful "ballpark" of the patient's clinical status [11]. In more severe grades of HE, the Glasgow Coma Scale (GCS) [99] may be a useful adjunct, supplying additional information about ocular and motor responses and thus allowing for wider separation among patients in grades 3 and 4 [62]. In less severe grades, and particularly in minimal HE, neurocognitive tests and neurophysiological measures are recommended [12].

Because some of the items in the WHC are not operationally defined and do not correspond well to the progression of HE, Ortiz and colleagues [91, 100] developed the Clinical Hepatic Encephalopathy Staging Scale (CHESS) . The CHESS consists of nine manifestations of HE that can be easily recognized and categorized into dichotomous groups (see Table 41.7) and was

Table 41.7 Clinical Hepatic Encephalopathy Staging Scale (CHESS)

1. Does the patient know which month he/she is in (i.e., January, February)?	
0. Yes	1. No, or he/she does not talk
2. Does the patient know which day of the week he/she is in (i.e., Thursday, Friday, Sunday, etc.)?	
0. Yes	1. No, or he/she does not talk
3. Can he/she count backward from 10 to 1 without making mistakes or stopping?	
0. Yes	1. No, or he/she does not talk
4. If asked to do so, does he/she raise his/her arms?	
0. Yes	1. No
5. Does he/she understand what you are saying to him/her? (based on the answers to questions 1–4)	
0. Yes	1. No, or he/she does not talk
6. Is the patient awake and alert?	
0. Yes	1. No, he/she is sleepy or fast asleep
7. Is the patient fast asleep, and is it difficult to wake him/her up?	
0. Yes	1. No
8. Can he/she talk?	
0. Yes	1. He/she does not talk
9. Can he/she talk correctly? In other words, can you understand everything he/she says, and he/she doesn't stammer?	
0. Yes	1. No, he/she does not talk or does not talk correctly

Table 41.8 Hepatic Encephalopathy Scoring Algorithm (HESA)

	Time __ __ : __ __ 24 Hour Clock
4	○ No eyes opening ○ No verbal/voice response ○ No reaction to simple commands
	All applicable ⇒ Grade 4 ○ otherwise continue examination
3	○ Somnolence ○ Confusion ○ Disoriented to place ○ Bizarre Behavior / Anger/Rage ○ Clonus/Rigidity / Nysatgmus / Babinsky □ Mental Control = 0
	3 or more applicable⇒Grade 3 ○ otherwise continue examination
2	○ Lethargy ○ Loss of time ○ Slurred Speech ○ Hyperactive Reflexes ○ Inappropriate Behavior □ Slow Responses □ Amnesia of recent events □ Anxiety □ Impaired Simple Computations
	2 or more ○ and 3 or more □ applicable ⇒ Grade 2 ○ otherwise continue
1	○ Sleep disorder / Impaired Sleep Pattern ○ Tremor □ Impaired complex computations □ Shortened attention span □ Impaired Construction ability □ Euphoria or Depression
	4 or more applicable ⇒ Grade 1 ○ otherwise Grade 0
	HE Grade __

Note: ○ indicates symptoms assessed using clinical judgment, and □ indicates symptoms assessed using neuropsychological measures

designed to provide a means to monitor the severity of HE. The CHESS provides a score from 0 (low) to 9 (high), which reflects the severity of HE, not the grade. Factor analysis supported two factors corresponding to "mild" and "severe" HE, which is consistent with recent proposals to classify HE into more clinically meaningful categories of "low-" (grades 1 and 2) or "high-grade" (grades 3 and 4) rather than trying to make fine-grained differentiations among grades. Like the WHC, the CHESS should be augmented with the GCS for more severe HE and with neurocognitive and/or neurophysiological measures for less severe grades.

A modified version of the WHC, the Hepatic Encephalopathy Scoring Algorithm (HESA), was developed by Hassanein and colleagues in an attempt to improve its objectivity and sensitivity [64]. The HESA combines the clinical exam with neuropsychological tests to determine HE grade, relying heavily on subjective clinical evaluation in the more severe grades where neuropsychological testing is not possible and more heavily on objective testing in the less severe grades where dysfunction may not be as evident on clinical exam (see Table 41.8). Initial findings confirm increased sensitivity and accuracy of the HESA compared to the WHC in grading HE [64].

Laboratory Findings

Blood ammonia levels are often elevated in patients with overt HE but do not always correlate with HE grade [101, 102]. However, significantly elevated blood ammonia levels (>150–200 μmol/l) in a comatose patient without a history of recent seizures are strongly suggestive of HE [59]. It is important to perform the assay within 30 min of drawing blood, or levels may be artificially inflated [103].

Neuroimaging

The primary role of neuroimaging in evaluation of HE is to rule out other possible etiologies of neurobehavioral changes [104] and to establish the presence of cerebral edema, particularly in acute liver failure. Because clinical symptoms of increased ICP (e.g., hypertension, bradycardia) may not be present, ICP monitoring devices may be helpful to identify cerebral edema early and prevent herniation until liver transplantation can be performed [105]. Typical neuroimaging findings in HE include hyperintensities in the globus pallidus on magnetic resonance imaging (MRI) T1-weighted images (see Fig. 41.1), elevated glutamine/glutamate peaks and decreased myo-inositol and choline signals on proton magnetic resonance spectroscopy (1H MRS), and white matter abnormalities on MRI fast fluid-attenuated inversion recovery sequences (FLAIR) and diffusion-weighted images (DWI) [106]. In cirrhotic patients with minimal HE, T2 hyperintensities along the corticospinal tract (see Fig. 41.2) are suggestive of mild edema [107, 108] and have been found to relate to abnormalities in central motor pathways that resolve (as do some cognitive difficulties) after liver transplantation [109]. In patients with HE due to portosystemic shunt and no liver disease, MRI can be especially helpful as dietary manganese that is not cleared by the liver accumulates in the basal ganglia and is detected as hyperintensities on T1-weighted images when exam may have found mild Parkinson-like movement changes only [103]. Qi, Zhang, and Zhong et al. [110] used fMRI and found that there is disrupted influence between the globus pallidus and the anterior cingulate cortex, which affects both cognitive and emotional processing [110]. This study confirmed previous investigations indicating decreased functional connection between the globus pallidus and the cuneus. They also reported an increase in connectivity from the pallidum to the precuneus that may indicate a compensatory mechanism in play and decreased input from the globus pallidus to the right inferior temporal gyrus and left superior temporal gyrus that may explain visual deficits.

Neurophysiological Measures

Advantages of neurophysiological measures are that they are not influenced by demographic variables, such as gender, education, or cultural background, and they are easy to administer by staff without extensive training. Electroencephalogram (EEG) has been used to diagnose HE since the 1950s [111]. However,

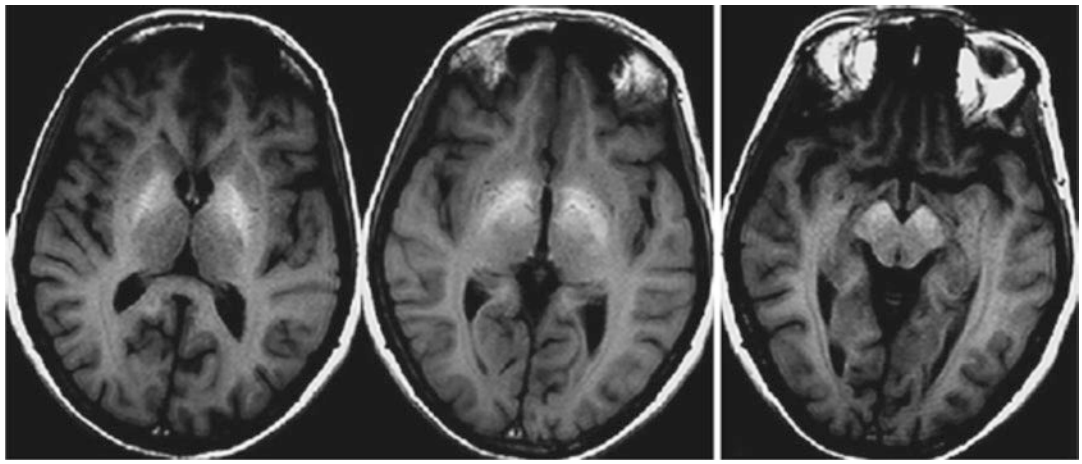

Fig. 41.1 Hyperintensities in the globus pallidus secondary to hepatic encephalopathy. Transverse T1-weighted MR images of the brain in a patient with chronic liver failure and parkinsonism. Observe the bilateral and symmetric high T1 signal-intensity change involving the globus pallidus and the anterior midbrain

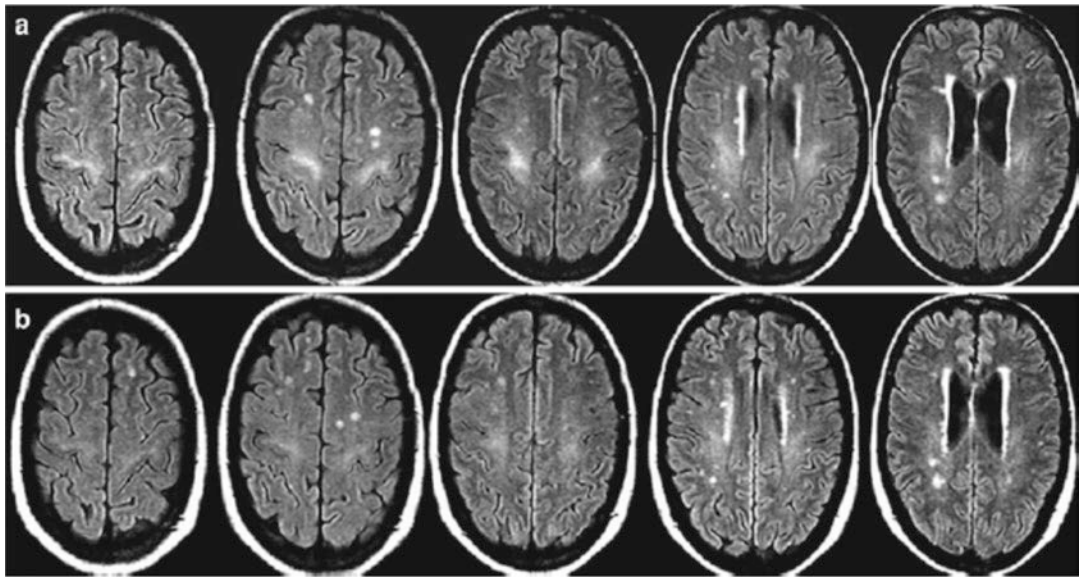

Fig. 41.2 Hyperintensities in the corticospinal tract secondary to hepatic encephalopathy. (**a**) Transverse T2-weighted fast FLAIR images obtained in a patient with liver cirrhosis during an episode of hepatic encephalopathy. Observe the symmetric areas of increased signal intensity along the corticospinal tract in both cerebral hemispheres. (**b**) This signal-intensity abnormality almost completely reverses on a follow-up study obtained few months later, when the patient showed no signs of overt hepatic encephalopathy

because findings are not specific to HE, EEG and other neurophysiological measures are most useful in the comatose patient [112], when the diagnosis is uncertain (i.e., focal neurological signs or seizure activity is present or the patient has "normal" mental status) or when evidence of worsening HE is needed [113]. The most common EEG findings in HE are slowed mean dominant frequencies, and in minimal HE, you may see relatively slowed activity within the δ (delta) and θ (theta) frequency bands [114]. In patients with minimal HE, changes in EEG have been shown to be predictive of developing overt HE and thus may have prognostic utility [115]. EEG has been criticized for use in detecting HE because it measures cortical rather than subcortical activity, which is where most of the pathology in HE is hypothesized to exist.

Other neurophysiological measures that have been used to identify HE include evoked potentials (EPs) and critical flicker frequency (CFF). EPs, the latency between presentation and detection of a stimulus, may be slightly delayed in patients with minimal HE, shown most often using P300 oddball paradigms [116–119], but findings are not specific and often confounded by alcohol use or diabetes, which also delay EPs, and are frequently found in patients with cirrhosis [120]. In CFF, the patient is asked to press a button when a steady light has changed into a flicker and when a flickering light has become a steady, fused light. Patients with minimal and lower grades of HE have shown reduced ability to detect the light flickering or fusing [76, 121, 122]. A recent meta-analysis of the diagnostic accuracy of the CFF revealed sensitivity of 61% (95% CI, 55–67) and specificity of 79% (95% CI 75–83) [123].

Neuropsychological Assessment

Neuropsychologists are most likely to encounter HE in the context of liver transplant evaluations. Pretransplant evaluations usually are conducted on an outpatient basis, but occasionally they must be performed while the patient is hospitalized and awaiting transplantation. Of course, the pos-

sibility of HE, particularly minimal HE, must always be considered in patients with cirrhosis, regardless of reason for referral or inpatient versus outpatient status. Neuropsychologists also are called upon to assess for HE in the context of clinical trials for management of HE and when insertion of TIPS for management of portal hypertension is planned [124]. TIPS for management of portal hypertension is planned. Onset or worsening of HE is common after placement of TIPS, occurring in 35–55% of patients within the first year [125]. Baseline assessment and subsequent monitoring are important for identifying and treating HE before it escalates and the patient's status becomes critical, particularly in the first 3 months, since 90% of post-TIPS HE occurs in this time frame [125, 126]. The level of neuropsychological assessment will depend on the severity of HE, with more comprehensive testing reserved for those with covert HE. It often is difficult for patients with grades 2 and 3 to participate reliably for more than 10–15 min. Fatigue is also frequently a factor, even in patients with no or minimal HE, so full-day evaluations are not routinely employed.

There is evidence that cognitive impairment may remain after the treatment and resolution of overt HE. Bajaj and colleagues examined 226 cirrhotic patients and found that patients with a history of overt HE were more likely to have persistent cognitive problems and patients with further episodes of overt HE displayed deficits in multiple areas of cognition [63]. Given growing evidence of cumulative effects of recurrent overt HE on neuropsychological functioning, the role neuropsychologists plays in educating patients and families about the effects of neuropsychological impairments on daily functioning cannot be understated.

