Practiced neuropsychologists and those just entering the field will benefit greatly from this collection of well-written chapters from experts providing concise up-to-date reviews of neuropsychological methods and a number of important neurological disorders and syndromes. This will be a valuable addition to any bookshelf.

—*William Barr, PhD,*
Director of Neuropsychology,
New York University School of Medicine, New York

In providing a ready reference and manual, Parsons and Hammeke go beyond the criteria for a handbook. This third edition also serves as an exceptional conduit to supplementary resources addressing the science that is the foundation of clinical neuropsychology and its best practice. The profession will welcome this updated treasure trove of information.

—*Sandra Koffler, PhD,*
Professor of Clinical Neuropsychology,
Drexel University, Philadelphia, PA

Clinical Neuropsychology

Clinical Neuropsychology

A POCKET HANDBOOK *for* ASSESSMENT *Third Edition*

Michael W. Parsons and
Thomas A. Hammeke, *Editors*
Peter J. Snyder, *Founding Editor*

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To Elizabeth, Laurel, and Nick for your support, love, and advice.
—Michael W. Parsons

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—Thomas A. Hammeke

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Clinical Neuropsychology

Michael W. Parsons

About This Handbook

The publication of the third edition of *Clinical Neuropsychology: A Pocket Handbook for Assessment,* fully 15 years after Peter Jeffrey Snyder's original edition, marks a transition to a new era in the field. Massive changes in the domains of psychology (e.g., the release of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*), neuroscience (e.g., the development of imaging biomarkers for neurologic diseases), and public policy (e.g., the Affordable Care Act) will influence clinical neuropsychology over the next several years. As clinical neuropsychologists face the challenges of the future, we are reminded that our core responsibility has not changed. The role of the neuropsychologist is to apply the understanding of brain–behavior relationships to individuals with cognitive and behavioral problems to improve the diagnosis and treatment of the conditions and their symptoms. These activities are accomplished primarily through the use of assessment methods developed over centuries (see the discussion of the methods of Luria, Broca, and Wernicke in the following chapters).

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Clinical Neuropsychology: A Pocket Handbook for Assessment, Third Edition, Michael W. Parsons and Thomas A. Hammeke (Editors)

Just as the goals of neuropsychology remain true to their roots, the purpose of this handbook has not changed. As stated by Peter Jeffrey Snyder in the prior edition, the goal of the handbook is to be

> a ready reference to assist the busy clinician or doctoral level trainee selecting from among the many hundreds of tests and assessment techniques that are widely available. The principal aim of this reference book is to help guide the clinician in developing tailored, hypothesis driven approaches for the assessment of patients with a broad range of common neuropsychological syndromes or neurological disorders. . . . [The handbook] should provide what already exists for most other medical or health care specialties: a diagnostic guide that fits into the lab coat pocket . . . a ready source of information for the differential diagnosis of clinical syndromes.

As with earlier editions, we hope that this book will serve as a diagnostic starting point, providing a roadmap for evaluation and additional avenues for exploration with every patient.

Although the core purpose of the handbook remains the same, the reader will see that the approach to this material, much of the content, and the design of this book have changed substantially. Specifically, the book is now accompanied by an online resource (http://pubs.apa.org/books/supp/parsons) that provides a wealth of supporting and additional material. As you read through the chapters, I encourage you to open the website and explore the information you find there. Chapter 2, which describes methods for neurobehavioral examination, is supported by a video demonstration of these techniques, which will allow the reader to truly get the feel of using the qualitative methods. Chapter 4, on neuroimaging, is accompanied by a large library of brain images that allows readers to familiarize themselves with different imaging modalities and types of pathology. Chapter 18, on aphasia, is accompanied by audio files providing examples of different forms of speech disturbances. These resources, in addition to numerous tables, suggested readings for specific topics, and figures help bring the material herein to life.

The content of this book has been significantly updated. Not only are there new topics covered in their own chapters (e.g., Chapter 7 on cultural neuropsychology, Chapter 25 on drug abuse and impulse control disorders, Chapter 27 on somatic symptom disorders) but also each chapter integrates the latest developments in the field. This includes information regarding *DSM–5* in relevant chapters and studies of functional brain imaging throughout the book.

In addition to the novel design and new content, the organization of *Clinical Neuropsychology* has been updated. The handbook

consists of four sections: The chapters in Part I, Clinical Neuropsychology: General Issues, are procedural and methodological in nature, and follow this general organizational framework:

- Relevance to neuropsychological evaluation
- Methods
- Interpretation
- Integration with neuropsychological evaluation
- Innovations, Trends, and Contemporary Issues

Parts II (Neurological Disorders, in which many of the most common neurologic problems that neuropsychologists evaluate are reviewed), III (Neuropsychological Syndromes, describing the core features and assessment of the "wheelhouse" of neuropsychology), and IV (Psychiatric Disorders and Behavioral Syndromes, in which the most common psychiatric problems that neuropsychologists evaluate are reviewed) are focused on clinical assessment of the disorder or syndrome. They are organized, giving allowances for variation in the complexity of the various topics, as follows:

- Definition/Classification
- Functional Neuroanatomy
- Neuropsychological Evaluation
- Treatment, Integration, Comorbidity, and Other Issues

Although the book covers a broad range of neuropsychology topics, the reader should be aware that the specific disorders and problems faced by children (and hence pediatric neuropsychologists) receive lighter treatment than adult disorders. The growth in pediatric neuropsychology has been tremendous, and attempting to cover the entire life span in a single volume is simply not feasible. We have included chapters on the core issues in the assessment of children (Chapter 6) and a chapter on the most common developmental disorders that neuropsychologists evaluate (Chapter 22), as well as discussing relevant pediatric issues in certain disorders (e.g., Chapter 9). However, it is my opinion that the field will benefit from a handbook specifically devoted to the neuropsychological evaluation of children.

Thomas Hammeke, my coeditor and mentor, has been an invaluable partner in the development of this volume, which would not have come to pass without his guidance and help. I would also like to thank the Founding Editor, Peter Snyder, for the opportunity to take over management of this well-respected book. Susan Reynolds, my editor at APA Books, has guided me through the process of development, and I thank her for her patience and assistance.

PART I

CLINICAL NEUROPSYCHOLOGY: GENERAL ISSUES

Chapter 1

Alexander Rae-Grant and Michael W. Parsons

Neuropsychology in the Clinical Setting: Conceptual and Practical Issues

As noted in "About This Handbook," the practice of neuropsychology is constantly evolving and changing. Many factors influence this evolution, including developments in neuroscience and brain imaging technology, growing awareness of cultural issues, and changes in the mechanics of clinical practice, such as the development of electronic medical records (EMRs) and structure of reimbursement for neuropsychological services. As neuropsychologists change their practices to keep pace with these challenges, the importance of strong collaborative relationships with physicians, psychologists, and other health care providers continues to grow.

This chapter focuses primarily on the relationship with *neurologists*, arguably the neuropsychologist's most important partner in multidisciplinary teams, clinics, and hospitals. We first discuss the process of identifying and preparing for the evaluation on the part of the neuropsychologist. Next, we discuss the approach and perspective of the neurologist, including the neurologic exam. Finally, we discuss the collaborative relationship between our disciplines.

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I. NEUROPSYCHOLOGICAL EVALUATION: PREPARATORY STAGES

The medical record review process is changing rapidly because of the growth in use of the EMR, which is likely to be ubiquitous within the next few years. Although the format of the medical record may be changing, the core responsibility of the neuropsychologist, development of an understanding of brain–behavior relationships in each individual patient, remains as central to our functioning as it has ever been. The first step in the process of developing that understanding is to identify the reason for referral. Although this may sound straightforward, it is often more obscure than we might like. Busy clinicians in neurology, psychiatry, or other medical practices often consult neuropsychologists when they hope that additional testing will clarify the nature of the patient's problem. They may not take the time to specify a "question" to be answered by the neuropsychologist, and reasons for referral may be as open-ended as "memory loss" or "evaluate." If it is possible to clarify the needs of the referral source through direct communication or through interview with the patient, doing so will almost always improve the use of the neuropsychological evaluation. When evaluating a patient who is referred from within a hospital system where there is a shared or connected EMR, even if no formal "referral question" is received, the needs of the referral source can often be divined by reading through the report of the referral source that coincides with the date of referral. Developing strong collaborative relationships with your most frequent referrers will facilitate communication about individual cases as well as help you to understand the perspective of those who refer to you. Neuropsychologists do well to educate their referral sources about the kind of question that results in clear answers.

Critical items to identify in the medical record review include the list of patient medications. These must always be confirmed with the patient or a reliable collateral source, as the accuracy of these lists is only as good as the conscientiousness of those who are responsible for keeping them up-to-date. Most medical record systems now provide a facility for reviewing brain imaging results and often the images themselves (see Chapter 4, this volume, for an introduction to image interpretation). Laboratory results can also be found readily in electronic medical records and are often of relevance to the neuropsychological question at hand (see Chapter 3 for a thorough review of laboratory tests that are most important to neuropsychologists). In inpatient hospital settings, the EMR is also making inroads, though paper charts still are the norm in many

locations. As the paper record fades into history, problems like poor handwriting will become less frequent, though poor grammar will remain a source of confusion, and factors like errors in voice recognition software for those systems that use it will provide entertaining turns of phrase into the future.

II. THE PERSPECTIVE OF THE NEUROLOGIST

Neuropsychology and neurology have faced many of the same evolutionary pressures as the practice of medicine has entered the modern era. In the late 1970s when computed tomography (CT) scanning of the brain emerged, many neurologists were told by their internal medicine colleagues that they would no longer be needed. All the internist had to do was to do a CT scan, get the answer, and dispense with the neurological process. For reasons that evade reckoning, neurologists continued to practice and in most cases to thrive. In the late 1980s when magnetic resonance imaging (MRI) scanning of the brain and spinal cord emerged, many neurologists were again threatened with extinction at the hands of a superior technology. In fact, now that we are well into the 2nd decade of the 21st century, there is a shortage of neurologists in clinical practice. Although many new technologies and tests continue to come onto the scene (e.g., AV45 imaging for amyloid deposition as a marker of Alzheimer's disease and ocular coherence tomography as a marker for optic neuritis), there continues to be a need for a sound evaluation of each case using the neurological method. The following patient example provides some insight into the clinical perspective of the neurologist:

> Mrs. Abel Body is a 62-year-old woman who comes to the neurologist's office. She has no prior medical problems and is on no medications. She was referred for transient ischemic attacks (TIAs; usually a warning sign of stroke). Her internist (or family physician, nurse practitioner, physician assistant, etc.) heard a story of episodic visual symptomatology and ordered carotid ultrasounds, a magnetic resonance angiogram of the head and neck, MRI of the brain, a CT angiogram of the head, a full coagulation panel, an echocardiogram, and an electrocardiogram. The internist has Mrs. Abel Body booked to see a cardiologist for a transesophageal echo.
>
> The neurologist takes a history and finds that in her 20s Mrs. Abel Body had episodic pounding headaches with photophobia and sonophobia, lasting hours, often related to her menses. About 10% of these headaches would be

preceded by a visual phenomenon of zigzag lines, which began in the center of both visual fields and expanded to a central area of visual loss. The present TIAs are exactly the same phenomenon as her visual symptoms in her 20s, but Mrs. Abel Body does not get headaches with them. Her neurological exam is completely normal. The neurologist makes a diagnosis of migraine equivalents—the neurological component of migraine without headache—and reassures her that these are not a significant risk factor for stroke. She or he follows this up by reviewing the literature and finds that migraine aura without headache becomes more common in postmenopausal women and is frequently confused with TIAs. He or she notes that the neurological evaluation (charged to insurance $345 for a 45-minute evaluation) would have avoided the costs of the testing done (estimated charges to insurance $10,945, charge to patient 20% of same) and would have been much more reassuring and satisfying to the patient.

What are the issues here? It turns out that many neurological problems are solved by the history and/or examination, not by technical testing, illustrating the importance of the integration of symptomatology with knowledge of the nervous system. Although the literature on this point is limited, it is common knowledge that many neurological diagnoses do not depend on an imaging or laboratory component, including essential tremor, migraine, back pain, trigeminal neuralgia, and in most cases Parkinson's disease. These entities are diagnosed from the history and exam and would not be solved by testing. Take another example:

Mrs. Iva Drawpfut is a 54-year-old woman who comes to the neurologist with weakness of the right foot. They could test this with a variety of studies, including electromyography, evoked potentials, myelography of the lumbar spine, MRI of the spinal cord and brain, electroencephalography, or a leptomeningeal biopsy, among a plethora of other possibilities.

Instead, the neurologist astutely takes a history and finds that the patient does yoga 3 days a week and Mrs. Iva Drawpfut noticed this weakness 1 day after she fell asleep sitting in the lotus position for an hour. On examination, the neurologist finds weakness and sensory change in the distribution of a single nerve (peroneal nerve). He or she taps over the nerve at the lateral border of the knee, finding that Mrs. Iva Drawpfut experiences a tingling sensation

(Tinel's sign). The neurologist makes a clinical diagnosis of compression of the peroneal nerve at the head of the fibula and recommends stretching, wearing a foot brace when walking long distances, and reporting back in 1 month. When Mrs. Iva Drawpfut returns, her foot is stronger and the sensory change is improving. The neurologist does not do any testing.

Both of these cases emphasize that the neurological method is powerful, focused, and capable of diagnosing many conditions accurately without the aid of extensive testing. In fact, the variety of neurological structures that can be affected and the number of disorders that can affect them is so wide that nothing but a well-defined clinical approach can adequately limit testing enough to avoid a blunderbuss approach.

In neurology, as in neuropsychology, there are two schools of thought when it comes to the examination. The comprehensive school aims to do the full neurological exam on all patients and then correlate this exam with the history and differential diagnosis. The hypothesis-driven school is one in which the neurological exam is driven largely by the history and focuses on the specific components of the exam that will most sharply support or refute the working diagnosis. These schools are mirrored in neuropsychology by the fixed battery versus hypothesis testing approach to evaluation. Both approaches have pluses and minuses, but neither works in all cases. As you will see from the examples that follow, we favor the hypothesis testing approach in both neurology and neuropsychology. We teach the medical students that neurology is, really, a very simple specialty. With only three questions to answer, for the medical student, it becomes clear what to test and how to proceed.

1. *Is there a neurological syndrome?* Although this is probably the simplest of the three questions, it is crucial to answer. There is nothing more foolish than testing a patient with a conversion disorder for acute intermittent porphyria or treating a patient with hyperventilation using anticonvulsants. Recognizing that an issue is outside of the scope of one's practice is a key to ultimate success.
2. *Where in the nervous system is this problem?* This is a crucial question for neurological disorders. Without understanding where in the nervous system the problem is, one cannot understand the cause of the disorder or move forward in therapy. Lesions can either be located at a *level* in the nervous system (e.g., cortex, brainstem, peripheral nerve), or affect a particular neurological *system* (e.g., cerebellar disorder, motor

system disorder). Some diseases affect multiple levels in the nervous system (e.g., multiple sclerosis).

A working knowledge of basic *neuroanatomy* helps in localizing problems in the nervous system. Understanding the anatomy of the major ascending and descending pathways (spinothalamic tract, dorsal columns, corticospinal tract), the major cranial nerves and their brainstem connections, the visual system, and the major anatomic areas of the cortex (language areas, sensory cortex, visual cortex, motor cortex) assists in localizing lesions in the central nervous system (CNS). A working knowledge of the major root, plexus, and peripheral nerve anatomy allows effective localization of peripheral nervous system disorders.

Each level or system within the nervous system has characteristic symptoms and signs. When listening to the history or examining the patient, the examiner should consider how the signs and symptoms correlate with different nervous system locations, in an effort to focus on the problem area. Table 1.1 lists different locations in the nervous system, what symptoms are typical for this location, and what signs may be seen with deficits in this location in the nervous system.

In addition to locations in the nervous system, there are systems that may be involved that do not respect anatomic boundaries. For example, amyotrophic lateral sclerosis is the archetypical *system disorder*, affecting motor neurons both in the motor cortex of the brain and in the spinal cord. Each system disorder also has typical symptoms and signs, as seen in Table 1.2.

3. *What is the etiology or mechanism of the neurological problem?* Once the location or system is known, the etiology can be considered. Important data from the history include the time course of the problem. Events occurring over seconds to minutes suggest stroke, migraine, or epilepsy. Events occurring over hours to days suggest stroke, infection, rapid mass lesions, or inflammation. Events occurring over weeks to months suggest rapidly growing mass, chronic infection, or a degenerative process. Events occurring over years suggest a degenerative process or slow mass lesion.

   Epidemiological, demographic, and family data from the history are very helpful. Older patients are more likely to have stroke, Alzheimer's disease, lumbar spinal stenosis, and a variety of other disorders than younger patients. Patients from tropical areas are more likely to have malaria than those from Finland. Patients who have diabetes, hyperlipidemia,

Table 1.1. Localization of Lesions in Neurologic Exam

Location in the central nervous system	Typical symptoms	Typical signs
Cortex	Cognitive, visual, language, neglect, behavior, motor, sensory, seizures, myoclonus	Field cut, aphasia, neglect, cortical sensory loss, apraxia, dementia
Brainstem	Diplopia, dysarthria, imbalance, facial weakness or numbness, weakness, altered consciousness	Combination of cranial nerve findings and long tract findings
Spinal cord	Sensory and motor symptoms below a level, bowel and bladder symptoms, stiff legs	Sensory level, motor and sensory deficits below level, reduced anal reflexes, hyperreflexia below level and upgoing toes
Nerve root	Pain down root distribution, weakness, numbness limited to root involved	Weakness, sensory loss, and reflex loss in root distribution
Plexus	Focal weakness usually in shoulder girdle or hip girdle muscles on one side, with sensory loss	Weakness of proximal muscles on one side, sensory loss in similar area not in root distribution, reflex loss
Peripheral nerve	For generalized neuropathy, sensory symptoms in feet and hands, weakness, imbalance. For focal neuropathy weakness, numbness, pain in nerve distribution	"Stocking and glove" sensory loss feet–hands, decreased reflexes, distal weakness. For focal neuropathy weakness, sensory loss, reflex loss in nerve distribution

(continued)

Table 1.1. Localization of Lesions in Neurologic Exam *(Continued)*

Location in the central nervous system	Typical symptoms	Typical signs
Neuromuscular junction	Fluctuating weakness, usually proximal, diplopia, dysphagia, neck weakness. No sensory symptoms or bowel and bladder symptoms	Fatiguable weakness of various muscles, normal reflexes, sensory, and other neurological examination
Muscle	Weakness, usually difficulty arising from chairs, going up stairs, combing hair	Weakness of muscles, atrophy, normal sensory, reflex, and other neurological examination

and hypertension are at risk of cerebrovascular disease. Patients with a family history of Huntington's disease are at a well-defined risk for this autosomal dominant disease.

Once a differential diagnosis of the etiology and mechanism is developed, a rational strategy to confirm the diagnosis can be developed. Without a stepwise analysis of each case, answering these three key questions, it is difficult to effectively treat neurological disorders.

III. METHOD: THE NEUROLOGIC EXAM

The methods of neurological examination have not changed significantly over time and probably lag far behind the developments in technological studies or neuropsychological batteries. Some quantitative and validation studies have been undertaken, but these studies are limited, and more has been done on the general medical examination than the neurological one. Chimowitz, Logigian, and Caplan (1990) assessed the accuracy of bedside diagnosis and showed that it increased with years of clinician experience. Half of the time laboratory testing was negative and a diagnosis depended on the clinical examination. Kamel et al. (2011) investigated the sensitivity and specificity of a screening neurological examination versus a hypothesis-driven one, and they showed a higher sensitiv-

Table 1.2. System Disorders in Neurology

System involved	Symptoms	Signs
Motor system	Weakness, spasticity, muscle twitching, dysphagia	Hyperreflexia or hyporeflexia, fasciculation, atrophy, weakness
Sensory system	Tingling, burning, sensory loss, unsteady gait, difficulty feeling things	Loss of pin, touch, temperature, position, vibration sensation, reflex loss
Autonomic nervous system	Blurred vision, dry mouth, loss of sweating, bowel and bladder dysfunction, postural lightheadedness	Altered pupil responses, postural hypotension, loss of R-R variability
Basal ganglia	Gait disorders, unusual limb movements, dysphagia, dysarthria	Parkinsonian symptoms, choreoathetosis, hemiballismus
Cerebellar	Unsteadiness, incoordination, slurred speech	Ataxic gait, nystagmus, incoordination, intention tremor, reduced reflexes

ity to a hypothesis-driven exam at the expense of some specificity as well as a more rapid exam. However, they used medical students who would be likely to have a less well-defined hypothesis-driven exam than more experienced clinicians.

Many articles on the neurologic exam focus on a specific sign (Carter, Wasser, Statler, & Rae-Grant, 2004; Guarino, 1982; Hancock, Koes, Ostelo, & Wilco, 2011; Luzzi, Fabi, Pesallaccia, Silvestrini, & Provinciali, 2011). Because neurologists use a grouping of multiple signs combined with history, taking a single exam sign out of context may not adequately assess the process used or the diagnostic accuracy of the exam as a whole. Recently, certain signs have been subjected to systematic review, indicating a higher level of scrutiny

of the features of the neurological exam (Dros, Wewerinke, Bindels, & van Weert, 2009). Given the ubiquity of the neurological exam and the relatively limited data on the validity, reproducibility, sensitivity, and specificity in any given disorder, more work needs to be done on this aspect of neurological diagnosis.

Neurologists either incorporate their neurological examination into a general physical examination or separate these into two different elements. Thus, a neurologist may start with a head and neck examination, including the cranial nerve examination; move on to the trunk and abdomen, incorporating motor, sensory, and coordination of the limbs and sensory testing of the trunk; then finally assess the limbs, adding in reflexes and the Babinski sign. The mental status exam may be done before, during, or after the neurological exam. Gait testing is either done as the patient walks into the office or later in the exam. As is the case for neuropsychological evaluation, the hypothesis-driven neurological exam will be modified depending on the specific issues and patient circumstances. For example, in a patient suspected of having multiple sclerosis (MS), particular attention will be paid to fundus examination, visual fields and acuity (for optic nerve disorders), eye movements (commonly affected in MS), reflexes, sensory and motor (for long tract signs and sensory levels), and Babinski sign and gait (for spasticity or ataxia). In the case of a patient suspected of a cerebellar tremor, specific evaluation of eye movements for overshoot dysmetria, gaze-evoked nystagmus, and other eye signs of cerebellar disease would be helpful. Most neurologists have a screening evaluation that they modify depending on the specific patient circumstance. The general organization of the neurological examination includes (a) bedside mental status testing; (b) cranial nerve examination; (c) motor examination, including coordination; (d) sensory examination; (e) reflex examination, including frontal release signs; and (f) gait and stance testing.

A. Bedside Mental Status Testing

There is no set mental status testing protocol for neurologists. There are various tasks that the neurologist is called on to achieve, and mental status can be modified to suit the particular task at hand. Neurologists are more concerned about defining the location of lesions or presence versus the absence of disease than about quantifying cognitive deficits. Critical issues to evaluate with the mental status exam include (a) altered mental status (coma, delirium, inattention), (b) dementia (presence and severity), (c) psychiatric syndromes (e.g., psychosis, depression, mania), and (d) identifying focal abnormality of cortical and subcortical systems.

1. ALTERED MENTAL STATUS

Often neurologists see patients in the hospital who are delirious, confused, or even comatose. Bedside testing for these conditions is limited by the alteration of sensorium. *Coma* has been variably defined, but the simplest definition is a patient who is neither asleep nor awake but is still alive. That is, comatose patients cannot visibly emerge to a conscious state even with stimulation, but they are not in a normal sleep state either. The mental status exam in coma is limited to assessing the level and type of response: Does the patient respond to voice? to light stimuli? to painful stimuli? If so, how?

Exam of a comatose patient encompasses three domains: brainstem signs, motor function, and level of consciousness. The goal of the exam is to define depth of coma and to determine whether there is a supratentorial lesion, infratentorial lesion, or diffuse lesion. A neurologist may be able to examine cranial nerve functions in coma, including papillary response to light (CN II and III), corneal response (touching with a cotton swab; V in, VII out; eyes may roll up, III), the so-called doll's eyes (turn head briskly to side, *normal;* comatose response eyes roll away from turn; VIII, III, VI). A neurologist may also perform ice water caloric stimulation, using a large bore syringe to place 200 cc of cold water in each ear. When cranial nerves III, IV, VI, and VIII are intact, the eyes will tonically deviate to the side stimulated. Gag reflex may be examined to test CNs IX and X. The examination of motor response in a comatose patient allows the neurologist to localize the level of damage. Lateralization of lesions can be established by asymmetries (e.g., one side weak, other normal). The presence of *decorticate posturing* (flexing of arms and extending of legs to painful stimulus) indicates a higher brainstem lesion. *Decerebrate posturing* (extension of arms and legs) suggests a lower brainstem lesion. Level of responsiveness in the comatose patient is typically reported by the neurologist in a few words that describe what the patient does either spontaneously or in response to a stimulus.

Delirium can be defined as a subacute onset of a confused state with associated positive symptoms of hallucination, restlessness, or agitation. It is common in the hospital setting and in the dementia population ("beclouded dementia," with subacute delirium on top of a demented baseline). Delirious patients are inattentive, have difficulty maintaining a stable level of arousal, tend to have trouble following mental status testing, and may alert to environmental stimuli in the room or outside the room inappropriately. Frequently, patients in the hospital are confused but may not show the restless or hallucinatory phenomena of delirium. Such patients are still part of the

encephalopathy spectrum, implying altered brain function based on a variety of causes (medication, infection, fever, sleep deprivation, withdrawal states, metabolic abnormalities, focal brain injuries of various types). Bedside assessment of attention and arousal consists of observing the patient during history taking. Often patients drift off to sleep or become distracted by other events in the room. Basic maneuvers such as asking the patient to say the months backward or digit span testing can be useful to determine where the patient's behavior veers from normal responses.

2. PRESENCE OF DEMENTIA

As part of the neurological exam, the neurologist is often called to assess the presence and severity of dementia. The history from an informant is critical to documenting a progressive cognitive decline affecting memory, executive functions, visuospatial function, and language function. Many patients with dementia lack insight into their problem, which may be a specific sign of the disruption of cognitive perspective with the brain disease. The informant may be asked by the neurologist to provide information either through informal interview or through standardized questionnaires, such as the Alzheimer's Disease–8 scale (Galvin, Roe, & Xiong, 2006).

Simple bedside tests of cognitive function are commonly used by time-pressed neurologists. The Mini-Mental State Examination (Folstein, Folstein, McHugh, & Fanjiang, 2001) is most commonly used but may miss many visuospatial, subtle memory, and executive dysfunction issues on examination. The Montreal Cognitive Assessment (http://www.mocatest.org) is a more recently developed measure used in the bedside assessment of dementia or mild cognitive impairment. It interrogates attention, memory visuospatial function, language function, and abstraction. Montreal Cognitive Assessment testing is more sensitive to the presence of mild cognitive impairment than the Mini-Mental State Examination. There is a host of bedside mental status evaluations that can be used, depending on the need for a rapid screen (e.g., the MiniCog) or a more comprehensive bedside evaluation (e.g., the Short test of mental status; Kokmen, Naessens, & Offord, 1987). A comprehensive elaboration of these tests is beyond the scope of this chapter, but a variety of reviews are available to assess the types and utilities of various mental status screens (e.g., Borson, Scanlan, Chen, & Ganguli, 2003; Kokmen et al., 1987; Petersen et al., 2001). In general, neurologists prefer rapid, simple tests over complex, time-consuming ones, reflecting the accelerating pace of their practice. More subtle cognitive syndromes are often the source of appropriate referrals for evaluation by neuropsychological colleagues.

3. PRESENCE OF PSYCHIATRIC SYNDROMES

Neurologists may be called to see patients who ultimately have a psychiatric syndrome, and they need to know how to recognize these syndromes. These are usually identified during the interview with the patient and observers as there are certain cardinal symptoms or behaviors that point in this direction. The presence of hallucinations (visual, auditory, other), or delusions (thoughts of control, thought withdrawal, beliefs inconsistent with reality), and tangential thought may all point to a psychotic disorder. The presence of a negative mood, vegetative symptoms, self-denigrating thoughts, and suicidal thoughts or intentions may point to a major depression. Rapid flight of ideas speech, lack of sleep, and impulsivity may all suggest mania. In such patients, the mental status exam helps support the presence of cardinal manifestations as well as interrogates the underlying thought process. Screening self-reported tests such as the depression module of the Patient Health Questionnaire (Kroenke, Spitzer, & Williams, 2001), the Beck Depression Inventory–II (Arnau, Meagher, Norris, & Bramson, 2001), or the Geriatric Depression Scale (Lesher & Berryhill, 1994) may be useful in screening for depression, particularly in populations such as the MS or memory disorders clinic populations, in whom a high prevalence of depression is seen (see Chapter 26 for an extensive review of emotional measures). Once again, the role of the neurologist is to determine whether a psychiatric disorder is the cause of the patient's presenting problem; when in doubt, referrals to neuropsychology or psychiatry ensue.

4. IDENTIFYING FOCAL ABNORMALITY OF CORTICAL AND SUBCORTICAL SYSTEMS

An aspect of the neurological examination that overlaps with the neurobehavioral examination (described in Chapter 2) is the attention to the presence and quality of focal cortical and subcortical abnormalities. This examination can be as simple as interacting with the patient in history taking or as complex as focused inquiry on cortical function in detail (e.g., extensive apraxia testing).

The neurologist may be alerted to the possibility of a focal cortical disorder by the history, with stories of behaviors that appear odd to family members but are readily interpreted by the behaviorally oriented neurologist. For example, "he doesn't seem to recognize faces of familiar people anymore" (prosopagnosia, inferior occipitotemporal lesions), or "his personality has changed, he's just not the same" (prefrontal, orbitofrontal), or "he doesn't seem to use his left arm, and when we walk in the room he doesn't seem to see us when we are on the left side of the bed" (right parietal syndrome, neglect). Focal findings associated with lesions to various cortical or

subcortical regions of the brain are as important to neurologists as they are to neuropsychologists. They are not listed here, given that these signs and symptoms are essentially the content of this book (e.g., amnesia, Chapter 17; aphasias, Chapter 18; visuospatial disorders and agnosias, Chapter 19; attention and executive deficits, Chapters 20 and 21). Neurologists follow up precise examination with imaging or neuropsychological evaluation to correlate with clinical suspicion.

B. The Cranial Nerve Exam

Neurologists test the cranial nerves for specific reasons. They are eloquent components of the nervous system that show evidence of pathology readily. They may be affected in meningeal, base of the brain, brainstem, and peripheral nerve syndromes. In addition, some cranial nerves have neuromuscular and muscular components (e.g., facial nerve, oculomotor nerves, lower cranial nerves) and therefore may show evidence of disorders of these systems. Although cranial nerves one and two are part of the cranial nerve test, they are really components of the CNS and particularly the optic nerve (ii) may be profoundly affected by cortical and subcortical disease. (See Table 1.3 for a listing of cranial nerves, major function, and examples of diseases that may affect each.)

C. Motor Examination

Although many neurologists do the same motor testing for each patient, the questions to be answered vary from patient to patient, and therefore the exam should be tailored to be sensitive to specific findings. Patients with parkinsonian syndromes will have specific changes in muscle tone (rigidity, cogwheeling) but will not have weakness per se. Patients with a hemiparesis have a specific pattern of weakness based on the muscle systems, which are more affected by the corticospinal tract (e.g., weakness of hip flexion and ankle dorsiflexion more than knee extension and foot plantar flexion) and will show altered tone with increased muscle resistance to passive force.

The components to be examined in the motor exam include bulk of the muscle, tone, power (graded on Medical Research Council [1981] scale 0–5; see Table 1.4), coordination, and abnormal movements (e.g., chorea, myoclonus). It makes sense to include coordination in the motor exam as there are various generators of ataxia other than the cerebellum (descending frontocerebellar paths, sensory afferent traffic, white matter paths). Although many neurologists

Table 1.3. The Cranial Nerves

Cranial nerve	Function	Example of disorders affecting nerve
Olfactory nerve	Sense of smell	Orbitofrontal mass, Parkinson's disease
Optic nerve	Vision, afferent pupil innervation	Multiple sclerosis
Oculomotor nerve	Eye movement, lid elevation, pupil constriction	Berry aneurysm compressing nerve, diabetes
Trochlear	Eye adduction	Head trauma
Trigeminal	Facial sensation, mastication	Trigeminal neuralgia
Abducens	Eye abduction	Increased intracranial pressure
Facial	Facial movement, taste	Bell's palsy
Acoustic	Hearing, vestibular function	Acoustic neuroma
Glossopharyngeal	Gag, posterior tongue taste	Jugular foramen mass
Vagus nerve	Swallowing, autonomic	Gag
Accessory	Neck movements	Carotid surgery may injure
Hypoglossal	Tongue movement	Skull base masses

separate out a cerebellar examination, in fact, they do not lift out the cerebellum and examine it but infer from the exam what the location of pathology may be. The exam suggests possible localizations, but neurologists should probably not presume localization until all the data are analyzed. Occasionally, specific findings on the motor exam may suggest certain pathologies, for example, the presence of fasciculations pointing toward amyotrophic lateral sclerosis or myotonic hand grip, suggesting the possibility of a myotonic dystrophy.

Table 1.4. Medical Research Council Muscle Grading Scale

0	I	2	3	4	5
No movement	Flicker of movement	Moves but not against gravity	Moves against gravity, not resistance	Moves against resistance but weak	Normal

Neurologists may test for the presence of apraxias of various types. *Ideomotor apraxia* is usually tested by asking patients to perform a unilateral task (throw a ball, brush your teeth, comb your hair), a bilateral task (drink tea from a saucer), or full body task (hit a home run, swing a golf club). *Ideational apraxia* is tested by giving patients the object and seeing how they use it. *Gait apraxia* is tested by watching patients walk and seeing if they hesitate initiating and proceeding. If there is gait apraxia, patients can usually do bicycling movements lying down without difficulty as opposed to ataxia, which would affect both equally. Other more specialized testing occurs depending on the clinical context and often serves to help localize or to elaborate on pathological findings in a region of the brain. The TULIA apraxia screening test (Vanbelligen et al., 2010) is a simple bedside measure that is easily scored and has been validated as a sensitive and specific measure of the presence of apraxia.

D. Sensory Testing

Tactile sensory testing again varies from a brief screen of sensation in four limbs and face to a detailed mapping of a focal sensory or multifocal sensory deficit. Sensory modalities traditionally tested include light touch, pin, temperature (hot, cold), two-point discrimination, vibration threshold, and position sense. A hypothesis-directed sensory exam is likely to yield more useful data than a standard exam, as it allows neurologists to raise or lower the likelihood of a specific localization if the exam concurs with the hypothesis. For example, if a neurologist is considering a generalized peripheral neuropathy, a graded distal sensory loss in the feet and hands would be consistent but a focal sensory level at the trunk would not. In a posterior cord syndrome, specific alteration of vibration and position sense would be consistent (dorsal columns of spinal cord), but spinothalamic sensory

disruption (ventrolateral cord) would not be. Sensory testing validation has been performed in some situations such as vibration sensation in MS (Carter et al., 2004) and distal sensation in diabetes (Dros et al., 2009).

E. Reflex Examination

Reflexes are usually divided into muscle stretch reflexes and pathological reflexes. Muscle stretch reflexes are based on a simple reflex arc with an afferent and efferent component. They are graded from 0 to 4 and can be elicited from any muscle but are usually checked in certain muscles. Neurologists use them to determine whether there is a generalized neuropathy (reduced reflexes); corticospinal tract disorder (increased reflexes below the level of the lesion); lateralized CNS disorder (asymmetric reflexes); or a focal root, nerve, or plexus disorder (focal reflex change reflecting specific root, plexus, or nerve disorder).