Clinical Interview

Changes in cognitive and motor functioning secondary to minimal HE are often subtle and result in cognitive inefficiencies rather than frank impairment but still significantly affect daily functioning, including ability to work and drive. With regard to driving, patients with minimal HE report more traffic violations and motor vehicle accidents than those without cognitive dysfunction [14, 15, 127]. Common cognitive complaints include trouble paying attention, concentrating, remembering, and completing tasks. Aphasia, significant memory problems such as repeating stories or forgetting recent events even when reminded, and lateralized motor problems (i.e., weakness or motor abnormality on one side only) are uncommon and usually indicate another etiology. Patients often have difficulty pinpointing when the symptoms began but usually indicate that they are not worsening significantly over time. Report of gradual cognitive decline over time in the absence of recurrent episodic HE is suggestive of possible neurodegenerative disease process, psychological factors, or medical conditions other than minimal HE contributing to cognitive complaints.

Additional complaints often include fatigue and changes in appetite, sleep, energy, and activity levels. Patients with minimal HE report reduced HRQOL, such as limited social interactions and recreational pastimes and difficulties managing home and work duties [13, 16, 17, 128]. Although the patient may endorse affective symptoms, it is important to establish that these changes do not occur in conjunction with increasingly depressed or anxious mood.

As with any patient referred for neuropsychological assessment, ruling out other possible causes of cognitive impairment, including stroke, seizure disorder, traumatic brain injury, or other neuromedical condition, is necessary. Gathering information about psychiatric and substance use histories, academic and social functioning, and family medical history also is important for differential diagnosis. Information from a collateral source is helpful when assessing patients with minimal HE due to the possibility of poor insight and/or awareness [127] and essential when assessing patients with overt HE who often cannot report reliably.

Test Selection

Selection of measures will depend on the setting (inpatient vs. outpatient), severity of HE, and reason for evaluation (e.g., pretransplant, monitoring of HE in clinical trials, or following TIPS). In the case of pretransplant outpatient evaluations, most patients are either unimpaired or have minimal HE, so comprehensive neuropsychological evaluation is appropriate. Assessment of current intellectual or estimated premorbid functioning, language, visuospatial/constructional skills, attention and processing speed, executive functioning, learning and memory, emotional status, and HRQOL is recommended. Because one of the purposes of the pretransplant evaluation is to rule out neurodegenerative diseases, such as Alzheimer's disease, it is important to include tests that can distinguish cortical from subcortical patterns of deficits. A couple of studies have found support for the utility of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [129] in pretransplant evaluations [67, 130], with one study confirming the expected subcortical pattern of deficits using the Randolph Cortical–Subcortical Deviation Score detailed in the RBANS manual [67]. When pretransplant evaluations must be conducted on an inpatient basis and the patient can tolerate more detailed assessment (i.e., is at grade 2 HE or less), the RBANS may be a good choice since it taps multiple cognitive domains, can be administered in less than 30 min, and is easy to transport.

With regard to emotional status, brief self-report measures rather than longer measures of psychopathology (e.g., Minnesota Multiphasic Personality Inventory-2) [131] are used to minimize fatigue. Of course, if there are concerns about significant psychopathology, particularly in the context of pretransplant evaluation, the use of a more comprehensive measure of psychological functioning may be warranted. For HRQOL, the Medical Outcomes Study Short Form (SF-36) [132] is commonly used and enables comparisons to other chronic diseases, but disease-specific measures also are available, including the Chronic Liver Disease Questionnaire [133], the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)—Quality Assessment [134], and the Liver Disease Quality of Life Instrument [135]. Recently, a measure of HRQOL for use specifically with minimal HE patients showed promising initial validity [136]. Table 41.9 displays a sample outpatient pretransplant battery and suggested modifications for inpatient status.

Table 41.9 Sample neuropsychological battery for pretransplant evaluation

Wechsler Test of Adult Reading [137]
Repeatable Battery for the Assessment of Neuropsychological Status [129]
Trail Making Test [138]
Stroop Color and Word Test [139]
Boston Naming Test [140]
Controlled Oral Word Association Test [141]
Animal Naming [141]
Wisconsin Card Sorting Test—64-Card Version [142]
Finger- Tapping Test [138]
Grooved Pegboard [143]
Beck Depression Inventory-II [144]
Beck Anxiety Inventory [145]
Chronic Liver Disease Questionnaire [133]

Note: For inpatient evaluations, suggest administration of the first three tests only

When monitoring HE in the course of clinical trials, you want to select measures that can be completed by patients with more severe HE but also are sensitive enough to detect subtle changes in cognition in the less severe grades. This was one of the goals of the HESA, which allows one to measure changes in HE severity across all grades and is now required in Federal Drug Administration (FDA)-sponsored studies [64]. Although more validation of the HESA is needed, particularly in the lower grades, it is a viable option for clinical trials, as the neuropsychological measures administered are well known and widely used with modifications to ensure feasibility of administration and scoring in the inpatient setting while maintaining sensitivity for detecting impairment.

When the goal is to identify the presence of minimal HE outside the context of pretransplant evaluation or clinical trials, such as when conducting evaluations pre- and post-TIPS insertion or for monitoring risk of developing overt

HE during clinic visits, a comprehensive battery may not be necessary or appropriate. The consensus statement generated by the 1998 working group mentioned previously [12] recommended at least two of the following four measures be used to assess for minimal HE: Parts A and B of the Trail Making Test (TMT) [138] (also known as the Number Connection Test), block design test, and digit symbol test. Also recommended was the Psychometric Hepatic Encephalopathy Score (PHES) [70], which has been validated in several languages across several countries, including Germany, Italy, and Spain [146]. The PHES is a composite score based on demographic-adjusted *z* scores from Parts A and B of the TMT, digit symbol, line tracing, and serial dotting. Scores ≤ -4 are considered to reflect minimal HE.

The PHES, along with the RBANS, also was recommended recently by a group of experts convened by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) for use in patients at risk for developing minimal HE [147]. One limitation of the PHES for use in the United States is that line tracing and serial dotting have not yet been normed in the United States. A limitation of the RBANS is that it has not been systematically studied as a method for detecting or monitoring HE [148]. Computerized cognitive measures are another method beginning to be used, with the inhibitory control task (ICT), a computerized variant of the continuous performance test, showing good initial validity [14, 149, 150], including ability to predict future car crashes and traffic violations [127].

Case Example: Characterization of Overt and Minimal HE [133]

Following is a case example of a 46-year-old non-Hispanic White man with end-stage liver disease (ESLD) secondary to hepatitis C virus and alcoholic hepatitis. Mr. J graduated from high school and worked primarily as a machinist until he became disabled from ESLD. He was being followed in a hepatology clinic at a university hospital and agreed to participate in a research study examining quality of life in persons with chronic liver disease. As part of this research protocol, a brief neurocognitive battery consisting of a modified version of the Rey Complex Figure Test (RCF) [151], Digit Cancellation (DC) [151], Trail Making Test (TMT), and the written version of the Symbol Digit Modalities Test (SDMT) [152] was administered during a routine clinic visit. Mr. J completed this battery on three occasions: once during an episode of overt HE judged to be grade 1, once during minimal HE, and once 5 months post-transplant. His raw scores on these measures at each of the three time points are presented in Table 41.10.

Table 41.10 Mr. J's cognitive test performances over time

	Pretransplant 7 months Grade 1 HE	Pretransplant 5 months Grade 0 (Minimal) HE	Post-transplant 5 months
Modified RCF copy	3.5	20	19
Modified RCF learning	5	16	19
Modified RCF% forgotten	50.0	6.3	5.6
DC total time (s)	278	225	200
DC total errors	31	9	9
TMT-A (s)	85	40	34
TMT-B (s)	>300	110	60
SDMT	18	31	44

Note: RCF Rey Complex Figure, *DC* Digit Cancellation, *TMT* Trail Making Test, *SDMT* Symbol Digit Modalities Test (written version)

Cognitive performance on all measures during Mr. J's episode of overt HE was more than three standard deviations below the normative mean, and he evidenced a mild tremor while performing tasks. He exhibited significant difficulty copying this version of the RCF, which was modified to be more simplistic than the original figure. Even after having viewed the figure three times, his learning score (i.e., raw score = 5) revealed that he did not encode much additional information beyond that encoded on the initial (copy) trial (i.e., raw score = 3.5). Moreover, he forgot half of the details of the figure after a 20-min delay. On a measure of selective attention, Digit Cancellation, he required a long time to complete the task and made a significant number of errors (both omission and commission). He was able to complete the TMT, albeit very slowly, and he made several cognitive-switching errors on Part B. On the SDMT, he performed very slowly and made a few errors. His cognitive and motor findings during this episode of overt HE are typical of those seen in patients with grade 1 HE [153].

A couple of months later, after his episode of overt HE had resolved, Mr. J's performance on this brief battery was significantly improved. His action tremor was gone, and his test scores were essentially within normal limits, except for SDMT, which was approximately 1.5 standard deviations below the normative mean. Five months post-transplant, Mr. J exhibited continued improvement, particularly on measures relying on executive function (i.e., RCF learning, TMT Part B, and SDMT). Although some of these improvements may have been due to practice effects, others were too significant to be attributed to practice effects alone. The contrast between test performances during minimal HE and post-transplant suggests that although Mr. J generally performed within normal limits on all but one task (i.e., SDMT) pre-transplant, he was still performing below his baseline. The pattern of findings also is consistent with the literature showing compromised frontal–subcortical circuits.

Case Example: Overt HE in Post-TIPS and Continued ETOH Use

Identifying information in the following case example was altered to protect the patient's privacy. Mr. H is a 36-year-old, divorced, Caucasian man with 13 years of formal education and a significant history of heavy drinking. He had been admitted to the hospital for HE after an accidental overdose of Tylenol and was referred for neuropsychological evaluation to characterize neurocognitive functioning, provide treatment recommendations, and educate family members about his behavior and prognosis.

Past medical history was noteworthy for hospitalization 13 months earlier for HE associated with recent heavy drinking. Mr. H's hospital course was complicated by pneumonia and acute respiratory failure, requiring intubation. Liver biopsy revealed cirrhosis, and he had portal hypertension, which was treated with TIPS. Mr. H recovered and was discharged. Although he was independent with his activities of daily living, he did not return to his premorbid level of functioning and remained unemployed post-discharge. Mr. H was being followed by cardiology for alcoholic cardiomyopathy.

Upon admission for the current episode of HE, toxicology screens were negative for substances including alcohol. He had an elevated ammonia level (78 umol/L) and a MELD score of 39. Neuroimaging revealed mild dilation of the ventricles and sulci, compatible with generalized cerebral volume loss, and abnormal T1 hyperintensities in the bilateral basal ganglia, which the radiologist interpreted as consistent with a history of elevated manganese levels (See Figs. 41.3 and 41.4). As noted earlier, the inability of the liver to clear manganese from the diet often manifests as T1 hyperintensities, particularly in the context of portosystemic shunt, suggesting that the patient's current episode of HE may have been a complication of TIPS [154]. Mr. H was disoriented and agitated and was treated with lactulose and rifaximin. After approximately 2½ weeks, Mr. H's medical status had stabilized, including normalization of

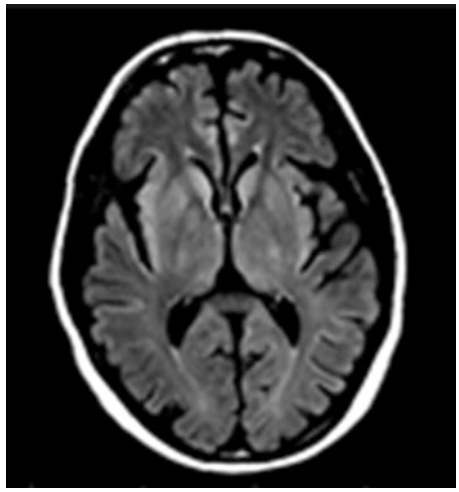

Fig. 41.3 MRI of patient indicating generalized cerebral volume loss

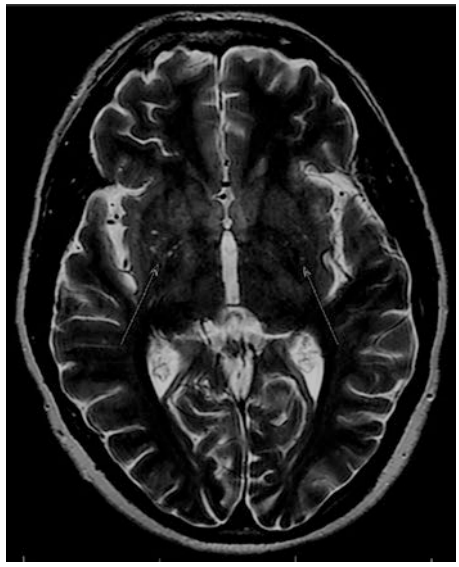

Fig. 41.4 MRI images with TI hyperintensities in bilateral basal ganglia

ammonia levels, and he was transferred to a locked psychiatric unit. While his neurocognitive abilities had improved, staff reported that he continued to hallucinate and become confused during the evening hours.

At the time of the clinical interview, Mr. H had been in the locked psychiatric unit for 9 days. He was alert and oriented and ambulated independently. He had significant yellowing of his sclera. His speech was fluent but tangential and nonsensical at times and noteworthy for word-finding problems and confabulatory responses. He was an inconsistent historian and had difficulty relaying the sequencing of his medical history. Of note, Mr. H denied having had alcohol since his hospital admission for HE the previous year; however, his mother indicated that she had found empty liquor bottles in the house and that his friends had told her that he had resumed drinking. He reportedly has gotten lost while driving and had unexplained scrapes on his car. There was no history of previous neuropsychological testing.

During neurocognitive testing 3 days later, he appeared motivated to perform well, which was confirmed by performance validity measures (see Table 41.11). Mr. H's performance on the Brief Cognitive Status Exam, a cognitive screening measure, was within normal limits, although he struggled with the inhibition task and made multiple commission errors. Intellectual test results ranged from borderline to average. His ability to define words was a significant weakness, and difficulties with naming and category fluency were apparent although phonemic fluency was intact. He also struggled with duplicating designs using blocks and tended to copy designs in a sloppy fashion, with decreasing accuracy noted when the precepts became complex. His free recall of previously copied figures after a delay was impaired, but he was able to accurately identify all of the previously copied designs in a recognition format. Memory for verbal information was intact. On measures of timed visual scanning, sequencing, attention, and inhibition, Mr. H exhibited difficulties, performing in the impaired range after correcting for age and education.