Pathological reflexes include the *Babinski sign*. The Babinski sign is obtained by stroking the lateral border of the sole of the foot with a sharp object. The normal response is a flexor movement of the great toe. The Babinski sign shows an upgoing great toe with fanning of the smaller toes and occasionally flexion of the knee and hip (triple flexion response). The Babinski sign reflects alteration in corticospinal tract function anywhere from the motor cortex to distal thoracic spinal cord. Other primitive reflexes include the rooting reflex, palmomental, snout–pout response, grasp response, and Glabellar tap and are discussed more extensively in Chapter 2.

F. Gait Evaluation

Perhaps the most useful aspect of the neurological exam after the mental status test is gait evaluation. Neurologists tend to have the patient walk up and down the hall and then subject them to a variety of stress maneuvers (e.g., tandem gait, Romberg test, hopping on one foot, standing on one foot, balancing with arms folded across the chest and one foot in front of the other). Watching the spontaneous gait can tell the neurologist many things: whether there is a parkinsonian syndrome, ataxia, choreiform gait, hemiparesis, spastic paraparesis, foot drop, muscle disorder (so called Trendelenberg gait), or a hysterical gait disorder. Some neurologists will do the gait exam first to get clues on what to watch for when doing the formal neurological examination. Various methods of classification of gait disorders that reflect system involvement and diagnosis have been proposed (Jankovic, Nutt, & Sudarsky, 2001).

Quantitative studies of gait may be used in a variety of neurological settings. Disorders with prominent gait components such as Parkinson's disease, MS, and normal pressure hydrocephalus benefit most from such measures. Simple quantification measures such as timed 25-foot walk (T25FW) or 6-minute walk can provide a longitudinal measurement to guide therapy (Goldman, Marrie, & Cohen, 2008; Kragt, van der Linden, Nielsen, Uitdehaag, & Polman, 2006). Recent observations that gait disorders are associated with the development of dementia in older patients have increased the need for more carefully validated measures of gait (e.g., Martínez-Martin, Ossa-Ruiz, Gómez-Conesa, Olazarán, & RSGE-CD Validation Group, 2012). Portable analytic devices such as the GAITrite (Bilney, Morris, & Webster, 2003) may be useful for developing therapeutic programs for gait disorders.

IV. INTEGRATION WITH THE NEUROPSYCHOLOGICAL EVALUATION

The neurological examination allows deductions to be made about the localization of pathology in the nervous system. Those aspects that affect cognitive function dovetail with the neuropsychological evaluation in terms of localization, severity of deficit, and presence of psychiatric components. An effective hypothesis testing neurological examination can guide or limit the necessary scope of the neuropsychological evaluation by narrowing the field of hypotheses to be considered by the neuropsychologist. As noted earlier, communication about the specific referral question can greatly aid in the use of the neuropsychological evaluation, enhancing the relationship between the referral source and the consulting neuropsychologist. Furthermore, the overlap between the two forms of examination can serve to provide independent samples of data that can support (or refute) a specific localization or neurological syndrome.

Neurologists look upon the neuropsychological examination as an extension of their own history and physical exam. They use the neuropsychological evaluation in much the same way as they use the mental status examination but to get a more detailed interpretation of cognitive function. Thus, they find evaluation useful for dementia or other memory complaints or to assess for other focal features in the cortical and subcortical exam. At times they look for whether the features of the neuropsychological exam assist with differential diagnosis among similar neurological syndromes (e.g., dementia subtypes). Although a neuropsychological result that confirms the clinical suspicion is comforting, perhaps more useful is one that is at

odds with the clinical diagnosis, leading the neurologist to rethink the case or pursue different avenues of testing or treatment.

The avenue for communication of the opinion of the neuropsychologist is the neuropsychological report. Thus, the quality and use of the evaluation are entirely dependent on the quality of the report. This does not mean that the report has to be lengthy; rather, it must be clear and accurate and meet the needs of the referral source. For many neuropsychologists, this means that flexibility in report style is a necessity: Reports to a consulting neurologist on an inpatient service will be very different from those written for a patient and family to support accommodations in a work or school environment (see Chapter 6 for a discussion of the special issues that come into play in the assessment and reporting of pediatric neuropsychological evaluations). Of course, many reports have multiple audiences, including the patient and family. The neuropsychologist often needs to balance the goal of simplicity and clarity to the referral source with comprehensible and compassionate communication to the patient about their symptoms.

V. INNOVATIONS, TRENDS, AND CONTEMPORARY ISSUES

The production of reports in the era of the EMR can be greatly facilitated by taking advantage of the capability of these systems to produce templates that incorporate information that is already present in the system (e.g., demographics, medication lists, past medical diagnoses, family medical history). Of course, this information must be confirmed: Neuropsychologists are always responsible for the content of their report, and including erroneous information just because it was already erroneous in the system is illegitimate. Report templates are particularly useful in the context of multidisciplinary clinical settings where the audience for the report, the patient population, and the referral questions are fairly homogenous.

A developing trend within health care funding is the concept of *bundled payment* for certain conditions or problems. For example, a health care insurer may contract with a hospital system to provide all the care necessary for a medical event (e.g., epilepsy surgery, newly diagnosed high grade brain tumor). The system will be paid a fixed sum for all of the procedures (e.g., imaging, electroencephalography, surgery, neuropsychological evaluation). Under this framework, the neuropsychologist will be pressured to provide relevant information for as little cost (in terms of neuropsychologist time) as possible, to maximize the information–cost ratio. As the pressures imposed by health care finance reform require neuropsychologists

to provide more service in less time, increased efficiency in report will become critical.

Recently, bedside neurological testing has begun to enter the computer age along with everything else. Various "apps" for tablets and smartphones are available with scoring measures for examination (e.g., National Institutes of Health stroke scale, Unified Parkinson's Disease Rating Scale, Glasgow Coma Scale), as well as specific tests such as Ishihara plates (used at times in optic nerve disorders), opticokinetic tapes (used to evaluate abnormal nystagmus in temporoparietal disorders), and others. In addition, computerized cognitive tests are used, as covered in many chapters in this volume (e.g., as discussed for traumatic brain injury in Chapter 10).

As neurologists and neuropsychologists move together into the new era of health care, it is our opinion that their importance to the care of patients with many disorders will continue to grow. Many diseases that were once quickly terminal are becoming more like chronic conditions (for example, oncological conditions; see Chapter 14). As medical advances improve, providing longer life, the neurologic and cognitive sequelae of disease (and treatments) will become more relevant issues to the patient. Through the use of efficient hypothesis-testing approaches, the neurologist and neuropsychologist of the future will be able to affect these patients' quality of life.

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Chapter 2

Ekaterina Keifer and Marc W. Haut

Neurobehavioral Examination

The goal of this chapter is to provide a how-to guide for the administration and interpretation of one variation of a neurobehavioral examination. We begin with historical background to put the examination in the proper context. A brief review of scientific evidence is also included, although a comprehensive review is not the primary goal of this chapter. We hope that by the end of this chapter, readers will have a basic understanding of the examination and will then perfect their knowledge and interpretation with experience.

The theoretical guidance and procedures in our interpretation and use of the neurobehavioral examination were inspired by the pioneers of the qualitative approach to neuropsychology, Alexander Luria and Edith Kaplan. Luria was a Russian neuropsychologist (1902–1977) who through his clinical and scientific work developed a set of procedures to elicit manifestations of brain dysfunction. The theoretical underpinnings and practical guidance for the procedures are outlined in his book, "The Highest Cortical Functions of Man" (Luria, 2008). In preparing to write this chapter, one of the authors

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(Keifer) read Luria's book in its original Russian version. It is interesting that in his book, Luria referred to his examination as *neuropsychological*, whereas the laboratory-based standardized procedures commonly used by neuropsychologists were referred to as the *neuropsychometric* approach. For the purpose of clarity, we use the term *neurobehavioral* to refer to the examination.

Luria valued the neurobehavioral examination and regarded it as a qualitative tool. He believed that this method provides a greater depth of understanding of the patient's primary or core deficits and syndromes. He referred to his procedures as *structuro-dynamic*, reflecting the combination of structured tasks combined with a dynamic and evolving nature of the examination. Luria believed that the examination should include assessment of a range of functions from basic to more complex. He highlighted that the tasks were specifically designed to present patients with certain conditions that would allow them "an opportunity to exhibit with maximal clarity the deficit" (Luria, 2008, p. 343). Our interpretation of this is that the examination needs to be administered in a manner that allows and gives the patient every opportunity to show the existing pathology. This is particularly important for tasks eliciting frontal or executive dysfunction where excessive direction, guidance, and structure from the examiner can mask the existing deficit. We elaborate on this point throughout the chapter.

Luria believed that the neurobehavioral examination should consist of tasks that are easily achievable by all healthy individuals regardless of level of education. The examination may begin with standardized procedures to "orient" the examiner to the patient's deficits. Subsequently, the nature of the examination becomes dynamic as the examiner begins to tease out different elements of poorly performed tasks, varying task difficulty to elicit the core deficit. This is the "creative" and "individualized" part of the examination, requiring curiosity and ingenuity on the part of the examiner. He acknowledged that, because of its qualitative nature, the interpretation and administration of the exam requires experience and knowledge about brain function on the part of the examiner.

Around the same time, Edith Kaplan (1924–2009) and her colleagues developed the Boston process approach "based on a desire to understand the qualitative nature of behavior assessed by clinical psychometric instruments" (Milberg, Hebben, & Kaplan, 1996). Milberg et al. (1996) developed new procedures or changed existing ones to elucidate the quality and process by which patients arrive at a given quantitative test score. The methods and philosophy of the Boston process approach have had a strong influence on the practice of neuropsychology and on the nature of the neurobehavioral examination as we use it.

In the following sections, we present the procedures for conducting the neurobehavioral examination in a step-by-step fashion,

as well as guidance for interpretation and scientific findings associated with some of the tasks. The exam will be presented starting with the hardwired functions associated with primary cortical areas and will move on to more complex functions and regions of the brain. Additional procedures or in-depth assessment of particular functions may be added to the examination as appropriate based on the patient's situation (e.g., in-depth apraxia examination). The order of the procedures may be changed to accommodate time constraints and/or to focus the exam in the context of a known lesion location or pathology. For a video demonstration of the assessment techniques described in this chapter, please see the online resources at http://pubs.apa.org/books/supp/parsons.

The purpose is not to do a thorough neurological evaluation, particularly if the patient is followed by a neurologist. Rather, the purpose is to perform a behavioral neurological examination, concentrating on behavioral aspects of the examination, in which neuropsychologists have unique expertise. During the neurobehavioral examination, parts of existing standardized measures may be used, but the examiner should not be driven to administer a particular measure from start to finish unless it is deemed to be informative. The point is to screen a variety of abilities, detect the core deficits, and elaborate on them. The examiner should be able to do this exam with only a piece of paper and a pen even though the examination covers the typical domains addressed by a more comprehensive and formal neuropsychological evaluation.

Finally, we mention some general guidance for the interpretation of the neurobehavioral exam. Given the qualitative nature of this examination, it is important to be mindful of over- or underinterpreting patients' performances. As Luria (2008) pointed out, reliability of findings in such evaluations is often established through recognizing patterns of behavior across different tasks. For example, an examiner would not necessarily interpret one perseverative error as a sign of brain pathology or executive dysfunction. However, if a patient is perseverative and is also stimulus bound or intrusive on other tasks, it strengthens the evidence for the presence of frontal–executive dysfunction. It is important to observe the patient closely and recognize subtle aspects of performance that may tell you about function in a different domain from the one that is being explicitly tested. Signs of frontal–executive dysfunction can be observed on virtually every task of the examination, and the examiner's task is to let them occur and recognize them. For example, if right-handed patients begin motor tasks with their left hand (hand closest to the demonstration by the examiner seated across from the patients), this suggests stimulus-bound behavior. Other examples of subtle performance aspects will be elucidated in the specific sections of the exam.

I. METHOD: ADMINISTRATION GUIDELINES AND PROCEDURES

A. Orientation and Insight

Just as in a traditional neuropsychological evaluation, the neurobehavioral exam should be interpreted in the context of the patient's background and presentation. Assuming that the examiner collects basic historical information, the examination should begin with assessing the patient's orientation (time, location, personal information), awareness of the patient's current circumstances, and appreciation of any cognitive difficulties (insight).

B. Motor Functions

As a general guideline, motor tasks should be administered bilaterally, and examiners should look for asymmetry in task performance. Although there are formal measures of motor function, such as the hand dynamometer (Reitan & Wolfson, 1993) to measure strength and the Finger Oscillation test (Halstead, 1947) for fine motor facilitation and speed, observing asymmetry without using the formal measures is indicative of more prominent difference in strength that is more likely to be functionally meaningful for patients. In other words, if examiners cannot detect a difference in grip strength by having patients squeeze their fingers, it may be too subtle to be functionally meaningful. Finally, it is important to keep in mind that people tend to perform slightly worse with their nondominant hand but not notably so.

1. STRENGTH OF GRIP

The strength of grip procedure involves examiners extending their arms toward the patients and asking them to squeeze the examiners' hands as hard as possible. We usually have patients squeeze only two fingers (index and middle), which are crossed to prevent pain from a very strong grip. Examiners have to be vigilant about the patient showing stimulus-bound behavior on this task. For example, some patients will mimic the actions of the examiner (e.g., stretch out their arms with their fingers crossed) or pull the examiner's hands toward themselves.

2. PRONATOR DRIFT

For pronator drift, examiners ask patients to stretch out their arms with palms up (perpendicular to their body), close their eyes, and hold the arms up (like they are holding a pizza box). One of the

arms may be slowly drifting or turning inward, suggesting decreased strength in that extremity. Their arms may need to be adjusted to be symmetrical with which to start. Examiners should be aware if the patients resist and push back when adjusting their arms, as this may also suggest stimulus-bound behavior.

3. MANUAL FACILITATION AND SPEED

For the manual facilitation and speed task, examiners ask patients to tap on the desk or knee with their palm as fast as they can, while briefly illustrating the action. To assess more fine motor skills, examinees are asked to tap their thumb and index finger together as fast as possible. An altered administration of this procedure is to ask patients to tap their thumb and all other fingers in order as fast as possible. Alternating palm movements is another task to assess fine motor facilitation. It involves asking patients to put one hand on top of the open palm of the other hand and quickly turn the hand that is on top from palm up to palm down. The examiners are observing asymmetry in performance, which may include speed as well as the ability to maintain the behavior, and the smoothness–effortfulness with which the behavior is performed.

With each of these three tasks, examiners are typically assessing the integrity of the primary motor cortex, the corticospinal tract, or in some cases the basal ganglia. If performance is noticeably and consistently asymmetrical, this suggests possible dysfunction in the contralateral motor pathways in the brain.

Additional motor tasks include the finger-to-nose test to check for dysmetria and intention tremor resulting from cerebellar dysfunction. The finger-to-nose test involves asking patients to touch their nose and then touch the examiner's finger. The examiner may move the position of the finger to make the task more challenging. An apraxia examination may be warranted to examine the patient's ability to perform skilled purposeful movements (Heilman & Gonzalez-Rothi, 2012).

C. Motor Tasks Assessing Executive Function

As previously mentioned, the neurobehavioral examination can be very rich with observations about patients' executive functions. The next several tasks are a good illustration of this point. They are motor tasks used primarily to assess frontal lobe function. These include tasks of motor sequencing, repetitive drawing, and behavioral inhibition. Luria (2008) outlined several variations for each of these tasks, and here we highlight several that we frequently use. Luria believed that disrupted performance on these measures results

from dysfunction in the premotor areas of the frontal lobes, which are involved in the planning and execution of movement.

1. MOTOR SEQUENCING

The motor sequencing task consists of showing the patient a sequence of three hand movements: touching the table first with a fist followed by the edge of the palm and then an open palm face down on the table. This task has also been called the Fist-Edge-Palm test in the literature (e.g., Fama & Sullivan, 2002). The examiner demonstrates the sequence to the patient three times in a smooth fashion. The patient is then asked to perform the task on their own with each hand. Indications of poor performance include errors in sequencing, self-corrections, or both. The most common sequencing error is to go from a fist to a palm, leaving out the edge or catching this error and self-correcting. Luria (2008) highlighted the importance of "smooth" and "melodic" completion of the task, with choppy and effortful performance being an indicator of frontal lobe dysfunction. If the patient is struggling to perform the task after the initial demonstration, the examiner can vary the conditions to assist the patient and assess the degree of structure and cuing the patient requires. In other words, you systematically introduce structure or act as the frontal lobe for the dysfunctional patient. Progressive increases in structure can include asking the patient to do the task with the examiner or introducing a verbal cue ("fist, chop, slap") to cue the patient to the sequence. On occasion, patients will make paraphasic intrusion errors, such as saying "flap" instead of "slap." The demonstrated sequence was initially presented three times. It is meaningful if the patient perseverates beyond the demonstrated three examples. As with all motor tasks that are performed bilaterally, the examiner should watch for subtle signs of stimulus-bound behavior, such as beginning the task with the hand that is closest to the demonstration by the examiner rather than with the dominant hand. For this reason, examiners do not indicate with which hand the patient should start.

Scientific investigations examining this task are limited, but we review several examples next. Beatty and Monson (1990) and Sullivan et al. (2001) found that patients with Parkinson's disease (PD) and schizophrenia both had significantly fewer correct movement sequences on the motor sequencing task compared with normal controls, although rigidity was found to significantly contribute to poor performance in patients with PD. Fama and Sullivan (2002) concluded that motor rigidity and cognitive nonmotor executive abilities both significantly influence motor sequencing performance in these patients. In contrast, patients with multiple sclerosis (MS) were found to perform normally on the motor sequencing task (Beatty & Monson, 1994).

2. GO/NO-GO

Immediately after the motor sequencing, examiners should assess behavioral inhibition with a go/no-go procedure. The reason for this is that both tasks involve movements of the hand, and this allows a better opportunity to observe intrusions from one task to another. There are different versions of the go/no-go task. Examiners are partial to telling patients that they will hit the table hard or soft and having the patients do the opposite. (i.e., the examiner says, "When I hit the table hard, you hit it soft and when I hit the table soft, you hit it hard." As the examiner is explaining this, he or she is demonstrating a hard and a soft hit for the patient.) It may be necessary to ask the patient to demonstrate soft and hard hits so that the examiner can tell the difference. It is important to perform an adequate number of trials with each hand (at least 10). As with the motor sequencing, the go/no-go procedure is performed bilaterally, and the examiner watches for asymmetry in performance. Poor performance on the go/no go procedure is usually characterized by the patient being pulled to the stimulus presented by the examiner and imitating it rather than inhibiting the response in favor of the correct one. Stimulus-bound patients often hit the table the same way as the examiner or have multiple self-corrections. Some patients can inhibit their stimulus-bound response, but it is visibly effortful and time consuming, which is also notable. As previously mentioned, the examiner may observe the patient intruding hand positions from the motor sequencing task into the go/no-go task. For example, the patient may hit the table with his or her fist or edge of the palm, as he or she would during the motor sequencing task. These motor intrusions are meaningful because they demonstrate perseverative and inflexible tendencies. Starting tasks with the hand closest to the examiner's demonstration or almost hitting the examiner's hand as it is pulled to stimulus are other examples of stimulus-bound behaviors observed with this task. Alternative go/no-go procedures include asking the patient to raise one finger when the examiner raises two and vice versa or asking the patient to hit the table if the examiner says "red" and do nothing if the examiner says "green."

There is a fair amount of scientific literature examining go/no-go procedures, particularly because the task lends itself well to functional neuroimaging. Overall, human lesion and functional neuroimaging studies consistently support frontal lobe involvement in response inhibition (Picton et al., 2007; Simmonds, Pekar, & Mostofsky, 2008). Picton et al. (2007) found that patients with frontal lobe lesions, particularly in the superior medial region, had increased stimulus-bound responding on go/no-go compared with age-matched normal controls. With regard to laterality, results of lesion studies are more variable, whereas functional neuroimaging

studies point to a predominantly right hemisphere network, including the presupplementary motor area, middle–inferior frontal gyrus, bilateral inferior parietal regions, occipital regions, and premotor cortex (Simmonds et al., 2008).

3. REPETITIVE DRAWINGS

Another way to assess frontal lobe function is to use a task of repetitive drawings to elicit perseverations. There are several ways to administer this task, and we concentrate on a couple of them: repetitive drawings of loops and ramparts. The administration consists of the examiner drawing three figures, each consisting of three loops (see Figure 2.1) at the top of the page, and asking the patient to draw them as fast as possible. The instructions are minimal to avoid overstructuring the task, thus masking the patient's potential pathology. In particular, we do not instruct the patient when to stop drawing. There are usually two types of perseverations observed on the loops task: Patients draw more than the original three designs and/or they add extra loops to each or some designs. In severe cases of perseveration, we have seen patients cover the whole page with loops, turn the page over and continue on the other side or draw over the loops again and again.

During the ramparts task, the examiner draws a continuous sequence of square and triangular elements and asks the patient to draw them as quickly as possible, again providing minimal directions (see Figure 2.2). It is important to mention that we do not use the ramparts design from the Dementia Rating Scale–2 (Jurica, Leitten, & Mattis, 2001) because it includes horizontal bridges

Figure 2.1. Continuous perseverations on the repetitive loop drawings.

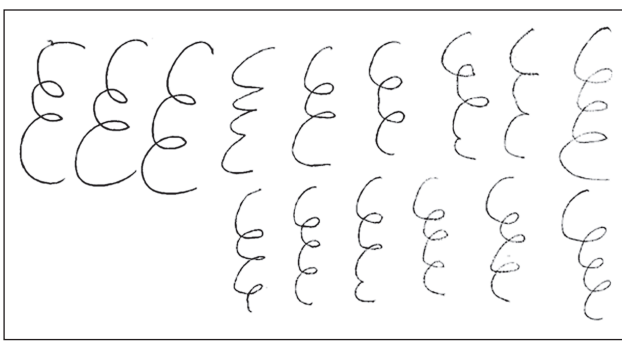
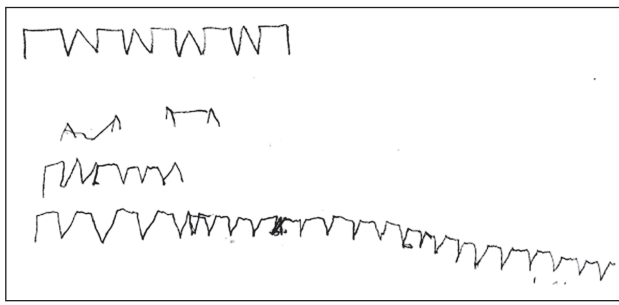


Figure 2.2. Continuous perseverations on the repetitive ramparts drawing.



between designs, which we believe serves as a transition that allows the patient to switch set and limit perseveration. Therefore, we use a continuous string of square and triangular elements, and we often see patients insert a horizontal transition between the elements, which we believe reflects a perseverative element from the rectangular part of the design. In addition to the inserted horizontal transition between elements, this task elicits other indications of perseveration elicited by this task. They include difficulty switching from one element to the other, resulting in the patient drawing the same element in a row multiple times. Another indication of perseveration is continuing the design beyond the demonstrated example. In severe cases, patients will run off the page and have to be asked to stop drawing (see Figure 2.2). Patients may also draw several sets of the original ramparts design after having drawn several sets of three loops.

Luria (2008) also provided examples of assessing motor perseverations by verbally asking patients to draw different geometric shapes. A patient with perseverative tendencies may continue drawing the same shape despite being given directions to draw a different shape. Luria believed that these motor tasks assess frontal lobe dysfunction, particularly in the dorsolateral–premotor areas.

Motor perseverations are hypothesized to represent dysfunction in the motor system controlling the timing or "when" to start, stop, or continue movements (Annoni, Pegna, Michel, Estade, & Landis, 1998). Difficulty stopping movements results in motor perseveration. Several taxonomies for identifying types and neuroanatomical correlates of perseverative errors have been proposed. The best-known ones are by Sandson and Albert (1984) and Goldberg (1986). Sandson and Albert identified recurrent, continuous, and

stuck-in-set types of perseverations. *Stuck-in-set* perseverations are defined as "continuous and inappropriate maintenance of a current set or framework" (p. 717), with the best example being perseverative errors on the Wisconsin Card Sorting Test (Berg, 1948). "Unintentional repetition, after cessation, of a previously emitted response to a subsequent stimulus" (Albert & Sandson, p. 717) was referred to as a *recurrent* perseveration, an example of which would be repeating the same word several times throughout a phonemic fluency task. Perseverations observed on the repetitive drawings of loops and ramparts are most often considered *continuous*, defined as "continuous and inappropriate repetition of a current behavior" (Sandson & Albert, 1984, p. 717). This type of perseveration was proposed to be most common in patients with a disturbance of "motor output," particularly related to subcortical pathology. There have been some scientific investigations of perseveration localization. For example, Annoni et al. (1998) used graphomotor tasks to assess perseveration in patients with brain lesions. They found that the frequency of perseveration was significantly increased in patients with lesions in a variety of brain regions compared with normal controls. Perseveration frequency was not significantly different between patients with frontal and nonfrontal lesions. Ryan et al. (1995) found that graphomotor perseverations occurred more frequently in patients with Alzheimer's disease who were identified as "wanderers." Bilder and Goldberg (1987) evaluated motor perseverations in a small sample of patients with schizophrenia. Of 12 patients, nine were found to show motor perseverations. Finally, Ramage, Bayles, Helm-Estabrooks, and Cruz (1999) found that continuous perseverations are the least common perseveration type to occur in normal subjects.

D. Examination of Sensory Functions

1. SIMPLE TACTILE STIMULATION

For simple tactile stimulation, examiners ask patients to close their eyes and put their hands palm down on the desk. They then touch each hand, asking patients to identify which hand is being touched (right or left). Obviously, this requires patients to have accurate right–left orientation, and if there is any doubt, examiners should formally examine that (Denburg & Tranel, 2012). If patients cannot verbally respond, examiners should ask them to move the hand slightly in response to touch. To make the procedure slightly more challenging, examiners can do directional tactile stimulation, which involves stroking patients' hands one at a time in an upward or downward direction and having them identify the

direction (up or down). If patients have no difficulty with simple tactile sensation but struggle with directional identification, this may point to dysfunction in the sensory association areas rather than the primary somatosensory area. On occasion, when we have begun the task, we have observed some patients having difficulty keeping their eyes closed, suggesting impersistence, another sign of frontal or executive dysfunction. This impersistence can be more formally assessed (Benton, Sivan, Hamsher, Varney, & Spreen, 1994).

2. DOUBLE SIMULTANEOUS TACTILE STIMULATION

Tactile extinctions on double simultaneous stimulation are commonly considered a part of hemispatial neglect or inattention resulting from contralateral brain damage (Tucker & Bigler, 1989). The phenomenon was initially described by Jacques Loeb (Benton, 1956) and involves poor perception on the side contralateral to the lesion with simultaneous stimulation in the context of preserved perception with unilateral stimulation. Extinctions can be assessed in both the tactile and visual domains. A common assessment of tactile extinctions includes having the patient close her or his eyes while the examiner lightly touches the dorsal surface of the patient's hand and asks him or her to identify which hand is being touched. Although extinctions are classically associated with lesions in the contralateral parietal lobe, they have also been reported following damage in other areas, such as the cingulate gyrus, frontal lobes, thalamus, and the basal ganglia (Tucker & Bigler, 1989). We find that extinctions are sometimes easier to detect with habituation: if the affected hand is stimulated several times in a row, followed by simultaneous stimulation of both hands, it is possible to detect reliable extinctions that were not detected by simple bilateral stimulation without prior habituation. The habituation procedure can be done with the simple touch and with directional stimulation. However, sometimes this may lead to bilateral extinctions. In other words, the patient will be pulled to the most salient stimuli regardless of the side. Thus, if the examiner touches the right hand twice and then both hands and the patient extinguishes to the right, the examiner might think that there is a lesion on the left. However, if the examiner touches the left hand twice and then both hands and the patient extinguishes to the left, this may represent stimulus-bound responding, as on each occasion the patient is pulled to the most recent new stimuli. There have been other perspectives and methods proposed in the literature regarding the effects of priming the affected side. For example, Birch, Belmont, and Karp (1967) proposed that delayed information processing in the affected hemisphere plays a role in the expression of extinctions.

E. Visual–Spatial Functions

1. VISUAL FIELDS

To check for restrictions in visual fields, the examiner positioned him- or herself directly in front of the patient and asks the latter to fixate her or his eyes on the examiner's nose. The examiner then slowly brings a pen from behind the examinee's head toward the face (mid face–eye level) and instructs the patient to indicate when she or he first sees the tip of the pen in the corner of her or his eye. The testing should be done for the right and left visual fields. The examiner would initially bring the pen directly to the right or left of the patient's head and subsequently test the four visual quadrants, while continuing to ask the patient to fixate the gaze on the examiner's nose. For a detailed description of the procedure, see Blumenfeld (2010). The examiner is watching for asymmetry in the patient's visual fields. Assuming there is no other plausible explanation (e.g., glaucoma), asymmetry in the visual fields may signify lesions at various points in the visual system. As a general rule, lesions in the optic nerve result in ipsilateral blindness, lesions in the optic chiasm result in bitemporal hemianopia, whereas lesions to the entire optic tract result in homonymous hemianopia. Quadrantic hemianopia usually results from contralateral damage to the optic radiations in the temporal and parietal lobes. For a more in-depth discussion on visual field defects, see Afifi and Bergman (2005). The examiner should also watch for stimulus-bound behavior manifested by the patient being unable to maintain his or her gaze on the examiner's nose and instead being pulled to look at the examiner's pen or hand. Sometimes the stimulus-bound behavior is so prominent that it becomes nearly impossible to assess visual fields.

2. DOUBLE SIMULTANEOUS VISUAL STIMULATION

The procedure to check for visual extinctions is similar to that for assessing tactile extinctions. The examiner asks the patient to fixate his or her gaze on the examiner's face while the examiner positions his or her hands at the edges of the patient's visual fields. The examiner then stimulates each visual field separately by wiggling his or her fingers, followed by bilateral simultaneous stimulation. The patient is directed to identify by saying or pointing to the hand that is wiggling. As with basic visual field testing, double simultaneous visual stimulation should be done bilaterally and in the four visual quadrants. For example, to test for extinctions in the upper visual quadrants, the examiner may position his or her hands in both visual quadrants and wiggle his or her fingers on one side at a time, followed by bilateral stimulation. It is important to alternate the pattern of stimulation between hemifields and quandrants, so that it does not become predictable for the

patient. The examiner can use the habituation procedure described in the previous section to assess visual extinctions. Although it occurs less commonly than with tactile extinctions, we have observed bilateral stimulus-bound visual extinctions.

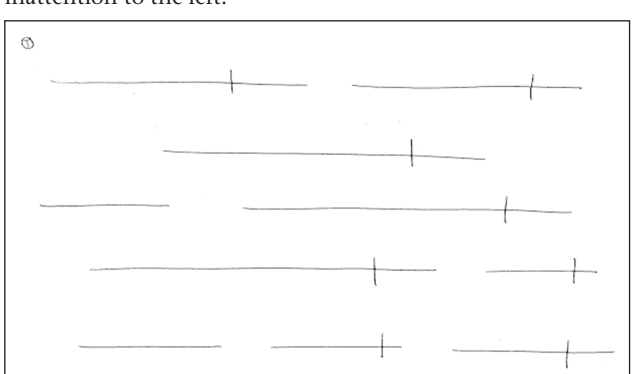
3. LINE BISECTION

To assess for hemispatial inattention or neglect, examiners can do a simple line bisection task (Butter, Mark, & Heilman, 1988; Schenkenberg, Bradford, & Ajax, 1980) in which multiple lines of different lengths are drawn on a piece of paper and the examinee is asked to bisect the lines. Typically, the paper is held in landscape orientation and lines of varying lengths are drawn symmetrically on both sides of the page. If the bisecting line is consistently shifted to one side, this suggests inattention and a contralateral lesion, typically in the parietal or occipital lobe (see Figure 2.3).

4. VISUAL CONSTRUCTION

Examiners can perform an assessment of basic visual–constructional skills by asking patients to copy designs of varying difficulty. Examples of designs include a Greek cross, the overlapping pentagons from the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), a cube, or a clock, depending on the patient's performance and depth of the examination. We prefer to initially use the Greek cross to start, as an easier design allows the examiner to determine whether the patient's basic visual–perceptual skills are

Figure 2.3. Line bisection demonstrating hemispatial inattention to the left.



preserved. If the patient's copy is ambiguous or the examiner suspects a visual–spatial integration deficit, presentation of other designs, such as cube or clock drawing, is warranted. When an examinee is drawing the cross and other designs, the examiner should watch not only for poor visual-constructional skills, such as segmentation or drawing left to right, but also for indications of hemispatial inattention (see Figure 2.4). In addition, some patients may draw their design on top of the original, thus exhibiting stimulus-bound behavior, or they may perseverate and draw multiple copies of the design (see Figure 2.5).

Deficits in visual construction are not easily localized and can result from a wide range of conditions with both focal and more widespread pathology. Assuming that a motor deficit impairing constructional abilities is excluded, close observation of the patient's approach to copying designs can reveal information about which process may be at the core of disrupted visual construction. These processes may include visual perception, spatial integration deficits, and organizational and attentional problems. Beginning with simple

Figure 2.4. The top designs are illustrations by the examiner. Design A: Cross copy of a patient with a left occipital-temporal glioma. Design B: Cross copy of a patient with a right fronto-parietal glioblastoma (notice the lacking left side of the design, suggesting neglect).

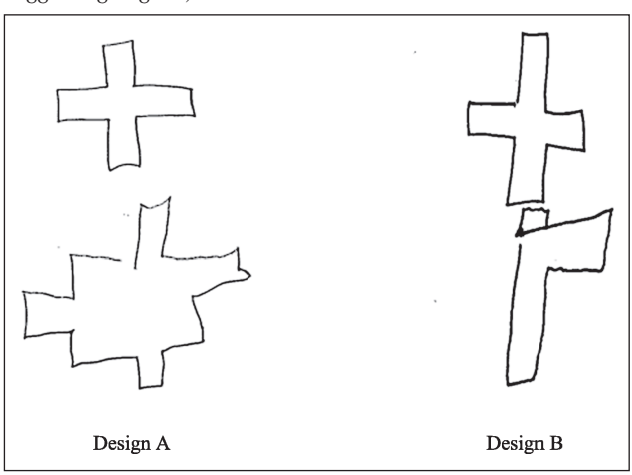
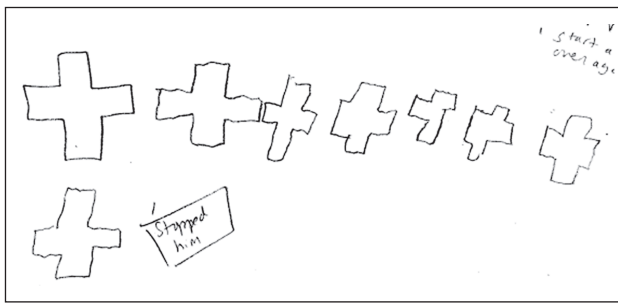


Figure 2.5. Perseverations of the Greek cross copy (the first cross is the examiner's example).



designs and increasing task difficulty helps to differentiate some of these processes. With more complex designs, the examiner may wish to look for right versus left hemisphere signs. For example, constructions lacking in details and grasping mainly the gestalt of the design can be associated with left hemisphere dysfunction, whereas detailed but slavish and disorganized constructions are typically associated with right hemisphere damage (Farah & Epstein, 2012).

5. BODY SCHEMA DISTURBANCES

For a more in-depth investigation of perception and spatial skills, examiners may evaluate for the presence of finger agnosia (Reitan & Wolfson, 1993) and agraphesthesia. *Finger agnosia* refers to difficulty with finger localization. The phenomenon is typically thought of as a disruption in body schema associated with left parietooccipital dysfunction. It has been observed in people with focal lesions as well as dementia, aphasia, and visuospatial deficits (Denburg & Tranel, 2012), but it can also be a marker for abnormal development. In-depth evaluation of finger agnosia can involve several levels of complexity (Benton et al., 1994). For the purposes of the neurobehavioral examination, we use the procedure of having the patients put their hands palm down on the table and assign a number one through five to each finger. The patients then close their eyes, and the examiners lightly touch the dorsal surface of their fingers one at a time, asking the patients to say the number of the finger that was touched. The procedure is performed bilaterally. *Agraphesthesia*, another task classically associated with dysfunction in the left parietal lobe, is defined as difficulty with perception of

figures drawn on the skin (Bender, Stacy, & Cohen, 1982). The task is usually performed by asking patients to close their eyes while the examiner draws a letter or a number on the ventral or dorsal surface of their hand and asks the patients to identify it. Bender et al. (1982) found that all patients who had impaired perception of directional stimulation also had agraphesthesia. The condition has been frequently reported in individuals with corticobasal degeneration in association with unilateral apraxia (Drago, Foster, Edward, Wargovich, & Heilman, 2010).

F. Language

Language screening should consist of assessing various aspects of language that follow the typical behavioral neurological assessment for aphasia (Benson, 1993). These aspects include observation of spontaneous speech, measures of auditory comprehension, naming, repetition, reading, and writing. The measures used to assess different areas of language have been outlined in the widely used aphasia assessments (e.g., Boston Diagnostic Aphasia Examination [BDAE]; Goodglass & Kaplan, 1983). For the purpose of the neurobehavioral examination, an abbreviated assessment of each domain may be sufficient. As with most measures, if a difficulty is observed in one domain, the examiner should investigate it further by varying the demands of the task and providing cues when necessary to assess the extent and nature of the difficulty. For example, to assess auditory comprehension, the examiner could use commands of varying difficulty (e.g., "Point to the ceiling," "Point to the ceiling after you point to the door"). Examiners tend to start with the most complex command that includes three elements with a conditional clause and right–left crossing ("With your right hand, touch your nose after you touch your left ear") because if patients can follow these types of commands, examiners can easily assume comprehension is at least relatively preserved. If an error is made, we back up to three-step conditional midline commands ("With your left hand, touch your nose after you touch your chin"). Examiners will continue to simplify the command until it is a single step and then shift over to items from Complex Ideational Material on the BDAE (e.g., "Do two pounds of flour weigh more than one?" "Is a hammer good for cutting wood?") until a base level of auditory comprehension can be determined. As a general rule, deficits in auditory comprehension are typically associated with posterior superior temporal lobe lesions. Similarly, to assess repetition, the examiner may ask the patient to repeat phrases or sentences. It is useful to start with a phrase of medium difficulty and subsequently provide more or less complex material based on the patient's performance (e.g., begin with "1776"

and vary the complexity to easier items, such as "purple" and "It's six o'clock," to more complex items, such as "The spy fled to Greece" or "The Chinese fan had a rare emerald"). The BDAE has many good items that are sensitive to these deficits with repetition. Deficits in repetition are typically associated with the disruption of the arcuate fasciculus, which is a white matter tract connecting posterior and anterior language areas. To assess naming, the examiner may point to different items in the room. The items should vary in difficulty and frequency of use (e.g., glasses, thermostat). Localization of naming deficits is more complex but typically includes anterior temporal or posterior inferior temporal regions. Reading can be assessed by asking the patient to read out loud signs in the room or an excerpt from a nearby newspaper or magazine. Finally, writing can be assessed by asking the patient to write any spontaneous sentence. If this is unsuccessful, the examiner can ask the patient to write letters to dictation and copy letters or a sentence to further define the nature of the deficit. Reading and writing deficits are typically associated with dysfunction in the posterior temporal–occipital-parietal areas such as the occipital lobe, including the splenium of the corpus callosum for reading and the angular gyrus for writing. As a guideline, in typically organized brains, language deficits result from left hemisphere dysfunction. It is important to highlight that this description of the aphasia examination and interpretation of the results is relatively brief and simplified. It is meant to be used as a screen. It will allow the examiner to gain a basic understanding of the patient's language skills and help with localization. For a more detailed and nuanced guidance on the aphasia examination and interpretation of the findings, please refer to the previously mentioned chapter on aphasia by Benson (1993).

G. Attention and Working Memory

Attention and working memory are important areas to assess because they underlie other cognitive abilities. There are a variety of attention and working memory tasks to choose from or modify for the use in the neurobehavioral examination. Although these tasks may be derived from standardized measures, the examiner can choose parts of a task for the neurobehavioral examination instead of administering the whole task to arrive at a score. For example, the examiner could pick several items from the Wechsler Adult Intelligence Scale—Fourth Edition (Wechsler, 2008) Digit Span subtest or use the spelling forward and backward method from the MMSE. Additional useful measures of attention and working memory are items from the Mental Control subtest of the Wechsler Memory Scale—Third Edition (Wechsler, 1997). For example, we often begin by asking the

patient to recite months of the year forward and backward. Although most patients will be able to recite months in forward order without significant difficulty, reciting months backwards is usually much more effortful for patients with deficits in attention and working memory. Common indications of a deficit include skipping months, self-corrections, long response times, or loss of set by reverting to months forward. If recitation of months proves to be too difficult, the examiner could simplify the task by asking the patient to recite days of the week forward and backward. If the lesion is localized to one hemisphere, it may be useful to evaluate whether the patient has lateralized attentional difficulties in verbal versus nonverbal domains. For this, the examiner could use tasks suggested by Edith Kaplan as part of her original modification of the Wechsler Memory Scale (Milberg, Hebben, & Kaplan, 1996). These tasks include asking the patient to say the letters of the alphabet that rhyme with "tree" or "key" (e.g., b, c, d) and those that have a curve when printed as a capital letter. If one is significantly more challenging than the other, this suggests a domain-specific deficit, enhancing lateralization to the left (greater difficulty with rhyming) or the right hemisphere (greater difficulty with curved letter).

H. Memory

The neurobehavioral exam should include a brief memory screening, unless patients are undergoing a full neuropsychological evaluation. This screening can be done simply by giving patients three words to remember (e.g., "apple, table, penny"; "car, tree, bed"), having patients repeat the words to ensure registration, and asking them to recall the words several minutes later. Although this can be done by another professional, neuropsychologists have a distinct set of skills to explore the nature of the memory impairment if it exists. For example, if after 5 minutes the patient can spontaneously recall only one of three words, the neuropsychologist can devise a cuing-and-recognition procedure. For example, if the patient could not remember the word *table*, the examiner could prompt by providing a semantic cue: It was a piece of furniture. If the patient provides an incorrect response or no response, the examiner can provide multiple choices, such as *couch*, *table*, or *chair*, or a forced choice, such as *table* or *chair*. This test will help determine in which part of the memory process (encoding, consolidation, or recognition) the deficit may lie. It is possible to give more words to challenge the memory capacity. It is also advisable to ask individuals to recall the words two or three times during the examination to establish whether they are able to benefit from repetition and whether they consolidate the information. Research indicates that the recall of only one of three words after 5 to 10 minutes

is indicative of a memory deficit for individuals of all ages. Recalling two words is also likely indicative of a memory impairment, particularly for middle-aged and younger individuals (Lezak, Howieson, Bigler, & Tranel, 2012). It is important to mention that the choice of the words used by examiners can be a complex decision, as different dimensions need to be taken into account. These dimensions include but are not limited to the words' frequency, level of abstractness, familiarity, and emotional salience (see Lezak et al., 2012, for a discussion of this issue). If examiners are interested in testing visual memory, an easy way to do this is to ask patients to recall the designs the examiners had them draw during repetitive drawings and visual-constructional evaluation (e.g., loops, ramparts, cross, cube).

II. CONCLUSION: INTEGRATION WITH THE NEUROPSYCHOLOGICAL EVALUATION

We have provided a basic background, procedural guidance, and scientific support for the neurobehavioral examination. It is important to highlight that only the basic examination was discussed, and examiners should feel free to individualize the procedures to each patient and explore areas in more depth if necessary. Also important is creating conditions that allow patients to show underlying pathology, which means reducing structure and direction of the evaluation and carefully observing the patient's behavior.

We use an abbreviated version of the neurobehavioral examination with most patients referred for neuropsychological evaluation. If patients are to complete a full formal evaluation, testing of constructional skills, attention, and memory may be unnecessary because these areas will be assessed in depth. However, it is useful for neuropsychologists to get a brief sense of patients by using the neurobehavioral examination, particularly if another person is administering the rest of the measures. In addition, the neurobehavioral examination is useful in generating hypotheses regarding patients' main areas of impairment that could inform and streamline the formal neuropsychological evaluation, thus increasing efficiency. The neurobehavioral exam's brevity and ease of administration lends itself well to the demands of inpatient consultations when patients may be more impaired and less able to tolerate formal testing. Finally, the neurobehavioral examination is also useful in a setting of a multidisciplinary clinic where the neuropsychologist has a limited amount of time to assess cognitive and psychological function.

The neurobehavioral examination is qualitative in nature, which is its asset and potential drawback. As many in our field move more toward standardized and normed measures, research investigating qualitative methods has declined since the times of Luria and

Kaplan. Although some aspects of the examination have been well established and validated, other tasks would benefit from additional scientific investigation and rigor. This does not necessarily mean standardizing and developing normative data because that would defeat the flexible nature and original purpose of the exam, but rather increasing knowledge about interpretation of performance characteristics. As an example, we recently retrospectively compared 113 patients with primarily psychiatric or neurological conditions referred for neuropsychological evaluations to our clinic on the number and frequency of perseverations on repetitive drawings of loops and ramparts. We found that perseverations are common in both types of patients, but older patients with neurological conditions tend to make these errors most frequently. It is unclear whether this is because of the effects of age, condition, or both. We are currently investigating this issue with a prospective study. These types of studies are relatively easy to do in a busy clinical practice and will provide insights into the nature of brain behavior relationships as intended by Dr. Luria.

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Chapter 3

Harry W. McConnell

Laboratory Testing in Neuropsychology

Laboratory tests provide useful clues in the neuropsychological evaluation of a patient. Whether they provide a pathognomonic test for a given diagnosis or are used to rule out alternative diagnoses, it is critical for the neuropsychologist to be fluent in their use and abuse in clinical neuropsychology. The neuropsychologist also needs to be aware of how alterations in these blood tests can directly affect an individual's performance in neuropsychological testing.

This chapter focuses on the role of laboratory testing in assisting the neuropsychologist in diagnosis and treatment monitoring. Although in most institutions it is the neurologist, psychiatrist, or physician who routinely orders such testing, it is also important that the neuropsychologist be aware of and actively participate in the ordering of such tests, because their results may greatly affect the results of neuropsychological testing. The neuropsychologist may also have important input into the ordering of such tests as a result of insight gained from the neuropsychological examination. For example, the neuropsychologist examining a patient with epilepsy

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must be aware of the antiepileptic drugs (AEDs) that the patient is taking, because a number of AEDs affect neuropsychological function. He or she must also be aware of the relevance of the AED blood levels and, possibly, relevant metabolites (e.g., 10,11-epoxide levels in patients taking carbamazepine), because AED toxicity can influence the results of neuropsychological testing. Conversely, the results of cognitive impairment found on testing may be compatible with a pattern seen in AED toxicity and may thus be a reason to check laboratory parameters.

I discuss, first, the general use of some tests and then look at their use in specific psychiatric presentations. The techniques discussed in this chapter focus primarily on tests of blood and other bodily fluids, as well as electroencephalography (EEG). Neuroimaging is not covered here; see Chapter 4 for a thorough discussion of neuroimaging techniques.

I. BLOOD TESTS

A. Hematologic Tests

The main tests to be looked at with respect to neuropsychology are the complete blood count (CBC) and erythrocyte sedimentation rate. The CBC consists of the red blood cell (RBC), white blood cell (WBC), and platelet counts, as well as the WBC differential (which has to be ordered separately in many laboratories), and the hemoglobin, hematocrit, RBC indices (e.g., mean corpuscular volume; see Table 3.1), and peripheral blood smear. These tests are useful for (a) detecting anemia, polycythemia, infection, or an inflammatory state that might present with an alteration of mental state and (b) monitoring for possible toxic effects of medications (e.g., carbamazepine, clozapine), which can cause bone marrow toxicity and thus may affect these indices. Routine measurement of the WBCs is mandatory in patients taking clozapine. Regular checking of platelets is also indicated in patients on sodium valproate.

Other hematologic tests used in neuropsychology include tests for folate and vitamin B12 (deficiency of which may cause marked mental state changes even in the absence of anemia) and of ferritin and total iron-binding capacity, which are all of use in the routine evaluation of anemia. These can also be affected by medications (e.g., valproate, carbamazepine, phenytoin) and should routinely be supplemented if these tests are not checked regularly. Coagulation tests are useful in evaluating liver disease and in monitoring anticoagulation therapy. These tests are outlined in Table 3.1.

Table 3.1. Hematological Tests of Relevance in Neuropsychology

Test	Clinical relevance
WBC count and differential	For evaluating the possibility of (a) infectious diseases, (b) leukemia, and (c) leukopenia from psychotropic medications; WBC differential is important for evaluating abnormality of WBC, characterizing components of WBC
RBC count	Important for evaluating anemia and polycythemia
Hemoglobin	Important for evaluating anemia
Hematocrit	Important for screening, follow-up, and evaluation of anemia and polycythemia
Mean corpuscular volume	Average volume of an RBC; useful in establishing whether an anemia is macrocytic (i.e., increased, such as in alcoholism and folate or B12 deficiency) or microcytic (i.e., decreased, such as in iron deficiency anemia)
Mean corpuscular hemoglobin concentration	Measured in grams/liter of hemoglobin; similar to mean corpuscular hemoglobin in evaluating anemia
Red cell distribution width	For evaluating whether an anemia is a combination of microcytic and macrocytic anemias
Peripheral blood smear	For abnormal RBCs, platelets, and WBCs such as atypical lymphocytes seen in mononucleosis, hypersegmented neutrophils seen in folate and B12 deficiency, and abnormal RBCs such as in sickle cell disease
Reticulocyte count	Indicative of RBC production and, hence, bone marrow activity; increased in anemia due to blood loss/hemolysis; decreased in anemias due to impairment of RBC maturation (e.g., folate, B12, iron deficiency anemias)

(continued)

Table 3.1. Hematological Tests of Relevance in Neuropsychology *(Continued)*

Test	Clinical relevance
Platelets	May be decreased due to drugs (e.g., valproate, clozapine, phenothiazines) or medical illness, either on its own or along with other cell lines (pancytopenia)
Erythrocyte sedimentation rate	Index of inflammation; elevated in infectious, neoplastic, and inflammatory illness (e.g., vasculitis, lupus)
Coagulation tests	May be elevated in liver disease; prothrombin time, international normalized ratio to monitor warfarin therapy; partial thromboplastin time and activated partial thromboplastin time for heparin therapy
Serum folate and vitamin B12 levels	Screen for deficiency, with or without anemia in psychiatric or neurological problems; deficiency may be due to impaired absorption or intake, medication effects (e.g., antiepileptic drugs); Schilling test, antiparietal cell antibodies and serum intrinsic factor used to evaluate B12 deficiency in pernicious anemia; monitor both B12 and folate as treatment with folate alone may reverse hematological abnormalities (macrocytic anemia) without reversal of neurological deficits; RBC folate is more indicative of overall status than are serum levels
Serum iron	Used to evaluate iron deficiency anemia along with total iron-binding capacity and ferritin levels

Note. WBC = white blood count; RBC = red blood count.

B. Endocrinologic Tests

Disturbances of endocrine function may present with virtually any type of mental state change. Table 3.2 summarizes the main endocrinologic tests used in evaluating mental state changes. The most important of these is the testing of thyroid status. This should be tested in every patient presenting with psychiatric illness for the

Table 3.2. Endocrinologic Tests of Use in Neuropsychology

Test	Clinical relevance
Thyroid function tests	Thyroid-stimulating hormone is best screening test; T3, T4, reverse T3, T3 resin uptake, free T4, free thyroxine index, and antithyroglobulin antibodies and microsomal antibodies are also useful in the evaluation of thyroid illness; both hypothyroidism and hyperthyroidism may present with psychiatric illness including depression, hypomania, cognitive changes, personality changes, anxiety, delirium, and psychosis. Improvement in mental state often lags behind improvement in biochemical parameters; thyroid testing should also be done to evaluate possible medication-induced thyroid disease (e.g., carbamazepine, lithium)
Plasma cortisol level	Useful in assessment of adrenal function, especially in evaluation of Addison's disease (low cortisol) and Cushing's disease (high cortisol), both of which frequently present with mental status changes
Dexamethasone suppression test	Measurement of serum cortisol checked at specific times prior to and after the administration of 1 mg of dexamethasone, thought by some to be a biological marker for depression; its only recognized clinical indication is in differentiating between the different causes of hypercortisolemia

(continued)

Table 3.2. Endocrinologic Tests of Use in Neuropsychology *(Continued)*

Test	Clinical relevance
Prolactin level	Used to evaluate patients on antipsychotics with galactorrhea or to evaluate compliance because antipsychotics characteristically increase prolactin; of limited use in evaluating NESLEs if psychotropics are controlled for and if sample is obtained within 20 min of a seizure; a normal value, however, should not be interpreted as representing a NESLE, because there may not be a rise in levels in seizures related to epilepsy; a clear rise in baseline within 20 minutes of a seizure is useful as an indication of epilepsy; exercise, increased muscular activity and intramuscular injections can produce false positive tests
Plasma catecholamine levels	Plasma epinephrine and norepinephrine levels are useful in evaluating pheochromocytoma, which may present with paroxysmal anxiety or other mental state changes
Parathyroid hormone level	Useful in evaluating mental state changes related to hypo- or hypercalcemia or related to changes in phosphorous levels; sometimes occurs after thyroid surgery
Insulin and C-peptide levels	Useful in the evaluation of paroxysmal hypoglycemia to rule out insulinoma, a rare tumor that may present with paroxysmal anxiety or other mental state changes

Note. T3 = serum triiodothyronine; T4 = thyroxine; NESLEs = nonepileptic seizure-like events.

first time, because thyroid disorder is an important and common reversible cause of psychiatric illness, presenting as depression, psychosis, dementia, or essentially any change in mental state. It is critical to be aware of the different thyroid function tests available and their meanings with respect to a given patient, because this is one of the most common causes of neuropsychological impairment and psychiatric presentation from a specific endocrinologic cause. Both hypothyroidism and hyperthyroidism can present with mental state changes, including depression, psychosis, and cognitive impairment. Treating the underlying thyroid disorder is critical for recovery, but these symptoms may persist for some time after a patient has been medically treated and is euthyroid. Addison's and Cushing's diseases may cause depression, mania, psychosis, anorexia, and other mental state changes. Endocrine disorders may be a manifestation of an underlying genetic or autoimmune disorder (e.g., polyglandular autoimmune syndromes) or paraneoplastic syndromes.

C. Biochemical and Immunologic Tests

Disturbances of electrolytes are common in psychiatric patients either as a presenting cause of mental status change (e.g., delirium in hyponatremia) or as secondary to the disease (e.g., hypokalemia in bulimic patients, related to bingeing) or its treatment (e.g., hyponatremia with carbamazepine). Liver and renal disease may also be a primary cause of presentation (e.g., hepatic or uremic encephalopathy) or, alternatively, secondary to the primary illness (e.g., liver failure in alcoholism) or its treatment (e.g., liver dysfunction secondary to use of AEDs). The serum glucose may give valuable information in cases of suspected diabetes mellitus or hypoglycemia presenting with mental status changes. All these tests, outlined in Table 3.3, can be quickly obtained (often within a matter of minutes if requested urgently), are inexpensive, and provide valuable routine laboratory screening and follow-up information in psychiatric populations. The rest of the tests discussed in Table 3.3 are commonly obtained as well in a neuropsychiatric population, but they are generally reserved for more specific clinical situations rather than used for general screening purposes.

The interested reader is referred to the review of Jacobson (2011).

II. CEREBROSPINAL FLUID TESTS

The cerebrospinal fluid (CSF) is a valuable adjunct to diagnosis in specific clinical situations. It offers little information in the setting of routine screening of general psychiatric or neurological populations. The CSF bathes the entire central nervous system (CNS) and thus has

Table 3.3. Biochemical and Immunologic Evaluation Relevant to Neuropsychology

Test	Clinical relevance
Electrolytes	Sodium, potassium, chloride, and bicarbonate are useful tests in psychiatric illness and should also be monitored in patients on psychotropics (especially carbamazepine and antidepressants), which may cause hyponatremia; hyponatremia is also seen in medical illnesses and in SIADH and psychogenic polydipsia; hypokalemia is common in people with bulimia and anorexia related to laxative and diuretic abuse and to bingeing
Liver function tests	Useful in psychiatric patients; also should be monitored in patients on psychotropics, which may affect liver function (especially antiepileptic drugs); includes alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, GGT, and lactate dehydrogenase, which has five isoenzymes and may be elevated in other medical conditions as well; GGT is the most sensitive of these; bilirubin (total, direct, and indirect) is useful in evaluation of hepatobiliary disease and hemolytic anemia and is ordered separately in some laboratories
Renal function tests	BUN and creatinine are elevated in renal failure; should be monitored in patients on lithium, gabapentin, levetiracetam and amantadine; electrolytes also frequently abnormal in renal failure, especially hyperkalemia; BUN also elevated in dehydration
Amylase and lipase levels	Used to evaluate pancreatitis and pancreatic carcinoma; should be screened in patients on valproate with gastrointestinal symptoms; because amylase is also elevated in disease of the salivary glands, monitor serum lipase levels as well (more specific to pancreatic abnormalities); amylase levels elevated in patients with bulimia may be used to monitor compliance concerning binge behaviors

Table 3.3. Biochemical and Immunologic Evaluation Relevant to Neuropsychology *(Continued)*

Test	Clinical relevance
Glucose level	Important in evaluating the possibility of diabetes mellitus or hypoglycemia, which has many causes and may present with mental state changes, including delirium and psychosis
CPK level	Useful in evaluating possible neuroleptic malignant syndrome, a severe toxic reaction to antipsychotic medications; elevated in muscle injury, after exercise or intramuscular injections and from muscle disease; CPK isoenzyme MM is used to evaluate skeletal muscle elevations, and MB fraction used to evaluate patients with suspected myocardial infarction.
Copper and ceruloplasmin levels	Used to diagnose and evaluate Wilson's disease, an inherited alteration in copper metabolism that presents with personality change, cognitive and affective symptoms, psychosis, and movement disorder, usually in adolescents and young adults
Porphyrins	Porphobilinogen, aminolevulinic acid, and other porphyrins and metabolites are used to diagnose porphyria, an inherited metabolic disorder that can present with intermittent psychosis, seizures, and other neuropsychiatric manifestations
LE prep	Used along with other tests, including antinuclear antibodies, anti-dsDNA antibodies, lupus anticoagulant, and complement levels, in the diagnosis of systemic LE, which may present with depression, delirium, psychosis, or dementia; phenothiazines, among other drugs, may cause false positive results

(continued)

Table 3.3. Biochemical and Immunologic Evaluation Relevant to Neuropsychology *(Continued)*

Test	Clinical relevance
RBC transketolase level	Test for the diagnosis of WE; WE is a medical emergency, commonly occurring in alcoholics (but also in other groups) deficient in thiamine; usually presenting with mental status changes; sometimes associated with ophthalmoplegia, ataxia, or both; because transketolase and thiamine levels take days or weeks to obtain, WE should be diagnosed and treated on clinical grounds in the emergency room, with the tests as confirmatory; glucose should not be given until parenteral thiamine and other B vitamins have been administered
Rapid plasma reagin test	Screening test for syphilis; also used is the venereal disease research laboratories test for screening; important screening test because neurosyphilis presents with many neurological and psychiatric symptoms
HIV antibody testing	Screening test for HIV infection, which has been termed the "great masquerader" because it can cause so many different neurological and psychiatric symptoms and thus mimic many syndromes; pre- and posttest counseling must be given to the individual, and consent must be obtained
Toxicology screens	Multiple drugs can be screened for at once; useful for suspected drug abuse and for suspected overdoses of an unknown substance; specific drugs may also be requested
Drug levels	Quantitative values with reference range of therapeutic drugs; in the case of psychotropics, they are particularly useful in assessment of compliance and in patients with a poor response to standard doses; reference ranges for lithium, clozapine and for the standard AEDs, e.g. carbamaezpine, phenytoin may be more useful in guiding dosage but should not be interpreted apart from the individual's response and tolerance of the drug

Table 3.3. Biochemical and Immunologic Evaluation Relevant to Neuropsychology *(Continued)*

Test	Clinical relevance
Heavy metal screens	Many neuropsychiatric symptoms have been associated with lead, mercury, manganese, arsenic, and aluminum poisoning; these should be tested if a patient with psychiatric presentation has any suggestion of a history of exposure to them

Note. SIADH = syndrome of inappropriate antidiuretic hormone; GGT = gamma-glutamyl transaminase; BUN = blood urea nitrogen; CPK = creatinine phosphokinase; LE = lupus erythematosus; WE = Wernicke's encephalopathy; RBC = red blood cell; AED = antiepileptic drugs.

the potential of offering a unique window into the biochemistry of various neuropsychiatric disorders. It is obtained by means of lumbar puncture (LP) for analysis; a small needle is inserted at the level of approximately L3–L4.

The CSF is made up primarily of water and has been called a "modified tap water"; its study in schizophrenia has been likened to the augur's examination of animal entrails. Although it is true that 99% of the CSF composition is water and that the many hundreds of studies looking at neurotransmitters and other markers in schizophrenia have not to date produced any useful clinical test, the remaining 1% of its composition has the potential to provide vast amounts of information to the clinician.

Although it has been more than a century since the first LP, the routine clinical tests performed on the CSF have not changed from the first one. Color, pressure, cell count, protein, and glucose levels are measured routinely with every specimen and together give the *CSF profile*, indicating more specific diagnoses. In bacterial meningitis, in which the LP is most useful, increases in pressure, WBC count, and protein are seen, as well as a decrease in glucose. The WBC count is usually greater than 1,000 per cubic millimeter with a predominance of polymorphonuclear cells. In viral meningitis, there is predominantly monocytic CSF pleocytosis with normal glucose levels and modest elevations in protein. Fungal and tuberculous meningitis are characterized by a predominant lymphocytic pleocytosis with increased protein and decreased glucose levels. The various causes of infection of the CNS can be differentiated by specific staining techniques and cultures along with measurement of antibodies, antigens, or both; other immunologic tests; and the use of the newer

polymerase chain reaction. In suspected neurosyphilis, the CSF profile is nonspecific, but the CSF venereal disease research laboratory is a specific test used for making the diagnosis.

Apart from infections, CSF finds its greatest use in the evaluation of suspected paraneoplastic conditions, demyelinating disease, especially multiple sclerosis and acute and chronic inflammatory polyradiculoneuropathies. Examination of the CSF is indicated in acute mental status changes when an infectious or other neurological cause is suspected and neuroimaging has ruled out the possibility of increased intracranial pressure. LP is indicated in many cases of delirium and dementia but should not be done as a routine screening procedure in psychiatric patients. Its yield is low, and it should only be performed for the above specific indications. In the case of suspected meningitis or encephalitis, it can be an essential and potentially life-saving test, guiding both diagnosis and treatment.

A. Contraindications

LP is contraindicated in the following circumstances:

1. if there is suspicion of increased intracranial pressure with a mass lesion or ventricular obstruction—in such instances, neuroimaging should always be obtained first;
2. in the presence of complete spinal subarachnoid block;
3. in the presence of significant coagulation defects; and
4. if there is evidence of local infection at the site of the LP.

In the case of known bacteremia, one should also be extra careful with LP because it has been associated with the occurrence of secondary meningitis.

B. Indications

Currently, the major indication for LP in neurology and psychiatry is to exclude CNS infection. Although many hundreds of studies have been done in psychiatric patients, there is still no recognized indication clinically for the procedure in the field of psychiatry except to exclude neurological illness. However, because meningitis and encephalitis often present with mental status changes, patients with these diseases may see a psychiatrist or neuropsychologist first in the evaluation process.

1. In adults, LP is indicated in the evaluation of the following conditions:
   a. Suspected infections or postinfectious illness (bacterial, tuberculous, viral, and fungal meningitis; aseptic meningitis; infectious polyneuritis; cysticercosis; toxoplasmosis and rickettsia infections; amebic infections; neurosyphilis; Lyme borreliosis; rubella panencephali-

tis; subacute sclerosing panencephalitis; HIV and herpes simplex encephalitis; encephalitis of uncertain cause),
   b. multiple sclerosis (oligoclonal bands, IgG index, and myelin basic protein),
   c. intracranial hemorrhage (better evaluated first with neuroimaging; CSF may be diagnostic for subarachnoid hemorrhage even if neuroimaging is negative, however),
   d. meningeal malignancy (pleocytosis, protein, glucose, specific tumor markers),
   e. paraneoplastic syndromes (specific neuronal nuclear and Purkinje cell antibodies are detectable),
   f. pseudotumor cerebri (to identify increased pressure and to exclude meningitis),
   g. normal pressure hydrocephalus (may be useful to predict response to shunting),
   h. amyloid angiopathy (cystatin C, amyloid beta-protein),
   i. neurosarcoidosis (CSF angiotensin converting enzyme),
   j. evaluation of dementia,
   k. stroke (better evaluated first with neuroimaging; CSF is useful in suspected subarachnoid hemorrhage, when CNS vasculitis or septic emboli are suspected, in patients with positive syphilis or HIV serologic studies, and in young patients with unexplained strokes), and
   l. other (systemic lupus erythematosus, hepatic encephalopathy, vitamin B12 deficiency; in seizures to exclude CNS infection or bleeding, and for intrathecal therapy).
2. In children, LP is indicated in the following clinical situations:
   a. suspected meningitis (CSF changes may be less specific and initially normal),
   b. other infections (as in adults; most show nonspecific changes except for antibody titers in subacute sclerosing panencephalitis, measles, rubella, and progressive rubella panencephalitis),
   c. febrile seizures (only if clinical evidence of meningitis is present, except in infants <12 months, in whom clinical signs may be absent and CSF should be examined),
   d. intracranial hemorrhage in neonates,
   e. pseudotumor cerebri,
   f. lead encephalopathy,
   g. CNS neoplasia (as in adults; best evaluated first with neuroimaging),
   h. lysosomal storage diseases (measurement of specific glycosphingolipids), and
   i. therapeutic LP (intrathecal therapy).

The interested reader is referred to the reviews of McConnell and Bianchine (1994) and Jacobson (2011).

III. URINE TESTS

The most common test of urine used in psychiatric patients is the routine urinalysis and culture to detect infection or renal disease. The test reveals the cell count (increased with infections), the protein (increased in renal disease) and glucose (increased in diabetes mellitus) levels, as well as the specific gravity and microscopic analysis. Urine culture is often needed to establish the cause of infection and the susceptibility of the organism to various antibiotics. Detection of urine infections is important because their presence may exacerbate other changes in mental state and may, in elderly patients, even present with delirium and other acute mental state changes. The creatinine clearance test is also used sometimes in psychiatric patients when starting lithium therapy as a sensitive baseline of renal function should the question of renal impairment arise on follow-up. This is particularly important in patients with a history of renal disease. The creatinine clearance is calculated from a 24-hour urine collection using serum values as well. Estimates can be obtained through serum tests.

Other, more specific tests of urine of use in neuropsychiatry include urine toxicology (for suspected drug abuse), trimethylamine (for trimethylaminuria), porphyrin screens (for porphyria), catecholamine and metabolites (for pheochromocytoma), osmolality (for the syndrome of inappropriate antidiuretic hormone), and urine myoglobin (in suspected rhabdomyolysis, such as in neuroleptic malignant syndrome, severe electrical shock, or muscle crush injury).

The interested reader is referred to the review of Jacobson (2011).

IV. ELECTROENCEPHALOGRAPHY

EEG is a measure of electrical activity taken from surface electrodes on the scalp. In certain circumstances (e.g., in the evaluation of patients for epilepsy surgery), intracranial electrodes may also be used. Anterior temporal and sphenoidal electrodes may also be helpful in evaluating suspected complex partial seizures. Photic stimulation, sleep, and hyperventilation are all useful activation procedures. Although hundreds of EEG studies have been done in primary psychiatric illness, the abnormalities found are generally nonspecific, and the EEG is used primarily to exclude neurological illness within psychiatry (McConnell, Andrews, Binnie, & Rogers, 2003). The EEG is the one test that relates directly to attention and mental state, however, and therefore it is of particular interest to neuropsychologists.

The EEG is not clinically indicated for the general screening of psychiatric patients or for the evaluation of primary psychiatric ill-

ness, although it is of some academic interest in these conditions. During electroconvulsive therapy (ECT), EEG monitoring is useful to establish seizure duration and may also be useful in evaluation of patients prior to ECT. The EEG is also useful in suspected drug toxicity and in evaluating suspected lithium toxicity in patients who develop mental symptoms at therapeutic levels, suspected AED toxicity, and suspected intoxication from other psychotropic drugs.

The main indication for an EEG, however, is in the evaluation of suspected epilepsy. It is also useful in the evaluation of episodic behavioral disorders when epilepsy is in the differential diagnosis (e.g., atypical panic attacks, atypical paroxysmal affective or psychotic symptoms, transient cognitive impairment or inattention in children). Ambulatory or video EEG is often helpful as well in these situations; these tools provide for prolonged monitoring and for correlating the EEG findings with the clinical behavior. Sphenoidal or anterior temporal leads are used if a temporal focus is suspected. It should be noted that a normal EEG does not rule out epilepsy, nor does an abnormal EEG rule it in, and the results of an EEG must always be taken within the clinical context. Deep foci, especially frontal, may have normal surface EEG findings even ictally.

Another indication for the EEG is the evaluation of the acute confusional state. In these situations, the EEG is useful for establishing the diagnosis and following the course of delirium. In the assessment of other cognitive impairment, it is useful in the diagnosis of dementia and of cognitive impairment related to depression or to medication effects.

Long-term EEG monitoring can be very useful in patients with fluctuating or intermittent mental status changes. Ictal and postictal states can present with many psychiatric symptoms. Ambulatory and video-EEG can help elucidate whether a given behavior or symptom is ictal in nature and is an essential tool with a very high yield in a neuropsychiatric population.

EEG is indicated for a variety of other illnesses presenting with psychiatric symptoms. This is particularly so when findings in the history, mental state examination, physical examination, or laboratory tests suggest a neurological or medical basis for the patient's symptoms; examples include an unusual course of illness (unusual onset, rapid deterioration), a history of known neurological illness such as epilepsy, and atypical mental state findings or focal abnormalities on neurological examination. Table 3.4 shows the primary EEG findings in psychiatric disorders and in neurological illness presenting with psychiatric symptoms.

The interested reader is referred to the reviews of McConnell et al. (2003) and Boutras, Galderisi, Pogarell, and Riggio (2011).