Mr. H represents a complex case in terms of differential diagnosis for the etiology of his neurocognitive dysfunction. He had two documented episodes of overt HE requiring hospitalization in the 14 months prior to neuropsychological evaluation, but the contribution of continued alcohol use cannot be ruled out entirely in spite of negative toxicology results at

Table 41.11 Mr. H's cognitive test performance

TEST	Raw score	Converted score Comment
Test of Memory Malingering		
Trial 1	49	Pass
Trial 2	50	Pass
Brief Cognitive Status Exam	49	Borderline
Wechsler Adult Intelligence Scale-IV		
VCI	23	87
PRI	19	79
WMI	17	92
PSI	16	89
FSIQ	75	82
Subscales		**Scaled scores**
Arithmetic	11	8
Block design	20	5
Digit span	26	9
Coding	59	8
Information	13	10
Matrix reasoning	15	8
Similarities	22	8
Symbol search	29	8
Visual puzzles	8	6
Vocabulary	16	5
Boston Naming Test	44	HAECT score = 26
Verbal Fluency		
Animals (raw)	17	HAECT score = 37
FAS (raw)	51	HAECT score = 56
Wechsler Memory Scale-IV		**Standard score**
Immediate memory (LMVR)	18	93
Delayed memory (LMVR)	9	67
Auditory memory (LM)	19	98
Visual memory (VR)	8	67
Subscales		**Scaled scores**
Logical memory I	28	11
Logical memory II	17	8
Symbol span	24	11
Verbal paired associates I	39	14
Verbal paired associates II	14	7
Visual reproduction I	33	1
Visual reproduction II	0	9
Stroop Color and Word Test		
Color task	112	
Color-word task	82	< 24th percentile
	(4 errors)	
Trail Making Test		
Part A	29"	HEACT score = 38
Part B	162"	HEACT score = 19
	8 errors	

Note: HAECT Heaton Age and Education Corrected T-scores

the time of his most recent hospitalization. Neuropsychological testing indicated impairment in areas of attention, language, managing complex information, visuospatial abilities, and visual memory. While this pattern of dysfunction is generally consistent with findings associated with minimal HE, it is also generally consistent with findings associated with recent alcohol detoxification [155]. As Mr. H was tested within 1 month of onset of HE, continued improvement is expected as long as he remains abstinent from alcohol. Long-term follow-up, along with reliable verification of alcohol-free status, is needed in order to establish the etiology and stability of his neurocognitive dysfunction.

Clinical Pearls

- HE is associated with impaired abilities to perform complex tasks (e.g., driving), reduced HRQOL, and poor outcome, including death.
- Severity of HE is usually graded on a scale from minimal to 4 (coma), and sometimes distinctions among grades are difficult to determine due to fluctuations in a patient's status or limitations in the methods available for grading HE.
- Overt HE typically requires hospitalization and quick identification and treatment of precipitating events to prevent continued deterioration and death.
- Blood ammonia levels may not correspond to clinical severity of HE and have little clinical significance if serially followed.
- Minimal HE is present in 50–80% of cirrhotic patients and usually undetected unless tested with neuropsychological or neurophysiological measures.

- Although HE should be high on the list of diagnostic possibilities in delirious patients with cirrhosis, other causes of mental status change, such as alcohol withdrawal, occult gastrointestinal bleed, infection, and dehydration, must be ruled out since they are also common in patients with cirrhosis.
- In patients with worsening of HE but no clear precipitating factor, check for noncompliance with lactulose or other HE treatments since patients sometimes are not compliant due to unpleasant drug side effects or poor memory.
- In patients with minimal HE, a frontal–subcortical pattern of deficits and cognitive inefficiencies is a characteristic; aphasia, significant forgetting such as that seen in Alzheimer's disease, and lateralized deficits suggest another etiology.
- Traffic violations and motor vehicle accidents are more common in cirrhotic patients with minimal HE than those without, so careful inquiry about driving is needed, and physician recommendation for the patient to stop driving may be advised.
- Gut dysbiosis is an emerging area of research and has demonstrated a relationship with HE-related cognitive impairment.
- NAFLD is estimated to become the main reason for liver transplant.
- Neuropsychological evaluation can aid in decisionmaking for priority placement for liver transplant.

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Late-Onset Schizophrenia

42

Tracy D. Vannorsdall and David J. Schretlen

Symptoms of psychosis, including delusions, hallucinations, loosening of associations, and thought disorder, are prevalent in geriatric populations. In a Swedish community sample of 347 non-demented adults who were 85 years old at study entry, 10.1% were found to have at least 1 psychotic-type symptom. The most common of these were hallucinations (6.9%), paranoid ideation (6.9%), and delusions (5.5%) [1]. Earlier studies reported that psychosis was present in more than 25% of older patients admitted to inpatient geropsychiatric units [2] and more than 33% of older adults admitted to a hospital for psychiatric treatment for the first time [3]. Psychosis can occur in a variety of conditions and disorders of late life with etiologies including acute conditions such as delirium or the effects of substance use or withdrawal. Alternatively, psychotic symptoms may arise from chronic degenerative conditions such as moderate to severe Alzheimer's disease or Lewy body dementia. Finally, a variety of late-life psychiatric illnesses including delusional disorder, mood disorder with psychotic features, bipolar disorder, and both early- and late-onset schizophrenia (LOS) can also be accompanied by prominent psychotic features.

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History and Terminology

Most individuals with schizophrenia develop symptoms of psychosis in late adolescence or early adulthood. As a result, our understanding of thought disorders primarily stems from these early-onset patients. However, it has long been recognized that such symptoms can emerge for the first time later in life. Unfortunately, late-life psychosis has historically been inconsistently described, imprecisely defined, and understudied. Manfred Bleuler, who first brought attention to the study of late-life psychosis, crystallized these difficulties with an often-cited quote [4, 5]:

> One can hardly deal with late onset schizophrenic pictures without being reminded again and again how right Kraepelin was when he called the science of psychoses of old age 'the darkest area of psychiatry'. Indeed, today as in earlier times the ground seems to shake under our feet, and our basic psychiatric terms seem to lose their meaning, when one grapples with late onset schizophrenias. (p. 259)

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In fact, the rigorous study of late-onset psychotic symptoms started with M. Bleuler who, in 1943, observed that 15% of the patients with schizophrenia he examined had an onset of symptoms after 40 years of age and another 4% developed symptoms after age 60 [5]. Noting that nearly half of his late-onset cases evidenced symptoms that were consistent with those seen in the early-onset schizophrenia, Bleuler coined the term "late-onset schizophrenia" to reflect a disorder with an onset of schizophrenia-like symptoms occurring at age 40 years or later. However, this classification did not immediately take hold in the USA or Great Britain. Rather, the term "late paraphrenia" was more commonly used to reference onset of all schizophrenia-like symptoms and delusional disorders with onset after age 55 or 60 [6, 7].

Late paraphrenia was included as a diagnosis in ICD-9, and in ICD-10, the term was included as a part of the diagnosis of delusional disorder. Despite the lack of data to support an age cutoff, in the DSM-III, schizophrenia was defined as having an onset *before* age 45, thus reflecting the "praecox" view of Kraepelin with typical disease onset in late adolescence and early adulthood. As evidence that schizophrenia can emerge after age 44 accumulated, the age cutoff was eliminated and replaced with a late-onset specifier in the DSM-III-R. Subsequent revisions removed the late-onset specifier, and DSM-IV-TR simply noted that an onset after age 45 is both possible and associated with certain characteristics including female preponderance, better premorbid functioning, more paranoid delusions and hallucinations, and less disorganization and negative symptoms than are characteristic of early-onset schizophrenia. Neither the most recent iteration of the DSM (DSM-5) nor ICD-10 contains separate codes differentiating the late-onset of symptoms.

An International Late-Onset Schizophrenia Group met in 1998 in order to encourage greater consistency in the recognition, classification, and treatment of late-life schizophrenia. Although there were still no data to justify specific age cut points for diagnostic classification, it was felt that some delineation of age groups was necessary in order to stimulate further research in this area. In the resulting consensus statement [8], it was concluded that there was sufficient evidence to justify the adoption of two illness classifications: LOS and very-late-onset schizophrenia-like psychosis (VLOSLP). The former was conceptualized as a subtype of schizophrenia with an onset occurring after age 40 years. VLOSLP was defined as having an onset after age 60 and applies when the symptoms cannot be attributed to an affective disorder or a progressive structural brain abnormality. It was so named in order to reflect the relative diagnostic uncertainty that arises when attempting to identify a primary psychotic disorder at an age in which the risk for dementia-related psychoses begins to rise.

Epidemiology

Despite the findings and age cutoffs recommended by the consensus conference statement, the terms LOS and VLOSLP have yet to be uniformly adopted, and the ages used to define "late onset" still vary across studies. Not surprisingly, gaining an accurate estimate of the incidence of LOS and VLOSLP has proven difficult. The issue is further complicated by the fact that many studies assessing the epidemiology of schizophrenia do not include older adults, and those that do make varying levels of effort to exclude individuals whose psychotic symptoms might be due to such causes as dementias or delirium. Other studies that do focus on psychosis in adulthood often collapse across non-affective psychotic conditions, making it impossible to determine which characteristics are specific to LOS/VLOSLP.

The available evidence suggests that the 1-year prevalence rate of schizophrenia, irrespective of age of onset, in people ages 45–64 is 0.6% [9]. The proportion of individuals with schizophrenia whose symptoms emerge after age 40 (i.e., LOS) has most recently been estimated to be 36.4% [10] with only 3% developing symptoms after age 60 (i.e., VLOSLP) [11]. The community prevalence estimates for those age 65 and older range from 0.1 to 0.5% [12–14], and the incidence of VLOSLP is estimated to be in the

Table 42.1 Comparison of patient characteristics by age of onset

Characteristic	Early-onset schizophrenia	Late-onset schizophrenia	Very-late-onset schizophrenia-like psychosis
Age	<40	41–59	60+
Sex differences	M > W	W > M	W > M
Negative symptoms	Prominent	Perhaps less prominent	Uncommon
Positive symptoms	Prominent	Prominent	Prominent
Thought disorder	Prominent	Uncommon	Uncommon
Partition delusion	Uncommon	Less common	Common
Family history of schizophrenia	Common	Less common	Uncommon
Early-life maladjustment	Common	Less severe	Uncommon
Cognitive dysfunction	Common	Uncommon	Uncommon
Cognitive decline over time	Absent	Uncommon	Uncommon
Efficacious antipsychotic dose	Greater	Lower	Lower

Adopted from Reeves and Brister [18] and Palmer and colleagues [19]

range of 17–24 per 100,000 [15]. Greater age tends to confer greater risk for the disorder, as data from first admission reports for patients age 60 and above indicate the annual incidence of schizophrenia-like psychosis increases by 11% with each 5-year increase in age [16]. Further, while most individuals with LOS or VLOSLP first develop symptoms in their 50s, 60s, and 70s, Cervantes, Rabins, and Slavney [17] reported a woman who, after detailed examination, was found to have developed LOS at the age of 100. Thus, it appears that LOS/VLOSLP can develop at any age in late adulthood.

Clinical Features

The symptoms of schizophrenia, regardless of the age of onset, can include the positive symptoms of delusions, hallucinations, and disorganized speech and behavior, along with negative symptoms such as affective flattening, alogia, and avolition. According to DSM criteria, in order to justify the diagnosis of schizophrenia, these symptoms must disrupt a person's ability to function in major life roles, not be accompanied by prominent mood symptoms and not be due to substance use. Numerous similarities have been noted between the clinical presentation of LOS/VLOSLP and early-onset schizophrenia. In fact, they are often described as being more similar than different, particularly with respect to their positive symptom presentation [8]. On the other hand, evidence suggests that early- and late-onset cases are not identical conditions in terms of their clinical phenomenology (see Table 42.1).

Late-Onset Schizophrenia

There are a number of relative, and sometimes subtle, differences in symptom presentation that differentiate early- and late-onset schizophrenia. One of the most notable and reliably reported differences, particularly among earlier studies, is the relative paucity of classic negative symptoms such as affective flattening or blunting in persons with LOS [20–22]. Almeida and colleagues [23] found that only 8.5% of participants in their cohort evinced negative symptoms, and those that did appeared only mildly affected. In contrast, more recent investigations of large numbers of well-characterized subjects suggest that while individuals with LOS still show greater negative symptoms than age-matched healthy controls [19], EOS and LOS groups show similar negative symptom severity [2, 3, 24, 25], suggesting that early- and late-onset groups may be more similar in this regard than has previously been appreciated.

Individuals with LOS have historically been found to be markedly less likely to experience formal thought disorder (e.g., loosening associations, circumstantiality, etc.) than those who

develop schizophrenia in adolescence or early adulthood [20, 22]. For example, Pearlson and colleagues [20] looked at individuals who had an onset of symptoms after age 45 and found that formal thought disorder was present in only 5.6% of cases. In contrast, thought disorder was present in 51.9% of young adults with early-onset schizophrenia and in 54.5% of older early-onset cases. Pearlson et al. also found that the overall occurrence of formal thought disorder decreased as age of onset increased, such that individuals with the latest onset (i.e., VLOSLP) showed markedly lower rates of disordered thinking.

With respect to positive symptoms, patients with LOS are more likely to report visual, tactile, and olfactory hallucinations than are those with early-onset schizophrenia [20, 26], Alzheimer-type dementia with psychosis, or major depression [27]. When auditory hallucinations are present in LOS, they are more likely to consist of a third person, running commentary and accusatory or abusive content [22]. The content of the delusions in early- and late-onset schizophrenia may also differ, with LOS patients being more likely to experience persecutory and partition delusions (i.e., the belief that people, objects, or radiation can pass through what would normally constitute a barrier to such passage) [20, 22]. Such delusions frequently involve the belief that people or animals invade one's residence at night. For example, we had one patient with VLOSLP who was convinced that the light on a distant power line actually was a device being used to monitor her behavior at home. It has also been reported that some Schneiderian first-rank symptoms, such as delusions of control and thought insertion, thought withdrawal, or thought broadcasting, are far more likely to occur in LOS than in dementia-related psychosis [27].

Very-Late-Onset Schizophrenia-Like Psychosis

Relatively few studies have focused on the presentation of patients who develop psychoses for the first time in very late life and whose symptoms meet criteria for VLOSLP. Nonetheless, available evidence does suggest some unique and identifying symptoms in these patients. For example, there is a high prevalence of sensory deficits including a notable preponderance of conduction deafness [7, 28] and social isolation in those with VLOSLP [7].