Table 3.4. Primary EEG Findings in Psychiatric and Neurological Illness Presenting With Psychiatric Symptoms

Psychiatric or neurological disorder	EEG findings
Schizophrenia	Nonspecific findings; low mean alpha frequency, nonspecific findings in sleep staging
Depression	Nonspecific changes in waking EEG; sleep EEGs more useful than waking EEG; decrease in REM latency often seen, especially if delusions and depression are present; also decreases in Stages III and IV and in sleep continuity
Anxiety disorders	Nonspecific changes in anxiety disorders, often with predominant muscle artifact; although the EEG changes in panic disorder are also nonspecific, panic may also occur as an ictal phenomenon; ambulatory monitoring is helpful, especially in cases refractory to traditional treatment and atypical cases
Delirium	Severity relates to extent of slow-wave abnormality; causes include various medical and neurological conditions: toxic, metabolic, vascular, infectious, postsurgical, traumatic
Dementia	Nonspecific slowing most common; EEG relates somewhat to degree of impairment; lag behind cognitive impairment in Alzheimer's disease; focal EEG changes suggest multi-infarct dementia or NPH; changes often mild or absent in Pick's disease; characteristic triphasic complexes in CJD
Epilepsy	Ictal EEG changes useful in assessing diagnosis and location of focus; sharp and slow activity may also be seen interictally; interictal changes generally do not correlate with psychiatric symptoms; ambulatory and video-EEG monitoring often useful

Table 3.4. Primary EEG Findings in Psychiatric and Neurological Illness Presenting With Psychiatric Symptoms *(Continued)*

Psychiatric or neurological disorder	EEG findings
Tumors	Focal slowing may be seen; psychiatric presentations and EEG findings depend on location and nature of tumor
Metabolic and toxic conditions	Triphasic waves in hepatic and renal coma; nonspecific EEG abnormalities in vitamin B12 deficiency, with cognitive impairment and nonspecific slowing in hypothyroidism
Infections	Herpes encephalitis: temporal sharp complexes Diffuse slowing in encephalitis of various causes; focal or generalized slowing or paroxysmal discharges in AIDS Localized slow waves over area of abscess in localized CNS infection; EEG findings do not generally correlate with psychiatric symptoms

Note. CJD = Creutzfeldt–Jakob disease; EEG = electroencephalography; NPH = normal pressure hydrocephalus. From "The EEG in Psychiatry," by H. McConnell, C. Andrews, C. D. Binnie, and T. D. Rogers, 2003, *Clinical Neurophysiology, 2*, pp. 372, 383. Copyright 2003 by Elsevier Science. Adapted with permission.

V. USE OF TESTING IN SPECIFIC PSYCHIATRIC PRESENTATIONS

Laboratory testing must always be considered within the context of the clinical presentation. The appropriate ordering of tests depends on an accurate assessment of each individual presentation. Some of the most difficult clinical evaluations in neuropsychology are the evaluation of dementia, atypical affective disorder, and atypical psychosis. Exhibits 3.1 and 3.2 show the laboratory evaluation of these clinical conditions, which must be individualized depending on the

Exhibit 3.1. Laboratory Evaluation of Dementia

Assessment of dementia in elderly patients
Blood tests:
CBC, ESR, electrolytes, glucose, calcium and phosphorus, TSH, serum B12, RBC folate, RPR
Neuroimaging:
MRI
Systemic tests:
Chest X ray, ECG, urinalysis
Optional tests:
Lumbar puncture
EEG
SPECT
Antiphospholipid antibodies
HIV testing
Toxicology screen
Heavy metal screening

Assessment of dementia in children and young adults
(Preceding tests as in older adults)
Blood tests:
Serum cholestanol (cerebrotendinous xanthomatosis)
Serum copper and ceruloplasmin (Wilson's disease)
Serum HIV antibodies (AIDS dementia)
Serum very long chain fatty acids (adrenoleukodystrophy)
Serum lactate and pyruvate levels (mitochondrial encephalopathies)
WBC arylsulfatase A (metachromatic leukodystrophy)
WBC galactocerebroside beta galactosidase (Krabbe disease)
WBC sphingomyelinase (Niemann–Pick disease)
WBC Gm1 beta-galactosidase (GM1 gangliosidosis)
WBC hexosaminidase A (GM2 gangliosidosis)
WBC alpha galactosidase (Fabry's disease)
WBC alpha-*N*-acetylglucosaminidase (mucopolysaccharidosis)
Urine:
Urinary dolichols (ceroid lipofuscinosis)

Exhibit 3.1. Laboratory Evaluation of Dementia *(Continued)*

Other:
- Skin biopsy (polycystic lipomembranous osteodysplasia; pseudoxanthoma elasticum)
- Liver biopsy (Lafora's disease, Niemann–Pick disease)
- Skeletal muscle biopsy (Lafora's disease)
- Brain biopsy (ceroid lipofuscinosis)
- Hand X rays (polycystic lipomembranous osteodysplasia)
- Nerve conduction studies (neuroacanthocytosis)

Note. CBC = complete blood count; ECG = electrocardiogram; EEG = electroencephalography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; RBC = red blood count; RPR = rapid plasma reagin; SPECT = single photon emission computed tomography; TSH = thyroid-stimulating hormone. From *Neuropsychiatry and Behavioral Neurology* (p.167) by J. L. Cummings and M. R. Trimble, 1995, Washington, DC: American Psychiatric Association. Copyright 1995 by the American Psychiatric Association. Adapted with permission.

Exhibit 3.2. Laboratory Tests to Consider in the Evaluation of Atypical Psychosis or Affective Disorder

Blood tests:
- CBC, electrolytes, glucose, renal and liver function tests, thyroid function tests, serum B12 and RBC folate, RPR, calcium and phosphorus, HIV serology in those with risk factors, ESR and ANCA if vasculitis suspected, antineuronal antibodies (including NMDA receptor antibodies) if paraneoplastic syndrome suspected.

Systemic tests:
- Chest X ray
- ECG

Urine tests:
- Urinalysis
- Urine toxicology
- Urine porphyrin screen

Neurophysiological assessment:
- EEG

Neuroimaging:
- MRI

Note. ANCA = antineutrophil cytoplasmic antibodies; CBC = complete blood count; ECG = electrocardiogram; EEG = electroencephalography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NMDA = *N*-methyl-D-aspartate; RBC = red blood cell; RPR = rapid plasma reagin.

nature of the presenting symptoms. In some instances a more detailed assessment than that noted in the table would be indicated, such as when there is a family history of a certain metabolic or degenerative disorder that may present with psychosis or affective disturbance or when there is an indication from either the history or the physical examination of other CNS disease.

Other psychiatric presentations may require a different emphasis from that noted in Exhibits 3.1 and 3.2. Although the tests in Exhibit 3.2 would be appropriate for the evaluation of atypical anxiety disorder, a history of atypical panic attacks might warrant the use of ambulatory EEG because complex partial seizures may present in this manner. The occurrence of symptoms seen commonly in seizure disorders with a temporal lobe focus would indicate further evaluation with EEG. If the history showed the finding of urine changing color, a porphyria screen may be appropriate; if a history of drug abuse were suspected, a toxicology screen would be important. If the presentation were extremely atypical with an excess of autonomic signs, such as hypertension, associated with episodes of behavioral disturbance, the clinician should consider measuring serum and urine catecholamines and metabolites to evaluate for possible pheochromocytoma, a rare tumor that may present with such symptoms. It is clearly not practical or cost-efficient (or clinically necessary), however, to screen every patient with panic attacks, which is one of the most common psychiatric presentations, for rare tumors. The laboratory workup must be geared toward the history and physical findings to avoid the ordering of unnecessary tests.

The age of the patient is also an important consideration in the laboratory assessment. The evaluation of dementia in children and young adults, for example, is very different from that in elderly adults with the same clinical presentation. This is because different disorders tend to start at different ages, and the evaluation should be geared toward the possible causes for the relevant age group. It would be inappropriate, for example, to screen an older adult presenting with psychosis or dementia for congenital metabolic illness that presents only in childhood. The differential diagnosis is not the same in these situations, and the laboratory evaluation should always be geared to the differential diagnosis for an individual patient rather than set protocols for every patient with a given presentation. Protocols do have a use in routine screening of psychiatric patients, such as set laboratory tests ordered on admission to a psychiatric hospital. In these instances, one can be sure that certain common treatable causes of psychiatric illness (e.g., hypothyroidism) will not be missed, but these tests should not replace a full clinical evaluation including a history and physical examination.

VI. CONCLUSION

It is important for the neuropsychologist to be aware of laboratory testing because he or she is one of the principal members of the team involved in the evaluation of the patient's mental state. Laboratory tests must be ordered and interpreted within the clinical context of the patient, with patient consent and following an appropriate history and mental status, neurological, and physical examination. This chapter has summarized the major laboratory tests of interest to the neuropsychologist. The suggested readings contain further readings concerning the specificity, sensitivity, indications, and contraindications for various laboratory tests.

It is critical for all members of the treatment team to be aware of the laboratory tests available and to be wary of third-party payer algorithms for the laboratory evaluation of neuropsychological illness. Whereas screening protocols have some use in this population, it is important to consider laboratory tests for individual patients within the context of their presenting symptoms, age, family history, past medical and psychiatric history, and clinical examination and to put this information in the context of a differential diagnosis and management plan for the patient. There have been many brilliant careers wasted looking for specific laboratory tests for primary psychiatric illness. Instead of relying on sometimes misleading laboratory tests, such a clinical diagnosis is best made on the basis of an extensive patient history. The primary role of laboratory tests in neuropsychology is to look for treatable neuropsychiatric causes of a patient's clinical presentation.

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Chapter 4

Michael W. Parsons, Stephen E. Jones, and Thomas Krewson

Structural and Functional Brain Imaging for the Neuropsychologist

The explosion of brain imaging technology over the past 2 to 3 decades has changed the face of the clinical neurosciences. Although a major role of neuropsychology during the development and history of the field has been to localize lesions, the speed, power, and sensitivity of current neuroimaging techniques have greatly reduced the relevance of neuropsychologists in that role (though not eliminated it). However, one of the revelations that has come with more sensitive imaging techniques is that there is a vast difference in presentation of patients, even when their brain lesions are quite similar on imaging studies. "Treat the patient, not the picture" is a common teaching point for neurological specialty medical doctors, and it is precisely that role that has defined the importance of comprehensive neuropsychological evaluation of the patient. Despite the lack of a perfect correspondence between brain imaging and cognitive function, it has become imperative that the neuropsychologist have at least a moderate level of familiarity with brain-imaging techniques, defining the goal of this chapter.

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Clinical Neuropsychology: A Pocket Handbook for Assessment, Third Edition, Michael W. Parsons and Thomas A. Hammeke (Editors)

I. INTEGRATION OF NEUROPSYCHOLOGICAL DATA WITH STRUCTURAL IMAGING

Neuropsychologists are in the ideal position to determine whether or not cognitive deficits correspond with an imaging finding. The phrase "Correlate with clinical findings to determine significance" is tailor made to be answered by a neuropsychological evaluation. Consider the following scenario:

> A 67-year-old woman complains of memory problems to her primary care physician, who orders a brain magnetic resonance (MR) image. The imaging has revealed a "falcine meningioma" according to the primary care physician, who has now referred the patient to your facility to be evaluated by a neurosurgeon for resection. The surgeon has reviewed the imaging, met the patient, and is now consulting you to determine whether or not her memory problems are likely to be caused by the meningioma. If so, she will recommend resection of the mass in hope of relieving the patient's cognitive symptoms. If not, they will likely opt to observe with serial imaging.

In such a situation, the appearance of the lesion on imaging can provide a wealth of data when integrated with your neuropsychological evaluation. Let us assume that the assessment reveals a marked consolidation-based memory impairment, as well as milder but significant signs of language dysfunction. The history notes a gradual and insidious decline in cognitive function over the past 3 years, and the patient has a family history of dementia in her mother. When you review the imaging, you see that the mass is about 1 cm in diameter, positioned along the interhemispheric fissure abutting the falx, near the frontal poles, with no surrounding parenchymal reaction and minimal mass effect (see Figures 4.1i–4.3i in the online resources). With this confluence of findings, you can inform the surgeon that it appears likely that the patient may be developing the early stages of a neurodegenerative disorder, possibly Alzheimer's disease (AD). Furthermore, you could suggest that resection of the mass would be unlikely to improve her cognitive symptoms. A referral to a neurologist and a course of watchful waiting may be the best plan, rather than subjecting this patient to surgery (likely unnecessary).

Other advantages of developing a familiarity and comfort with imaging include the possibility that specific imaging findings will allow you to plan and select your neuropsychological test battery to evaluate certain hypotheses. Lesion location and size will predict to

some extent the nature and severity of deficits you may expect to encounter and allow you to tailor your battery for maximum sensitivity to those issues. Furthermore, you may be able to predict consequences of intervention (e.g., surgery) more accurately if you can integrate imaging findings. For example, a patient who is a candidate for left temporal lobectomy for epilepsy may be at greater risk of memory decline if they do not have evidence of left hippocampal sclerosis on their imaging (see Chapter 9 in this volume for a full discussion of this issue). Not all imaging reports will contain this detail, particularly if not done with knowledge of the surgical issue involved.

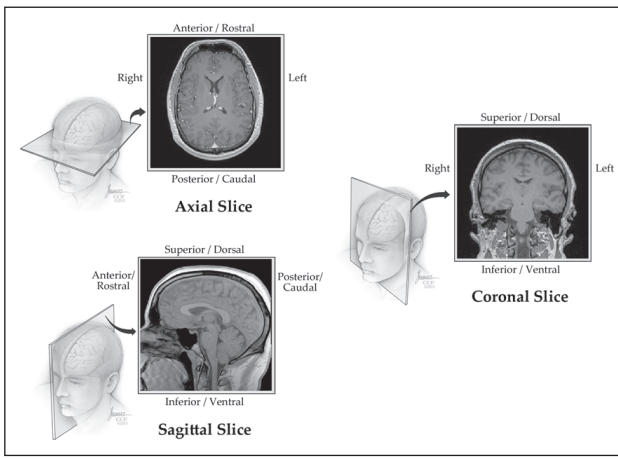
Neuroimaging is a vast subject and cannot be covered in its entirety in a chapter of this depth. This is meant to be an introduction to the topic for a neuropsychologist. It is our hope that this chapter will provide a basic understanding of the neuroimaging modalities and thereby allow the reader to become comfortable viewing images and discussing them intelligently with their colleagues. The best method for developing a comfort with neuroimaging is to make the review of neuroimaging a part of everyday clinical practice, ideally with a neuroradiologist available for consultation and education. With that goal in mind, we offer this chapter. We cover the basics of the structural imaging techniques and touch on functional imaging methodologies. Electroencephalography (EEG), which is discussed in Chapter 3, is not reviewed here, but we briefly discuss magnetoencephalography (MEG). Throughout the chapter, you will find references to the online resources (http://pubs.apa.org/books/supp/parsons) that will provide images and image sets to bring this material to life. We recommend that you sit by your computer with this book in one hand and your mouse in the other to take advantage of the image library we have compiled.

II. NEUROIMAGING: THE METHODS

A. Structural Neuroimaging Techniques

Central to brain imaging is spatial resolution and contrast sensitivity to discriminate anatomical and pathological features. As the methods have evolved over the past 4 decades, images have improved dramatically on both fronts. In addition, the imaging methods have become faster and safer. A common issue in all imaging modalities is the trade-off between image resolution, contrast (or signal to noise), and imaging time. The trade-offs become particularly acute for imaging a three-dimensional (3D) object, which then adopts the strategy of approximating a 3D "image" as a stack of 2D images. The images

Figure 4.1. Standard imaging planes and accompanying directional terms (T1-weighted magnetic resonance imaging).



are typically viewed in conventional planes (axial, coronal, sagittal; see Figure 4.1). A typical MR image has a slice thickness of 5 mm and covers an area of 24×24 cm. Each slice is discretized into an imaging matrix typically of size 256×256, thereby producing voxels (volume + pixel) with an in-plane size of almost 1×1 mm. With a slice thickness of 5 mm, each voxel actually has a skinny rectangular shape. To increase the resolution of the image, one must either increase the size of the matrix (e.g., to 512×512) or decrease slice thickness (e.g., down to 1 mm). Each time this is done (within the limits of the resolution of the technology), the brain image is divided into more and more voxels, reducing the signal-to-noise ratio (and therefore contrast) in each voxel and also increasing the acquisition time.

It is important to remember when you are looking at these spectacularly detailed images that you are not looking at the brain itself; you are seeing an image of the brain, subject to distortion, error, and insensitivity. For example, a common artifact of images known as *volume averaging* arises from the methodology described above: Tissue is imaged in predefined rectangular cubes of space, averaging together the various characteristics of the tissue within that volume. Because virtually no structures in the human body conform to that shape, the image necessarily averages together a

variety of underlying tissue types (e.g., gray matter, white matter, bone, cerebral spinal fluid [CSF]) within a single voxel, which can lead to confusing imaging characteristics. It is important not to mistake such artifacts as pathology, a skill dependent on the knowledge and experience of the image interpreter. For this reason among many others, it is important for the neuropsychologist to recognize that the material in this chapter is provided to help you become an informed consumer of imaging data, not to become a neuroradiologist!

B. Computerized Tomography

Computerized tomography (CT) scanning depends on a well-collimated beam of X rays that are incident on a patient, with transmitted X rays collected by sensitive detectors. The CT scanner rotates the X-ray source and the detector on a gantry around the patient, obtaining images at hundreds of angles, and thereafter using a computer to reconstruct a plane (or tomogram). First developed by Sir Godfrey Hounsfield, the final intensity of the image at any point is directly related to the tissue's physical density, whose scale is known as the Hounsfield unit (HU). The intensity of water was set to 0 HU and air to –1,000 HU. Typical tissue types range in intensity from about –100 HU (fat) to about 1,000 HU (cortical bone).

Although CT was invented over 40 years ago, technological improvements continue unabated. Today, CT is the mainstay examination for quick and inexpensive neuroimaging, especially because it is sensitive to many of the types of pathology that require emergent detection and management. Common examples are the rapid detection of skull fracture, intracranial bleeding, mass lesions, and acute territorial stroke. Iodine-based contrast agents can be used in CT to identify areas of breakdown in the blood–brain barrier, such as those that occur in high-grade brain lesions, infections, and inflammation. In addition, contrast combined with high-resolution imaging permits CT angiography, revealing aneurysms, clots, and other vascular diseases. Last, aside from a small but nonnegligible radiation dose, there are relatively few contraindications to CT, in distinction to magnetic resonance imaging (MRI) which has numerous contraindications, including pacemakers and other implants.

Common applications of CT include the following:

- rapid detection of damage secondary to traumatic brain injury (TBI),
- fracture (Figure 4.4i),
- identification of foreign bodies that may be metallic (Figure 4.5i),
- intracranial bleeds (subarachnoid hemorrhage, subdural hematoma; Figures 4.6i–4.9i),

- placement of intracranial electrodes (Figures 4.10i; 4.11i),
- detection of calcified lesions (Figure 4.12i),
- bony disease,
- CT perfusion and angiography, and
- when MRI is contraindicated.

C. MRI

MRI relies on a complex interplay between the magnetic moment of a proton and applied magnetic and radiofrequency (RF) forces. A thorough description of the physics of MRI is beyond the scope of this chapter and probably unnecessary for the purposes of a neuropsychologist. The interested reader can find a comprehensible description in Chapter 2 of the textbook *Functional Magnetic Resonance Imaging* by Huettel, Song, and McCarthy (2004). Briefly, MRI essentially depends on three components: a superconducting electromagnet that maintains a powerful static magnetic field, multiple gradient coils that slightly alter the static magnetic field in any direction, and powerful coils that apply strong RF power to flip a proton's magnetic moment and then record the signal when the moment returns to equilibrium. All of these features are intricately orchestrated by a computer, which also reconstructs an image.

Whereas CT scanners provide image contrast based solely on tissue density, MRI can provide numerous forms of contrast depending on the mode of operation. The two most common forms, T1-weighted (T1W) and T2-weighted (T2W) sequences, derive their contrast from the details of how magnetic moments relax to their equilibrium state. Proton density sequences provide contrast based on proton density, which does not vary much in the brain, and such sequences find their greatest use in musculoskeletal imaging. Fortunately, different types of tissue within the human body have different characteristics in terms of T1W and T2W, particularly including the brain, which provides the exquisite tissue contrast seen in neuroimaging (see Figures 4.13i through 4.18i for examples of tissue contrast in normal brain MRI; see Table 4.1 for the MRI characteristics of various tissue types and pathology).

Perhaps the most frequently referenced type of MR images are the fluid-attenuated inversion recovery images (FLAIR; Figure 4.17i). FLAIR images are created from a T2W sequence with an additional step that removes all signal emanating from watery material, such as CSF. The technique (which radiologists have nicknamed *T2 for neurologists* because of the ease with which abnormally increased concentrations tissue water can be seen) allows the areas of more subtle T2W hyperintensity to stand out in contrast to the relatively dark tissue, particularly around the pial and ventricular margins.

Table 4.1. T1 and T2 Characteristics of Tissue and Pathology in Magnetic Resonance Imaging

Tissue type/ pathology	T1 weighted	T2 weighted	Contrast agent
Fat	Bright	Bright	N/A
Bone	Dark	Dark	N/A
Air	Very dark	Very dark	N/A
Cerebrospinal fluid	Dark	Bright	N/A
Grey matter	Dark grey	Light grey	N/A
White matter	White	Dark grey	N/A
Recent infarct (Figures 4.19i–4.22i)	Abnormally dark	Abnormally light	Subtle, patchy
Old infarct (Figures 4.23i–4.27i)	Dark	Light	No
Hemorrhage (Figures 4.28i–4.36i)	Bright	Bright	No
Low-grade tumor (Figures 4.37i–4.40i)	Dark	Bright	No
High-grade tumor (Figures 4.41i–4.44i)	Dark	Bright	Yes
Multiple sclerosis plaque (Figures 4.49i–4.56i)	Dark	Bright	Acute/ subacute

Note. N/A = not applicable.

Other than suppressed CSF signal, which also increases image noise, the characteristics of FLAIR images are similar to those of T2W images.

1. DIFFUSION WEIGHTED IMAGING

Diffusion imaging is based on the sensitivity of MRI to proton motion and hence to the transport of water molecules. In simple terms, diffusion weighted imaging (DWI) takes advantage of diffusive transport of water molecules within the brain's tissues, both intracellular and extracellular. In a uniform medium such as CSF, diffusion occurs equally in any direction and is called *isotropic*. Within tissues

the diffusion is much reduced and is less isotropic. In various disease states, such as acute infarct, diffusion becomes so reduced—or restricted—that the enormous conspicuity of DWI hyperintensity has revolutionized the diagnosis of acute stroke. In particular, the apparent diffusion coefficient (ADC) within each voxel can be measured. ADC is sensitive to areas of cytotoxic edema that occur in the context of a recent infarction (within minutes to hours), the detection of which is the most important clinical use of DWI (Figures 4.21i and 4.26i).

2. DIFFUSION TENSOR IMAGING

Although to first approximation the diffusion within tissues shows various degrees of isotropy, detectable and reproducible directional differences do exist. Within a structured system, such as that created by the physical boundaries of neurons, membranes, and fiber bundles, diffusion varies in directions that reflect the underlying structure of boundaries, and the diffusion becomes *anisotropic*. By clever application of gradient fields in different directions (at least six parameters are required), a diffusion tensor can be generated, which efficiently described the orientational dependence of diffusion in every voxel. More complex imaging protocols, involving the measurement of diffusivity in many directions (e.g., 25–150+), are used to map out finer details of the directional diffusivity and are known as *high angular resolution diffusion imaging*. Using the hypothesis that the major direction of diffusivity in any voxel reflects the major underlying direction of axons or white matter tracts, one can connect paths between voxels that may reflect long-range white matter tracts, a procedure known as *tractography*, which produces familiar and fantastic images (Figure 4.65i).

3. CONTRAST AGENTS

Gadolinium is a contrast agent with paramagnetic properties that is used in MRI to identify areas of blood–brain barrier breakdown. In these regions, the contrast agent seeps through the capillary bed and into surrounding brain tissue. The magnetic properties of gadolinium make it appear brighter than normal on T1W imaging, a feature known as *contrast enhancement*. The degree to which a lesion will enhance with gadolinium administration (Table 4.1) can be affected by a number of features of the lesion, including the permeability of blood vessels in the lesion and the vascularity of the lesion, as well as details of the injection of the contrast agent itself, including the volume of agent injected and the timing of injection in relation to the particular scan being viewed. Gadolinium is most commonly used in the identification of brain tumors, vascular lesions (Figures 4.40i and 4.44i), infections and abscesses, and inflammation (e.g., newly developing plaques in multiple sclerosis; Figures 4.52i & 4.56i).

Gadolinium has also proven useful in examining important aspects of brain blood flow. In magnetic resonance angiography, the flow-sensitive characteristics of MRI are amplified to create images of the major intracranial vessels. Although this method does not have the ability to show the small vessels that can be demonstrated through conventional angiograms, it has the marked advantage of being much less invasive and not requiring any intravenous injection of contrast. The images are valuable in detecting vascular occlusions, malformations, or aneurysms. Another application of contrast enhanced MRI is perfusion imaging (Figures 4.45i & 4.48i). This technique is used to measure the rate of microscopic blood flow in the brain's tissues (in distinction to the larger vessels), based on the transient signal changes from a bolus injection of contrast. Three-dimensional maps are produced showing cerebral blood flow (CBF), cerebral blood volume (CBV), and the mean transit time. It can be used to discriminate areas of tissue with high CBV (e.g., rapidly growing brain tumor) from those with low CBV (e.g., necrosis due to radiation therapy), despite the fact that that the tissues may not be discriminable on conventional contrast-enhanced MRI.

4. MR SPECTROSCOPY

Spectroscopy is the use of the MR scanner to identify the chemical composition of tissue within a given voxel or set of voxels. Not to be confused with single photon emission computed tomography (SPECT) scanning (see the next section), MR spectroscopy can be useful in identifying the type of pathology apparent on an image. In most clinical uses, spectroscopy interrogates the chemical composition of a limited area of brain and focuses on three molecules with the highest signal and relevance to the brain: creatine (Cr), a marker of cellular metabolism, choline (Cho), an indicator of cellular membrane synthesis, and N-acetyl aspartate (NAA), a marker of neuronal density and integrity. Another molecule seen during states of local ischemia is lactate, and its presence often indicates a necrotic tumor, abscess, or metabolic disarray. The technique divides the chemical composition of the voxel into a spectrum, with the relative concentration of these molecules displayed as "peaks" on a histogram (Figure 4.66i).

D. Metabolic and Functional Neuroimaging

1. SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT measures regional cerebral blood flow (rCBF), which can be considered to be a surrogate for neuronal activity under the proper circumstances (for a thorough review of this issue, see Van Heertum,

Tikofsky, & Ichise, 2010). Technetium-99m (^{99m}Tc) is a gamma-emitting radionuclide that, when combined with hexamethylpropyleneamine oxime (HMPAO [^{99m}Tc-HMPAO]) and injected intravenously, is taken up by brain tissue in a manner proportional to CBF. Assuming a tight correlation of CBF with neuronal activity, SPECT images form functional maps of brain activity. The tracer is then contained in the cells as the ^{99m}Tc decays with a half-life of 6 hours. Perhaps the most common application of this technique is in the identification of seizure foci within the brain. If the bolus is injected immediately at the onset of the seizure, ^{99m}Tc is taken up preferentially near the focus due to hyperperfusion, which can then be conveniently scanned using SPECT a short while later. One of the advantages of SPECT imaging is the ability to radioactively label chemicals related to specific neurotransmitter systems. This technique has been used to develop radiopharmaceutical labels for the presynaptic dopamine transporter, which can be used clinically to identify dopamine abnormalities in Parkinson's disease.

2. POSITRON EMISSION TOMOGRAPHY

The imaging of cellular metabolism with 18-flourodeoxyglucose (FDG) has been of greatest clinical use in the identification of hypermetabolic tumors throughout the body. Positron emission tomography (PET) imaging has the distinct advantage of using a radiolabeled glucose analogue to directly measure cellular metabolism, as opposed to other techniques (SPECT, functional MRI), which depend on blood flow as the index of activity. The methodology depends upon a cyclotron to produce the radioactive pharmaceuticals, which are then administered intravenously. The PET camera takes advantage of the physical properties of positrons (negatively charged electrons), whose annihilation emits two characteristic gamma rays in opposite directions. Current scanners commonly conduct PET imaging and CT scanning in the same session, to allow for spatial localization of metabolic activity imaged by PET. As noted above, the most common clinical use of PET is to locate areas of malignant hypermetabolism. Within the brain, PET can be used to discriminate high-grade from low-grade neoplasms or to distinguish a high-grade neoplasm from radiation necrosis. Beyond oncology, FDG-PET is also approved by the U.S. Food and Drug Administration (FDA) as a technique for the differential diagnosis of dementia (e.g., AD vs. frontotemporal dementia; Ibach et al., 2004). The more recent development of PET radiotracers capable of labeling amyloid in the brain has been shown to be a highly sensitive and specific biomarker for AD (e.g., Mikhno et al., 2008). In patients with epilepsy, FDG-PET imaging is often used to identify regions of cerebral hypometabolism that might reflect a seizure focus in the interictal

state. When coupled with ictal SPECT, these technologies can provide precise localizing information.

Most of the studies of cognitive function that use PET imaging use a different radionuclide, ^{15}O in labeled water. This chemical is administered intravenously and provides an index of rCBF. Because of its short half-life (2 minutes, as opposed to nearly 2 hours for ^{18}F), repeated imaging sessions can be conducted in a single scanning session, allowing the research to compare rCBF during different cognitive tasks or conditions. Such studies allow for the use of "activation" tasks and have had a role in advancing cognitive neuroscience, which has now largely been eclipsed by functional MRI (see the following section).

Although many potential applications of metabolic imaging technology in other conditions have been discussed (e.g., psychiatric disorders, addiction, mild TBI), few are currently in mainstream clinical use. The interested reader is directed to Hillary and DeLuca (2007) for a thorough and thoughtful review of appropriate use of functional neuroimaging techniques in clinical populations. As a neuropsychologist, you may be asked about the ability of one or another functional imaging technique to "diagnose" a condition. Although there is some debate on the topic, claims to do so should be treated with careful empirical consideration.

3. FUNCTIONAL MAGNETIC RESONANCE IMAGING

The development of fMRI in the early 1990s has been perhaps the most influential technological advance in the field of cognitive neuroscience. Research into brain function with fMRI has shaped the thinking of the current generation of neuropsychologists and continues to be the driving force in understanding how the brain functions. To fit within the scope of this book, this discussion of fMRI will be limited to a brief description of the method and clinical applications. For neuropsychologists with an interest in the technique, *Functional Magnetic Resonance Imaging* (Huettel et al., 2004) is a good introductory text on the topic, and other books are provided in the online resources (http://pubs.apa.org/books/supp/parsons).

a. FMRI Methodology

Although a thorough discussion of fMRI physics is beyond the scope of this chapter, it is important to understand the basic underpinnings of the technique. The technique is based on an effect termed *blood oxygen level dependence* (BOLD), which refers to the fact that local neuronal activity indirectly affects the fraction of deoxygenated hemoglobin in the blood. It takes advantage of the natural MRI contrast created by the different magnetic properties of oxy- and

deoxyhemoglobin. Put simply, as neural ensembles become active, the elevation of the local field potentials cause the local entering arterioles to dilate and supply neural tissue with an overabundance of oxygenated blood within about 5 seconds of the change in neural activity. The relative concentrations of oxy- and deoxyhemoglobin in the active region change, creating a subtle change in magnetic signal (about 1% to 2%) that can be detected by the special MRI pulse sequences.

Structural MRI and fMRI scanning differ in several important ways. Whereas a high-resolution structural image is a single image in time, acquired over several minutes, fMRI scans consist of multiple images taken sequentially over time, with much lower resolution. It is useful to consider an analogy: Standard structural MRI scans are similar to early photographs from the 19th century, taking several minutes to acquire (which is why movement produces so much blurring in the image). In contrast, an fMRI scan is more like a movie, with perhaps hundreds of images taken in sequence, each of which is acquired in a small number of seconds. The rapid pace of image acquisition permits the measurement of change in BOLD fMRI signal intensity over time as the subject performs a task. However, the consequence of such rapid imaging is markedly decreased spatial resolution (e.g., larger voxel size) than is obtained in standard structural imaging (recall the discussion about trade-offs between imaging time and resolution from earlier in this chapter).

The earliest fMRI studies used very simple behavioral tasks and designs to demonstrate the viability of the technique as a measure of brain activity. The simple paradigms required participants to alternate between an active or target condition (e.g., tapping fingers, listening to words, tactile stimulation) and periods of rest. A cross-correlation method was used to identify voxels within the whole brain image that showed fluctuations in BOLD signal intensity that were temporally correlated with the stimulation (Figures 4.67i–4.69i). Although the design and analysis of fMRI paradigms has become much more complex and subtle, the basic principle of using BOLD signal changes as an index of blood flow from which one can infer brain activation remains at the core of fMRI.

b. Functional Connectivity

Low-frequency BOLD fluctuations is a newer technique that uses fMRI methodology to measure the degree to which disparate brain areas are functionally connected, which does not require the patient to perform any task. The technique takes advantage of a discovery by Biswal, Yetkin, Haughton, and Hyde (1995), which demonstrated that fMRI can measure spontaneous variations in brain

blood flow during periods of alert rest. Although these variations appear to have a different random pattern in every voxel, buried within this noise, the patterns show statistically significant correlations between regions that can be very far apart. Furthermore, the maps of these correlated regions appear to recapitulate known underlying functional relationships. For example, the bilateral motor regions show significant correlations, which have a strong known anatomic connectivity, although on opposite sides of the brain. Functional connectivity is proving to be a powerful and sensitive measure of pathology in a number of patient populations that have previously been difficult to study with other imaging methods, such as AD and mild cognitive impairment (see Supekar, Menon, Rubin, Musen, & Greicius, 2008). Disruptions in functional connectivity have been correlated with structural measures of white matter damage in patient populations (see the suggested readings list). A critical advantage of functional connectivity studies over fMRI activation tasks is that the subject or patient does not need to do anything in the scanner; the image series simply requires an alert resting state for up to 10 minutes to acquire data. Currently, the method is being used in studies of many neurologic and psychiatric disorders, including blast-related mild TBI, multiple sclerosis, chemotherapy-related cognitive problems, major depression, and others (see the suggested readings list). These studies are demonstrating meaningful relationships between connectivity measures and cognitive or emotional symptoms of the disorders. It is not unlikely that this technique will find a role as an "imaging biomarker" for certain disease processes or disorders in the near future.

c. Application of fMRI in Clinical Neuropsychology

As is noted above, the most important role of fMRI has been in the advancement of cognitive neuroscience, in which neuropsychologists have played no small role. The clinical utility of fMRI has been explored in many domains, including differential diagnosis of various neurologic and psychiatric conditions (Hillary & DeLuca, 2007), the effect of drugs on the brain, and the potential utility of fMRI as a method for detecting deception. What these studies have accomplished has been to add to the understanding of the differences in brain activity that may be associated with these conditions or symptoms. However, such studies typically compare groups of subjects with a given pathological condition with groups of unaffected individuals, and use of the technique to perform individual differential diagnosis is only beginning.

The only role for fMRI that has received approval from the U.S. FDA in the clinical care of individual patients is the use of cognitive

paradigms to identify functionally critical brain regions to assist in neurosurgical planning. Over the past 15 or more years, neuropsychologists and neuroradiologists have worked together to develop paradigms for the activation of specific brain regions that are likely to produce significant functional deficits if damaged during surgical intervention (for a review, see Parsons, Moran, & Boling, 2008). Numerous studies have demonstrated that fMRI has the capability to provide valuable information for surgical planning in the setting of epilepsy, brain tumor, and cerebrovascular conditions. Specific examples of clinically robust tasks are those that activate motor functions, language networks, and primary visual cortex (Figures 4.67i–4.69i). In order to be useful in this role, the activation paradigms must be highly replicable, simple in design, and powerful at producing activation on the BOLD images. Many examples of such tasks are currently available in the literature and have been widely propagated through imaging centers. It is not at all uncommon for cognitive activation and analysis paradigms to be included as part of the software that is purchased with MRI scanners. These "turnkey" paradigms have their limitations, but they can often be effective when used properly by neuropsychologists, neurologists, and neuroradiologists with appropriate training and experience.

Through the diligent work of a group of neuropsychologists who were involved in the development of the fMRI techniques, it is now possible for practicing clinical neuropsychologists to perform and submit professional bills for clinical application of fMRI on a par with physicians in the specialties of neuroradiology or neurology (American Psychological Association Division 40 Taskforce, 2004). Of course, in order to perform this procedure ethically, the neuropsychologist must have the appropriate training and experience. Collaborative relationships between neuropsychologists and neuroradiologists tend to produce the most effective and efficient clinical fMRI programs.

E. Magnetoencephalography

The laws of electromagnetism show how electric fields and magnetic fields are intricately related, and neuronal activity causes both. MEG is a technology with the ability to measure the magnetic field signature of cortical neuronal activity, which is parallel to the ability of scalp EEG to measure the electric field signature of neuronal activity. They view the same phenomenon—the local field potential—but they view it differently, and there are advantages and disadvantages to each. MEG has a distinct advantage over other functional imaging modalities because it directly measures neuronal activity, rather

than through a surrogate such as blood flow or metabolism, as discussed in the other methods above. In contrast to scalp EEG, MEG is able to provide superior localization of neuronal activity since magnetic fields are not dissipated through the meninges, skull, fat, and skin (unlike electric fields; see Papanicolaou, 2009, for a full discussion). Although MEG represents a significant technological advance, there remains a near-intractable problem of converting the external magnetic recordings into an internal source localization. This mathematical "inverse" problem requires considerable modeling and today remains an active area of research.

The most common clinical application of MEG is in the localization of epileptic foci. This is done by modeling abnormal interictal spikes as a magnetic source using a single dipole model, with a resulting specified location and orientation. Because it can localize magnetic dipoles below the cortical surface, MEG can complement invasive intracranial EEG using depth electrodes. The measurement of evoked magnetic fields parallels that of other stimulus-triggered activation techniques and allows the localization of cortical regions critical for the processing of specific stimuli (e.g., visual, tactile, language). These maps can be used along with other functional imaging modalities to identify lateral dominance for language function or locate critical regions of eloquent cortex near brain tumors or vascular malformations. Not only can these maps provide localizing information that can be used to guide surgical approaches to lesions, but the advantages of MEG also provide for fascinating maps that can demonstrate the temporal sequence of activation within a neural system with exquisite temporal resolution.

III. CONCLUSION

Brain imaging, once thought of as a threat to the job security of neuropsychologists (and neurologists, for that matter) has become an indispensible ally in the understanding of brain–behavior relationships. A working understanding of the various imaging modalities is critical to neuropsychologists, particularly those practicing in medical settings, neurology clinics, or neurosurgical practices. Although we have briefly surveyed the methods here, and provided images for visualization purposes, a familiarity with imaging is dependent upon diligent study of the images, the underlying neuroanatomy, and the basic principles of the imaging modalities. As neuropsychologists move into the future, productive relationships with neuroradiologists will form an essential collaboration that will enhance the neuropsychological health of our patients.

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Chapter 5

Glenn J. Larrabee

Assessment of Performance and Symptom Validity and the Diagnosis of Malingering

Neuropsychological evaluation depends on the use of tests that are valid tests of core neurobehavioral functions such as language, perceptual, and spatial skills, sensorimotor functions, attention, processing speed, verbal and visual learning and memory, intellectual and problem-solving skills, and personality and emotional functioning (Board of Directors, 2007). In this sense, *test validity* refers to adequate coverage of the construct being evaluated by the test (i.e., whether the Rey Auditory Verbal Learning test adequately measures verbal learning and memory) and whether the test predicts to external criteria in a meaningful way, such as detection of the presence or absence of cognitive deficits in a disorder such as Alzheimer's disease, or relate in a dose–response pattern to accepted criteria of severity of brain trauma, such as duration of coma. It is noteworthy that tests of abilities such as the Rey Auditory Verbal Learning Test (Rey, 1964; Schmidt, 1996) depend on the examinee giving a full effort, and tests of personality such as the Minnesota Multiphasic Personality Inventory—2 (MMPI–2; Butcher, Graham, Ben-Porath,

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Tellegen, & Kaemmer, 2001) depend on accurate endorsement of symptoms actually experienced by the examinee, in order to obtain valid measures of the examinee's actual abilities and symptom experience. This identifies a second type of validity that is distinct from test validity: the validity of an examinee's performance and symptom endorsement, which can be defined as *performance validity* and *symptom validity*, respectively. Performance validity tests (PVTs) address whether or not the test performances obtained are an accurate measure of the examinee's actual abilities, and symptom validity tests (SVTs) address whether or not the test scores on self-report instruments such as the MMPI–2 are accurate measures of the examinee's actual symptom experience. (Note that I am using *SVTs* in a way different from how this term has previously been used to identify two-alternative, forced-choice testing; see Larrabee, 2012 for this rationale, as well as for the rationale for not referring to performance validity assessment as assessment of "effort.")

Invalid examinee performance can substantially alter expected associations of neuropsychological test performance with external criteria. For example, olfactory identification was only correlated with measures of brain injury severity such as the Glasgow Coma Scale in those subjects passing a PVT (Green, Rohling, Iverson, & Gervais, 2003); California Verbal Learning Test scores did not discriminate traumatic brain injury (TBI) patients with abnormal computed tomography or MRI scans from those with normal scans until those patients failing PVTs were excluded (Green, 2007). The expected association between neuropsychological test performance and presence or absence of brain injury only was demonstrated in patients who passed PVTs (Fox, 2011).

The most common sources of invalid examinee performance or symptom endorsement are those related to strong external incentives, such as monetary gain in personal injury litigation, Social Security disability payment, or avoidance of prosecution and/or mitigation of punishment in criminal court proceedings (Mittenberg, Patton, Canyock, & Condit, 2002). Across these different contexts, the frequency of invalid performance or symptom exaggeration can be 40% to 50% or more (Larrabee, Millis, & Meyers, 2009).

I. DEFINITIONS AND CLASSIFICATION OF MALINGERING

Malingering is defined as the intentional production of false or grossly exaggerated physical or psychological symptoms that is motivated by external incentives such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or

obtaining drugs (American Psychiatric Association, 2013). Criteria have been proposed for the diagnosis of malingered neurocognitive dysfunction (MND; Slick, Sherman, & Iverson, 1999) that define MND in a manner similar to that of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM–5):* volitional exaggeration or fabrication of cognitive dysfunction for the purpose of obtaining substantial material gain, or avoiding or escaping formal duty or responsibility. Slick et al. (1999) presented multiple criteria, similar to what are used in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM–IV–TR;* American Psychiatric Association, 2000) criteria for various psychiatric disorders, including a gatekeeper criterion A, the requirement for a substantial external incentive; B criteria based on atypical performance on measures of neurocognitive ability (PVTs); C criteria based on invalid symptom report (SVTs); and D criteria, which require ruling out failure of B criteria PVTs and C criteria SVTs due to bona fide neurologic disorder (e.g., severe TBI with prolonged coma, resulting in the need for 24-hour supervised care), psychiatric disorder (e.g., poorly controlled schizophrenia), or significant developmental disorder (e.g., mental retardation requiring a supervised living setting). The Slick et al. criteria allow for probabilistic conclusions regarding the presence of malingering, including definite MND, defined by significantly worse-than-chance performance on two-alternative, forced-choice testing; probable MND, defined by failure of multiple B criteria PVTs or B criteria PVTs in association with C criteria SVTs; and possible MND, defined by failure of C criteria SVTs alone or demonstrating multiple PVT and SVT failure, but the D criteria for ruling out neurologic, psychiatric, and developmental criteria cannot be met.

The Slick et al. (1999) criteria were modified by Bianchini, Greve, and Glynn (2005) to establish diagnostic criteria for malingered pain-related disability (MPRD), including a gatekeeper requirement for a substantial external incentive (A), cognitive (neuropsychological) test performance (PVTs; C), symptom report criteria (SVTs; D), and rule-out criteria for neurologic, psychiatric, and developmental explanations for atypical performance and symptom complaint (E). Drawing on clinical examination procedures specific to evaluation of pain patients, Bianchini et al. (2005) included an additional category for results from a physical examination of the patient (criteria B; e.g., Waddell's signs for nonorganic physical examination findings; see Waddell, McCulloch, Kummel, & Venner, 1980); presence of a significant discrepancy between behavior when the examinee is aware of being observed vs. behavior when unaware of observation, with significant discrepancies referred to as "compelling inconsistencies" (e.g., observation of an examinee jogging while under video surveillance despite needing a cane to walk, with difficulty, in

the examining physician's office). Of course, there is an additional powerful external incentive for pain patients: obtaining narcotic analgesic medications.

My colleagues and I (Larrabee, Greiffenstein, Greve, & Bianchini, 2007) have described several common features of the Slick et al. (1999) MND criteria and the Bianchini et al. (2005) MPRD criteria. These include (a) the requirement for a substantial external incentive; (b) the requirement for multiple indicators of performance invalidity and/or symptom exaggeration; and (c) test performance and symptom report patterns that are atypical in nature and degree for bona fide neurologic, psychiatric, or developmental disorders. As we concluded, it is the combined improbability of findings, in the context of external incentive, without any viable alternative neurologic, psychiatric, or developmental explanation, that establishes the intent of the examinee to malinger (Larrabee et al., 2007).

II. METHODS: MEASURING PERFORMANCE AND SYMPTOM VALIDITY

PVTs and SVTs are an important part of reaching a diagnosis of malingering, but performance on these tests alone does not determine the presence of malingering. Context is key; without the presence of a substantial external incentive and the exclusion of reasonable alternative explanations of PVT and SVT failure, malingering cannot be concluded. For example, factitious disorder, wherein there is no external incentive but in which the patient deliberately feigns symptoms (SVTs) and deficits (PVTs) for taking on the role of a sick person, is distinct from malingering because there is no substantial external incentive. Failure of SVTs and PVTs in the absence of meeting other criteria for malingering remains significant, as PVT failure has been reported to reduce global measures of function such as the Overall Test Battery mean (Miller & Rohling, 2001) by more than a full standard deviation (Green, Rohling, Lees-Haley, & Allen, 2001). In the presence of PVT failure, low neuropsychological test performances are likely due to factors related to performance invalidity, whereas normal range scores themselves may be underestimates of actual level of ability, irrespective of whether or not the examinee meets the Slick et al. (1999) MND or the Bianchini et al. (2005) MPRD criteria.

Formal evaluation of performance validity dates to Rey's work with the Dot Counting Test (Rey, 1941) and the 15-Item Test (Rey, 1964), and Spreen and Benton's work on simulation of mental deficiency on the Benton Visual Retention Test (BVRT; Benton & Spreen, 1961; Spreen & Benton, 1963). This early work highlights two features of PVTs. First, PVTs can be stand-alone measures of performance

validity that only address the issue of performance validity (Dot Counting Test, Rey 15-Item Test), or PVTs can be derived from clinically atypical patterns of performance on standard neuropsychological tests such as the BVRT. The early stand-alone PVTs such as the Dot Counting and the Rey 15-Item Test were designed to be sufficiently easy that persons with bona fide neurologic impairment could perform normally on these tasks. The atypical performance of simulated mental deficiency on the BVRT was similarly determined so that the pattern would not be confused with the legitimate performances of patients with bona fide mental impairment; however, variability in performance precluded recommendation for routine clinical application of these patterns of simulated impairment. Thus, the focus of these early investigations was twofold: (a) determine patterns of feigned impairment in noninjured persons instructed to feign impairment, and (b) establish that these feigned patterns are distinct from those patterns produced by patients who had bona fide clinical impairment.

Similarly, formal evaluation of the validity of symptom report dates to the original publication of the MMPI (Hathaway & McKinley, 1943). In its original format, there were three validity scales: Cannot Say (representing the unanswered items), L, and F. Subsequent research on the F scale demonstrated its particular relevance to detection of malingering of severe psychopathology. In this regard the F scale demonstrates one of the key features of detection of malingered symptom report: overendorsement of rare or unusual symptoms. Over time, it became obvious that symptom exaggeration on omnibus personality tests such as the MMPI can occur in areas other than the overreport of rarely endorsed symptoms that is characteristic of exaggeration of severe psychiatric disturbance. As a result, Lees-Haley, English, and Glenn (1991) developed the FBS Symptom Validity Scale to detect exaggeration of nonpsychotic emotional and physical complaints; the Fs scale was developed for the Minnesota Multiphasic Personality Inventory—2 Restructured Form (MMPI–2–RF) to detect somatic symptom overreporting (Ben-Porath & Tellegen, 2008; Tellegen & Ben-Porath, 2008); and the Response Bias Scale (RBS) scale of the MMPI–2–RF was devised to detect symptom report characteristic of examinees who failed PVTs (Gervais, Ben-Porath, Wygant, & Green, 2007). The F scale, developed to detect items rarely endorsed by the MMPI normative sample, has been augmented by the Fp scale, developed to detect items rarely endorsed by an inpatient psychiatric sample (Arbisi & Ben-Porath, 1995). A cogent review of the MMPI/MMPI–2 and MMPI–2–RF validity scales is provided by Ben-Porath (2012).

It is noteworthy that the development of individual PVTs and SVTs has focused on keeping false-positive identification at a mini-

mum; in other words, avoiding characterizing a clinical patient with bona fide symptoms and neuropsychological test performance as demonstrating invalid symptom report and/or ability test performance. This goal is achieved through the use of simulation research designs and criterion group research designs (also referred to as known groups designs; see Heilbronner et al., 2009; Rogers, 1988). The typical simulation group design compares the performance on a PVT or SVT of a group of noninjured persons instructed to feign impairment in order to successfully pursue a claim in an imaginary personal injury case with the PVT/SVT performance of a group of nonlitigating, or non–compensation-seeking individuals, usually with a history of moderate-to-severe TBI (note that in some instances this group may also be in litigation or compensation-seeking, but these subjects have successfully passed a series of PVTs and SVTs, independent of the particular PVT/SVT being validated in the specific investigation). In this fashion, one can determine those features of performance/symptom endorsement typical of a feigning sample (known to be feigning because they have been instructed to do so) that are not characteristic of bona fide symptoms/test performance in a clinical sample known to manifest abnormalities due to serious brain injury (moderate and severe TBI, typically with histories of coma and abnormal CT and/or MRI of the brain). In the criterion groups or known groups design, a group of persons, typically with uncomplicated mild TBI (who would not be expected to manifest persistent impairment; cf. McCrea et al., 2009) and who meet objective criteria for presence of malingering using the Slick et al. (1999) MND criteria or the Bianchini et al. (2005) MPRD criteria for presence of external incentive and multiple PVT/SVT failure, is contrasted with a group of patients suffering moderate/severe TBI regarding performance on the particular PVT or SVT being validated. Both of these designs have their strengths and weaknesses. Simulation designs are useful since the feigning group is known to be feigning because they have been instructed to do so, but this design raises issues of generalizability of findings because the incentives for feigning in a simulation study do not match the potentially large financial incentives present for persons in real-world litigation. Criterion group designs include a malingering group with definite real-world incentives, but this group may be more representative of gross symptom exaggeration and underperformance, rather than manifesting more subtle degree of impairment. Criterion group designs are only as good as the criteria used for group formation (e.g., when using subjects with bona fide injury who are also in litigation, this group must be carefully screened to exclude malingerers). The one feature that is typically constant in both simulation and criterion group designs is the comparison group of moderate-to-severe TBI, which provides a

good control against misidentifying bona fide performance as evidence of malingered impairment.

Research on PVT and SVT development using simulation and criterion group designs has yielded multiple stand-alone PVTs, as well as multiple embedded and derived PVTs and SVTs. Stand-alone PVTs range from non–forced-choice tests such as the Rey 15-Item Test, requiring "memorization" of a large number of items that actually are easily categorized into much smaller chunks of information, rapid circling of a specific letter of the alphabet (b Test; Boone, Lu, & Herzberg, 2002a), and counting of grouped and ungrouped dots (Dot Counting; Boone, Lu, & Herzberg, 2002b), to two-alternative, forced-choice tests appearing to assess memory but placing no real demand on memory, such as the Portland Digit Recognition Test (PDRT; Binder, 1990, 1993), Test of Memory Malingering (TOMM; Tombaugh, 1996), Victoria Symptom Validity Test (VSVT; Slick, Hopp, Strauss, & Spellacy, 1996), and Word Memory Test (WMT; Green, 2003).

Two-alternative, forced-choice testing, often referred to as *symptom validity testing*, originated with the work of Pankratz (1979). Initial use of this paradigm focused on identification of significantly worse-than-chance levels of performance, which Pankratz characterized as the "smoking gun of intent" (see Pankratz & Erickson, 1990). For someone to perform significantly worse than chance, it is assumed that they had to know the correct answer to avoid choosing this response, because someone with zero ability would be expected to perform at chance. It soon became apparent that most persons suspected of malingering actually performed significantly better than chance but at a level below the performance of neurologic patients with bona fide central nervous system dysfunction. For example, on the TOMM, the average correct on Trial 2 for noninjured persons feigning deficit (simulators) is 71%, which is significantly greater than chance, but the average correct for 22 TBI patients who had coma of at least 24 hours was 98.2%. Consequently, most two-alternative, forced-choice tests use empirically determined cutoffs set to keep false positives at 10% or less (90% specificity; see Boone, 2007; Larrabee, 2007).

In addition to stand-alone PVTs, various embedded and derived PVTs have been developed on the basis of patterns of performance that are atypical in either pattern or degree of abnormality. Heaton, Smith, Lehman, and Vogt (1978) were the first to apply discriminant function analysis to differentiate between patterns of performance characteristic of feigned impairment and those patterns of performance characteristic of severe TBI. In particular, their research demonstrated relatively poorer performance of their noninjured, feigning (simulating) subjects on measures of motor function (Finger

Tapping), and attention (Seashore Rhythm and Speech Sounds Perception) than seen in the severe TBI subjects. Mittenberg and colleagues (Mittenberg, Rotholc, Russell, & Heilbronner, 1996) replicated these findings and developed discriminant function equations for the Wechsler Adult Intelligence Scale–Revised (showing particularly poor performance on Digit Span; Mittenberg, Theroux, Zielinski, & Heilbronner, 1995) and Wechsler Memory Scale–Revised (showing particularly poor performance on Attention Concentration relative to General Memory; Mittenberg, Azrin, Millsaps, & Heilbronner, 1993) for simulating (feigning) subjects compared with patients with histories of significant TBI.

Other patterns that are atypical for bona fide neurologic disorder but frequently seen in persons feigning impairment include particularly poor performance on recognition memory measures derived from supraspan verbal learning measures (Barrash, Suhr, & Manzel, 2004; Millis, Putnam, Adams, & Ricker, 1995) and poorer gross motor function (Finger Tapping, Grip Strength) compared with fine motor function (Grooved Pegboard; Greiffenstein, Baker, & Gola, 1996). I have developed a PVT for the Continuous Visual Memory Test (CVMT; Trahan & Larrabee, 1988), a recognition memory test, based on identifying test items on which a group of patients with moderate-to-severe TBI outperformed a group of litigants with alleged uncomplicated mild TBI who also performed significantly worse than chance on the PDRT, meeting Slick et al. (1999) criteria for definite MND (Larrabee, 2009).

In summary, persons feigning neuropsychological impairment typically perform less well on measures of simple perception, gross motor function, attention/working memory, and recognition memory compared with the performance of persons with significant neurologic dysfunction such as that produced by moderate and severe TBI. Often, persons feigning deficit perform in patterns that are atypical for bona fide neurological disorder, such as poorer gross motor compared with fine motor ability, poor attention with normal memory, and poorer recognition than recall on memory testing procedures.

As noted earlier, identification of exaggerated symptom report has moved far beyond the use of the F scale of the MMPI. The bulk of identification of patterns of atypical symptom report has been conducted on the MMPI and MMPI–2, as well as on the newer MMPI–2–RF. Originally, omnibus personality tests such as the MMPI or Personality Assessment Inventory (PAI; Morey, 1991) relied on measures of overreporting of rarely endorsed items by normal subjects, a strategy that was far better suited to detection of exaggeration of severe psychiatric disturbance. Scales such as the F and Fp scales of the MMPI–2 and the Negative Impression Management (NIM) scale

of the PAI are thus more sensitive to detection of exaggeration in settings wherein demonstration of psychosis is useful in achieving an external incentive such as mitigation or avoidance of punishment in criminal court or avoidance of military duty (a more frequent occurrence during the period of the compulsory military draft but still a factor in the modern military; see Kennedy & Moore, 2010).

Malingering in civil forensic settings takes on a different picture because the litigant is usually attempting to appear sick or hurt rather than crazy (Larrabee, 2003b). Consequently, scales such as F, Fp, and NIM are not sensitive to this type of exaggeration. These observations led Lees-Haley et al. (1991) to develop the FBS, which did indeed prove more sensitive to detection of feigned symptoms of injury and illness while at the same time proving insensitive to the presence of bona fide neurological and medical disease (see Greiffenstein, Fox, & Lees-Haley, 2007, for a more detailed review of the FBS). Extensive subsequent research substantiating the validity of the FBS as an SVT led to the incorporation of the FBS Symptom Validity Scale as one of the standard validity scales of the MMPI–2 (Ben-Porath, Graham, & Tellegen, 2009). FBS investigations have also stimulated research in the development of additional measures of exaggerated symptoms other than those associated with exaggeration of severe psychiatric disturbance. The RBS was developed by Gervais et al. (2007), based on identification of those MMPI–2 items that discriminated disability claimants who failed PVTs (e.g., WMT, Computerized Assessment of Response Bias, Test of Memory Malingering) from those disability claimants who passed PVTs. Moreover, the RBS was more sensitive in discriminating the PVT-pass from PVT-fail subjects than F, Fp, or FBS. In a subsequent investigation, the RBS was more closely associated with exaggerated memory complaints than F, Fp, or FBS (Gervais, Ben-Porath, Wygant, & Green, 2008). Recently, the RBS has been included as a standard validity scale in the MMPI–2–RF (Ben-Porath, 2012). The Fs scale was developed for the MMPI–2–RF MMPI–2 by selecting those items endorsed by 25% or fewer of men and women in several large medical samples (two large general medical patient samples and one large chronic pain sample; Ben-Porath, 2012; Tellegen & Ben-Porath, 2008).

In an interesting investigation, Wygant et al. (2007) found differing patterns of MMPI–2 validity and clinical scale endorsement in evaluees failing the WMT or the TOMM in civil versus criminal forensic settings. FBS was associated with PVT failure in both civil and criminal settings, but Fp was the only other MMPI–2 validity scale associated with PVT failure in the criminal sample. Both the civil and criminal evaluees elevated FBS and RCI, but only the criminal defendants elevated Fp and RC8. Wygant et al. concluded that criminal defendants demonstrated a more global pattern of exag-

geration and feigned cognitive impairment, whereas civil litigants restricted exaggeration to somatic complaints and feigned cognitive impairment.

Research is beginning to accumulate on the relationship of PVTs and SVTs to malingered pain (MPRD). Meyers, Millis, and Volkert (2002) developed a composite validity index for the MMPI–2 that was sensitive to exaggerated symptom report in chronic pain patients. Failure of PVTs was associated with receiving/seeking disability in fibromyalgia cases (Gervais et al., 2001). SVT failure (MMPI–2 validity scales) discriminating those subjects meeting MPRD criteria from those not meeting criteria has been reported (Bianchini, Etherton, Greve, Heinly, & Meyers, 2008). Similarly, Greve, Ord, Curtis, Bianchini, and Brennan (2008) reported on the association of PVT failure with presence of MPRD. Exaggerated symptom endorsement in association with MND has been reported for the Pain Disability Index (PDI; Tait, Chibnall, & Krause, 1990) and Modified Somatic Perception Questionnaire (MSPQ; Main, 1983), with large effect sizes for discriminating probable malingerers from published data on chronic pain samples (d = 1.08 for PDI; d = 2.92 for MSPQ; Larrabee, 2003c). Patients failing computerized dynamic posturography (CDP) with nonphysiologic (i.e., feigned) patterns of performance produced significantly higher scores on the MSPQ than persons with physiologic patterns of performance on CDP (Brasseux, Greve, Gianoli, Soileau, & Bianchini, 2008).

III. INTERPRETATION: DIAGNOSTIC ACCURACY OF PVTS AND SVTS IN RELATION TO PROBABILITY OF MALINGERING

Modern PVT and SVT research typically sets specificity, the absence of invalid performance or symptom report, at 90%, representing a false-positive rate of 10% (Boone, 2007; Larrabee, 2007). This results in much lower sensitivity to detection of invalid performance or symptom report; for example, Vickery, Berry, Inman, Harris, and Orey (2001) in a meta-analysis of PVTs reported a 95.7% specificity, but only a 56% sensitivity. It is noteworthy that positive predictive power (PPP), or the probability of a diagnosis, is more dependent on specificity than on sensitivity because the general calculation of PPP is True Positives/(True Positives + False Positives; see Straus, Richardson, Glasziou, & Haynes, 2005). Hence, the smaller the false-positive rate, the higher the PPP. Two separate investigations, both using criterion group designs, have demonstrated that requiring multiple PVT and/or SVT failures increases the probability of correctly identifying the presence of malingering (Larrabee, 2003a; Victor, Boone, Serpa,

Buehler, & Ziegler, 2009). At a 40% base rate of malingering, PPP for failure of two PVTs/SVTs was .91 (Larrabee, 2003a) and .90 (Victor et al., 2009), and PPP for failure of three PVTs/SVTs was 1.00 (Larrabee, 2003a) and .96 (Victor et al., 2009), respectively.

The finding of increased probability of malingering as a function of increasing number of PVTs/SVTs failed is understood by the methodology of chaining of likelihood ratios (Grimes & Schulz, 2005). The positive likelihood ratio is defined by the ratio of sensitivity to the false-positive rate. Consequently, a score falling at a particular PVT cutoff with an associated sensitivity of .50 and specificity of .90 yields a likelihood ratio of .50/.10 or 5.0. If this value is multiplied by the base rate odds of malingering (a base rate of .40 converts to odds of .40/(1 – .40), .67), the result is .67 × 5.0 or 3.35, which represents the posttest odds of malingering, given a base rate of .40 and a test with a sensitivity of .50 and specificity of .90. The posttest odds of 3.35 can be converted back to a probability of malingering by the formula: odds/(odds + 1), 3.35/4.35 = .77. Chaining can be applied with administration of a second PVT/SVT that is independent of the first one. If the second PVT/SVT has a similar sensitivity of .50 and specificity of .90, this again yields a likelihood ratio of 5.0, which now can be multiplied by the posttest odds obtained following application of the first PVT/SVT, 3.35. This yields a new posttest odds of (3.35) × (5.0) = 16.75, which can be converted back to a probability of malingering by 16.75/17.75 or .94. If a third, independent PVT/SVT with a sensitivity of .50 and specificity of .90 is failed, the posterior odds of malingering become (16.75) × (5.0) = 83.75, which convert to a posterior probability of malingering of 83.75/84.75 or .99. I provide more detailed discussion of this methodology in Larrabee (2008).

Chaining of likelihood ratios demonstrates, quite nicely, the power of aggregating PVT/SVT failures. The greater the number of PVT/SVT failures, the greater the probability of malingering. There are certain precautions; for example, the methodology requires independent measures; otherwise the probabilities are inflated (Grimes & Schulz, 2005). As I have shown, this assumption can be met due to the rare occurrence of PVT/SVT failure in patients with bona fide neurologic and psychiatric disorder, with the five PVT and SVT variables from Larrabee (2003a) intercorrelating .175, on average (see Larrabee, 2012). Of course, one would only select one measure from each PVT or SVT to chain; for example, if both the Test of Memory Malingering Trial 2 and Retention Trial fell in the invalid performance range, only one score would be used, and similarly, if the FBS-r and RBS were both elevated on the MMPI–2–RF or MMPI–2, only one score would be used for chaining of likelihood ratios. Obviously, in circumstances where multiple scores from a single PVT

or SVT are invalid, one would choose the single score with the best likelihood ratio to use in the final chaining of likelihood ratios.

Also, chaining of likelihood ratios assumes that each PVT/SVT is equally sensitive to the presence of feigned impairment, which may not be the case. An alternative to chaining independent tests is to use a logistic regression including multiple PVTs and SVTs. Logistic regression allows for the presence of predictor intercorrelation as well differential weighting of salient variables (e.g., if Reliable Digit Span is a more sensitive PVT than Failure to Maintain Set on the Wisconsin Card Sorting Test, it would receive a greater weighting in the logistic regression formula; see Heilbronner et al., 2009). Logistic regression formulas have been published for the multiple scores on the CVLT–2 (Donders & Strong, 2011; Wolfe et al., 2010), as well as for the tests comprising the Pearson ACS Assessment of Suboptimal Effort (Miller et al., 2011). Of course, one can only rely on validated logistic regression equations that are available for the particular set of tests used, which can be a limiting factor given the absence of a consensus battery of neuropsychological tests.

IV. PVTS, SVTS, AND THE VALIDITY OF THE SLICK ET AL. CRITERIA

My colleagues and I have reviewed PVT and SVT research based on simulation studies and criterion (known) group designs, in order to address the validity of the Slick et al. (1999) criteria (Larrabee et al., 2007). First, we demonstrated the equivalence of PVT performance of simulators to that of litigants with definite MND (defined by worse-than-chance performance), noting that this similarity supports intentional underperformance in the definite MND group, because they are performing like those subjects who are known to be intentionally underperforming because they have been instructed to do so. Then, we demonstrated the equivalence of PVT and SVT performance of persons with definite MND and those with probable MND, supporting the validity of the probable MND criteria. We also discussed how the article by Bianchini, Curtis, and Greve (2006), which demonstrated a dose–effect relationship between PVT failure and amount of external incentive, supports that intent is causally related to PVT failure; in other words, greater PVT failure is associated with larger external incentive. By extension, this supports the primary thesis of the MND criteria: Multiple PVT and/or SVT failure, in the context of substantial external incentive, without any viable alternative explanation, establishes the intent of the examinee to malinger. This argument can also be extended to support the MPRD criteria, which are developmentally linked to the MND criteria. As we also suggested, my results (Larrabee,

2003a, 2008) and the results of Victor et al. (2009) support simplification of the MND criteria to two PVT or one PVT and one SVT failure to provide psychometric support for probable MND (Larrabee et al., 2007). Last, we suggested that there be greater symmetry to the Slick et al. criteria so that two independent SVT failures without associated PVT failure should meet criteria for probable MND, rather than the current characterization of SVT failure alone as representing possible MND.

V. INTEGRATION: USE OF PVTS AND SVTS IN THE INDIVIDUAL CASE

Both the National Academy of Neuropsychology (Bush et al., 2005) and the American Academy of Clinical Neuropsychology (Heilbronner et al., 2009) recommend the use of PVTs and SVTs as part of a comprehensive neuropsychological evaluation. This is particularly important in contexts with substantial external incentives, wherein PVT and SVT failure occurs at a greater frequency (Mittenberg et al., 2002). Continuous sampling of performance validity is also recommended (Boone, 2009), as validity can fluctuate over the course of the examination. Continuous sampling is enhanced by the availability of measures of embedded and derived PVTs for many standard measures of motor function, attention, working memory, verbal and visual learning and memory, and problem-solving skills (Boone, 2007; Larrabee, 2007; Morgan & Sweet, 2009; in particular, see Appendix A in Morgan & Sweet, 2009). In this fashion, performance validity can be assessed throughout the entire neuropsychological evaluation.

Interpretation of PVT and SVT results needs to consider the context of the evaluation. A diagnosis of malingering requires presence of external incentive, no other viable explanation of PVT and SVT failure, and presence of multiple failures on PVTs and SVTs, according to the Slick et al. (1999) MND criteria and Bianchini et al. (2005) MPRD criteria.

As noted earlier, individual PVTs and SVTs typically have specificities of 90% or greater, yielding false-positive rates of 10% or less. PVT test manuals frequently include comparison groups of nonlitigating, non–compensation-seeking patients with serious neurologic, psychiatric, or developmental conditions; for example, the TOMM manual (Tombaugh, 1996) contains comparison groups of patients with aphasia, documented neurologic disorder associated with cognitive impairment (e.g., stroke, Korsakoff's syndrome), moderate and severe TBI, and dementia. With the exception of the dementia group, very few of these patients performed in the invalid range on the TOMM; for example, 21 aphasic patients averaged

98.6% correct on Trial 2, a value similar to that produced by 22 TBI patients with 24 hours or more of coma, who averaged 98.2% correct, including one individual with a right frontal gunshot wound and right frontal lobectomy, who scored 100% correct. Boone's group has included comparison groups of patients with depression, head injury (with brain lesions documented by CT or MRI), schizophrenia, and stroke for the b Test (Boone et al., 2002a), and for these same groups plus an additional group of mild dementia patients for the Dot Counting Test (Boone et al., 2002b). TOMM scores were not affected by psychiatric disorder such as depression (Rees, Tombaugh, & Boulay, 2001), depression and anxiety (Ashendorf, Constantinou, & McCaffrey, 2004), or depression and chronic pain (Iverson, Le Page, Koehler, Shojania, & Badii, 2007). Acute pain did not affect performance on the TOMM (Etherton, Bianchini, Greve, & Ciota, 2005) or affect performance on Reliable Digit Span, another PVT (Etherton, Bianchini, Ciota, & Greve, 2005). Goodrich-Hunsaker and Hopkins (2009) reported three cases of anoxic encephalopathy with radiologically confirmed hippocampal damage who scored in the valid performance range on the WMT, a widely used PVT.

As Boone and Lu (2003) illustrated, with independent PVTs having false-positive rates of 10%, failure of one PVT has a false-positive rate of 10%, but failure of two PVTs has a false-positive rate of $.10 \times .10$ or .01, and failure of three PVTs has a false-positive rate of $.01 \times .01 \times .01$ or .001. Victor et al. (2009) and I (Larrabee, 2003a) both reported essentially zero false positives in association with failure of three PVTs. Even at low base rates of malingering, such as .10, PPP can be greater than .90 for failure of three PVTs (Larrabee, 2008). Moreover, current PVT and SVT research emphasizes reporting the characteristics of those examinees who fail these measures due to bona fide, legitimate neurologic, psychiatric, and developmental conditions (Larrabee, 2003b; Victor et al., 2009). Typically, factors associated with false-positive results on individual PVTs include severe neurologic conditions (coma, structural lesions in the brain; Larrabee, 2003a; unequivocally severe and obvious neurologic symptoms, Merten, Bossink, & Schmand, 2007) or neurologic, psychiatric, or developmental conditions requiring 24-hour supervision of the examinee (Meyers & Volbrecht, 2003). As a result, protection is provided against making a false-positive diagnosis of malingering by requiring multiple PVT and SVT failure, in the context of external incentive, with consideration of published identification of examinee factors likely to be seen in association with false-positive identification due to bona fide impairments that are not a consequence of invalid performance or symptom report.