Perhaps even more so than in LOS, formal thought disorder and negative symptoms are extremely rare in those with onset at age 60 or later [4, 23, 29]. Nevertheless, most, if not all, positive symptoms of early-onset schizophrenia can also appear in those with VLOSLP. Helping to differentiate VLOSLP from psychotic symptoms arising due to other etiologies are the partition delusions that occur in up to 70% of VLOSLP cases [20, 30, 31] but are less common in early-onset schizophrenia. The nature and pattern of positive symptoms of schizophrenia seen in VLOSLP also tend to be rather unlike the psychotic symptoms seen in the so-called *organic* psychoses of aging such as Alzheimer's disease and Lewy body dementia. A more characteristic delusion of patients with Alzheimer-type dementia is that others are stealing personal effects that the patient actually has misplaced or hidden and forgotten. Unlike dementing conditions wherein delusions and hallucinations tend to be less organized and persistent, the psychotic symptoms of VLOSLP tend to be more organized, fully formed, and stable features of the condition. As is discussed below, also unlike psychoses in dementia, the psychotic symptoms of VLOSLP are not invariably associated with a decline in cognition over time.

When considering the positive symptoms of schizophrenia evident in VLOSLP, there is a high prevalence of visual hallucinations [22, 29, 32]. Multimodal hallucinations are also quite common in this group. In a well-characterized cohort of persons with VLOSLP from south London, Howard [4] found visual hallucinations in 40% of the sample, with 32% experiencing these as well-formed visual hallucinations. Further, approximately 20% had what were described as Charles Bonnet-type complex recurrent visual hallucinations (sometimes described as "Charles Bonnet syndrome plus" [33]). Also common,

reported in 59.4% of the sample, were visual misinterpretations and misidentifications. In comparison with the prominent visual disturbances, auditory hallucinations were even more common in the London cohort, as 70% of those with VLOSLP were noted to have nonverbal auditory hallucinations. Another sizable proportion of participants (49.5%) endorsed auditory hallucinations consisting of third-person voices or voices speaking directly to the patient. Hallucinations in other modalities were common as well, with 30–32% reporting olfactory, gustatory, or tactile hallucinations with delusional elaboration. Finally, equally notable were the high rates of delusions of persecution (84.2%) and reference (76.3%) seen in VLOSLP.

Risk Factors and Associated Features

A number of studies have examined risk factors for the development of LOS and VLOSLP including gender, age, premorbid functioning, family history of schizophrenia and dementia, APOE genotype, pharmacological treatment response, and neuroimaging characteristics.

Gender

Perhaps the most consistent risk factor for the development of schizophrenia or psychotic symptoms in late life is gender. Unlike early-onset schizophrenia in which there is a male predominance, considerable evidence indicates that a disproportionate number of individuals diagnosed with LOS and VLOSLP are female [14, 23, 24, 29, 30]. In one early study of gender differences in schizophrenia onset across the lifespan, Castle and Murray [14] found a male to female ratio of 1.56:1 in the 16- to 25-year age group. The ratio was roughly equal among those with onset around age 30. However, for those whose psychosis emerged for the first time between 66 and 75 years of age, the male to female ratio declined to just 0.38:1.0. Further, this difference appears to persist even after accounting for gender differences in social role expectations and care-seeking behavior [34, 35].

Age

Age also appears to be a risk factor, particularly for developing VLOSLP. The risk of developing schizophrenia is highest in adolescence and early adulthood. It declines during mid-adulthood but then increases again after age 60, at which time very LOS-like psychoses occur with increasing frequency. VLOSLP has been found to occur in 10 individuals per 100,000 adults in the 60–65 age bracket. Thereafter, the rates rise steadily to 25 per 100,000 among adults aged 90 and above [16].

Premorbid Functioning

Although some studies suggest poor childhood adjustment in both early- and late-onset schizophrenia [36], many investigations have found notable differences in rates of successful social and role functioning between early- and late-onset cases. Generally, individuals who develop psychosis late in life tend to have better premorbid educational attainment, greater occupational success, and less impaired psychosocial functioning than is seen in early-onset schizophrenia [21, 37, 38]. For example, in one study [14], half of those with early-onset schizophrenia were judged to have poor premorbid work adjustment as compared to only 15% of the LOS group. Similarly, while 43% of early-onset subjects were rated as showing poor premorbid social adjustment, only 22% of those with LOS were rated as such. Rates of marriage were also twice as high among LOS compared to early-onset cases (66% vs. 33%).

While later onset of schizophrenia and psychosis may be associated with better psychosocial functioning and perhaps a less severe form of the disease, evidence suggests that those who do develop schizophrenia/VLOSLP in late life are more likely to have a history of mild premorbid

schizoid or paranoid personality traits that do not meet criteria for a personality disorder [7, 20, 21]. Further, evidence suggests that while their psychosocial deficits are not as severe as those with early-onset schizophrenia, they still have greater rates of general psychopathology and functional disability than healthy normal controls [24].

Family History

Family studies of LOS and VLOSLP tend to be small and have methodological shortcomings. There is some evidence that those with LOS may have higher rates of schizophrenia among relatives than unaffected individuals [37]. However, studies also have found lower rates of schizophrenia among relatives of those with late-onset compared to early-onset schizophrenia [20, 39]. There does not appear to be an increased rate of schizophrenia among relatives of patients with VLOSLP [19] nor does there appear to be an increased prevalence of family history of Alzheimer's disease, vascular dementia, Lewy body dementia, or APOE ε4 alleles in LOS or VLOSLP [40]. Consistent with this, LOS patients do not show the hallmark neuropathological indicators associated with neurodegenerative dementias on autopsy [41].

Pharmacological Treatment Response

At present, there is no good randomized clinical trial evidence on which to base treatment guidelines for LOS/VLOSLP [4, 42]. Despite the lack of well-controlled, double-blind trials and overreliance on case reports or series, available evidence indicates that LOS and VLOSLP often respond well to antipsychotic medications. Further, effective treatment can often be reached at doses that are a fraction of those used for early-onset cases. Based on open-label observations, Howard [8] found that LOS can often be effectively managed on antipsychotic doses that are approximately 40% as high as that needed for younger patients. Similarly, Barak [38] reported that 71.4% of individuals with VLOSLP reached a favorable response to an atypical antipsychotic (risperidone) as compared to just 57.1% of older patients with early-onset schizophrenia. Despite its apparent efficacy, recent data suggests that less than half of VLOSLP patients are started on an antipsychotic at time of diagnosis and only about one quarter are receiving pharmacological treatment at 1 year post-diagnosis [43]. More careful monitoring and greater efforts to enhance treatment engagement may be warranted in this population. As in all populations, antipsychotic side effects can include sedation, anticholinergic effects, extrapyramidal effects, weight gain/diabetes, hyperglycemia, tardive dyskinesia, and neuroleptic malignant syndrome.

Neuroimaging

Neuroanatomic investigations of individuals with schizophrenia have generally failed to detect consistent characteristics that differentiate LOS cases from early-onset schizophrenia. Anatomic brain imaging studies of individuals with LOS have found increased ventricle-to-brain ratios in LOS/VLOSLP compared to matched healthy controls [38, 44, 45]. Semiquantitative analyses of brain MRI scans have demonstrated larger thalamic volume in LOS compared to early-onset schizophrenia [46] and smaller third ventricle volumes compared to age-matched controls [47]. Focal changes, such as reduced volumes of the left temporal lobe and superior temporal gyrus, are also similar to those found in early-onset cases [45, 48]. With respect to white matter abnormalities, some early studies reported that large subcortical white matter hyperintensities were common in LOS [49]. However, subsequent studies that carefully controlled for organic cerebral disorders failed to replicate these earlier findings among late-onset cases [38, 50, 51]. More recent diffusion tensor imaging findings also failed to find significant differences in fractional anisotropy or mean diffusivity between those with VLOSLP and age-matched unaffected adults, arguing further against structural white

matter abnormalities as a potential etiology for psychotic symptoms late in life [52].

Early functional neuroimaging studies found lower perfusion of the frontal and temporal lobes in LOS as compared to EOS and healthy controls [53], as well as preliminary evidence of higher D2 receptor density in those with LOS compared to age and gender norms [45]. More recently, Wake [54] compared regional cerebral blood flow (rCBF) in EOS in their 30s to LOS patients and found different patterns of rCBF between the patient groups. While the EOS group showed reduced precentral and inferior frontal gyri rCBF, those with LOS demonstrated bilateral postcentral gyri reductions. The LOS group generally demonstrated more strongly localized temporal lobe hypoperfusion. While these findings suggest that differences in rCBF may be related to the age of disease onset, the age difference between the patient groups introduces a significant methodological limitation. Furthermore, the study was cross-sectional in nature, and it remains unclear whether any LOS participants showed signs of an incipient dementia syndrome that might account for the observed temporal hypoperfusion.

In light of the known association between elevated inflammatory biomarkers and risk of schizophrenia, Wium-Anderson and colleagues [55] conducted a large case registry review and found that elevated C-reactive protein at baseline was associated with a 6- to 11-fold increase in the risk of LOS and VLOSLP in the general population. These associations held even after removal of participants who went on to develop dementia in the 2 years following their diagnosis of schizophrenia.

Cognitive Profile and Course

Contrary to Kraepelin's notion that schizophrenia involves a progressive "dementia praecox," there is now compelling evidence that early-onset schizophrenia is a neurodevelopmental disorder that rarely involves progressive dementia. While the development of schizophrenia in early life certainly is associated with widespread cognitive dysfunction, it does not predict worsening cognitive decline in late life relative to age-matched controls [56, 57]. Some experts have suggested that the emergence of psychotic symptoms late in life may signal the onset of a neurodegenerative process [58]. Further, given that LOS/VLOSLP arises at a time in which rates of dementia begin to rise, differentiating the cognitive pattern of a primary psychiatric disease from the psychoses that can accompany dementia is important from a treatment planning perspective.

Persons with early-onset schizophrenia show severe and pervasive deficits across virtually all domains of cognitive functioning. The most pronounced impairments typically appear to involve psychomotor speed, verbal memory, and attention [59, 60]. Beginning in the mid-1990s, studies began finding that both early- and late-onset schizophrenia involve cognitive dysfunction [21, 56] and that early- and late-onset groups tended to perform quite similarly to one another on cognitive testing. In these early studies, the primary differences seen between the early- and late-onset groups tended to occur on tests of learning/memory and abstraction/mental flexibility, with later age of onset being associated with better performance on these tasks.

Vahia and colleagues [24] replicated the finding that outpatients with both early- and late-onset schizophrenia performed more poorly than healthy controls on most cognitive tests but that those with LOS showed less severe dysfunction on most measures and these differences in cognitive impairment were accompanied by notable functional differences. Their early- and late-onset groups were equivalent in terms of crystallized verbal abilities and working memory as assessed by Wechsler subtests (Wechsler Information, Vocabulary, Similarities, and Arithmetic subtests). However, the LOS patients showed less severe impairment than early-onset cases on tests of processing speed (Digit Symbol), visuoconstruction (Block Design), executive functioning (WCST perseverative responses), and verbal memory as assessed by CVLT long-delay free recall (when adjusted for Trial 5 learning). In addition to showing less severe cognitive deficits, the LOS group performed better than early-onset patients on performance-based measures of functional capacities, social skills, and health-related

quality of life. More recent work by Brichant-Petitjean and colleagues [61] found similar results when comparing a group with EOS, those with LOS who were <65 years old and had MMSE >27, and healthy matched controls across a brief cognitive battery. Here the LOS group demonstrated intermediate cognitive functioning, outperforming the EOS group on Digit Span forward, phonemic verbal fluency, and delayed recall of the Rey Complex figure while consistently underperforming relative to the controls.

Most studies examining the cognitive profile of schizophrenia emerging in late life have combined patients with LOS and VLOSLP or combined across late-life psychosis diagnostic categories. As a result, less is known about whether there are any unique VLOSLP-related cognitive deficits. Those studies that do address this issue have found that the cognitive deficits associated with VLOSLP are widespread, with no pronounced differences in cognition between LOS and VLOSLP [8]. Similarly, when considering the full spectrum of schizophrenia-spectrum disorders (i.e., schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychotic disorder NOS), Hanssen [62] found that non-demented very late-onset patients were similar to non-demented early-onset patients in terms of IQ, attention, memory, and executive functioning.

Of critical importance is determining whether the onset of psychosis late in life signals the presence or onset of a dementing condition. Available evidence suggests that the pattern of cognitive deficits seen in early- and late-onset schizophrenia differ from those seen in Alzheimer's disease, with schizophrenia of any age of onset showing a pattern of deficient learning coupled with intact retention [21, 56, 63, 64]. This contrasts with the impairments seen in Alzheimer's disease, which involve both learning and retention.

Several longitudinal studies have sought to determine whether LOS/VLOSLP might herald the development of a progressive dementia syndrome. Most of these [57, 65, 66] have found a pattern of stable cognition over a period of several years. For example, a careful review of the longitudinal cognitive literature failed to yield any conclusive evidence that cognitive trajectory of EOS and LOS patients differs over time [67]. A longitudinal [68] study of patients with early- or late-onset schizophrenia, mild Alzheimer's disease, Alzheimer's disease with psychotic features, and healthy controls found that both dementia groups showed steep cognitive declines over a 2-year period, whereas both schizophrenia groups and the normal controls remained cognitively stable over the same interval. However, the finding of stable cognitive functioning over time in LOS is not uniform. A few studies with longer follow-up periods have reported that a proportion of patients decline over time. For example, Holden [15] conducted a retrospective chart review and found that 35% of people with LOS developed dementia within a 3-year follow-up period. Brodaty and colleagues [58] reported that 9 of 19 (47%) older adults with LOS subjects developed dementia over a period of 5 years, whereas none of the 24 healthy controls developed dementia over the same period. In the largest study to date, Korner and colleagues [69] conducted a retrospective cohort study of patients in Denmark who were first hospitalized with a diagnosis of schizophrenia late in life. Both late and very late first-contact patients were several times more likely to develop a dementia syndrome over the 3–4.5 years following hospitalization when compared to both the general population and to a somatic (osteoarthritis) control group. Finally, a longitudinal study of psychogeriatric clinic patients, Rabins and Lavrisha [27] examined the rates of conversion to dementia (as indicated by declines in MMSE of ≥4 points and fulfillment of DSM-IV criteria for dementia) in 28 cognitively intact, non-depressed patients with LOS; 48 patients with depression but not dementia or psychosis; and 47 patients with dementia and psychosis. While approximately half the LOS cases developed dementia by 10-year follow-up, those with LOS were no more likely to develop dementia than those with late-life major depression. These findings suggest it may be the late-onset of a psychiatric disorder, rather than the late-onset of schizophrenia specifically, which may portend the onset of a dementia syndrome in some individuals.