Last, a particularly vexing problem is the occurrence of malingering in persons who have actually sustained significant brain illness

or injury of sufficient severity to have produced suspected permanent problems (Bianchini, Greve, & Love, 2003; Boone & Lu, 2003; Paniak, 2009). Of course, when multiple PVTs and SVTs are failed, one cannot rely on low performances as being accurate measures of actual reduction in abilities. Normal performances on sensitive measures such as Trail Making B and the Auditory Verbal Learning Test take on increasing importance in this regard, for they demonstrate, at best, low estimates of actual abilities which, in this example do not provide evidence for acquired impairment. In the cases where insufficient information is available to rule out significant sequelae, the clinician is forced to rely on published data on outcome from various neurologic disorders. Consider the example of one of my previous forensic cases of the personal injury litigant who sustained severe TBI producing a month of coma who also presented with evidence of multiple PVT and SVT failures and performed in a uniformly poor manner on all neuropsychological tasks. Also, this person did not require 24-hour supervised care and could use public transportation, making it likely that the multiple PVT and SVT failures did not represent false-positive findings. In this particular example, I referred to return-to-work data published by Dikmen et al. (1994). These data show that only 8% of patients sustaining TBI followed by at least 1 month of coma had returned to work by 24 months after injury. Thus, in the current example of malingering in a severe TBI patient, although the test data could not be relied on to ascertain whether he would have been part of the 8% to return to work, the odds certainly were against the possibility of gainful employment based on the Dikmen et al. outcome data.

VI. SUMMARY

This chapter reviewed suggested diagnostic criteria for malingering, described measures of performance validity (PVTs) and symptom validity (SVTs), and discussed the use of PVTs and SVTs in the diagnosis of malingering (see Table 5.1). Current practice in neuropsychology encourages use of PVTs and SVTs as a standard, accepted practice. Diagnosis of malingering is a probabilistic determination, requiring the presence of a substantial external incentive, multiple PVT and SVT failure and no viable neurologic, psychiatric, or developmental explanation for such failure. The probability of the accuracy of the diagnosis of malingering increases as a function of the number of failed PVTs and SVTs, reaching the .90s with two failures, and approximates .99 with three failures. Definite malingering is seen in association with significantly worse-than-chance performance

Table 5.1. Summary of Main Points

Validity of actual level of ability must be measured with PVTs, and validity of actual symptom experience must be measured with SVTs in every neuropsychological evaluation.
PVTs may be free-standing (i.e., only measuring performance validity, such as the Test of Memory Malingering or Word Memory Test), or may be derived from neurologically atypical patterns of performance on standard measures of core neuropsychological abilities such as Finger Tapping or the Auditory Verbal Learning Test.
SVTs can be specifically designed on omnibus personality tests such as the MMPI–2–RF, including measures of exaggerated/rare/atypical symptom report of psychotic symptoms (F, Fp) or somatic, health or injury symptoms (Fs, FBS-r, RBS), or may be derived from excessive symptom endorsement on pain scales such as the Modified Somatic Perception Questionnaire.
PVTs and SVTs are developed with the goal of achieving 90% specificity per test; i.e., the false-positive rate, per test, is 10% or less.
The presence of multiple PVT and/or SVT failures in the context of a powerful external incentive, such as financial gain in personal injury litigation or avoidance or mitigation of punishment in the criminal setting, with no viable alternative explanation (e.g., need for 24-hour supervision, obvious serious brain damage documented by prolonged coma and objective evidence of CT scan abnormality, or mental retardation or severe psychopathology such as acute schizophrenia) is consistent with malingering, the exaggeration or fabrication of deficit to achieve an external incentive.
The Positive Likelihood Ratio, obtained by dividing sensitivity, typically about 50%, by the false alarm rate, typically 10%, yields a ratio of 5.0, which, when multiplied by the pretest odds of malingering (i.e., the base rate odds) of .67 (in mild TBI cases), yields posttest odds of malingering, which can be transformed to probabilities of malingering, reaching .94 for failure of two PVTs/SVTs and .99 for failure of three PVTs/SVTs.

(continued)

Table 5.1. Summary of Main Points *(Continued)*

In the presence of multiple PVT and or SVT failure, poor neuropsychological test scores are more likely the result of invalid performance. whereas normal range scores themselves may be underestimates of actual level of ability.

Note. PVTs = performance validity tests; SVTs = symptom validity tests; MMPI–2–RF = Minnesota Multiphasic Personality Inventory—2 Restructured Form; FBS-r = Symptom Validity Scale; RBS = Response Bias Scale.

on two-alternative, forced-choice testing, which Pankratz, a PVT pioneer, referred to as the "smoking gun of intent" (Pankratz & Erickson, 1990).

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Chapter 6

Amy Heffelfinger

Issues in the Assessment of Children

Having a rudimentary understanding of the similarities and differences in assessing children versus adults is essential, regardless of whether an individual's practice actually includes child assessment. Notably, children are not just "little adults," and the development of neural systems is not simply the opposite of late-life neural system loss. A neuropsychologist needs to have a general understanding of the developmental trajectories of neuropsychological functions from birth to death to truly comprehend the utility and variability of these functions at any age of interest. Please see Exhibit 6.1 for a brief review of considerations for testing children.

I. RELEVANT DEVELOPMENTAL ISSUES IN NEUROPSYCHOLOGICAL EVALUATION

A. Types of Patients

Children are referred for neuropsychological assessment for many reasons, but the goal of most assessments is to identify general level

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Exhibit 6.1. Basic Considerations for Child Neuropsychological Assessment

Consent regarding limits of confidentiality
- Need to have consent to conduct the evaluation from the child's legal guardian.
  - If not, do not proceed with the evaluation.
- Know state rules on when a child becomes a legal adult.
  - Prior to that age, the parents (or parent) provide consent, and feedback is directly provided to them.
  - After becoming a legal adult, the patient needs to provide consent, and results are provided directly to the individual.
  - In order to communicate with the parents, the patient has to sign a release of information.

Clinical interview
- Conduct with parents primarily.
- Conduct a brief clinical interview with the child.
- Complete parent and child interviews separately.

Content of clinical interview
- Understanding of neuropsychological areas of strength and weakness.
- Presence or absence of the symptoms of emotional, behavioral, or social problems.
- Achievement of developmental milestones and academics.
- Birth history.
- Medical history.
- Current living and academic situation.
- Family history of developmental disorders, medical illness, and neurological problems.

Test selection
- Confirm intact sensory and motor function.
  - If not intact, design battery so it is not reliant on impaired function.
- Choose tests that are appropriate for developmental level and chronological age.

Test environment
- Warm and comfortable but void of stimulating or distracting objects.
- Quick appraisal of child and parent emotional state upon meeting.
- If child is anxious, talk quietly and reassuringly to parent first.

(continued)

Exhibit 6.1. Basic Considerations for Child Neuropsychological Assessment *(Continued)*

- If child is hyperactive, talk to child first and immediately begin managing behaviors.

Testing session

- Model positive affect.
- Use consistent and clear behavior modification.
- Provide frequent reassurance when the child is working appropriately.

of intellectual functioning, determine whether neuropsychological strengths and weaknesses are consistent with a neurobehavioral syndrome, and appropriately plan for treatment, education, and intervention. Broadly speaking, most referrals are one of two types, neurological/genetic/medical or developmental.

There are a multitude of neurological disorders that affect neural system development and function. Some of the most prevalent are epilepsy, hydrocephalus, spina bifida, brain tumor, traumatic brain injury (TBI), pre- and perinatal complications, and infectious diseases in brain tissue. Neurological disorders directly impact the development of neuropsychological functions by altering or harming the brain cells or systems during development. Many genetic disorders result in altered neuropsychological functions by disrupting the actual development of brain tissue and systems (e.g., Down syndrome, Williams syndrome, neurofibromatosis Type I, sickle cell disease, phenylketonuria, and storage diseases). Finally, many other medical diseases and conditions have a secondary impact on the development of neural system functions and often benefit from assessment (e.g., cardiac, kidney, or liver disease, blood disorders, and endocrine dysfunction).

Although many children experience neurological, genetic, and medical disorders that influence brain system development, many more children experience developmental disorders. Developmental disorders result in delayed development of cognition, emotion, behavior, or social function. The most common disorders include attention-deficit/hyperactivity disorder (ADHD); developmental delays (especially in acquisition of language and motor milestones); learning disabilities, particularly reading disability and mathematics disability; and pervasive developmental disorders, or autism spectrum disorders. Each of these is considered developmental in nature when occurring outside of known neurological or genetic cause, but

the development of behavioral, academic, or social functions is abnormal. Although numerous genes have been identified in individuals with developmental disorders, there is not a specific gene or set of genes that can clinically be useful for diagnosis or treatment planning of developmental disorders. Rather, the abnormal development results from underlying genetic predisposition in conjunction with other multifactorial influences such as temperament, other individual characteristics, and environmentally based experiences, such as early parenting, socioeconomic factors, and social experiences.

Of important note, neurological/genetic/medical and developmental disorders are not mutually exclusive; nor are they always differentiable. First, many children who suffer from neurological disorders also have clear familial risk for developmental disorders, such as ADHD or learning disabilities. Although the risk is not necessarily additive, these children have increased risk for such problems or for increased severity because of their "double whammy" of both familial and biological risks. Of course, it is often possible that the cause of both originates from shared genetic risk, as can be the case for children with epilepsy and Neurofibromatosis type I. Second, one cannot separate out typical development from the abnormal development that results from having a neurological disorder that begins early in life, such as spina bifida or perinatal stroke. The individual child's development encompasses both. The damaged or abnormal systems develop in conjunction with systems developing typically. Typical and abnormal development become entwined and are one and the same. For this reason, such childhood neurological disorders are often considered to be neurodevelopmental disorders.

B. Referral Questions

Referral patterns for children tend to vary on the basis of the neuropsychologist's setting and location. Child neuropsychologists who practice in academic medical institutions, especially if affiliated with a children's hospital, have access to more children with neurological/genetic/medical concerns. Those who practice in university settings, private hospitals, private practices, and rural areas tend to see more children with developmental concerns. Child neuropsychologists in any setting, however, can improve their referral patterns by educating the local referring entities about how neuropsychological assessments can help their patients/students/clients. General practice physicians/pediatrics, neurologists, neurosurgeons, emergency room physicians who treat TBI, school districts, and therapists all work with children who may benefit substantially from

a neuropsychological evaluation. In any setting, a clinical child neuropsychologist can help define their own practice by developing these referral relationships.

II. METHODS IN THE ASSESSMENT OF CHILDREN

The basic methodology for a neuropsychological evaluation with children is similar to that for adults. The neuropsychologist should inform the patient about the evaluation procedures and limits of confidentiality. It is important to know state rules on when a child becomes a legal adult. Prior to that age, the parents (or parent) provide consent, and feedback is directly provided to them. After becoming a legal adult, the patient needs to provide consent, and results are provided directly to the individual. For the neuropsychologist to communicate with the parents, the patient has to sign a release of information. There are rare occurrences in which a parent is not available. In these situations, a legal guardian, caregiver, teacher, or therapist may have to provide background information and reason for evaluation. An important side note: The neuropsychologist needs to have consent to conduct the evaluation from the child's legal guardian, or he or she should not proceed with the evaluation.

A. Reason for Referral and Clinical Interview

The reason for referral guides the clinical interview, and the interview is essential for gathering pertinent information. Typically, the clinical interview is conducted with parents primarily, although most neuropsychologists conduct a brief clinical interview with the child as well. These should be completed separately when possible. It is very difficult for parents to talk about their child in front of the child, and detailed discussion of the child is not clinically advised with the child present. Additionally, the child may be more comfortable providing accurate, detailed information in his or her interview if alone than if the parents are present.

The primary goal of the interview is to understand the current and developmental history of the primary concerns resulting in neuropsychological evaluation. These concerns tend to be with cognitive, emotional, behavioral, academic, and social functioning. There are typically one to three areas of primary concern. The interview should flesh out the developmental course of these concerns and locations of functional problems, such as at home, at school, and in the community. Information should also be obtained to rule in or rule out differential diagnoses and related areas of concern. From the interview, the neuropsychologist gleans a clear understanding of neuro-

psychological areas of strength and weakness; presence or absence of the symptoms of emotional, behavioral, or social problems; achievement of developmental milestones and academics; birth history; medical history; current living and academic situation; and family history of developmental disorders, medical illness, and neurological problems. After completion of the interview, the neuropsychologist should have a clear set of differential diagnoses.

B. Test Selection

These differential diagnoses guide the test battery. The examiner must confirm that there are no severe sensory or motor impairments that will negatively impact test performance. As in any neuropsychological evaluation, the presence of a motor impairment requires alteration of the battery to minimize demand on motor function. Similarly, the battery for someone who is blind should not include measures requiring visual perception. Most batteries should be designed to include globally based assessment of cognitive development or intellectual functioning; some estimate of adaptive, behavioral, social, and emotional functioning; and evaluation of academic achievement in reading and math. The assessments also should include basic assessment of functioning in the areas of fine motor, attention, executive, visuospatial, language, and verbally and visually based learning and memory.

C. Chronological Versus Developmental Age

It can be challenging to consistently and accurately complete developmentally appropriate neuropsychological assessments, in part because no assessment tool is applicable throughout the full chronological and developmental course of childhood. First, one needs to always consider the chronological age of the normative sample when choosing tests. Representative normative sampling should include a sufficient number of children in the patient's age bracket, as well as the age brackets around it, to ensure accurate estimation of acceptable variability in performance for chronological age. Adequate normative sampling also means that other demographic variables relevant for the patient, such as ethnicity, race, and gender, were adequately present in the sample.

Understanding the child's developmental age for each area being assessed is one of the most difficult components of designing a battery and is of utmost significance. A child who is 9 years old, chronologically, but is functioning at a developmental age of a 2-year-old will not be able to perform tasks that were designed and normed

for 9-year-olds. If the neuropsychologist administers an intellectual measure for children ages 6 and older, such as the Wechsler Intelligence Scale for Children (Wechsler, 2004), the child will not be able to complete any of the items and will be frustrated. This is true for broad-based assessment measures, such as the Wechsler scales, but also for tests for specific neuropsychological functions, such as those assessed using the NEPSY–II (Korkman, Kirk, & Kemp, 2007) or the Delis–Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001).

This thought process needs to be applied for each neuropsychological domain. An intellectually average 7-year-old with significant impairment in executive functioning will have a developmental age for executive functioning of less than 7 years old. Therefore, the executive functioning tests for 7-year-olds might be too hard for him. The results will demonstrate what he cannot do but not what he can do. In this situation, the examiner needs to identify a test that included children of a younger chronological age in their normative sample to adequately assess actual developmental age. For example, the NEPSY–II (Korkman et al., 2007) has measures that can be administered to a child who is chronologically 7 years old but has a developmental age of 5 years old on executive functions.

Why is it important to actually know the developmental age of each neuropsychological function? It is not always sufficient to report that a child is functioning significantly below average in comparison with same-age peers, and this is an important distinction between adult and child neuropsychology. In childhood, each neuropsychological function is presumed to be developing. Knowing the developmental age of each function guides the intervention and education by the parents, referring physicians, teachers, and therapists. Promotion of optimal development requires knowledge of developmental level or stage in their areas of strength and impairment. It is much more valuable to tell the parents of the 7-year-old that their child has not yet learned to shift between different types of responding, what this means, and how to assist in developing the next-level skills than just to say that their child is impaired or delayed in executive functioning.

There are times when no measure is available that meets both the criteria of having adequate normative data for chronological age and assessing the developmental level. For example, if a child is 7 or older and functions at the developmental level of less than a 2-year-old, there is no appropriate cognitive measure. Administering normed IQ measures and most neuropsychological measures will result in standard scores that are <50 and age equivalents that are less than 6:0. This information is only mildly beneficial.

So how does one determine the appropriate battery? Typically, the referral question can drive this decision. For example, if the child has never been diagnosed with intellectual disability or mental retardation, an intellectual measure that can yield an IQ score should be administered. For example, the Stanford–Binet Intelligence Scales (Roid, 2003) has normative data down to 2 years of age. However, if a diagnosis of intellectual disability has been made previously and the referral question is to assist in school planning, choosing measures that provide an understanding of developmental age is the best choice. For example, if the child is functioning at less than a 2-year-old developmental level, an infant scale such as the Mullen Scales of Early Learning (Mullen, 1995) or Bayley Scales of Infant and Toddler Development (3rd ed.; Bayley, 2006) will provide detailed age equivalents for basic cognitive functions. For children estimated to be functioning in the 2- to 5-year developmental age range, measures such as the Beery–Buktenica Developmental Test of Visual–Motor Integration (Beery, Buktenica, & Beery, 2010), Peabody Picture Vocabulary Test (Dunn & Dunn, 2007), and NEPSY (Korkman et al., 2007) subtests can be useful for obtaining developmental age. Additionally, the Vineland Adaptive Behavior Scales (Sparrow, Cicchetti, & Balla, 2005) are an exceptional measure because they are able to assess adaptive functioning for all chronological and developmental ages.

Another important consideration in battery development is consideration of race/ethnicity (for a more comprehensive discussion of cultural neuropsychology issues, see Chapter 7). Briefly, if the normative sampling did not include a sufficient representation of race or ethnicity, result interpretation may be flawed. For example, the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was not well developed or normed for children of African American descent and will often underestimate language ability. A language measure such as the Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 2003) not only has adequate test item development but also normatively accounts for grammar and syntax differences due to culture.

D. Testing Environment

The testing environment is critical to obtaining optimal emotional response, cooperation, and attention. The testing rooms should be warm and comfortable, because most of the time the child will be separating from parents or caregivers for the testing. The testing room, however, also should be void of any stimulating or distracting objects.

A room should have few or no pictures on the walls, and if there are pictures, they should not be engaging for a child. Additionally, the room should be free of files or extraneous materials.

Possibly the most important moments for developing rapport on the testing day are those in the first encounter. The neuropsychologist and testing technicians need to be trained to quickly survey the emotional state of the child, as well as the parent, and navigate these often complicated emotions quickly and confidently. For example, a child feeling anxious will likely be close to the parent, sitting back in a chair, and making hesitant eye contact, whereas a child with high impulsivity will be elsewhere in the waiting area, eager to go with the examiner, and often overly willing to venture somewhere novel. For the anxious child, it is useful to use a softer voice, get down to the child's level, and make introductions but gear initial interactions to the parent first. Once the child perceives the parent as being comfortable with the examiner, this often results in less fearfulness. For the impulsive child, the parent often is the one who needs assurance that the examiner will protect the child from harm and manage the behaviors. One way to handle this is to direct introductions to the child, corral them using positive but clear behavior management strategies, and then address the parent quickly but confidently. Another common variation to be prepared for is parental anxiety or high need for control. Not managing the parent's emotions or personality can have deleterious effects on the testing as well.

During the testing session, an examiner cannot take on the same affect and presentation as may often be done when testing an adult. Children will typically mimic the affective state of the examiner, so that a child working with a stone-faced examiner will often appear to have flat affect. A disorganized tester allows the child to be more disorganized. The tester needs to model positive affect, use consistent and clear behavior modifications, and provide frequent assurance that the child is behaving appropriately, using comments such as, "You are working really hard."

III. INTERPRETATION OF NEUROPSYCHOLOGICAL ASSESSMENTS IN CHILDREN

Once the evaluation is completed, the differential diagnoses and hypotheses derived from the interview, parent and teacher reports, and testing observation drive test data interpretation. The test data do not drive the interpretation! The goal of the interpretation process is to explain the initial reason for referral and presenting complaints. Although each neuropsychologist has his or her own abilities to

complete this process, the most complete interpretation occurs when the neuropsychologist sees the evaluation as a puzzle, putting known pieces together and recognizing where there are missing pieces. Once the puzzle is complete, the neuropsychologist describes the puzzle in words for the feedback and the report. Typically, the goal is to "solve" the presenting complaints by describing the neuropsychological profile in the context of developmental, medical, familial, individual and environmental variables and provide recommendations regarding accommodations, treatment, and education for the areas of weakness, impairment, or limitations.

The interpretation process typically requires both broad-based and domain-specific analysis. Awareness of overall intellectual, adaptive, and academic functioning is vitally important to understanding the child. How the child compares to other same-age children in each of these functional areas is critical to understanding the neuropsychological domain tests, as well as educational and treatment needs. Typically, these three areas of functioning are relatively consistent with each other, and significant inconsistencies can speak to the child's experience. For example, academics > IQ may reflect a very hardworking personality or an exceptional school or home learning environment. Intelligence > adaptive functioning may reflect permissive or overwhelmed parents, an underperforming school, or substantial emotional/behavioral problems in the child.

Next, interpretation occurs for specific neuropsychological domains and their components. A basic but clear understanding of fine motor, speed-of-processing, and attention functions anchors test interpretation. These functions develop early chronologically. If they were impaired, then other neuropsychological functions were built on these impaired systems. Additionally, if these are impaired, performances on other tasks should be interpreted with caution. For example, fine motor impairment limits ability to complete psychomotor timed tasks, visual–motor integration tasks, and construction tasks. Speed-of-processing impairment also limits performance on timed tests. It also increases risk for fatigue from increased length of testing.

A. Neuropsychological Syndromes and Etiology

The next component of solving the puzzle is to determine whether the child has any neuropsychological syndromes by reviewing pattern of strengths and weaknesses. Common developmental disorders include ADHD, reading disability, and autism spectrum disorder. Children can experience classic neuropsychological syndromes as well such as ataxia, aphasia, and unilateral neglect, typically as a result of neurological injury or disorder affecting neural systems.

Finally, to complete the puzzle, the examiner needs to explain etiology for the pattern of strengths and weaknesses. Often, the cause is clearly neural injury or disorder. Many times, however, the neuropsychological weaknesses are not related to the medical reason for referral, and it is important for the neuropsychologist to assign causation only if it truly fits. Neural plasticity during development makes test interpretation and prediction of recovery highly complicated. It was long believed that younger age was related to better outcomes (Finger & Wolfe, 1988; Kennard & Fulton, 1942). Extent of, location of, and age at injury are important considerations. Children have better recovery if the injury is localized to a specific brain region versus widespread injury, as is often the case with severe TBI (Ewing-Cobbs, Prasad, Kramer, & Landry, 1999). Having remaining healthy tissue is believed to allow for greater neural reorganization. Healthy neurons that have not yet specialized for a specific neural function can take over for damaged neural functions (Johnson, Halit, Grice, & Karmiloff-Smith, 2002).

Age at injury and, more particularly, stage of neural system development are very important as well. If a certain neural function has not yet developed, that function can more easily be subsumed by neurons in a different region. Often devastatingly, neural systems that had already developed are not able to fully reorganize. Neural systems often have critical periods (exact time period) or critical windows/sensitive periods (broader time range) for development. If development does not occur in this time, it either is not going to develop or is going to develop abnormally or incompletely. If the injury occurs during or after these sensitive periods, development of that function is substantially harmed. For example, if the left frontal and temporal lobes are damaged in the first 6–8 months of life, the right hemisphere, along with remaining healthy left hemisphere systems, will likely support adequate, if not typical, language development. If the same injury occurs in a 4-year-old child, who had developed language typically, it is likely that language will not reorganize, at least not as completely.

Compensation is another wonder of childhood plasticity. A child who develops with significant impairments will naturally develop compensating behaviors for these impairments. For example, a child with a visual field cut learns how to function adequately despite the handicap and consequently often has limited awareness of the visual field cut. This makes sense because the young child does not have the memory of her or his vision being different. Another example of this is unilateral neglect. Young children often demonstrate neglect following perinatal strokes. When such patients are observed, these young children will often show full compensation, such as a natural ability to turn toward the neglected side or to create search strategies to scan around the perimeter.

To accurately interpret data, the neuropsychologist also needs to consider the course of normative developmental stages and how incongruent development across neural systems can cause functional difficulties for a brief time. For example, 4- to 5-year-olds generally have better developed learning and memory than executive functioning. At this age, children are often very good at remembering the rules, but they lack inhibitory control and switching to follow them appropriately and consistently. This will result in a period of time of seemingly purposeful rule breaking that tends to subside quickly.

Testing interpretation must account for all aspects of the child's environment as well. Does the child live in a home with few resources? A chaotic home? A home with environmental risks such as lead paint? What type of relationship does the child have with the parents? Is the discipline approach authoritative but positive or authoritarian or permissive? What languages are spoken in the home? What type of education is the child receiving? Each of these and many more factors has a significant impact on the development of neuropsychological functions. In fact, family and environmental factors often mediate or predict poor neuropsychological outcomes from neurological injury or disorder. The child's temperament and emotional/behavioral functioning can also impact neuropsychological development and performance. These can often cause poor performance on neuropsychological testing; both significant anxiety or inattentiveness reduce attentional focus and concentration.

B. Recommendations

A key aspect of a neuropsychological evaluation is the development of appropriate recommendations for the particular child. Recommendations should be provided for each neuropsychological syndrome or weakness. They should be individually crafted to use cognitive strengths to assist with areas of weakness or impairment. For example, a child with strong verbal abilities can learn to verbally mediate visual spatial tasks, such as reading graphs or maps. A child with strong planning and organizational skills can schedule extra time for practicing reading or writing, if the child has a reading disability. These recommendations should answer the referrer's primary questions. They also should tell parents, therapists, and school how to assist in optimizing development and recovery as well as provide accommodations for permanent deficits. Recommendations may also provide resources that are available in the community, online, and in books. Most important, the skilled neuropsychologist focuses on the whole child, addressing other areas that are negatively impacting neuropsychological development, such as recommending a psychologist to treat anxiety or teach parents more productive

behavior management strategies. Education on community resources to enhance an impoverished environment or to help choose a strong school is sometimes integral to the child's long-term success.

IV. INTEGRATION WITH ADULT NEUROPSYCHOLOGY

There are numerous life-span aspects of neuropsychology that should be understood by all neuropsychologists. Many chronic neurological, medical, or genetic disorders affect the individual throughout his or her life. A child-focused neuropsychologist is more knowledgeable and sensitive when aware of the life-span course of the disease. For example, many to most children who experience severe TBI continue to require supervision over aspects of daily living into adulthood. Many chronic neurological disorders are associated with reduced life spans. Intellectual disability in childhood continues to be intellectual disability throughout adulthood; parents benefit from honest education and preparation, allowing for optimal time to mourn the loss of expectations and proceed to work toward optimizing their child's daily living skills. An adult neuropsychologist needs to be aware of the developmental course of the patient's neuropsychological functions, as well as social, emotional, and environmental experiences.

A. Transition to Adulthood

Because more and more children with chronic conditions are surviving longer and thriving into adulthood, both child and adult neuropsychologists should be competent to assist with transition into adulthood and determination of need for guardianship. The time frame from 16 to 20 years marks many changes for a young adult and his or her family, who are faced with the question of what to do after high school. Does the child possess the ability to go to a traditional college? If so, he or she needs to participate in training courses for college entrance exams, receive extra support for taking the exams, and transition his or her special education plan from high school to college. Unlike even a decade ago, many colleges and universities provide substantial special education, with some even having designated school and dormitory living for young adults with a disability. The young adult not equipped for college may participate in specific trade-based education or job-learning programs. For many patients, the transition is into community-based programs for individuals with disability with assistance through community organizations.

B. Guardianship

Parents and young adults are often faced with the question of whether the individual requires guardianship. Guardianship is a legal definition awarded by the court that determines whether the individual either needs assistance in decision making or needs another to make decisions in a wide variety of areas, including finances, consent for medical treatment and participation in research, marriage and divorce, driving, voting, and even hunting and fishing. Although a neuropsychological evaluation is not necessary to determine guardianship, it is often helpful in determination. Additionally, many patients with chronic neurological conditions, such as brain injury or brain tumor early in childhood, will not be followed by other medical professionals anymore. The neuropsychologist may know the individual and the family better than anyone else in the position to determine need for guardianship. The assignment of guardianship can be for all or for specific domains of functioning (e.g., finances and marriage).

V. INNOVATIONS, TRENDS, AND CONTEMPORARY ISSUES IN CHILD NEUROPSYCHOLOGY

For the majority of the field's history, child neuropsychologists have had the option of practicing in an academic medical center or in private practice in major metropolitan areas. Currently, positions are increasingly available in private hospital systems, in smaller cities and rural medical centers, and in schools. This transition has been driven by the presence of more training programs specific for child neuropsychologists but also by increased education of medical professionals—such as pediatric neurologists, neurosurgeons, and pediatricians—on the value of a neuropsychological evaluation for their patients. Increased demand is resulting in increased work opportunities.

A. Outcome Prediction

Traditionally, neuropsychological evaluations have been requested to assess the outcome of an injury, disorder, or disability. A shift has occurred to view neuropsychological functions as predictors of broader outcomes, such as surgical, adaptive, academic, social, or emotional. Some examples of this shifting role of the evaluation are presented. In the past, the child neuropsychologist would document the final

neuropsychological outcome following TBI 6 or more months after the injury. In most centers, the neuropsychologist is now involved from the subacute phase to assist with education of parents on potential outcomes and variables that predict good outcomes, such as supportive environment, routine involvement in therapy, and absence of anxiety and depression. Education to teachers and friends on the course of recovery can help reduce the negative effects of returning to functioning with substantial deficits and losing social or academic position and confidence, even though a full recovery is expected over time. This is especially true for mild TBI and sports-related concussions. Intractible localized epilepsy may be treatable with hemispherectomy or lobectomy. Neuropsychological evaluation is useful in the determination of lateralized motor, language, and memory function that predicts functional loss following surgery. Establishing neuropsychological functioning and development can assist in classification of genetic disorders, which allows for prediction of disease course.

B. Rehabilitation and Treatment

Although neuropsychologists have traditionally had a presence on rehabilitation units, more neuropsychologists in other settings are being requested to have specialization in rehabilitation and treatment. An emerging trend is to implement therapy for injured attention, executive functioning, and memory following injury. These treatments are often administered and tracked empirically by the neuropsychologist.

C. Telemedicine

Another likely trend will be the need to practice telemedicine for children. Many children are too medically compromised to travel, or parents are not able to travel for treatment. Possible ways for evolution in this area include doing interview and feedback via phone or video conferencing, doing screening evaluations, or even testing via video conferencing. The ethics of this have been discussed primarily for adult neuropsychology, and methods are being developed.

D. Health Care Trends, Insurance Coverage, and Reimbursement

Changing and uncertain health care policy and reimbursement rates are likely the most pressing issues facing child neuropsychology. As in all of medicine, fewer patients pay for the complete charges for

an evaluation. Rather, insurance companies make payments for the evaluation. Each insurance company determines the market value for neuropsychological testing codes, and this can vary substantially between and within insurance companies. Many insurance companies negotiate these rates with the neuropsychologist or the organization. The contracted rate may differ on the basis of diagnosis (with mental health diagnosis receiving lower payments than do medical diagnoses at times) and may change from year to year. The practicing neuropsychologist needs to have a savvy understanding of such issues and of the impact they have on collection rate and overall practice budget.

The child neuropsychologist has an additional insurance-based concern: Medicaid and state-based government contracts. Although Medicare is a federally funded program, Medicaid is funded by individual states. This results in widely disparate coverage plans and reimbursement rates from one state to another. Because the majority of children with neurological, medical, and genetic disorders are covered by Medicaid, this can have a strong impact on a child neuropsychologist's ability to develop and maintain a successful business plan.

Child neuropsychologists also need to be aware of exclusions in coverage for neuropsychological assessment. For example, many companies have exclusions that restrict testing for learning disability (arguing that school districts should conduct these evaluations), ADHD (given that current state-of-the-art diagnosis and management are considered to be conducted by pediatricians), and even autism or developmental delay. These exclusions highly restrict the pediatric neuropsychologist's practice. Given the poor reimbursement rates for many children with neurological disorders covered by Medicaid, the child neuropsychologist often has to be creative in developing and maintaining a financially productive and sustainable practice.

E. Reducing Health Disparities

Consideration for justice in provision of services has to be a factor in practice development, even as financial success also has to factor into a child neuropsychologist's business development. As discussed, socioeconomically disadvantaged children and many children with neurological, medical, and genetic disorders are covered by low-paying insurance companies. The provision of their care can undoubtedly be a burden on the financial success of a clinical practice. Yet, these children often have the highest risk for neuropsychological impairment from both medical and family/environmental perspectives.

Children from disadvantaged environments have increased risk for lower intelligence, learning disability, and ADHD. Additionally, children with neurological, medical, and genetic disorders who live in families with lower socioeconomic status have poorer cognitive, emotional, and behavioral outcomes. These populations also tend to be educated in poorer school districts that are not able to meet the special education needs in any optimal manner. Developing a practice plan that allows for provision of neuropsychological services to these disadvantaged children is important.

VI. TRAINING OF CHILD NEUROPSYCHOLOGISTS

The training requirements are slightly different for a child neuropsychologist than for an adult neuropsychologist. Specialized knowledge in neuropsychology and child development and psychology is essential. Most child neuropsychologists attend graduate school in a clinical psychology program with emphasis on neuroscience or child psychology. Internship programs vary as well, but the student is advised to consider programs that result in at least 50% neuropsychology training and 50% pediatric psychology or child psychology. At some point in training, it is beneficial to be involved in adult-focused neuropsychology as well. Two years of postdoctoral training are strongly encouraged, with most or all time spent directly engaged in child neuropsychology didactic and practical learning. Such training will result in thorough understanding of brain development, neuropsychological function development, neuroanatomy, neuropsychological syndromes, and a vast range of neurological/medical/genetic disorders. Students considering a child neuropsychology specialization are encouraged to begin taking classes on neuropsychology and child psychology or development in graduate school. Practicum placement in child neuropsychology sites is highly valuable as well.

Child neuropsychology is a tremendously exciting field, requiring flexibility in thinking and desire to learn and integrate new knowledge. Research on brain development, neurological disorders, neurogenetics, and therapies to improve neural development is rapidly evolving, resulting in an always changing profession.

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Chapter 7

Xavier E. Cagigas and Jennifer J. Manly

Cultural Neuropsychology: The New Norm

When cultural and linguistic issues in neuropsychology are raised as a topic of discussion, most U.S.-based clinicians and researchers immediately begin to think of ethnic minority groups or people with limited English proficiency. Those who are familiar with recent literature may have associations related to level of acculturation, educational experience, and other variables that, if controlled, have the potential to improve the sensitivity and specificity of neuropsychological instruments in the diagnostic setting. In this way, the dialogue is frequently framed as having to do with the impact of culture and language *on* cognitive testing and is thus conceptualized as being relevant *only* to special populations.

I. WHAT WE DO AND SHOULD NOT

However, the everyday practice of neuropsychologists falls victim to folk beliefs that are unsubstantiated by empirical evidence, due in part to this limited view. For example, some neuropsychologists

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believe that if the conversational English of someone who learned English as a second language is "good enough," their cognitive abilities can be reliably assessed using a traditional battery of tests and related normative data developed on monolingual English speakers. This is particularly problematic because the assumption of "good enough" is made at the convenience of the neuropsychologist, and not necessarily in the best interests of the bilingual patient. How many neuropsychologists who are conversant in a second language, for instance, would be willing to undergo a neuropsychological assessment and have treatment decisions made on the basis of their conversational ability in a second language if they suffered the misfortune of acquiring a brain injury while visiting a foreign country? Other practitioners feel that it is sufficient to include a sentence that cautions the reader about the limits of interpretation due to a patient's cultural and linguistic background within one of their clinical reports, in order to justify use of the same typical instruments and norms that they were trained with during clinical internship or postdoctoral fellowship. Still, other students, and even professionals, feel competent to assess a non-English-speaking recent immigrant who suffered a traumatic brain injury after having completed a 6-hour continuing education seminar. The fact remains that most neuropsychologists will, at some point in their career, find themselves, stopwatch in hand, faced with a difficult decision: Is it appropriate to complete a neuropsychological assessment of a person whose culture they know nothing about, whose language they do not speak, and who otherwise does not reflect the characteristics of the standardization or normative sample of the measures available for the assessment? If they do not proceed, will they be denying that person access to a specialist in brain–behavior relationships and the impact of neurocognitive impairments on daily living?