Taken together, cross-sectional and longitudinal studies suggest that while individuals with LOS may perform more poorly than normal controls on tests of learning and memory, they can be differentiated from those with primary dementing conditions by the relative preservation of retention and recognition skills. Further, the psychosis of LOS and VLOSLP is not invariably associated with deteriorating cognitive abilities, and some patients remain cognitively stable over time. Given the variability in cognitive outcomes, a progressive dementia syndrome does not appear to be the primary underlying etiology of most cases of LOS/VLOSLP. Further research is needed to determine the pathology of most commonly experienced by those individuals with LOS/VLOSLP who do ultimately convert to a dementia syndrome.

Assessment

Given the age of the population in question, when a patient presents with symptoms of psychosis late in life, the referral question tends to focus on differentiating between late-life psychosis and a primary dementing illness. However, psychosis in late life can stem from several etiologies including acute conditions such as a delirium, degenerative conditions like moderate to severe dementia, or any of several psychiatric illnesses, including delusional disorder, mood disorder with psychotic features, bipolar disorder, and either early- or late-onset schizophrenia (see Table 42.2). In light of the differential course and survival rates for these various etiologies, an accurate diagnostic formulation is crucial to formulating the most effective treatment plan.

Table 42.2 Common differential diagnoses

Delirium
Substance use or withdrawal
Alzheimer's disease, moderate to severe
Lewy body dementia
Delusional disorder
Mood disorder with psychotic features
Bipolar disorder
Schizophrenia (early onset)

Clinical Interview and Symptom Assessment

As described above, the cognitive deficits of LOS/VLOSLP are relatively nonspecific and usually milder than those seen in older adults with early-onset schizophrenia. Thus, evaluation and proper diagnosis of these patients rely heavily on taking a thorough history of the patient's premorbid functioning and the nature and course of the psychotic symptoms. We have found that a knowledgeable informant can provide critically important data. This is particularly the case if a patient is experiencing intrusive psychotic symptoms at the time of the evaluation. However, the absence of an identifiable family member, friend, or caregiver who knows the patient well enough to provide such input suggests a level of social isolation that is fairly common in LOS patients. Determining the duration of symptoms can itself be a challenge given that these patients often lead relatively solitary lives. In fact, many such individuals only come to the attention of care providers after a neighbor becomes concerned about paranoid or other floridly psychotic behavior. For example, one of our patients repeatedly and angrily confronted the neighbor that she believed was breaking in and stealing money from her home. It was only after repeated unsuccessful attempts to convince the patient otherwise that the neighbor contacted the local police, which prompted the patient's admission to our geriatric psychiatry service.

As LOS and VLOSLP are associated with various premorbid characteristics, when taking a clinical history, particular attention should be paid to the individual's occupational and social functioning during midlife. Did the patient achieve a reasonable degree of occupational success by mid-adulthood, or is their work history characterized by difficulty maintaining employment, "underemployment" (working at jobs for which they are clearly overqualified), or recurrent problems working with others so that they quit jobs or were terminated? Since LOS and VLOSLP are associated with the presence of mild premorbid schizoid or paranoid personality traits, it can also be helpful to determine whether an individual has

a full and socially connected existence or gravitated toward solitary activities in their adulthood. Similarly, it is helpful to determine whether an individual's history suggests a lack of interest or success in forming romantic relationships or a general lack of relationships that could be characterized as close or warm. It is helpful to determine if the patient is described as mistrustful of others, quick to perceive slights or threats, or frankly suspicious. Although this is informative, the paranoia that often characterizes LOS/VLOSLP makes it difficult to obtain these details directly from the patient and sometimes from others as well. Rather, these individuals are often suspicious of the assessment procedures, reticent to disclose personal information, or unwilling to allow a knowledgeable informant to speak to the neuropsychologist or treatment team.

As was outlined above, LOS and VLOSLP are associated with common but not pathognomonic clinical features. These include prominent positive symptoms, such as auditory hallucinations of accusatory or abusive voices, visual hallucinations, and paranoid, persecutory, or partition delusions. Negative symptoms (i.e., alogia, avolition, and affective blunting) tend to be less prominent, and formal thought disorder is relatively rare. In our clinic, we augment our clinical interview with the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS). These semistructured interview/observation rating scales [70] can help quantify the severity of positive and negative symptoms. The SANS is a 25-item scale with five subscales: affective flattening, alogia, avolition/apathy, anhedonia/asociality, and inattention. The SAPS consists of 35 items and 4 subscales: hallucinations, delusions, bizarreness, and formal thought disorder. Both scales include a global rating, and symptoms are rated as they occurred over the preceding month.

Differentiating LOS/VLOSLP from Other Psychiatric Disorders

A thorough review of a patient's clinical and psychiatric history is essential to diagnosis, as the symptom presentation and cognitive deficits can be similar to other disorders. Affective disorders, including bipolar disorder and unipolar depression, also are common in older adults and can be accompanied by frank psychosis. The symptoms of LOS/VLOSLP do not couple tightly with fluctuations in a patient's mood. If psychotic symptoms resolve with return to a euthymic state or a patient exhibits mood-congruent psychotic features in manic and depressed states, LOS/VLOSLP should not be diagnosed, and consideration should be given to a diagnosis of depression with psychotic features or bipolar disorder. In our clinic, we routinely administer the 15-item Geriatric Depression Scale [71]. The diagnostic validity and reliability of this version are comparable to those of the original 30-item version [72, 73], and this appears to be the case for middle-aged adults as well [74]. Finally, although delusions can be a feature of LOS and VLOSLP, they differ from a late-life delusional disorder in that the latter is characterized by the presence of a nonbizarre delusion that occurs in the absence of prominent auditory or visual hallucinations. Further, delusional disorders are often associated with preserved premorbid personality, intact intelligence, and intact functioning in matters that are unrelated to the content of the delusion. This contrasts with the symptoms of LOS and VLOSLP in that the delusions may be bizarre, multimodal hallucinations are common, and both cognitive and functional deficits may be present.

Differentiating LOS/VLOSLP from Dementia Syndromes

Psychosis can occur in a variety of dementia syndromes such as Alzheimer's disease, Lewy body dementia, Parkinson's disease, and vascular dementia. However, there are several means of differentiating a primary psychiatric disorder from a primary degenerative cognitive disorder in an older patient. Because of the high rates of sensory deficits in LOS/VLOSLP, we often find it helpful to begin by evaluating the patient's auditory and basic visual-perceptual abilities. Hearing can be informally assessed during the clinical interview by performing basic comprehension and repetition tasks or by having the patient close

his or her eyes and indicate in which ear they hear the examiner's fingers rubbing lightly. If auditory deficits are present but mild to moderate, we often use a microphone and amplifier worn in the ear during cognitive assessment. More severe deficits may warrant delaying neuropsychological testing until after an audiology consultation. A pocket vision screener can be used to screen for problems with near visual acuity. We find it useful to keep a selection of magnifying reading glasses in various strengths for patients with decreased near visual acuity to use during testing. Finally, we often rely on the Judgment of Line Orientation, Hooper Visual Organization Test, and Boston Naming Test to detect the presence of visual misperceptions, which are common in LOS and VLOSLP.

Differentiating the psychosis of late-life schizophrenia from the psychosis that can accompany dementia should include a characterization of the initial symptoms and the temporal course of the condition. Hallucinations and delusions are rarely an initial symptom of dementia. Rather, in primary dementia syndromes, early cognitive decline is often the first indication of a disorder. These cognitive impairments tend to be at least moderately severe by the time psychotic symptoms emerge in patients with a primary dementing illness. In contrast, the psychotic symptoms of LOS and VLOSLP are often the first and most prominent manifestations of these conditions. While cognitive deficits often co-occur with the hallucinations and delusions, these deficits are usually not severe enough by themselves to bring a patient to clinical attention. Qualitatively, the hallucinations and delusions of LOS and VLOSLP tend to be more organized, elaborate, and stable than those seen in dementia. Finally, while not an essential feature of dementing illnesses, it is helpful to assess whether the patient has experienced a decline in cognition and if so, over what period of time. A decline in cognition and functioning over a period of months to years is often a sign of dementia. The cognitive weaknesses seen in LOS and VLOSLP, in contrast, tend to be stable features of the disorder and generally do not worsen over time, particularly when symptoms emerge between age 40 and 60 (i.e., LOS).

When attempting to diagnose an older patient with psychosis, it is also important to assess the presence of other symptoms that are characteristic of particular dementia syndromes, as their presence decreases the likelihood that the patient has LOS. Both LOS and VLOSLP are associated with a broad, generalized pattern of mild cognitive dysfunction. However, some features are generally not seen in these patients. Apraxia and naming deficits are not typical of LOS/VLOSLP, whereas they are prominent in Alzheimer's disease. Similarly, in a patient with visual hallucinations, the presence of axial rigidity, disproportionate impairment on tests of visual-perceptual or visual-constructional ability, and other Parkinsonian features would raise the suspicion for a Lewy body dementia and reduce the likelihood of LOS in the differential diagnosis. Several studies have found that patients with LOS or VLOSLP also be differentiated from those with dementia by their relatively preserved retention of newly acquired information as demonstrated by tests such as the HVLT-R or CVLT-II.

Medical Rule Outs and Recommendations

As with many conditions warranting a clinical neuropsychological evaluation in older adults, particular care must be taken to rule out the presence of delirium or another organic cause of psychosis when LOS/VLOSLP is in the differential. Learning about the course of the patient's symptoms can be illuminating. Unlike delirium in which hallucinations and delusions appear to wax and wane, the psychotic symptoms of LOS/VLOSLP tend to be stable and persistent. They rarely show marked fluctuations over time. We often recommend the patient undergo standard laboratory blood studies (e.g., complete blood count, glucose, TSH, electrolytes, BUN, creatinine, liver function, B12, folate, RPR, etc.) in order to rule out thyroid conditions, infections, glucose or electrolyte abnormalities, vitamin deficiencies, and other metabolic abnormalities. A toxicology screen should be considered, particularly if there is a suspected history of substance abuse. Any recent changes in drug use

should also be considered, as older adults can be particularly vulnerable to drug withdrawal. Similarly, it can be helpful to review the patient's medication history to assess for the potential effects of anticholinergic medications and adverse drug interactions. Brain imaging can be informative in determining whether any strokes, tumors, or other cerebral abnormalities might account for the late-onset of psychotic symptoms. Finally, given the increased rates of sensory deficits in patients with LOS/VLOSLP relative to older patients with affective disorder, early-onset schizophrenia, and age-matched controls [4, 20], recommendations for formal audiology and ophthalmology workups are often helpful to assess the extent to which sensory deficits might contribute to misinterpretations in older patients with psychosis. See Table 42.2 for common considerations in the differential diagnosis.

Treatment Recommendations

As outlined above, a substantial proportion of patients with LOS/VLOSLP show effective treatment response to relatively low-dose neuroleptics. For some patients, such treatment can limit their experience to a single acute episode. We have found that a geriatric psychiatrist is the most appropriate person to manage a patient's psychotropic medications. Further, if sensory impairments are present, attempts should be made to remedy these as well as possible, as they might contribute to perceptual aberrations. Even if full correction of sensory impairments is not possible, it can be helpful to educate patients about the potential contribution of hearing or vision impairments to their symptoms and difficulties with everyday functioning.

There are also a number of psychosocial interventions and recommendations appropriate in this population. These include supportive and cognitive-behavioral therapies. Aguera-Ortiz and Renese-Prieto [4] outlined a number of "tips and tricks" for the psychological management of patients with late-life schizophrenia. Even though patients may have difficulty forming an initial attachment to their treatment providers, attempts should be made to establish a good therapeutic relationship and a supportive atmosphere. It is not necessary to agree with a patient's delusional system, but rather to be empathic and understanding. Listening to psychotic complaints in a nonjudgmental manner may lessen the likelihood that they will act on their agitation (e.g., by confronting neighbors). It can also help address a patient's social isolation, especially if it leads to entry into a larger social sphere. More generally, we have found it important to educate family members and caregivers and to help create a network of persons (e.g., family members, friends, neighbors, church members) who can help ensure a patient's ongoing safety. In some instances, the establishment of a conservatorship or guardianship may be in the patient's best interest.

Clinical Pearls

- LOS/VLOSLP is associated with female gender, increased age, premorbid schizoid or paranoid personality traits, poor premorbid social and occupational functioning, social isolation, and sensory deficits.
- Symptoms tend to consist primarily of positive symptoms such as auditory or visual hallucinations or paranoid delusions. Partition delusions are particularly common and are fairly unique to LOS/VLOSLP. There is also often a lack of negative symptoms and formal thought disorder, particularly in those with very late onset.
- Similar to early-onset schizophrenia, LOS/VLOSLP is associated with a generalized, nonspecific pattern of cognitive dysfunction. However, the cognitive impairment tends to be less severe than early-onset schizophrenia. It differs from that seen in patients with dementia with psychosis by virtue of the relative sparing of memory abilities and the absence of cortical features and extrapyramidal signs. LOS and VLOSLP have been conceptualized as primarily non-dementing disorders, but patients with late onset of schizophrenia

probably are at increased risk of developing dementia.

- When an older patient presents with psychotic symptoms, it is important to first rule out delirium, identifiable medical etiologies, and the effects of medications or toxins, as well as prominent mood symptoms.
- Treatment, both psychosocial and pharmacological, can be successful in helping affected individuals maintain maximal functional independence and remain safe.

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Chronic Traumatic Encephalopathy

43

William B. Barr and Stella Karantzoulis

Introduction

The effect of repetitive head trauma on athletes participating in contact sports has become a highly publicized and controversial topic. But, just how serious a risk concussive (and even subconcussive or asymptomatic) cerebral trauma is in the long-term relative to other risk factors facing professional athletes remains uncertain. Media reports on the "concussion epidemic" and the potential link between repetitive brain injury and long-term cognitive and emotional problems in the brains of former athletes from contact sports have certainly generated much public fear and anxiety on the topic.