Assessing someone in a language that you do not speak has been fiercely and appropriately criticized (Artiola i Fortuny & Mullaney, 1997, 1998; Artiola i Fortuny et al., 2005). At the same time, clinicians faced with a linguistically different patient have a difficult ethical dilemma, especially when they do not have referral access to the very limited number of qualified multilingual neuropsychologists. The naïve neuropsychologist may view this as a "no-brainer" and decide to use an interpreter. The role of linguistic interpreters as a potential solution to this problem, however, has also been a topic of substantial debate in recent years, given the additional source of error that is introduced into the assessment process (Judd et al., 2009).

Two separate issues merit closer attention when considering linguistic differences in neuropsychological assessment. On the one hand, just because a psychologist, postdoctoral fellow, intern, or doctoral student speaks the patient's language, it does not uniquely

qualify them to assess patients who have limited English proficiency. Without an explicit knowledge of the strengths and weaknesses of available instruments and norms in that language, their linguistic assets alone would not be a true advantage in performing a meaningful and valid neuropsychological assessment. In fact, complicit participation in carrying out such an assessment could create the false illusion that this is "good enough," in the eyes of all parties involved (i.e., clinician, patient, family, and other allied health professionals). By contrast, a neuropsychologist who does not speak the language of the patient may actually have an adequate understanding of what the relevant issues are in assessing a person within that language but, without the ability to directly communicate with the patient, may miss certain key pieces of information for purely linguistic reasons (e.g., paraphasic errors) and in the end may be no better off than is the fluent clinician. Furthermore, though cultural knowledge often travels with linguistic knowledge, these factors can be independent, especially given the rising number of second-generation U.S. psychologists who grew up speaking a language other than English at home. Thus, even a clinician speaking the same language as does the client may miss subtle neuropsychiatric manifestations of a disorder not because of linguistic limitations or a lack of familiarity with instrumentation but rather because of how symptoms are expressed within the particular culture (e.g., culture-bound syndromes; Gone & Kirmayer, 2010; Kirmayer, 2006). This last point introduces the heart and soul of cultural neuropsychology as it is evolving, namely, that neurocognition is deeply embedded within a person's cultural practices and therefore can only be accurately understood and assessed by taking these practices into account.

Despite the recent publication of position papers and clinical handbooks with an explicit focus on serving diverse populations, there are those who still insist on trying to make do with what they have, or rather have had, within their immediate grasp. As was stated by the English jurist John Selden, "ignorance of the law excuses no man; not that all men know the law, but because 'tis an excuse every man will plead, and no man can tell how to confute him" [sic]. This stagnancy is further compounded by the tautological logic of our well-meaning ethics code with regard to the assessment of underrepresented minorities (Standards 2.01, 9.01, 9.02; American Psychological Association, 2010). How then does one validly assess those for whom valid assessments do not yet exist, or justify denial of services to a patient whose suffering could be alleviated with recommendations from a proper neuropsychological assessment? The inertia that such an ethical mandate creates has enabled numerous neuropsychological practices cloaked in the guise of "doing the best we can with what we have." However, this well-meaning, but often

misguided, approach has the potential to damage the very foundation upon which our assessment methods are built and lead to a different substandard of care for the historically underrepresented, given limited empirical evidence to contradict this unexamined status quo.

Test publishers and their products do not always clarify the muddied waters of assessment across diverse cultures and languages. Careful perusal of non-English assessment instruments newly available from publishers reveals that they are (a) assessments that are simple translations of the English edition on which they are based, with no changes to item content; (b) adapted assessments that are both translated and modified from the English edition to best suit the target population (e.g., editing certain items to make them more culturally appropriate/relevant, changing the placement of items to achieve a more uniform gradient of difficulty, or introducing new items that are more appropriate for the targeted population); (c) translations/adaptations that have English norms but lack norms in the new language and population; (d) translations/adaptations with available norms in the translated language collected among standardization samples living within the United States; or (e) translations/adaptations with available norms in the translated language collected among standardization samples outside the United States. The responsibility for the ethical and scientifically responsible use of these options, however, is ultimately left to the practicing psychologist. We must then seriously consider whether our training and experiences as neuropsychologists have adequately prepared us for deciding among these options. If an assessment instrument has been demonstrated to have adequate reliability and validity for a specific purpose in English, for example, its translation into another language will not necessarily possess the same psychometric properties. Furthermore, if normative data collected in English are applied to scores on the newly translated instrument, this also invalidates the "new" instrument's utility in clinical decision making. Linguistic equivalence in translation/adaptation is independent from psychometric equivalence or equivalence of the underlying construct. These examples illustrate the potential danger of relegating cultural and linguistic variables to practices that do not meet the highest standards of scientific and methodological rigor, even if one's intentions are to provide more desperately needed instrumentation for underserved linguistic groups.

This chapter presents a tentative guide for improving the quality of the discussion surrounding cultural neuropsychology and a suggested blueprint for improving the quality and accuracy of cognitive assessment across diverse populations in both clinical and research settings. Although some of the content of this chapter

focuses on what we do wrong (naïvely and sometimes decidedly well intentioned), we also show that our field possesses the basic building blocks for fixing these problems. In fact, many of the solutions are embedded within the writings and observations that represent the formative roots of the field of neuropsychology. In the following sections, we (a) define cultural neuropsychology, (b) briefly review efforts to address cultural differences in cognitive test performance, and (c) reframe old questions to address modern problems that challenge some of the basic tenets held by most neuropsychologists. We then (d) briefly review key historical underpinnings of cultural neuropsychology, (e) provide a short overview and critique of other "handbooks" for neuropsychological assessment across cultures, (f) review the implications of demographic adjustments to normative data, and (g) raise awareness of ongoing work to identify variables that potentially underlie cultural differences and may ultimately help us make more accurate decisions in the diagnostic setting. Finally, with the hope of increasing interdisciplinary collaboration, we (h) briefly review advances in other disciplines that have made considerable progress in understanding cultural differences in cognition from sociological, biological, and psychological perspectives. Although we offer some practical guidelines for trainees, early career neuropsychologists, and established professionals, we balance these guidelines with an attempt to reframe and refocus the discussion of cultural neuropsychology and thus challenge the field to find new and better solutions.

II. WHAT IS CULTURAL NEUROPSYCHOLOGY?

It has been over a decade since the term *cultural neuropsychology* first made its way into the research literature lexicon (Kennepohl, 1999). This prescient call "toward a cultural neuropsychology" emerged as neuropsychology itself began to suffer a rude awakening, becoming aware that the discipline's significant strides were hampered by a lack of generalizability and ecological validity in representing the global community, and also the diverse patient population emerging in the United States. Similar pleas had been made in the past (Mecacci, 1984), but not under the guise of neuropsychology, at least not explicitly (Mecacci, 2005). Cross-cultural perspectives in neuropsychology, on the other hand, have enjoyed a slightly longer tail stretching into the past and have been clearly articulated, if not broadly heard and assimilated (Ardila, 1996). Since Kennepohl's (1999) call, the last decade and a half has seen a significant uptick in manuscripts addressing cultural issues in neuropsychology, as are summarized in this chapter. The historical roots of a broader cultural

psychology have also been masterfully articulated previously (Cole, 1998), and now the term *cultural neuroscience* (Chiao, 2009) has also emerged in the research literature to present an alternative view to the dominant homogenized view of brain and behavior. As such, the reemergence of cultural neuropsychology in this time, as discussed below, is in line with an awakening cultural zeitgeist that is coloring, and perhaps shifting, the continued rise of neuroscience as a means for understanding the human experience.

It is perhaps worth briefly exploring the difference between cultural and cross-cultural perspectives, because this seemingly innocuous distinction inevitably leads to very different destinations (Greenfield, 2000). Whereas cross-cultural perspectives compare one cultural or ethnic group with another with the purpose of examining the differences between the two, cultural psychology is less interested in between-group comparisons and more interested in explaining within-group variability. There is also a hybrid form of cross-cultural approaches that does not focus exclusively on group-level differences but instead attempts to treat language/culture/ethnicity as an independent variable that is somehow reified and separated from cognition as a dependent variable. Cultural psychology, on the other hand, assumes that culture and cognition are inextricably linked and that one cannot fully be understood without the other simultaneously being taken into account (Cole, Levitin, & Luria, 2006). Cultural neuropsychology, therefore, can be defined as *the systematic study of brain behavior relationships within the context of human beings recursively engaging in specific cultural practices that organize the development, maintenance, and revision of their cognition and behaviors*. Unfortunately, modern neuropsychology within the United States has fallen somewhat behind in truly addressing all of these issues, and only recently has a cadre of scientists and clinicians begun to push for a more integrated neuropsychology (Rivera Mindt, Byrd, Saez, & Manly, 2010). The last decade and a half, for example, has witnessed tremendous strides in articulating the limits of an acultural neuropsychology (Manly, 2008). The irony, of course, is that cultural neuropsychology was present in a clearly articulated, though deeply embedded, form from its inception in the work of Luria, one of the founding fathers of neuropsychology (Bodrova, Leong, & Akhutina, 2011).

III. A RECAPITULATION OF VYGOTSKY'S "CRISIS IN PSYCHOLOGY" AND LURIA'S SOLUTION

Michael Cole's (1998) scholarly exposition of the historical roots of cultural psychology systematically traces the evolution of what Wilhelm Wundt called "the second psychology." Namely, this was

coined as a *Völkerpsychologie* that embraced the complexity and diversity of human experience, which was minimized by experimental psychology in order to give way to a more universalist perspective (Diriwächter, 2004). The tension between a universalist perspective of cognition focused on a nomothetic science of groups, and more contextualized approaches yielding idiographic laws capable of guiding interpretation of individual experiences, formed the cornerstone for what Lev Vygotsky termed "the crisis in psychology" (Cole, 2002). In essence, this crisis can be recast as dialectic between objective and subjective approaches, between fixed and process approaches, laboratory and field approaches, or phylogenetic and ontogenetic approaches. Though largely unheard, previous arguments have been forcefully made that most contemporary neuropsychologists are not exposed to these historical foundations in neuropsychology and its methods and thus cannot benefit from how this perspective may inform current practice (Ardila, 2002; Luria, 1967).

It is important to note that volumes have been dedicated to extrapolating Vygotsky's sociocultural or sociohistorical theory; however, it is a little known fact among most modern neuropsychologists that A. R. Luria, considered a father of neuropsychology by many, was part of this founding school that attempted to integrate the cultural and historical with a developmental view of cognition. What is even less appreciated is that his theory of the functional organization of the brain assumed a cultural historical approach as a point of departure (Kotik-Friedgut & Ardila, 2005). Even a cursory appraisal of Luria's prolific work—including his self-proclaimed introductory text to neuropsychology (Luria, 1976), two classic neuropsychological novellas (Luria, 1987, 1994), views on development (Luria, 1985), and approach to rehabilitation (Luria, Naydin, Tsvetkova, & Vinarskaya, 1969)—reveals a degree of depth that both has withstood the test of time and provides a type of treasure map for the modern cultural neuropsychologist with a formulation of the interpenetration of cultural practices and the workings of the human brain.

A simple yet telling example of this can be found in Luria's field work in Uzbekistan (Nell, 1999, 2000). Here he had the rare opportunity to study a geographically isolated rural community as the people there began to acquire literacy practices. Assessment of various cognitive processes with instruments available at the time revealed that these people were not susceptible to certain purportedly universal visual illusions and were unable or unwilling to categorize objects on the basis of abstract rules. They instead focused on the relationship of stimulus objects to their everyday lives and simply did not perform in the same way as most educated adults on

his battery of cognitive tests. Over time, however, as those in the community began to participate more in the cultural practice of acquiring literacy and "going to school," they began to perform in more predictable ways, though still differing qualitatively from those who had experienced a more normative upbringing. Luria and his contemporaries hypothesized that the historical shift in their cultural practices demonstrated just how tied was their way of thinking to their everyday cultural context and way of life. In other words, when the cultural practices that organized their everyday life shifted, so did their way of thinking and perception of the world around them.

IV. UZBEKISTAN REVISITED? A HISTORICAL SHIFT IN U.S. DEMOGRAPHICS

The 2010 Census demonstrated that the United States of America is currently undergoing a truly historical shift in demographics that is changing the face of the country (U.S. Census Bureau, 2011). As a result, the shortage of neuropsychologists equipped to tackle this oncoming multicultural wave exposes the fact that even the training that most neuropsychologists have already received with diverse populations is antediluvian (Echemendia, 2004; Rivera Mindt et al., 2010) and is consequently providing a similar opportunity to that presented to Luria in Uzbekistan. This has been recognized in theory for some time now by a segment of the neuropsychology community citing evidence from practice surveys (Echemendia & Harris, 2004; Echemendia, Harris, Congett, Diaz, & Puente, 1997), a lack of training opportunities (Allison, Echemendia, Crawford, & Robinson, 1996), a lack of structure for defining competency (Van Gorp, Myers, & Drake, 2000), and challenges in the recruitment and retention of historically underrepresented neuropsychologists (Byrd et al., 2010).

The historical shift described above has been framed as a need to address cultural and linguistic issues in the neuropsychological assessment of historically underrepresented minorities and has been met with the publication of various handbooks and position papers during the last decade. These first-response publications have been preceded by numerous special chapters within larger volumes dealing with assessment (Puente & Agranovich, 2004; Puente & Garcia, 2000). The first major handbook (Fletcher-Janzen, Strickland, & Reynolds, 2000) attempted to bring together a body of literature and perspectives that had never coexisted before with a broad focus toward orienting clinicians to relevant issues. This was followed by a second handbook that adopted a focus on specific minority

populations, trying to offer more practical advice for how to work with each of these groups (Ferraro, 2002). In a similar vein, Latino neuropsychologists also weighed in with the publication of a position paper (Judd et al., 2009), handbook (Pontón & Leon-Carrion, 2001), and volume more thoroughly examining contextual factors such as immigration trajectory, trauma history, and early childhood experiences of poor nutrition and poverty often observed within the highly heterogeneous Hispanic/Latino population (Llorente, 2008). Another population-specific handbook followed that focused on Asian-Americans and Asian nationals from different countries (Fujii, 2010). This volume in particular stressed the importance of understanding a particular subgroup's historical context, cultural norms, and adopting a hypothesis-driven and process approach in assessment that relies less on hard data, which of course does not currently exist. The most recently published generalist handbook adopted a more international cross-cultural perspective (Uzzell, Pontón, & Ardila, 2007). It too seemed to focus more on groups from different parts of the world closely following the lines of ethnicity rather than attempting to adopt a more cultural neuropsychology framework. All of these texts offer valuable information that helps to contextualize the assessment encounter and inform the clinician about important issues in working with specific cultural groups, but they all perpetuate an explicit focus on differences drawn along racial, ethnic, or geographical lines.

V. A SHIFT IN PARADIGM

It is, in fact, ironic that the word *cultural* should even have to be inserted ahead of neuropsychology to draw attention to the role that human cultural practices and diverse life experiences play in brain–behavior relationships. Fortunately, the context in which most U.S. neuropsychologists function is allowing for a more conscious awareness of the diversity that exists among people throughout the world, and particularly within our own borders. Conversations about the role of individual differences and systematic variability across groups are surfacing at unprecedented rates, perhaps partly because the modern clinical neuropsychologist is faced with serving populations that are not representative of the standardization samples for the armamentarium of instruments currently available. Yet in our fiercely egalitarian and politically correct society, the mere suggestion of functional brain differences among people from different backgrounds summons reactionary condemnation given the very real, dark, and not-so-distant past history of eugenics and psychology's complicit role in its promulgation (Gould, 1981). The swing of the pendulum,

however, has unwittingly led to the systematic marginalization of those who have not been represented in the research studies and clinics that have shaped the discipline and has raised the specter that perhaps we cling to an impoverished understanding of brain–behavior relationships that reflects the experience of only a select subset of the human population.

As previously alluded to, cultural and linguistic considerations in neuropsychological assessment are usually relegated to a footnote or expiatory caveat in clinical reports, stating that caution should be exercised in interpretation of the results given the unknown impact of possible cultural and linguistic factors. The cultural is, therefore, conceptualized as a constricting limitation that must be *accommodated* to justify the use of a system for understanding brain–behavior relationships and thus assumes a certain degree of uniformity in order to make inferences about individuals on the basis of group-level data. In the end, this inevitably leads to a different standard of care for those who do not fit within the current cadre of available measures.

Equally inherent in neuropsychology's history and practice, as well as neuroscience overall, is the legacy of Cartesian dualism and the reign of reductionist science in explaining human behavior and cognition (Nicolosi & Ruivenkamp, 2012; Oyama, 2000). Nevertheless, the en vogue response of "both" to the proverbial nature versus nurture question betrays a long-held implicit assumption in neuropsychology that brain begets behavior. After all, it has only been fairly recently that science has "discovered" brain plasticity and provided a viable mechanism for how the brain might also serve as a recursive dependent variable in the causal chain of cognition (Doidge, 2007). Modern methods in neuroscience have demonstrated the impact of everyday cultural practices on a protean brain that reflects the specialized expertise and unique experience of jugglers (Driemeyer, Boyke, Gaser, Büchel, & May, 2008), musicians (Gaser & Schlaug, 2003), taxicab drivers (Maguire et al., 2000), bilinguals (Bialystok, Craik, & Luk, 2012), and even people who experience perceived discrimination (Johns, Inzlicht, & Schmader, 2008). Notwithstanding, neuropsychological assessment instruments are not calibrated to adapt to baseline differences systematically shaped by specific lifetime experiences, which may impact both the diagnostic sensitivity and specificity of the measures. As evidence continues to accumulate, the need for a paradigm shift that incorporates the explicit study and integration of specific cultural practices into the study of brain–behavior relationships becomes more apparent, especially as humans continue to interact with ever-evolving forms of technology (e.g., computers, cell phones), which birth new, uncharted cultural practices.

VI. THE HISTORICAL ROLE OF DEMOGRAPHIC CORRECTIONS

The typical clinical neuropsychological evaluation occurs without the benefit of prior testing. In other words, the neuropsychologist is asked to determine whether there is some new, acquired impairment and whether there has been a decline in cognitive function without objective information about prior test performance. Therefore, one key purpose of collecting information about medical and demographic background is to help estimate premorbid level of function (Busch, Chelune, & Suchy, 2006). Neuropsychological test norms serve as a standard against which a person's performance can be evaluated and then interpreted (Mitrushina, Boone, Razani, & D'Elia, 2005) and also can be used for either descriptive or diagnostic purposes (Busch et al., 2006).

When an individual's performance is compared with that of a single reference group—for example, a group of people matched to the U.S. population on age, sex, region of residence, race, and years of schooling—the normative data are being used descriptively. Any population can serve as a reference if appropriate to the question at hand; for example, use of a standardization sample that is representative of the U.S. population may have value in predicting the ability to read, understand, and act on medical instructions given in English (Wilson, 2003; Youmans & Schillinger, 2003; Zarcadoolas, Pleasant, & Greer, 2005) or the likelihood of obtaining admission to college.

More relevant to neuropsychological assessment, however, is the circumstance in which normative data are used to diagnose cognitive impairment (Busch et al., 2006; Heaton, Taylor, & Manly, 2001). In this case, the purpose of norms is to provide a best estimate of an individual's premorbid or expected score to which the obtained score can be compared. If the normative sample was selected appropriately, cutoffs can be generated that should provide good diagnostic validity, using indices such as sensitivity and specificity, positive predictive value, and likelihood ratios (Smith, Cerhan, & Ivnik, 2003). It should be clear that when norms are used for diagnostic purposes, background variables are likely to be crucial determinants of premorbid ability. Just as crucial as demographic factors such as age, education, and sex, racial and ethnic background has been shown to have significant effects on verbal and nonverbal neuropsychological test performance (Manly & Jacobs, 2002). Because most standardization samples consist of well-educated, English-speaking, U.S.-born, culturally mainstream Whites, ignoring demographic differences within the standardization sample can cause

attenuated specificity of verbal and nonverbal neuropsychological tests, such that cognitively normal ethnic minorities are more likely to be misdiagnosed as impaired in comparison with Whites.

The problem of low specificity among racial and ethnic minorities has driven a new fervor for collection of separate norms for each racial/ethnic or language group. Although establishing separate test norms for each group may help with misdiagnosis (Miller, Heaton, Kirson, & Grant, 1997), there is still considerable variability of educational and cultural experiences within groups that may decrease the utility of these norms. A person's racial or ethnic classification reveals nothing about his or her cultural, socioeconomic, educational, or racial experiences. Race and ethnicity may be surrogates for, or be confounded by, other relevant and more meaningful variables such as socioeconomic status, language proficiency, or educational quality.

Available separate ethnic group norms do not always provide explanations about why the standards for normal function differ across groups, and unfortunately, this leads to misunderstanding and misinterpretations (Herrnstein & Murray, 1994; Jensen & Miele, 2002) that fall prey to social and political agendas. Furthermore, separate ethnic and linguistic group norms allow us to escape critically important limitations in the construct validity of our measures. In other words, even if norms provide the proper adjustments and comparison groups to the population being tested, the measures may not provide accurate assessment across cognitive domains because they do not capture how cognition is expressed within that culture. Finally, as racial and ethnic lines blur in the United States with new generations containing more biracial and multiracial children, as well as bilingual and multilingual speakers, sharp classifications along language and racial/ethnic lines will lose relevance and utility. It is also important to note that although problems with specificity are more readily acknowledged in the context of assessing the culturally and linguistically different, adequate diagnostic sensitivity should not be assumed. For example, aphasia manifests differently in Spanish than in English (Ardila, 2001), and language disturbances follow a different pattern of development and recovery in bilinguals (Paradis, 2004), and so assessment solely in English, even with effective demographic adjustments, does not ensure an adequate balance of diagnostic sensitivity and specificity, particularly in more high-risk contexts (i.e., neurosurgery).

In summary, demographically adjusted norms are appropriate when (a) the tests have construct validity, (b) the key question is diagnostic, (c) the examinee is a member of the population in which the norms were developed, (d) issues like selection bias or preclinical cognitive impairment do not invalidate the representativeness of

the normative sample, and (e) it has been demonstrated that demographic adjustments maximize diagnostic accuracy. If used properly, demographic adjustments improve specificity. However, the practical and theoretical limitations of these norms have raised questions about the behavioral, attitudinal, experiential, and psychological underpinnings of linguistic and cultural differences in cognitive test performance. Deeper exploration of these underlying variables will help to improve our understanding of the role of race, culture, education, and language on cognitive functioning.

VII. UNPACKING CULTURAL PRACTICES: WHAT MAY BE DRIVING DIFFERENCES BETWEEN AND WITHIN CULTURAL GROUPS

A. Translation of Tests

Improper translations of tests, including culturally inappropriate translations and use of inappropriate normative standards with well-translated measures, may be responsible for considerable linguistic and ethnic group differences on cognitive measures. As discussed above, it is common practice in dealing with non-English-speaking populations to simply translate English language measures into a new language. Even if translation and back-translation methodologies are used, they are of questionable value because these translations are often provided by people who are not neuropsychologists or have not obtained higher-education credentials in the target language. In general, practitioners should be wary of versions of tests that do not follow established guidelines for development and translation of tests into different languages (van de Vijver & Hambleton, 1996) and those that do not consider cultural equivalence alongside linguistic equivalence (Harris, Echemendía, Ardila, & Rosselli, 2001).

B. Bilingualism

The effects of bilingualism on cognitive development, including executive control and cognitive flexibility, have been well documented (Akhtar & Menjivar, 2012) and are also possible contributors to ethnic and linguistic group differences. Among adults, findings of lower scores on measures of vocabulary (Bialystok, Luk, Peets, & Yang, 2009), picture naming (Gollan, Fennema-Notestine, Montoya, & Jernigan, 2007), word comprehension and production (Ivanova & Costa, 2008), and semantic fluency (Gollan & Ferreira, 2009; Gollan, Montoya, & Werner, 2002) among bilinguals in comparison with

monolinguals are contrasted with studies demonstrating a bilingual advantage on measures of executive control and episodic memory (Bialystok, Craik, & Luk, 2008). There is now an emerging but controversial literature examining the effects of bilingualism on cognitive function among older adults. The claim is that the continuous task of managing competing representations of two languages provides the type of cognitive stimulation that leads to cognitive reserve (Bialystok et al., 2012). However, the results of these studies are mixed (Zahodne, Schofield, Farrell, Stern, & Manly, in press) and suggest that when bilinguals and monolinguals are properly matched with respect to educational experience and acculturation, the bilingual advantage for cognitive decline or risk of dementia is less clear. The impact of bilingualism on neuropsychological test performance is a relatively new, but incredibly exciting, area for future work, offering the opportunity to explore critical questions about how culture and language affect brain function, as well as challenge our instruments to a high standard for construct validity (Rivera Mindt et al., 2008).

C. Years of Education/Quality of Education/Literacy

Extreme differences in educational level are often found between ethnic minorities and Whites or between residents of developed and undeveloped countries. Although it is common for investigators to use covariance, matching procedures, or education-corrected norms to "equate" ethnic groups on years of education before interpreting neuropsychological test performance, these techniques ignore ethnic discrepancies in quality of education. Therefore, disparate school experiences could explain why many ethnic minorities obtain lower scores on cognitive measures even after controlling for years of education. Several studies have found that years of education is an inadequate measure of the educational experience among multicultural adults and that adjusting for quality of education may improve the specificity of certain neuropsychological measures across racial groups (Manly, Jacobs, Touradji, Small, & Stern, 2002).

D. Acculturation

Level of acculturation is another source of within-group cultural variability that may also explain differences in cognitive test performance across groups. *Acculturation* is defined as the level at which an individual participates in the values, language, and practices of his or her own ethnic community versus those of the dominant culture

(Landrine & Klonoff, 1996; Padilla, 1980). Previous studies have identified ideologies, beliefs, expectations, and attitudes as important components of acculturation, as well as cognitive and behavioral characteristics such as language and customs (Berry, 1976; Negy & Woods, 1992). Several prior studies have demonstrated the effect of acculturation on cognitive test scores, generally showing that individuals whose background and experiences are similar to the culture in which the tests were developed and normed obtain higher scores than do individuals whose cultural experiences are less mainstream and bound to their own ethnic culture (Artiola i Fortuny, Heaton, & Hermosillo, 1998; Manly et al., 1998).

E. Racial Socialization

Neuropsychologists must take into account that level of comfort and confidence during the testing session, as well as level of distractibility, may vary among test takers according to racial socialization and experience of stereotype threat. Stereotype threat describes the effect of attention diverting from the task at hand to the concern that one's performance will confirm a negative stereotype about one's group and has been described among African Americans (Steele, 1997; Steele & Aronson, 1995), women on math tests (Spencer, Steele, & Quinn, 1999), and among White males (when comparisons with Asians were invoked; Aronson et al., 1999). One study of college-age people suggested that the mechanism by which stereotype threat operates is through depletion of executive resources (Johns et al., 2008). Another study of older adults (Barnes et al., 2012) showed that African American older adults who reported more lifetime experiences of discrimination obtained lower scores on cognitive measures; however, this effect was mediated by level of depressive symptoms. The role of stereotype threat in neuropsychological testing is severely understudied and thus represents an exciting and much-needed direction for future research in cultural neuropsychology.

VIII. INNOVATIONS, TRENDS, AND CONCLUSION

Although Vygotsky and Luria were the first to hypothesize that higher cortical functions within the frontal lobes developed by means of extracortical cultural practices exerting their effects on brain circuitry, modern methods in brain science have given way to cultural neuroscience (Chiao et al., 2010) and a similar hypothesis that culture wires the brain (Park & Huang, 2010). Examples abound for how culture impacts emotion recognition (Derntl et al., 2012), facial

processing (Goh et al., 2010), visual object processing (Gutchess, Welsh, Boduroglu, & Park, 2006), free recall in aging (Gutchess, Yoon, et al., 2006), attentional control (Hedden, Ketay, Aron, Markus, & Gabrieli, 2008), and a host of other cognitive processes and their neural substrates. Neuroimaging evidence (Han & Northoff, 2008) is quickly amassing for cultural differences driven by differing degrees of individualism and collectivism (Way & Lieberman, 2010), personality traits and social identity (Sul, Choi, & Kang, 2012), educational practices (Ansari, 2012), and mechanisms for imitation (Losin, Iacoboni, Martin, Cross, & Dapretto, 2012). Though not without its critics (Martínez Mateo, Cabanis, Loebell, & Krach, 2012), cultural neuroscience is enjoying a fertile nascency. Drawing heavily on cultural historical theory, much has been advanced theoretically to guide this empirical explosion under the rubric of biocultural coconstructivism (Kolstad, 2012; Li, 2003, 2006, 2007, 2008). The next generation of culturally and linguistically competent young neuropsychologists, therefore, would do well to familiarize themselves with these developments in the interdisciplinary arena because cultural neuropsychology is uniquely positioned to bridge the gap between the neurosciences and clinical practice.

Our history shows that the principles of psychic unity and a unilateral reductionist explanatory model are deeply woven into the fabric of neuropsychology. As with so many things in science, however, the questions we ask today have been posed in the past. The limits of neuropsychology in explaining brain–behavior relationships, and neuroscience more broadly, are brought into sharper relief when some of the emerging cross-cultural evidence is examined. A true cultural neuropsychology, therefore, must go beyond simply making cross-cultural or ethnic group comparisons and instead attempt to understand an individual's brain as completely culturally constituted. This integrated approach thereby suggests that greater fidelity in understanding the functional human brain requires an uncompromising integration of cultural practices, cognition, and behavior. Cultural neuropsychology, therefore, challenges us to begin all assessment and inquiry into brain–behavior relationships with diversity as a point of departure, with a direct examination of a person's cultural practices, which provide the scaffolding for the development and continued execution of cognition in people's everyday lives.

Perhaps the vestigial legacy of lesion studies in birthing neuropsychology has kept cultural ghosts at bay by keeping things relatively simple until now. The lack of articulation of the voices for the historically underrepresented, however, seems to have finally broken through the mind-numbing chatter of neural homogeneity, clearing the way for a reclaiming and recasting of brain diversity

that is empowering and representative of all humans while also more scientifically rigorous and closer to the diversity found throughout neurobiology and anthropology. To begin to define cultural neuropsychology, therefore, is truly to define the identity of neuropsychology itself in the 21st century and beyond.

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PART II

NEUROLOGICAL DISORDERS

Chapter 8

David Nyenhuis

Cerebral Vascular Disease

Cerebral vascular disease (CVD) is heterogeneous and complex. It affects the function of both large and small cerebral blood vessels and can result in either sudden neurobehavioral change (e.g., from large artery stroke) and/or chronic cognitive and behavior decline (e.g., from small vessel disease). It can attack by itself or in combination with other disease states, such as Alzheimer's disease (AD). Vascular cognitive impairment (VCI), the cognitive and behavioral phenotype associated with CVD, is also heterogeneous and complex, with no single sensitive and specific identifying cognitive or behavioral pattern.

Additional resources that were consulted in the creation of this chapter may be found in the online resources at http://pubs.apa.org/books/supp/parsons, grouped as (a) Cognitive and Functional Correlates of CVD, (b) Epidemiology of CVD and VCI, (c) Neuropsychological Instruments Used in Patients With CVD, (d) Behavioral Disturbance Associated With VCI, and (e) Pharmacologic Treatment in VCI.

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Clinical Neuropsychology: A Pocket Handbook for Assessment, Third Edition, Michael W. Parsons and Thomas A. Hammeke (Editors)

Table 8.1. Medical Abbreviations Used in This Chapter

Abbreviation	Term
AD	Alzheimer's disease
AVM	arteriovenous malformation
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CSVD	cerebral small vessel disease
CT	computed tomography
CVD	cerebrovascular disease
FLAIR	fluid attenuation inversion recovery
MID	multi-infarct dementia
MRI	magnetic resonance imaging
SAH	subarachnoid hemorrhage
SICH	spontaneous intracerebral hematoma
VaD	vascular dementia
VaMCI	vascular mild cognitive impairment
VBM	voxel-based morphometry
VCI	vascular cognitive impairment
TIA	transient ischemic attack
WMH	white matter hyperintensity

This chapter is intended as a primer for both CVD and VCI. Its goal is to provide the reader with tools that will lead to appropriate test selection, administration, and interpretation when examining patients with potential cognitive and behavioral change related to CVD. Because of the large number of abbreviations used in the chapter, a summary reference table is provided (Table 8.1).

I. DEFINITION/CLASSIFICATION

A. Cerebral Vascular Disease Classification

Cerebrovascular disease (CVD) refers to any pathologic process to the blood vessels that results in brain abnormality (Ropper & Samuels, 2009). The most common forms of CVD are large artery ischemic

Exhibit 8.1. A Brief Classification of Cerebrovascular Disease

I. Stroke
   A. *Ischemic: lack of blood flow due to vessel blockage or damage*
      1. Embolic: *blockage by material brought to the blockage site by blood flow*
      2. Thrombolic: *blockage material formed at the blockage site*
   B. *Hemorrhagic: a rupture of the blood vessel*
      1. Intracerebral Hemorrhage: *bleeding from a ruptured vessel within the cerebrum*
      2. Subarachnoid Hemorrhage: *bleeding from a ruptured vessel in the subarachnoid space, usually in the ventral area around the Circle of Willis*

II. Small Vessel Disease
   A. *Lacunar Strokes: events caused by blockage of the small vessels (arterioles)*
   B. *White Matter Hyperintensities: diffuse, usually subcortical areas of chronic, incomplete ischemia of small vessels*
   C. *Microhemorrhages: Small vessel bleeds, either in lobar or subcortical regions*
   D. *Microinfarcts: Very small lesions, usually only visible at autopsy*

III. Other
   A. *Atrophy: Reduction in brain parenchymal volume, often associated with small vessel disease*
   B. *Transient Ischemic Attack: A brief, reversible stroke-like event*
   C. *"Silent Stroke:" A nonclinical stroke event*
   D. *Mixed Disease: A combination of cerebrovascular disease and other disease process, usually Alzheimer's disease*

stroke, hemorrhage, small vessel disease, and the co-occurrence of CVD and AD (see Exhibit 8.1).

A *stroke* is a clinically defined, sudden, focal loss of neurologic function (Ropper & Samuels, 2009). When due to CVD, stroke is caused by either a blocked vessel (*ischemic* stroke) or a burst vessel (*hemorrhagic* stroke). Stroke is common, with recent incidence estimates of 750,000 new strokes occurring in the United States each year. Stroke is the third most common cause of death in the United States and is a leading cause of both physical and cognitive disability. For many years, from the 1950s to the 1990s, the incidence rate of stroke declined, likely because of better treatment of stroke risk factors, such as hypertension. Stroke diagnosis has increased in recent years, perhaps because widespread use of neuroimaging has led to greater stroke surveillance (Ropper & Samuels, 2009).

Ischemic strokes are the result of a lack of blood flow due to vessel blockage or vessel damage. They account for approximately 80% to 85% of stroke events. Ischemic strokes may be further divided into embolic and thrombotic events. An *embolism* is thrombotic or other intravessel material brought to a place of blockage by blood flow. For example, a *cardioembolic* stroke refers to a blocked brain vessel caused by thrombi formed at or near the heart, often associated with atrial fibrillation, that are transported via the arterial system to the brain. By contrast, a *thrombotic ischemic* stroke is caused by a buildup of intravessel material at the site of the blockage, often in a previously *stenosed* (narrowed) area.