Although the concept of dementia resulting from sports competition might be thought provoking, the public fear on this topic has *far* outpaced the scientific evidence supporting its existence and the scope of its occurrence. To the best of our knowledge, the data supporting the presence of brain disorders resulting from contact sports participation has been based thus far on reports from a skewed sample of athletes in the absence of any reliable or objective means to diagnose the condition or any population-based parameters to determine its prevalence or incidence. To date, there is no proven mechanism for its cause.

The term chronic traumatic encephalopathy (CTE) is currently used widely to describe a condition that is alleged to be a specific form of tauopathy resulting from repetitive brain injury that purportedly leads to a distinct clinical profile of cognitive, behavioral, and motor symptoms. It is claimed that these symptoms are ultimately caused by a form of neuropathology that is distinct from what is encountered in other more common forms of neurodegenerative disease, such as Alzheimer's (AD) or Parkinson's disease (PD) [1].

While forms of dementia have been described in relation to participation in combative sports, such as boxing, for nearly 100 years, the type of dementia that is most publicized today has been extended to include participants from professional American football, ice hockey, wrestlers, and soccer players and even nonathletes (e.g., a circus clown, a self-injurer, and a patient with epilepsy) [2]. It has also been associated with cerebral trauma from blast exposure in soldiers [3]. The condition currently characterized as CTE is believed by its proponents to be progressive and incurable with associations to both aggressive and suicidal behaviors, extending to what might amount to as a public health crisis.

This chapter provides a critical review of the evidence-based literature examining the risks of

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repetitive brain injury on the cognitive and mental health outcome of professional athletes, with a particular focus on studies of American football. The topic is clearly one that remains provocative, confusing, and disturbing. As with the non-sports arena, research regarding the association between concussion and the likelihood of developing late-life cognitive and psychiatric conditions is beset by numerous methodological problems, including reliance on retrospective report of injury characteristics by the athlete or others, failure to control for confounding variables, and a tendency to generalize from the literature involving *moderate to severe* traumatic brain injuries (TBI) to those with *mild* traumatic brain injuries (MTBI) or concussion. The goal is to highlight the numerous methodological issues besetting the research on CTE while making recommendations for future studies.

Dementia Pugilistica

For over a century, it has been believed that repetitive blows to the head sustained in sport are linked with cognitive and behavioral impairments occurring later in life. One of the first formal scientific descriptions of this topic was provided in a 1928 paper by Martland, a New Jersey pathologist and medical examiner, who reported a cluster of characteristic signs and symptoms, including confusion, bradykinesia, tremors, and gait disturbance, which were hypothesized to have followed repetitive boxing-induced TBI, a condition that he termed "punch drunk" [4, 5].

In 1937, Millspaugh coined the more formal term *dementia pugilistica* (DP) to describe a disease marked by motor deficits and cognitive dysfunction observed primarily in boxers [6]. By the 1970s, a sufficient number of boxers believed to have DP had been studied pathologically, leading to the popular belief that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease, like AD.

Symptoms of DP were reported to manifest long after (anywhere from 7 to 35 years) the start of a boxer's career [7, 8]. In terms of its incidence, the condition was initially observed in 17% of retired professional boxers. Risk factors included retirement after age 28, participation in boxing for more than 10 years, fighting in more than 150 bouts, and greater sparring exposure. Additionally, the probability of developing DP is believed to be increased for boxers with a history of technical knockout or knockout [9], in "sluggers" rather than more "stylish boxers" [10], and in those with the *APOE* e4 allele [11]. The risk of DP in amateur boxers is noted to be substantially lower than those participating in the sport on a professional basis [12].

The defining neuropathological features of DP, as later described by Corsellis and colleagues [13], included (a) abnormalities (cavum, fenestrations) of the septum pellucidum (a thin, triangular, vertical membrane separating the anterior horns of the left and right lateral ventricles); (b) scarring on the inferior surface of the lateral cerebellar lobes (primarily in the tonsillar region), with loss of Purkinje cells in these areas; (c) degeneration of the substantia nigra with loss of pigmentation, neurofibrillary changes, and the absence of Lewy bodies; and (d) diffuse neurofibrillary tangles in the cerebral cortex (primarily medial temporal) and brain stem, with very few, if any, senile plaques. It was from this study that Corsellis and his colleagues concluded that DP pathology was generally similar to AD but because plaques were not observed in all cases (seen in 11/15 cases) that DP likely represented a *unique* form of pathology.

Neuropathological examination of the brains of former boxers with DP has also resulted in different findings over the years. In a review study of 11,173 boxers, McCown indicated that he did not find a single case of "punch drunk syndrome" [14]. While he did not dismiss the possibility that boxing can potentially injure the brain, he did not support the idea that there was a *distinct* neurological syndrome unique to former boxers. In a more idiopathic view of the condition, he believed that the clinical changes observed in former boxers were likely due more to factors inherent in the person rather than in the occupation itself.

Evolution of Modern Day CTE

CTE is essentially the newest term used to describe DP, popularized largely by the efforts of two groups of investigators. Dr. Bennett Omalu, a Nigerian-born neuropathologist, is often cited as the first to identify CTE pathology in an athlete retired from the National Football League (NFL). The second group includes members of the Boston Center for the Study of Traumatic Encephalopathy (BU CTSE), led by Dr. Ann McKee, a neuropathologist who has made many highly publicized proclamations on the clinical characteristics of CTE based on select postmortem case reports or studies from small samples of brain specimens obtained from autopsies of retired athletes.

Formal inquiry into the relationship between head injury and late-life changes in mood and cognition actually began with a series of questionnaire studies performed by Guskiewicz and colleagues [15]. This group analyzed data regarding memory changes from a general health questionnaire sent to 3729 retired professional NFL players in 2001. Based on the retirees' responses, it was found that those players with three or more concussions were five times as likely to have a clinical diagnosis of mild cognitive impairment (MCI) and three times as likely to have more significant memory problems as compared to retirees without a history of concussion. A trend toward earlier onset of AD was also noted along with observations of a higher disease prevalence in younger cohorts, relative to the general population. Although compelling, these data were limited by design as a cross-sectional retrospective self-report study [15].

As stated, Omalu and his colleagues, performing neuropathological studies on autopsy material, described the first cases of CTE in retired NFL players in 2005 and 2006 [16, 17]. Medical history in the first two patients included symptoms of cognitive impairment, mood disorder, and Parkinsonism after retirement. There was no family history of AD noted or other head trauma incurred outside of football. In the first case, a neuropathological examination was performed after approximately 12 years following retirement. On autopsy, the brain showed no cortical atrophy, contusions, or infarcts. There was mild neuronal cell loss noted in the frontal, parietal, and temporal neocortex. CTE was reported to be evident by the demonstration of tau in the form of neurofibrillary tangles in the hippocampus [17].

The second reported case of autopsy-confirmed CTE in a retired professional football player displayed neuropathological features that *differed* from the first reported case [16]. This case had a 14-year span of play in organized football starting at age 18. The athlete was diagnosed with major depressive disorder without psychotic features after retirement from professional football and, after several failed attempts, committed suicide. Upon examination, the postmortem brain was also noted to demonstrate evidence of tau-positive neurofibrillary tangles and neuropil threads, but contrary to the first case, amyloid plaques were completely absent. Reasons for the contrasting neuropathological features of these two cases have never been made clear.

The clinical and neuropathological profile of CTE described by McKee and her colleagues in Boston was based initially on a collection of case reports and a review of the existing literature [2]. The characteristics of CTE, as reported by that group, are described in terms of a progressive tauopathy, which follows a sequence of clinical changes and associated neuropathological changes. The reported cause of these changes is alleged to be repetitive closed head injury, which can occur in a variety of contact sports, non-sport-related accidents, or in the setting of military service. Interestingly, analysis of a case series from a convenience sample of 202 football players showed neuropathological features of CTE as defined by this group in the vast majority (87%) of its players coming to their center in Boston at autopsy [18].

The researchers from Boston argue that the neuropathological changes associated with CTE are distinct from those found in other forms of dementia [1, 19]. They describe a long list of changes, which may or may not be present. Gross changes include anterior cavum septum

pellucidum and typically posterior fenestrations. Enlargement of the lateral and third ventricles is also common. Additional gross features include atrophy of the frontal and temporal cortices, atrophy of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Microscopic changes include an abundance of neurofibrillary inclusions, in the forms of neurofibrillary tangles, neuropil threads, and glial tangles.

In 2013, Stern and colleagues [20] described two major clinical variants of CTE – one variant has predominant behavioral and mood features developing at a relatively early age, while the other variant exhibits predominant cognitive disturbance with a later age of onset. Impulsivity, explosiveness, and violence are some of the most compelling and highly publicized symptoms that have been associated with CTE, and these are the features that have been alleged to have caused premature deaths in an alarmingly high number of individuals included in the Boston autopsy series. More recent published work from the Boston group describes a wider array of clinical presentations of CTE, including groups characterized by specific behavioral, mood, and cognitive symptoms, in addition to those with presentations characterized by dementia with and without motor symptoms [21].

Based on their ongoing work, the Boston group has concluded that clinical and pathological changes in CTE evolve in a progressive manner along a spectrum where the neuropathology ranges in severity from focal perivascular epicenters of neurofibrillary tangles (Stage I) to a severe tauopathy affecting widespread brain regions (Stage IV) [1]. The group also hypothesizes that the neuropathological spectrum of changes is accompanied by parallel changes in overt clinical symptoms, ranging from initial features of headache and attentional disturbance (Stage I) to a full-blown dementia associated with word finding difficulty and aggression (Stage IV).

Their view is that CTE is distinguishable from AD, other age-related changes, and other neurodegenerative tauopathies because of differing distributions of tau pathology. While the clinical symptoms of CTE are acknowledged by this group to overlap with those of other neurodegenerative conditions, they claim that a number of historical and symptomatic features distinguish CTE from other conditions [20]. For one, there is the claim that those presenting with CTE are known to have a history of exposure to repetitive brain injury with a profile of symptoms that distinguish them from individuals experiencing prolonged forms of post-concussion syndrome. Secondly, those with CTE often exhibit an earlier age of onset as compared to those with dementia due to AD and have a less rapid course of progression than non-AD conditions such as the behavioral variant of frontal temporal lobar degeneration (FTL-bv). There are, however, no reliable blood, cerebrospinal fluid, or neuroimaging biomarkers yet identified to distinguish CTE from a large list of other similar neurodegenerative conditions with overlapping symptoms and pathology.

Methodological Challenges to the Study of CTE

Ongoing and extensive media coverage has provided the public with an impression that much is now well-understood about CTE, including its clinical characteristics and its causes. However, this is far from the truth. The facts are that, from a scientific standpoint, the study of CTE is still in a preliminary stage with much that remains to be learned. Critically important is that, at this point in time, it is unknown how many athletes truly exhibit the reported signs and symptoms of CTE (i.e., beyond the number of brains examined postmortem by the Boston group). Also, yet to be identified is exactly who is prone to developing the condition? While the onset of CTE has been linked to repetitive head injury, that association has *not* been demonstrated scientifically nor is there an established neurophysiological mechanism. Additionally, while stories of many athletes diagnosed with CTE are publicized, there are, as of yet, *no* established clinical criteria for making the diagnosis in living subjects. A brief review of the state of the science and existing challenges is provided in the paragraphs below.

Epidemiology

A review of the published literature on CTE reveals that the rate reported in some groups has been alarmingly high, with one recent report demonstrating CTE pathology in 110 of the 111 players (99%) who had formerly played in the NFL [18]. A closer look at these data, however, reveals that these figures are not based on randomly acquired samples nor are they compared to any existing control group. An athlete's entry into this study and similar investigations is influenced by highly biased recruiting methods, based on public responses to press releases and media reports – meaning that those athletes and families who are more likely to be experiencing some of the cognitive, mood, and behavioral changes described as associated with CTE are more likely to participate or become available for study at high-profile research sites. At the same time, those retired players who do not experience any of these reported changes prior to death are not counted as "negative" cases. This highlights the classic "denominator problem" – focusing on positive cases while ignoring negative cases, a problem that has long affected all levels of behavioral research in TBI and other neurological and medical conditions [22].

Another major issue is that studies examining the relationship between the more general category of TBI and dementia have produced mixed results over the years. Some have suggested an association between TBI occurring over the lifetime and an increased risk of AD in later life [23]. However, those associations have not been observed in more recent studies using both prospective and retrospective methods [24]. In fact, investigations into the relationship between MTBI and late-life dementia from systematic reviews and other carefully conducted reports have found this relationship to be negative or inconclusive [25, 26].

Efforts to study rates of dementia in retired athletes have produced mixed results thus far. One study demonstrated that, while the general death rate in retired NFL players was lower than what is observed in men from the general population, the rate of death associated with neurodegenerative disease such as AD, PD, or amyotrophic lateral sclerosis (ALS) was nearly three times higher. However, this study is limited by its reliance on a relatively limited number of deaths attributed to neurodegenerative causes (N = 17) and no conclusive link between these conditions and head trauma [27]. It is noted that this type of relationship was not found in a study of retired players from the Canadian Football League, raising questions about the generalizability of the findings [28]. Since that time, a range of pathologies have been reported in yet another small sample of retired professional soccer players (N = 14) [29]. There is clearly a need for more controlled studies using a larger sample of athletes before any firm conclusions can be made.

Interesting results have arisen from a brain bank study examining neuropathological changes in 1721 men reviewed for history of past brain injury or participation in contact sports [30]. The results showed the presence of tau pathology associated with CTE in 21 of 66 former athletes with none of these same changes in 198 individuals without any association with contact sports, including 33 individuals with documented single-incident TBI. While these findings raise a suspicion that CTE might exist in approximately 30% of those individuals exposed to contact sports, the study did not establish any link between the pathology and any cognitive or behavioral changes in those individuals. The findings also contrast reports of two studies demonstrating no increase in neurodegenerative disease later in life in those individuals participating in football many years earlier in life relative to control groups who did not play football [31, 32].

In light of the many discrepancies in published studies, it comes as no surprise that the prevalence of CTE remains unknown with estimated rates ranging widely, from 4% to 87%, depending on the source and sample of interest [18, 33]. Taking a commonsense view, one might ask, "could CTE really be affecting 99% of those men who formerly played in the NFL?" The answer is clearly no, as is well understood by anyone who has ever witnessed lucid and insightful discussions of the sport and other related topics

involving retired NFL players via sports broadcasts or by other means. Unfortunately, the publicity that has surrounded CTE has trumped many of the pivotal contributions that former NFL players have offered to fields of business and economics, politics, and the law.

It is also entertaining to extend the argument to examine the much larger population of former high school football players. Published estimates suggest that over 6 million males participated in the sport between 1970 and 1988, resulting in a cohort that is currently in the 45–60-year age group [34]. If one were to extend the 90% prevalence estimates to that number, memory clinics nationwide would be inundated with the need to treat cognitive, mood, and behavioral changes in over 5 million men given their prior participation in football alone – this is something that is certainly not happening. The lack of any current epidemic of former football players presenting to clinics with these overt behavioral presentations is yet further support for the fact that there really is no current public health crisis and that great strides need to be made for any real estimates of the true prevalence of CTE in football and all other contact sports can be made.

Causal Mechanisms

There is an assumption among laypersons, members of the media, and healthcare professionals of a strong link between CTE and concussions. This is, as repeatedly pointed out so far, not yet established. In fact, there is no clear link between history of discrete concussions and the development of any type of dementia, including CTE that has yet to be identified. Rather, there is a hypothesized link between CTE and brain injury in retired athletes and others propagated almost exclusively by one group of researchers that is based on cumulative exposure to repetitive injury, rather than any direct association to concussion, occurring either as a single event or through multiple occurrences. Some of the most highly publicized cases of CTE (approximately 20%) were not known to have sustained any concussions at all during the course of their football careers, although it is certainly possible that injuries that these players sustained were not reported [35].

Establishing a scientifically validated link between repetitive brain injury and CTE requires a specification of what type of injury is sufficient to cause the damage and how many injuries are needed to cause a recognizable pattern of symptoms and associated neuropathology. In response to this question, one must define what constitutes a "subconcussive blow," while specifying how this type of blow can be differentiated, on one hand, from the level of impact that causes a true concussion and, on the other hand, a totally benign blow to the head [36]. Use of the term subconcussive to describe the impact implies that we are already able to identify the occurrence of concussion in an accurate manner and understand the lower boundary threshold for development of its symptoms, which is clearly not the case [37].

At one point, there had been hope that questions about the physical and biomechanical characteristics of injury impacts would be answered through the use of helmet-based sensors. Such sensors could be used to characterize the kinematic features of concussive impacts and the number of head-impact exposures sustained by athletes during the course of routine sports participation. While the results from initial studies using this methodology provided valuable data regarding the range of severity and number of head impacts sustained by athletes in various settings, investigators were unable to establish a clear threshold of impact for concussive injury and therefore, by definition, what constitutes a subconcussive blow [38]. More recently, questions about the reliability of the data acquired from these devices and their oversensitivity to registration of other types of body movements have curtailed their use to a large degree, as evidenced by the NFL's decision to discontinue studies using these methods in 2015.

Another question that arises is whether results obtained from basic neuroscience research have provided a neurophysiological mechanism that establishes a link between repetitive brain injury and tauopathy in animal samples. While several studies have attempted to use traditional brain

injury paradigms to study CTE in animals, there has been variable success in replicating the profile of tau phosphorylation and progressive behavioral deficits that has been associated with the disorder [39]. While some interesting results are reported from one recent study [40], there has been little success, to date, in replicating a staged progression of tau pathology, beginning in superficial cortex and spreading to other regions, including the hippocampus, nor has there been any controlled laboratory production of TDP-43 immunoreactive nuclear inclusions in response to repetitive head impact, as hypothesized by the CTE proponents [1].

The issue of exposure is central to any theory linking repetitive brain injury sustained in contact sports to the development of neurodegenerative changes. However, it is clear that the issue of exposure is not simple, as is evident from the existence of autopsy-defined cases of CTE documented in an 18-year-old athlete with exposure limited to participation in high school football, to retired NFL players, aged 80 or older, who had played the game for many years. There are also cases of CTE pathology in individuals who had never played contact sports in addition to a lack of identified pathology in some retired athletes with many years of sustained competition at the professional level [41–43].

Studies of exposure to repetitive head impact can take two basic forms, with one focusing on the exposure resulting from positional play (e.g., running back versus offensive lineman) and the other cumulative exposure resulting from the total number of years of participation in the sport. The results from existing studies demonstrate that quarterbacks, running backs, and defensive backs are the players most susceptible to concussions, while offensive line is the position that is exposed to the most number of repetitive head blows during the course of a football season [44–46]. However, the relative risk of CTE occurring in linemen versus other players remains unknown. One study has attempted to combine exposure variables to compute a "cumulative head impact index" (CHII) with results showing that the index was effective in predicting subjective ratings for a number of individual clinical symptoms [47].

There has been some suggestion that NFL players who began their football careers through youth leagues before the age of 12 years exhibit greater levels of cognitive dysfunction and impaired neuropsychiatric functioning, although the studies have received criticism on methodological grounds [48–50]. At the current time, many more studies need to be performed before we can make any firm conclusions about any negative effects of exposure to contact sports.

Clinical Symptoms and Neurodiagnostic Findings

Nowadays, it is not uncommon to encounter media coverage of a retired athlete struggling with mental health and associated social issues that are attributed to a reported diagnosis of CTE. These accounts should come as a surprise to those who are aware of the current status of the science, as it is clear that the scientific study of CTE remains in its early stages, raising questions about the source and validity of the reported diagnoses. While there is some reported consensus on the neuropathological criteria used to make the diagnosis in postmortem brains, there remains no accepted diagnostic standard or consensus criteria for making a clinical diagnosis of CTE, based on symptoms or neurodiagnostic tests, in a living patient. Any efforts to establish a reliable set of symptoms will encounter obstacles in differentiating symptoms from those observed in overlapping conditions, bias from retrospective reporting of symptoms, lack of an established cause, and excluding psychosocial effects associated with substance abuse, marital discord, and employment-related factors.

The clinical presentation of CTE has been associated with a broad spectrum of cognitive, mood, behavioral, and motor symptoms that are believed to appear in advance of similar changes known to occur in a variety of other neurodegenerative conditions [20, 21]. The diagnostic challenge in these cases is to develop a reliable method for successfully distinguishing them from other known neuropsychiatric and neurodegenerative conditions, including AD, PD, ALS,

depression, and frontotemporal dementia (FTD), with some of these conditions having relatively high prevalence rates in the general population [51, 52]. There is clearly a need for establishing and validating a set of characteristic clinical symptoms and other features that would distinguish an individual with CTE from experiencing any of these other conditions with a high level of reliability and specificity.

There have been several attempts over the past several years to establish standardized clinical and research criteria for making a diagnosis of CTE. In 2013, Victoroff, for example, examined 436 published cases of CTE to establish criteria for "traumatic encephalopathy" [53]. He enumerated a number of critical signs and symptoms associated with the condition. Another set of clinical criteria emphasize classification into definite, probable, possible, and improbable CTE groups [54].

Two independent groups developed criteria for diagnosis of traumatic encephalopathy syndrome (TES), which comprise the reported clinical features of CTE. Both groups emphasized prior exposure to head injury in the context of outlining a set of more general symptoms [21, 55]. Efforts are currently being made to validate at least one set of these criteria in relation to other neuropathological and neurodiagnostic criteria [56]. In the meantime, there remain no established symptom-based criteria for making a diagnosis of CTE based on these or any other clinical criteria.

There has been much interest in establishing a biomarker that is effective for making a diagnosis of a neurodegenerative disorder, considered by many to be the "holy grail" of clinical neuroscience. To date, there has been little success in establishing any single reliable biomarker; limited gains have been made in the study of AD [57]. There has been no progress in developing a biomarker for CTE over and above what is used for other neurodegenerative disorders. Blood and cerebrospinal fluid candidate markers for tau pathology and inflammatory processes have been identified, although the study of these markers is in a very early stage [58]. There has also been some interest in structural imaging features, such as a cavum septum pellucidum, for aiding diagnosis of CTE [59], although that finding has been shown to lack sensitivity and specificity [60]. Another avenue of interest involves functional imaging techniques such as positron emission tomography (PET), using compounds sensitive to tau or amyloid deposition. While there have been preliminary reports of identified tau abnormalities in small samples [61, 62], there is a long way to go in establishing the specificity of those findings with the ability to distinguish CTE from other neurodegenerative conditions.

Accuracy of the Neuropathological Diagnosis

The practice of establishing a definitive diagnosis of neurodegenerative disease dates back to the nineteenth century and has been based on postmortem analysis with neuropathology – this has been considered the gold standard by which to gauge all other diagnostic tests. In the modern study of CTE, the earliest information in support of this condition came from the identification of unexpected neuropathological changes with known associations to other dementing conditions but in younger individuals with a history of exposure to contact sports. There continues to be controversies and criticisms regarding the specificity of the observed neuropathological changes associated with CTE.

In light of continued scientific advances, there is now some question regarding the accuracy of neuropathological diagnosis and its use as the gold standard for diagnosis [63]. The results from a recent large-scale study found that the specificity of the neuropathological diagnosis of AD, based on neuritic plaque densities and Braak neurofibrillary stages, ranged in various datasets from 44% to 70% compared to other clinical diagnoses, including FTD, Lewy body disease, cerebrovascular disease, and hippocampal sclerosis [64]. In another report, results from a survey of practicing neuropathologists showed that the majority feel unable to make a neuropathological diagnosis of AD without clinical data and only one in four reported using standardized diagnostic criteria on a regular basis [65].

In the study of CTE, the emphasis has been on identifying a pattern of tau deposition in the brain that is different from the pattern observed in other neurodegenerative conditions [1]. The more recent characterization of CTE suggests that symptoms progress along a spectrum and that the profile of tau deposition in younger individuals with mild symptoms (Stage I) differs in nature from normal age-related patterns of tau deposition, while the pathology observed in more chronic stages of illness (Stage IV) can be distinguished on reliable basis from AD and other advanced stage neurodegenerative conditions. Questions naturally arise on the reliability of the clinical symptoms documented in these cases, as most are based on retrospective reports from relatives with a strong potential to be influenced by hindsight bias. Criticisms are also made on the purity of the pathology obtained in many of the cases that have studied as most did not die as a result of the end stage of a neurodegenerative disease but rather from a range of other causes (e.g., hanging, gunshot wound, or drug overdose) [66].

Some have suggested that the focus on tau and its relation to the emergence of CTE symptoms is premature, given that the pathology has not been established as the cause of the symptoms [67]. Questions have also arisen as to whether the neuropathological features of CTE are necessary or sufficient for one to exhibit the clinical and symptomatic features of the disorder. In one summary analysis of neuropathological reports from some of the earliest published autopsy cases, it was found that only 20% of the cases demonstrated "pure" CTE pathology, while 23% of the cases with clinical symptoms exhibited no signs of neurodegenerative pathology [42]. An additional 5% of the studied cases exhibited signs of CTE neuropathology and no clinical symptoms, a finding that has been replicated in more recent studies demonstrating similar forms of pathology in 12% of older adults exhibiting no symptoms of neurodegenerative disorder [29, 41].

Research on CTE has also been limited by the lack of consistency in the neuropathological criteria that have been used to diagnose the disorder. As mentioned above, the relative patterns of amyloid and tau appearing in more recently reported cases of retired football players and others are reported to differ from what was described in earlier reports on retired boxers [42]. There have also been differences in the neuropathological characteristics reported by the modern CTE advocates. For example, in cases reported by Omalu and colleagues, there was more of a lobar cortical distribution of pathology [17], whereas the cases reported by McKee and colleagues were focused more on perivascular spaces and the depths of the sulci [1]. Additionally, the Boston group has described the spectrum of clinical and pathological changes in CTE, while Omalu and colleagues have focused more on a definition of four separate CTE phenotypes [68].

In 2016, a report was published which summarized results of a consensus panel of 7 neuropathologists who evaluated digitized images of neuropathological specimens from 25 cases of CTE and other tauopathies, concluding that CTE could be reliably distinguished from those other conditions [69]. However, when one looks more closely at the data, one finds that the reported agreement among reviewers was clearly not spectacular (Kappa = 0.78). Alzheimer's changes were reported by consensus members in 8 of 10 CTE cases, while CTE findings were identified in 8 of 15 cases without clinical features of CTE. In the end, while the consensus findings are commonly invoked to establish the validity of the neuropathological diagnosis of CTE, the data actually raise doubts about the specificity of the diagnoses made within the sample. There clearly needs to be continuing analysis of the accuracy and generalizability of the consensus study findings before those criteria can be used as the "gold standard" for CTE research.

Alternative Perspectives on CTE

As stated throughout this chapter, CTE is characterized as a progressive tauopathy that occurs as a consequence of repetitive mild traumatic brain injury. As a clinical syndrome, the cognitive impairment and many complex behaviors associated with CTE, including aggression and suicide, result from specific neuropathological

changes that are proposed to be distinct from those changes seen in other clinical conditions, including AD, FTD, and depression. Many of the assumptions associated with the clinical presentation of CTE might appear a little odd or extreme, to clinicians and social scientists, who typically consider a number of alternative medical and psychosocial factors before attributing the emergence of complex behavioral symptoms to the direct effects of neuropathology.

Much of what is described about CTE as a syndrome comes from neuropathological studies. This is not surprising given the leading and early role of neuropathologists in published work on CTE. However, with this focus on autopsy data, less (if any) attention is paid to critically important clinical data that other clinicians routinely consider. Skilled neuropsychologists, for example, routinely view complex behavioral symptoms in the overall context of a person's life and not as isolated symptoms. The aim of this section of the chapter is to provide alternative perspectives to the topic of CTE as a clinical condition, as demonstrated through results of neuropsychological studies and application of the biopsychosocial model.

Neuropsychological Studies

Neuropsychologists in clinical practice are often asked to evaluate cognitive and behavioral changes in older men with the aim of determining whether their presenting symptoms are representative of normal aging, neurodegenerative disorder, or other clinical condition(s). When one considers published base rates, the lifetime risk of developing dementia is 15% in older males from the general population and 10% in males reaching age of 45 years [70, 71]. This value is often ignored when estimating the prevalence of CTE in retired athletes. Overall rates of dementia are commonly reported in retired athletes – however, they are rarely viewed in the context of the existing base rates, where it must be demonstrated that the rate of dementia in this select population of retired athletes exceeds the rate that would be expected in individuals who were not theoretically exposed to the same risk factors for development of CTE. In other words, demonstrating that dementia develops in one of six NFL players actually tells us nothing, as that is the same rate expected over the course of any man's lifetime.

Based on a typical neuropsychologist's clinical knowledge and training, the primary aim when performing an evaluation of cognitive and behavioral changes in retired football players would be to rule out the presence of the most likely clinical conditions in this age group, which would be MCI or AD. In fact, as mentioned earlier in this chapter, it had been demonstrated through survey studies of retired football players that those athletes with multiple concussions were more likely to be diagnosed with MCI than those without a reported history of concussion with a trend toward earlier onset of AD in the multiple concussion group [15]. Perhaps the most important factors to consider with the clinical presentation of CTE are that cognitive and behavioral changes are being reported in individuals that are much younger than individuals who typically present to memory disorder clinics. This requires an explanation of why conditions such as MCI or AD would be presenting earlier in these individuals.

Based on these survey data and the availability of emerging data from accelerometer studies, Randolph and Kirkwood were among the first investigators to suggest that many years of repetitive head trauma from playing sports could result in diminished "cognitive reserve" [72], employing a concept developed by Yaakov Stern in the study of aging and dementia [73]. Using cognitive reserve as guiding concept, it was hypothesized that retired athletes are less able to compensate for normal age-related brain changes, as a result of cumulative head injury exposure, and are therefore more likely to exhibit cognitive changes earlier than would otherwise be expected for their age. If this were true, one would expect the early emergence of these clinical symptoms to resemble the changes associated with more prevalent conditions, such as MCI or AD, rather than any newly emerging clinical syndrome, such as CTE.

In the first published study employing neuropsychological tests to study retired professional football players, the resulting test profile was found to be very similar to what was observed in a control group of patients diagnosed with MCI [74]. The retired athletes were also significantly younger and somewhat less impaired overall in terms of their neurocognitive status. Furthermore, approximately 35% of the players' spouses provided subjective ratings of their husbands' behavior that were above the published figure associated with possible dementia (scores of >2 on a dementia screening index). Although these data were considered preliminary, they did support the hypothesis that repetitive head trauma from many years of playing football may lead to the earlier expression of late-life cognitive disorders that are similar in characteristics to what is more commonly observed in conditions such as MCI and AD. Since that time, other published studies have also provided data supporting the hypothesis that cognitive reserve mediates the clinical expression of CTE [18].

Additional studies using neuropsychological test batteries with retired NFL players have reported objective evidence of cognitive impairment (e.g., problems with memory and naming) and mood symptoms considered to be more consistent with diagnoses of MCI or depression than CTE. For example, in a study by Hart and colleagues [75], cognitive findings were associated with white matter abnormalities and regional cerebral blood flow differences demonstrated on neuroimaging, which is common among individuals with depression as well as MCI. In another study, this same group of researchers reported that concussion history in NFL athletes was associated with reduced hippocampal volume and lower verbal memory performance, which is typical of individuals with MCI [76]. Not surprisingly, the clinical profile observed in those athletes was attributed to MCI rather than CTE.

Results from another study of 42 former NFL players reported that players who had initiated their football playing careers before the age of 12 exhibited more evidence of late-life cognitive impairment on neuropsychological tests [50]. The findings were observed primarily on tests of executive functioning, memory recall, and estimated verbal intellectual functioning. The results of that study were criticized on several factors, including an emphasis on retrospective findings and a failure to control for premorbid cognitive differences in the two groups. In a similar neuropsychological study involving a different sample of NFL players [77], the data did not show greater impairment in NFL players who participated in youth football; importantly, the data were controlled for a number of clinical variables, and appropriate statistical corrections were applied.

Neurobiopsychosocial Perspectives

Over 40 years ago, there was a call to arms in medicine for increased recognition of the influence that social, psychological, and behavioral factors play in the development and manifestation of disease through development of a biopsychosocial model [78]. With the increasing focus on identifying diagnostic biomarkers, neuropsychologists have become increasingly vocal in their support for a more updated approach to that model, incorporating advances in imaging and neurobiology, through development of a neuropsychobiological perspective for assessing and treating the effects of concussion and its long-term consequences [79]. Several have criticized the degree to which existing studies and theories of CTE have failed to account for the influence that biopsychosocial factors are likely to exert on the presentation of symptoms in NFL retirees [51, 80–82].

In a critical review of the CTE literature, Asken and colleagues reviewed different factors that may potentially affect an athlete's risk for developing CTE, many of which are not recognized or controlled for, in most of the existing studies of CTE [80]. Prominent among these factors are biopsychosocial variables including developmental factors, demographics, drug/alcohol abuse, adjustment to retirement, and ongoing sleep difficulties. In the following paragraphs, we will further highlight the degree to which biopsychosocial factors potentially

influence complex behaviors including depression, suicide, and violence, which are considered among the most critical and highly publicized features of CTE.

There has been increased study of the mental health of elite athletes with an emphasis on depression and its relationship to concussion history [83]. Guskiewicz and colleagues were the first to demonstrate a relationship between concussion frequency and the emergence of depressive symptoms in retired NFL players, and this finding has been supported in research performed by this group and others [84–86]. However, there are other studies demonstrating increased rates of depression in NFL retirees arising from a host of other medical and psychosocial factors [87]. This group hypothesizes that chronic pain induced by musculoskeletal difficulties affects the retirees' physical activity and fitness levels to a degree that increases the risk for depression. The authors highlight the degree to which these factors interact with problems arising from employment issues, financial status, marital relations, and decreased social support. Other factors can result from retired players transition from a socially visible individual to a point of relative anonymity during retirement, with adjustment to retirement noted to be a significant predictor of many of the behavioral and emotional symptoms commonly attributed to CTE [81, 88]. What clearly emerges is a very complex interaction between health issues and a number of other important psychosocial factors when evaluating the occurrence of these behaviors in retired professional athletes.

Turning to the controversial topic of suicide and CTE, it is clear to most seasoned clinicians that suicidal ideation and associated behaviors are symptoms of depression and are typically not included among the diagnostic criteria associated with traditional neurodegenerative disorders, such as AD or PD. It is therefore disconcerting to see that suicidality is now included among the diagnostic features of TES without recognizing its primary link to depression [21, 55]. There is an overrepresentation of suicide as the cause of death for many of the younger postmortem cases that have been studied and found to have neuropathological evidence of CTE [68]. Some have hypothesized that impaired neurotransmitter homeostasis in the brain may explain the overrepresentation of suicides in studies of CTE [89], but this is with no apparent recognition of the undoubtedly large number of *other* possible factors that might have been responsible for suicides in those subjects.

Public health statistics show that across the nation there has been an increase in suicides over the past 20 years, with the greatest increase observed in males between the ages of 40–64 years. Job, financial, and legal problems are cited as the most common circumstances surrounding the suicides occurring in that age group [90]. One might notice that this is the same age group that characterizes the retired NFL players who have been included in CTE studies. While it might appear at first glance that former NFL players are at risk for suicide, the results of research investigations examining this topic have actually found that these players are at a lower risk for suicide than other males from their age group [91, 92].

Modern research has demonstrated that suicidal behaviors are heterogeneous in nature and result from a complex interaction of physical and social causes [93]. In detailed discussions of the relationship between suicide and CTE, Iverson concluded that there is no proven connection between CTE and suicide with observation that there are multiple underlying biopsychosocial causes for suicide and a belief that any conceptualization of suicide as a result of a progressive tauopathy as scientifically premature and potentially fatalistic [94, 95]. A recent study found that most professional football players who committed suicide in recent years suffered from multiple life stressors secondary to social, economic, and mental health factors [96].

There are many serious dangers of associating suicide and CTE. One can only imagine the many negative consequences that can result from informing an individual that their symptoms, including suicidal ideation, are the result of a progressive and "incurable" condition such as CTE, as opposed to a very treatable condition such as depression. Given the potential for contagion effects secondary to suicide reporting

in the media [97], it is very important that clinicians, scientists, and journalists seriously consider the continued reporting of a link between CTE and suicide, given the current status of the science and the potential to circulate misinformation rapidly through social media.

There has also been much attention placed on reports of violent behaviors in NFL players and retirees. Information obtained from media investigations has indicated that, while NFL players exhibit lower rates of arrest and violent crimes in comparison to the general population, there is a general increased rate of domestic violence arrests in this group, when controlling for other factors [98]. CTE researchers include agitation, explosivity, loss of control, and short fuse among the behavioral features associated with TES [21, 55]. Based on the proposed association between CTE and aggression, it has been easy for some to speculate that the domestic violence rates in NFL players might be due to an early expression of the neuropathological effects of that condition. As one might imagine, explaining this type of violence as the result of abnormal brain functioning resulting from head injury could have significant legal and societal implications [99].

As seen in studies of other complex behaviors, the research on domestic violence has clearly demonstrated that there is combination of psychobiological and sociocultural determinants underlying these behaviors [100]. While there might be many biological factors that render males more prone to aggressive behaviors in general, it is clear that domestic violence stems from a number of complex sociocultural factors that extend well beyond any pattern of hormonal expression or the effects of abnormal tau deposition in the brain.

One should remember that, to begin with, football is a violent sport, and those who excel in the sport might succeed because of their ability to express or channel aggression through the sport. Recent reviews have supported the notion that there are higher rates of violence in athletes, which is believed to be the result of a number of factors including masculine culture and social norms attached to certain sports [101]. Unfortunately, much of the macho culture associated with football and other sports includes negative impressions of women and glorification of some antisocial behaviors, including illicit drug use. The hope is that future attempts to curtail these behaviors will be focused more on rectifying the social contributions of violence as opposed to becoming distracted by any attempts to treat violence as a sole consequence of the underlying neurobiology.

Conclusion

Over the past 10–15 years, CTE has become one of the most highly publicized and controversial topics encountered in medicine and the clinical neurosciences. As reviewed in this chapter, the study of this condition started nearly 100 years ago with observations of cognitive, behavioral, and motor changes in professional boxers. Since that time, with the help of modern informational technology and social networking, a modern form of CTE has now been described, based on findings from autopsy studies performed primarily on retirees from professional contact sports. With this newer form of the condition, there has been emphasis on a more expanded list of behavioral changes, including high-profile behaviors such as suicide and violence and an accompanying pattern of underlying neuropathological changes that are proposed to be distinct from the original form of the condition seen in boxers and from changes associated with more prevalent conditions, including AD and PD.

It is unfortunate that the media coverage of CTE has extended well beyond the results of scientific studies, which remain preliminary, but has led the public nonetheless to have a false sense of what is known about CTE. As a result, there has been an outcry for changes in the sport with some calling for an outright ban on tackle football in younger athletes. While some of the proposed changes for football have been appropriate and have made the sport safer, many questions still need to be addressed before making any more radical changes. With all the enthusiasm for banning these sports, many are forgetting what might become unintended consequences of reducing

youth activities, including the potential for an even greater increase in childhood obesity and rises in associated conditions like early type II diabetes and hypertension. In the end, the increased risk for development of neurodegenerative disorders secondary to cerebrovascular factors could outweigh whatever risks were associated with participation in contact sports.

As summarized in this chapter, there remain several serious methodological flaws in existing studies of CTE, which continue to limit conclusions one can currently make about the incidence, cause, and characteristics of the condition. To date, there is no knowledge of the true frequency of CTE in the general population or any sense of who might be most affected. Existing studies have been based on autopsy series that have been limited through biased sampling methods and variable methods for defining the clinical symptoms and pathology found in the participants. At this point, while it is assumed that CTE is caused by exposure to repetitive head injury, that causal relationship has not been established scientifically. There also remains no validated method for diagnosing CTE in living subjects or distinguishing it from other neurodegenerative conditions, using clinical symptoms, neuroimaging, or neurobiological markers. While there has been an emphasis on the definition of a distinct pattern of neuropathological changes in CTE subjects, a closer look indicates that the ability to distinguish the condition from other neurodegenerative diseases is not as strong as advertised.

It is also becoming increasingly clear that there will remain a cost to limiting explanations of the clinical presentation of CTE to the effects of neuropathology without fully considering or exploring the degree to which other neurobiopsychosocial factors might be playing a causative role. The results of neuropsychological studies have focused more on conceptualizing cognitive and behavioral changes observed in NFL retirees in terms of an early expression of MCI or AD rather than as an effect of any newly emerging neuropathological condition. There has also been a focus on the role that depression plays in the manifestation of the changes reported in this population. It will be necessary to consider the full range of sociological and cultural factors influencing complex conditions and behaviors such as depression, suicide, and violence in order to make advances in our understanding of these conditions and any relation they might have to participation in contact sports. The good news is that neuropsychologists are well equipped, through their knowledge and combined use of neurobiological and psychosocial methodologies, to provide valuable insights and advances in the study of CTE. The hope is that neuropsychologists play a larger role in shaping the direction of CTE research in the future with results of a more balanced account of its characteristics and its causes.

Clinical Pearls

- Media coverage of CTE has extended well beyond the results of scientific studies, which remain preliminary and has led the public to have a false sense of what is known about CTE.
- The study of CTE is still in a preliminary stage with much that remains to be learned. At the current time, many more studies need to be performed before we can make any firm conclusions about any negative effects of exposure to contact sports.
- Estimates of the prevalence of CTE in retired athletes should be considered in the context of published base rates for dementia. The lifetime risk for developing dementia is 15% in older males from the general population and 10% in males above age 45. The questions should be whether the rate in retired athletes exceeds the rate that would be expected in individuals who were not theoretically exposed to the same risk factors for development of CTE.
- To date, there is no clear link between history of discrete concussions and the development of any type of dementia, including CTE, that has yet to be identified.
- While there is some reported consensus on the neuropathological criteria used to make the

diagnosis in postmortem brains, there remains no accepted diagnostic standard or consensus criteria for making a clinical diagnosis of CTE, based on symptoms or neurodiagnostic tests, in a living patient.

- While initial studies using helmet sensors provided valuable data regarding the range of severity and number of head impacts sustained by athletes, questions about the reliability of the data acquired from these devices and their oversensitivity to registration of other types of body movements have curtailed their use to a large degree.
- Neuropsychological studies have focused more on conceptualizing cognitive and behavioral changes observed in terms of an early expression of MCI or AD rather than as an effect of any newly emerging neuropathological condition. There has also been a focus on the role that depression plays in the manifestation of the changes reported in this population.
- Thus far, explanations of the clinical presentation of CTE have been limited to the effects of neuropathology without fully considering or exploring the degree to which other neurobiopsychosocial factors might be playing a causative role.
- Neuropsychologists are well equipped, through their knowledge and combined use of neurobiological and psychosocial methodologies, to provide valuable insights and advances in the study of CTE.

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