A *transient ischemic attack* (TIA) is caused by either an embolic or a thrombotic event and is defined by its duration time rather than the severity of its symptoms. Ischemic events that last 24 hours or less are arbitrarily defined as TIAs, though most TIAs last fewer than 15 minutes before symptom recovery is achieved. By definition, TIAs do not result in permanent brain lesions. TIAs increase risk for subsequent stroke; approximately 5% of persons who experience a TIA will experience a stroke within 1 year. A *"silent stroke"* is a nonclinical event discovered serendipitously at a later time, usually as a lesion on computed tomography (CT) or magnetic resonance imaging (MRI). One could say that silent strokes are actually neither "silent" nor "strokes." They are not strokes because of the lack of a clinical event, and they are not silent because of their potent risk for subsequent stroke, cognitive impairment, and dementia (Vermeer, Longstreth, & Koudstaal, 2007). Silent strokes outnumber clinical stroke events by greater than 10 to 1 and are estimated to have occurred in 11% of healthy elderly (Vermeer et al., 2007).

Hemorrhagic strokes account for the remaining 15% to 20% of stroke events. Cerebral hemorrhages may be further divided into *intracerebral* and *subarachnoid* events. Spontaneous intracerebral hematomas (SICH) occur in the absence of other trauma. Hypertension is by far the leading cause of SICH, followed by arteriovenous malformations (AVMs) and aneurysms. Hemorrhages may also occur after an ischemic stroke, especially after an embolic event. They often occur from the bleeding of small vessels, which form a hematoma, and in more severe cases may leak into the ventricles and/or subarachnoid space.

Hemorrhages that originate in the subarachnoid space most often are secondary to the rupture of a saccular aneurysm at the branching or bifurcation points of large arteries in or around the Circle of Willis on the ventral surface of the brain. Subarachnoid hemorrhages (SAH) may lead to delayed ischemia caused by *vasospasm*, or a constriction of the blood vessels. The onset of vasospasm

may occur several days after the hemorrhagic event, with peak frequency at about 5 to 7 days post SAH.

1. CEREBRAL SMALL VESSEL DISEASE

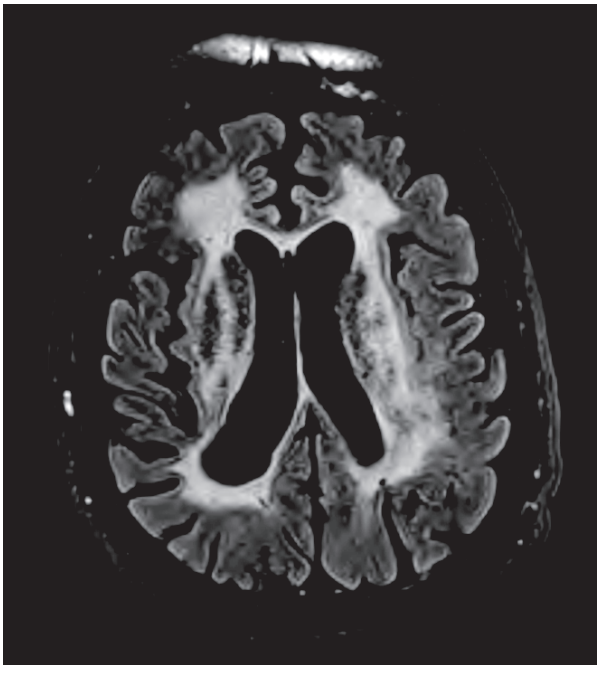
Although the clinical emphasis of CVD has traditionally been on overt large artery stroke, more attention is now being focused on small vessel, subcortical vascular pathology and its relationship to cognition. The most common form of VCI is the subcortical type (Pantoni, 2010). *Cerebral small vessel disease* (CSVD) refers to primarily subcortical gray and/or white matter pathology associated with distal penetrating arterioles most often branching from the middle, posterior, or basilar arteries. CSVD includes both focal arteriolar occlusion (lacunar infarction) and more diffuse white matter pathology, seen as nonspecific white matter hyperintensities (WMH) on T-2 weighted and fluid attenuated inversion recovery (FLAIR) MRI sequences. Lacunar infarcts are most often located in basal ganglia structures, in the thalamus, and in the area of internal capsule or deep hemispheric white matter and may be associated with focal syndromes, such as a pure motor or pure sensory loss event, the co-occurrence of dysarthria, and a "clumsy hand" or hemiparesis. Multiple bilateral lacunar infarctions are associated with *etat lacunaire*, a syndrome marked by cognitive impairment, incontinence, dysarthria, and gait disturbance.

WMHs are ubiquitous in elderly patients, with greater than 90% of community samples showing hyperintensities on MRI (de Leeuw et al., 2001). They may reflect different pathologic processes but are most often thought to be related to chronic, incomplete ischemia (perhaps venular based) in addition to incomplete arteriole occlusion (Black, Gao, & Bilbao, 2009). Axial T2 or FLAIR MRI often shows periventricular "caps" and "bands" of WMH (see Figure 8.1). Small vessel disease is also associated with brain atrophy, which in turn may be independently associated with cognitive impairment (Jokinen et al., 2012).

2. MICROHEMORRHAGES, MICROINFARCTS

Two additional types of cerebral small vessel disease recently have been described. *Cerebral microbleeds* are most often identified via gradient echo MRI sequences (T2*). Their etiology may depend on their location. *Lobar microbleeds* are likely associated with cerebral amyloid angiopathy, which in turn is associated with AD. Conversely, deep, subcortical microbleeds, primarily found in and around basal ganglia structures, are associated with stroke risk factors, most notably hypertension. Linkages between cerebral microhemorrhages and cognitive impairment are tenuous, though they are established risk factors for subsequent stroke and cognitive decline.

Figure 8.1. Periventricular caps and bands on axial FLAIR MRI.



Cerebral *microinfarcts* are very small lesions, difficult to visualize with conventional MRI techniques and most often identified at autopsy. They have been linked with cognitive decline and dementia. For example, a clinicopathologic study that is part of the Honolulu Asia Aging Study found microinfarcts to be the most common pathology at autopsy in study subjects identified prior to death as demented or possessing significant cognitive impairment (Launer, Hughes, & White, 2011).

B. Co-Occurrence of CVD and AD

Important linkages have been established between CVD and AD. Midlife stroke risk factors, such as hypertension and diabetes, are

associated with later life cognitive impairment and dementia (Gorelick et al., 2011). These dementia cases are not limited to vascular dementia (VaD); instead, there is also a higher incidence of AD in persons with midlife stroke risk factors, suggesting potential common pathologic pathways for AD and VaD. In addition, the most common pathology associated with late life dementia is a combination of AD and CVD pathology rather than either "pure" AD or "pure" CVD (James, Bennett, Boyle, Leurgans, & Schneider, 2012). Furthermore, neuropathologic study of the brains of subjects tested clinically prior to death suggests an additive influence of CVD and AD pathology to produce neurocognitive impairment. Thus, in research such as the Nun Study, less AD pathology was needed for cognitive impairment and dementia in persons who also showed pathologically defined CVD (Snowdon et al., 1997).

C. Cerebrovascular Disease Across the Life Span

Stroke and CVD are most often associated with middle-aged and elderly persons. However, pediatric stroke events also occur at the rate of 11 cases per 100,000 children per year, and stroke is one of the top 10 causes of death in children. Some of the more common etiologies for infant and pediatric CVD include sickle cell disease, coagulopathies, moya-moya disease, homocystinuria, and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes). In addition to the above, CVD in adolescence and early adulthood is associated with pregnancy, heart disease, arterial dissections, substance abuse, and migraine.

A midlife genetic cause of CVD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), with an age of onset between 30 and 50 years. CADASIL patients present with multiple small strokes, TIAs, cognitive impairment, and migraine headaches. The cognitive impairment often progresses to VaD. A mutation on chromosome 19 of the *Notch 3* gene is thought to be the culprit. CADASIL patients are an important source of information about the patterns and severity of VCI because of their relatively young age and lack of co-occurring pathologic processes such as AD.

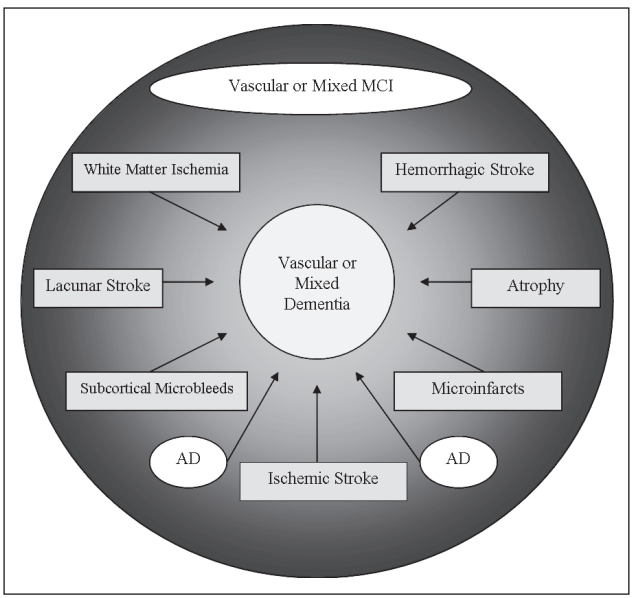
II. COGNITIVE IMPAIRMENT CLASSIFICATION

The construct of cognitive impairment and dementia that is associated with CVD has gone through many permutations, from multi-infarct dementia (MID) to VaD to the most commonly used term at present, VCI. VCI has been defined as "a syndrome with evidence of

clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain" (Gorelick et al., 2011, p. 2677). VCI is an umbrella term that encompasses the cognitive deficits from all of the subgroups of CVD discussed in the previous sections. It also includes all levels of cognitive severity, from vascular-based mild cognitive impairment (MCI) to full-blown vascular dementia. Finally, it also includes cognitive disturbance associated with both "pure" CVD conditions and "mixed" pathologies, such as the combination of CVD and AD (see Figure 8.2).

Differences of opinion remain on how best to classify VCI. There is general agreement on the foundational elements: (a) the presence of cognitive impairment, preferably defined by way of neuropsychological assessment; (b) the presence of CVD; and (c) a (preferably temporal) relationship established between the cognitive

Figure 8.2. A schematic drawing of vascular cognitive impairment. AD = Alzheimer's disease; MCI = mild cognitive impairment.



impairment and the CVD. The most common differences across the various sets of criteria include the number and type of cognitive domains required for impairment and the degree of relationship required between CVD and cognitive impairment. For example, the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) requires two areas of demonstrated cognitive impairment for VaD. One of the impaired domains must be memory. In contrast, the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia, which is currently the most commonly used criteria for clinical trial research, requires memory plus two other domains. A recent VCI statement by the American Heart Association–American Stroke Association (AHA-ASA) includes criteria for both VaD and vascular mild cognitive impairment (VaMCI; see Exhibit 8.2). Using the AHA-ASA criteria, both VaD and VaMCI require two areas of measured cognitive impairment. Memory does not need to be one of the impaired domains. The difference between VaD and VaMCI is the presence of functional impairments that are related to the cognitive deficits. There are also separate criteria for "Probable" and "Possible" VaD and VaMCI, dependent largely on the strength or certainty of the relationship between CVD and cognitive impairment/dementia. The AHA-ASA criteria also include "Unstable VCI," which refers to patients who shift from an impaired to an unimpaired cognitive state, perhaps as a result of stroke recovery (Gorelick et al., 2011). Finally, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) does away with the term *dementia* altogether. It is replaced with *major neurocognitive disorder* or *minor neurocognitive disorder*. A major vascular neurocognitive disorder requires demonstrated cognitive decline that interferes significantly with independence, coupled with evidence of a relationship between CVD and the neurocognitive disorder. Memory disturbance is not required.

A. Functional Neuroanatomy

The clinical picture of patients with VCI depends upon the underlying CVD pathology. When considering the relationship of CVD to cognitive and behavioral change, the clinician should consider three primary factors: infarcts (location, size, and number), small vessel disease (lacunar infarcts and WMH), and brain atrophy. If there are one or more clinical strokes, the location, number, and volume of the brain infarctions largely determine the pattern and extent of cognitive impairment and behavior change. In a seminal

Exhibit 8.2. Vascular Cognitive Impairment (VCI) Criteria From the 2011 American Heart Association–American Stroke Association Statement

1. *VCI* characterizes all forms of cognitive deficits from VaD to MCI of vascular origin.
2. Not to be used for subjects with any type of substance abuse in prior 3 months.
3. These criteria cannot be used for subjects with delirium.

Dementia

1. Diagnosis of dementia based on decline in cognitive function from baseline and deficit in 2 cognitive domains of sufficient severity to affect activities of daily living (ADL).
2. Diagnosis of dementia based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
3. Deficits in ADLs are independent of motor/sensory sequelae of the vascular event.

Probable VaD

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and:
   a. There is a clear temporal relationship between a vascular event (e.g., clinical stroke) and onset of cognitive deficits, or
   b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g., as in CADASIL).
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaD

There is cognitive impairment and imaging evidence of cerebrovascular disease but:

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (e.g., silent infarcts, subcortical small-vessel disease) and the cognitive impairment; or
2. There is insufficient information for the diagnosis of VaD (e.g., clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available); or
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g., annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as having probable VaD; or

Exhibit 8.2. Vascular Cognitive Impairment (VCI) Criteria From the 2011 American Heart Association–American Stroke Association Statement *(Continued)*

4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as:
   a. A history of other neurodegenerative disorders (e.g., Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
   b. The presence of Alzheimer disease biology is confirmed by biomarkers (e.g., PET, CSF, amyloid ligands) or genetic studies (e.g., *PS1* mutation); or
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.

VaMCI

1. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain.
2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.
4. The differences between probable and possible VaMCI are largely identical to corresponding differences between the probable and possible VaD.

Unstable VaMCI

Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having "unstable VaMCI."

Note. VCI = vascular cognitive impairment; VaD = vascular dementia; MCI = mild cognitive impairment; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT/MRI = computed tomography/magnetic resonance imaging; PET = positron emission tomography; CSF = cerebrospinal fluid; VaMCI = vascular mild cognitive impairment. From "Vascular Contributions to Cognitive Impairment and Dementia: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association," by P. B. Gorelick, A. Scuteri, S. E. Black, C. Decarli, S. M. Greenberg, C. Iadecola, . . . Council on Cardiovascular Surgery and Anesthesia, 2011, *Stroke*, *42*, p. 2672. Copyright 2011 by the American Heart Association. Adapted with permission.

study, Tomlinson, Blessed, and Roth (1970) suggested that total lesion volume plays a critical role in VaD, with significant and pervasive cognitive deficits following loss of a critical volume of tissue. However, studies investigating the cognitive effect of total lesion volume have been mixed. Lesion location appears to be at least as important as lesion volume, with lesions in the dominant (usually left) hemisphere leading to greater cognitive deficits than lesions in the nondominant (usually right) hemisphere. Focal cognitive deficits may be associated with specific lesion locations, such as lesions located in language (usually dominant hemisphere, fronto–temporo–parietal regions) or visuospatial (usually nondominant hemisphere, parietal region) brain regions. Executive dysfunction and behavior change are often associated with anterior lesions, such as after ruptured anterior communicating artery aneurysms. Similarly, well-placed lesions in thalamus or hippocampus, especially in the dominant (usually left) hemisphere may be associated with significant memory deficits. Multiple strokes may correspond with ever-deteriorating cognitive skills and are the source of so-called multi-infarct dementia. Subsequent chapters in this handbook focus on the localization of specific neurobehavioral syndromes, such as aphasia, amnestic syndromes, and neglect. Lesion analyses of stroke patients play a key role in this line of research.

Juxtaposed with the focal features of specific stroke-related lesions is the more diffuse pattern of cognitive impairment associated with subcortical small vessel disease, consisting of both lacunar infarctions and white matter hyperintensities. In fact, separate diagnostic criteria have been suggested to capture the clinical–cognitive and behavioral syndrome called *subcortical ischemic vascular dementia* (Erkinjuntti et al., 2000), including executive cognitive impairments and behavioral manifestations such as irritability, apathy, low mood, and gait difficulties.

Of the two components of small vessel disease, lacunar infarcts have a stronger relationship with cognitive function, and multiple lacunar infarcts may have an additive effect with respect to cognitive and functional impairment. Paired with the lacunar infarcts are the white matter hyperintensities, also known as *subcortical hyperintensities* and *leukoaraiosis*. The pathology underlying WMHs likely reflect multiple etiologies, including glial swelling, demyelination, enlarged perivascular spaces, spongiosis, amyloid angiopathy, and cyst formation (Pantoni, 2010). The relationship of white matter hyperintensities and cognitive function is debated. WMH are ubiquitous in elderly persons, with greater than 90% of a community sample showing at least mild degrees of WMH (de Leeuw et al., 2001). There appears to be a relationship between stroke risk factors, such as hypertension, dyslipidemia, and diabetes, and WMH

(Gorelick et al., 2011). But how much WMH is needed for it to affect cognitive function? Large community samples, such as the Rotterdam Scan Study and the Cardiovascular Health Study, support a threshold effect above which WMH is associated with cognitive impairment (Longstreth et al., 1996). In the Cardiovascular Health Study, a mild degree of WMH is not related to lower scores on the Modified Mini-Mental State Examination (MMSE). However, moderate and severe WMH are inversely related to cognitive function. Whether the location of small vessel disease is also important is less clear. Some studies report localized effects. For example, memory disturbance has been related to hyperintensities in the anteromedial thalamus, whereas hyperintensities involving cholinergic tracts appear to compromise executive functions (Swartz, Sahlas, & Black, 2003). Other studies have reported executive dysfunction independent of location (Reed et al., 2004).

Cerebral atrophy in the context of CVD is also related to cognitive impairment. Mungas et al. (2001) found cortical gray matter volume to be a stronger predictor of cognitive function than lacunar infarct volume in normal, cognitively impaired, and demented individuals with and without subcortical lacunar infarcts. In this study, white matter lesions independently predicted selected timed measures. However, there is an inverse relationship between brain size and the presence of white matter lesions. Some investigators have begun to address this issue by quantifying both atrophy and small vessel disease burden simultaneously. Although these studies agree that atrophy explains most of the variance for cognitive decline, lesion load also independently contributes (Swartz, Stuss, Gao, & Black, 2008). Localized atrophy may also be important. For example, Stebbins et al. (2008) used voxel-based morphometric measures (VBM) to show lower thalamic gray matter volume in poststroke patients with mild cognitive impairment than in poststroke patients with normal cognitive function.

B. Neuropsychological Examination

1. GENERAL CONSIDERATIONS

Stroke patients present special challenges to neuropsychological assessment that may require augmentation of standardized administration. For example, if a patient presents with focal cognitive deficits secondary to stroke, neuropsychological examination is often a two-step process:

1. Examine for the presence and extent of focal deficits related to the stroke location.
2. Examine other cognitive domains while minimizing the effects of the focal deficit(s).

The goal of the first step is to understand the extent of the focal deficit. For example, if a patient presents with language deficits secondary to a left hemisphere middle cerebral artery ischemic stroke, the first goal of the examination is to examine language, including an assessment of fluency, auditory comprehension, repetition, reading and writing (see Chapter 18 in this volume for a detailed description of an examination of aphasia). Once the examination of the focal deficit is complete, the second phase of the examination takes an opposite tack. During this phase, the goal of the examination is to assess the remaining cognitive domains while attempting to minimize the effects of the focal deficit. Of course, this may not be completely possible (e.g., it is not possible to remove the effects of language deficits from the examination). Still, the clinician may be able to minimize language by relying on tests that do not require normal verbal output, such as recognition memory paradigms. Clinicians may also wish to supplement a standard administration of a test by testing the limits of a performance. For example, the clinician may wish to allow extra time on a verbal fluency task for a patient with an expressive aphasia, score production during the standard time (usually 1 minute), and also record the raw score of what is achieved at 2 minutes to see if additional points are achieved when more time is allowed. Other ways to test the limits of a patient's abilities include paraphrasing the directions, allowing a patient to read the directions, pantomiming the directions, or (when examining patients with unilateral neglect) drawing attention to all areas of a visual stimulus (e.g., to all four pictures on a page from the Peabody Picture Vocabulary Test) or even cutting them out and presenting them in a vertical array. Although standard scores cannot be generated when altering the test administration, valuable qualitative information may be gained using this approach.

2. NEUROPSYCHOLOGICAL PATTERNS IN VCI

Given the heterogeneity of CVD that may lead to VCI, it is not surprising that there is no single neuropsychological pattern that is both sensitive and specific to CVD, and the clinician is cautioned not to diagnose VCI based on neuropsychological test results alone. Still, several studies have found that a pattern of slowed information processing, executive dysfunction, immediate memory deficits, and mood disturbance are common in patients with stroke and CVD. One of the complexities of VCI is that patients often present with a focal stroke or strokes superimposed on a foundation of long-standing small vessel disease. Thus, they show both the focal pattern of cognitive impairment dependent on the location of the infarction as well as the diffuse, subcortical pattern of executive dysfunction, slowed processing, and memory encoding deficits associated with the small vessel disease. Patients may also show evidence of concurrent AD,

such as anomia, rapid forgetting of newly learned information, and inconsistent orientation.

Although as in any neuropsychological examination it is important to sample all cognitive domains, two specific areas deserve special mention because of their prominence in VCI research. First, executive function, which refers to higher level cognitive skills such as planning, organizing, and synthesizing, is seen by many as a hallmark of VCI. In fact, some have suggested that executive dysfunction be a required feature of VCI. However, although tests of executive function are certainly sensitive to CVD related impairment (Nyenhuis et al., 2004), they have only inconsistently been shown to be specific to patients with CVD compared with patients with AD pathology (Reed et al., 2007). Memory is a second important cognitive domain. The NINDS-AIREN criteria for VaD require memory impairment. However, perhaps in fear of the "Alzheimerization" of all dementia, subsequent groups of VCI investigators have argued that memory should not be required (Hachinski et al., 2006), and the AHA-ASA criteria do not require memory impairment for diagnosis of VaD or VaMCI (Gorelick et al., 2011). Still, memory impairment is common in patients with VCI (Nyenhuis et al., 2004). The pattern of memory impairment in VCI may be qualitatively different from that of AD in that a rapid forgetting of newly learned information may not be seen in VCI patients for which there is not an AD component. Instead, patients with cerebrovascular disease often show inefficient encoding of new information, resulting in less information acquired.

3. NEUROPSYCHOLOGICAL PROTOCOLS

Given the hundreds of neuropsychological tests at their disposal, clinicians may find it difficult to choose which tests to administer to their patients with potential vascular cognitive impairment. Some guidance was provided by the neuropsychology committee at the VCI Harmonization Conference cosponsored by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network in 2005 (Hachinski et al., 2006). The committee examined the literature and chose tests with acceptable psychometric properties, a track record of research in patient groups with suspected VCI, involving relatively little cost and equipment, and conducive to studies across different languages and cultures. A list of the tests included in their recommended Sixty Minute Protocol is contained in Exhibit 8.3.

a. Screening examinations

The MMSE, although brief, may not be as sensitive to cognitive impairment associated with CVD as newer screening tools with better psychometric properties, such as the Montreal Cognitive Assessment Test (MoCA; http://www.mocatest.org) or, if more time is available

Exhibit 8.3. Sixty-Minute Protocol From the VCI Harmonization Conference

Executive/Activation
- Animal Naming (semantic fluency)
- Controlled Oral Word Association Test
- WAIS–III Digit Symbol-Coding

Trailmaking Test
- Future Use: Simple and Choice Reaction Time

Language/Lexical Retrieval
- Boston Naming Test, Second Edition, Short Form

Visuospatial
- Rey-Osterrieth Complex Figure Copy

Memory
- Hopkins Verbal Learning Test—Revised
- Alternate: California Verbal Learning Test—2

Neuropsychiatric/Depressive Symptoms
- Neuropsychiatric Inventory Questionnaire Version
- Center for Epidemiological Studies—Depression Scale

Note. VCI = vascular cognitive impairment; WAIS–III = Wechsler Adult Intelligence Scale, Third Edition. From "National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards," by V. Hachinski, C. Iadecola, R. C. Petersen, M. M. Breteler, D. L. Nyenhuis, S. E. Black, W. J. Powers, . . . G. G. LeBlanc, 2006, *Stroke*, *37*, p. 2223. Copyright 2006 by the American Heart Association. Adapted with permission.

for screening, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). In several studies, the MoCA has been shown to be more sensitive than the MMSE to detecting cognitive impairment in patients with suspected CVD, though some have noted that the test's sensitivity may come at the expense of specificity (Godefroy et al., 2011; Rossetti, Lacritz, Cullum, & Weiner, 2011) and that there is need for educational corrections when using the MoCA. Multiple studies have also demonstrated the validity of the RBANS for use with patients with stroke and CVD (e.g., Larson, Kirschner, Bode, Heinemann, & Goodman, 2005). The Five Minute Protocol from the VCI Harmonization Conference is designed to potentially be administered by telephone and includes the immediate and delayed five-word recall, the orientation items, and the one-letter phonemic fluency tasks from the MoCA (Hachinski et al., 2006). Its validity, however, has yet to be established.

b. Executive domain tests

The construct of executive dysfunction is complex and multifaceted. Speeded tests of executive function have been shown to be especially sensitive to patients with suspected VCI (Nyenhuis et al., 2004). The NINDS–Canadian Stroke Network (CSN) protocols include several speeded executive function tests, based on Donald Stuss and colleagues' initiation/activation factor of executive function. These tests include the Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale—Third Edition as well as phonemic fluency, semantic fluency, and the Trail Making Test.

c. Memory domain tests

The construct of memory encompasses a wide array of subdomains, depending on the material that is to be learned and recalled (e.g., verbal vs. visual memory), when it is to be recalled (e.g., immediate and delayed recall paradigms), the method of recollection (e.g., free vs. cued recall), and the neural system involved (e.g., declarative vs. procedural memory). Decisions of which memory test to choose will depend in part on patient characteristics, such as the severity of their cognitive impairment (e.g., choosing a 16-word vs. a nine-word list learning task), the location of their stroke lesion (e.g., left vs. right hemisphere), and the cognitive symptoms with which they present (e.g., topographical memory deficits). Much has been made of differences in the pattern of memory disturbance between patients with CVD and those with AD, with the former group showing the relative lack of rapid forgetting than the latter group, and the greater likelihood that patients with CVD will benefit from delayed recognition paradigms than those with AD. For these reasons, VCI neuropsychology protocols should include memory measures that include immediate, delayed free recall, and delayed recognition paradigms. The VCI Harmonization Committee recommended both the revised Hopkins Verbal Learning Test (HVLT) and the revised California Verbal Learning Test (CVLT), depending on the time available to complete the assessment; the HVLT takes less time than the CVLT but does not include potentially important components such as cued recall and an interference list. Potential tests of visual memory include the recall condition of the Rey Complex Figure and the Brief Visual Memory Test.

d. Language and visuospatial domain tests

Aphasic patients provide methodological challenges to the neuropsychologist because they frequently are unable to complete formal neuropsychological testing. As already mentioned, it may be required that the clinician use individualized, nonstandardized approaches with these patients. Aphasic patients should also be examined by the neuropsychologist or the speech pathologist with

standard aphasia protocols, such as the Western Aphasia Battery or the Boston Diagnostic Aphasia Examination.

Other than in patients with focalized lesions leading to aphasia, tests that measure primary language functions (e.g., confrontation naming, auditory comprehension, repetition skills) may not be as sensitive as tests in other domains in patient groups with suspected VCI. Verbal fluency tests have been sorted into both language and executive cognitive domains and indeed show aspects of both. In nonaphasic patient groups, however, the activation and working memory demands of the tasks make them ideal measures of executive function. Similarly, other than in patients with focal nondominant hemisphere frontoparietal lesions, tests of spatial function may not be as sensitive to cognitive impairment in patients with suspected VCI as tests in other domains. The VCI Harmonization Committee recommended the Rey Complex Figure, in part because it included both spatial and executive components.

e. VCI-related behavioral disturbance

Depression is the most common poststroke psychiatric disturbance. Approximately one third of patients with stroke experience clinical depression in the months following their brain attack. Vascular disease has also been linked with late life depression, also known as *vascular depression* (Samaras, Rossi, Giannakopoulos, & Gold, 2010). Finally, apathy or abulia, which may mimic depression, is a common symptom associated with diffuse subcortical small vessel disease. For these reasons, it is important to examine for depressive symptoms in patients with CVD. Although self-report screening examinations cannot formally diagnose depression, they may be used as an efficient way to gather mood-related information from patients. Commonly used screening tests in patients with suspected VCI include the Beck Depression Inventory, the Geriatric Depression Scale, and the Center for Epidemiologic Studies Depression Scale. Whichever scale is used, the clinician is cautioned not to overdiagnose depression because of the inclusion of vegetative symptoms that may be related to the patient's physical or cognitive state rather than their mood.

The Frontal Systems Behavior Scale (FrSBe), which examines for the presence and severity of dysexecutive, disinhibition, and apathy behaviors before and after an event such as stroke, can be useful in patients with stroke, especially when it is completed by a collateral source who knows the patient well. The Neuropsychiatric Inventory (NPI) also uses a collateral source and can provide a broad overview of the presence and severity of neuropsychiatric symptoms in patients with CVD. Finally, the Apathy Evaluation Scale (AES) is one of many that assess for the presence and extent of apathy–abulic tendencies.

4. TREATMENT

The majority of treatment studies have focused on either the effects of medications originally targeted for patients with AD or on control of stroke risk factors. Results in both areas of study have been modest and inconsistent. There is currently no FDA-approved medication for use in patients with VCI. Pivotal trials for cholinesterase inhibitors approved for use with patients with AD, such as donepezil and galantamine, have shown modest cognitive effects and inconsistent global or daily functioning differences when compared with placebo. A similar pattern of results was found with memantine, an N-methyl D-aspartate agonist. Several methodologic factors have made these trials difficult to complete and interpret, including the potential presence of AD in patients enrolled in the trials, the difficulty assigning cognitive versus physical cause for functional impairment, and the requirement for significant memory impairment for study entry, thus increasing the potential confound with AD. In addition, the cognitive tests used in these trials included only a limited assessment of executive function and therefore, may not have been sensitive enough to the presence and extent of cognitive impairment (Gorelick et al., 2011).

Risk factors for stroke are well known and include many modifiable markers, such as hypertension, dyslipidemia, diabetes, smoking, and heavy alcohol use (Gorelick et al., 2011). Strong linkages are demonstrated in large observational studies between midlife stroke risk factors and later life cognitive impairment and dementia (Birns & Kalra, 2009). These linkages are not only between risk factors and VCI but also with AD, leading some to postulate potential vascular precursors to AD. Clinical trials to date have found only inconsistent evidence that risk factor control later in life results in better cognitive outcomes (Birns & Kalra, 2009). Potential reasons for the apparent discrepancy between midlife and late-life studies include the following:

1. Cognitive test scores are often secondary endpoints to these clinical trials, with primary outcomes being other events, such as stroke or death. Trials may be halted before there is sufficient time and statistical power to the test the cognitive outcome.
2. The damage, such as cerebral small vessel disease and cognitive decline, may already have occurred prior to the onset of the clinical trial.
3. Relatively weak cognitive outcome measures, such as the MMSE, have been commonly used in these studies.

Current and future clinical trials have attempted to correct these shortcomings.

III. SUMMARY

Patients with stroke and CVD provide many challenges for neuropsychologists. Patients may present with both focal and diffuse deficits that range in severity from very mild to severe. Other disease processes, such as AD, may be part of the pathologic picture. Disability may be caused by physical symptoms, cognitive symptoms, or the combination of physical and cognitive symptoms. Behavior change, such as depression or anosagnosia, may affect cognitive performance. Through all of this, the neuropsychological clinician is in a unique position to provide a complete, efficient, timely and helpful report that can serve as a road map to the patient's cognitive and functional status, as well as an outline of their therapeutic and daily care needs. Although new imaging techniques and therapeutic agents may be developed, they will not change the need for a skilled neuropsychologist to interpret the cognitive and behavioral consequences of stroke and CVD.

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Chapter 9

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The Neuropsychology of Epilepsy

Epilepsy is a common neurological disorder defined by recurrent unprovoked seizures that can lead to cognitive morbidity and psychosocial issues. Epileptic seizures are brief periods of stereotyped altered behavior accompanied by paroxysmal electrical activity in the brain. The fields of neurology and neuropsychology have benefited greatly from studying the cognitive and psychological correlates of repeated seizures, the underlying etiology of the seizure disorder, and the pharmacologic and neurosurgical interventions for seizures.

A number of important brain behavior models and neuropsychological concepts have been derived from the study of epilepsy, including hippocampal models of memory, the sensorimotor homunculus, the plasticity of language, and the lateralization of cognitive functions (Loring, 2010; Novelly, 1992). Specialized cognitive testing in epilepsy surgery candidates such as during invasive electroencephalogram (EEG) monitoring, intraoperative mapping, intracarotid sodium amobarbital (Wada) testing, and functional magnetic resonance imaging (fMRI) have provided a window to the functioning

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brain. Neuropsychology plays a vital role in the evaluation of patients with epilepsy by measuring the effects of seizures on cognition and behavior and through the design and administration of cognitive tests during specialized brain mapping techniques.

I. EPIDEMIOLOGY AND CLASSIFICATION OF EPILEPSY

A. Incidence, Prevalence, and Etiology

The incidence of epilepsy is generally accepted as 50 cases per 100,000 persons per year in developed countries and between 100 and 190 cases per 100,000 persons per year in developing countries. Across studies, the prevalence of epilepsy is reported as five to 10 cases per 1,000 persons, with lifetime prevalence of seizures between 2% and 5% (Sander, 2003).

The etiology of epilepsy is thought to be related to numerous factors, including genetics, acquired conditions, geographic location, age, and sex. Of all cases of epilepsy, 68% have an idiopathic cause (i.e., genetic or an unknown cause; Annegers, Rocca, & Hauser, 1996), although the specific genes that may be responsible for the most common forms of epilepsy with a genetic origin are still largely unknown. Of the remaining acquired cases of epilepsy, cerebrovascular disease is the leading cause in adults (11%). Other etiological factors include developmental disabilities (5%), traumatic brain injury (4%), brain tumor (4%), degenerative central nervous system disease (3%), and perinatal factors and febrile seizures (5%). Additionally, infectious diseases, the contraction of meningitis in early childhood, extremely low birth weight (less than 1,000 g/27 weeks), and alcohol or drug use are associated with the development of seizure disorders (Borg, Testa, Levy, & Shinnar, 1996). Risk factors also include geographic location (cysticercosis in Latin America), race, socioeconomic status, type of setting (rural vs. urban), age (younger than 2 years or older than 65 years in developed countries), and sex (male; Sander & Shorvon, 1996).

B. Classifications of Seizures and Epilepsy Syndromes

According to the International League Against Epilepsy (ILAE), an *epileptic seizure* is a transient occurrence of signs and/or symptoms due to abnormal excessive and/or hypersynchronous neuronal activity in the brain. *Epilepsy* is a disorder of the brain characterized by recurrent epileptic seizures (two or more at least 24 hours apart) and

by its neurobiological, cognitive, psychological, and social consequences. An *epileptic syndrome* is a cluster of epileptic symptoms and signs that occur together but do not have a single known etiology.

During the past 20 years, the terminology proposed by the ILAE for the classification of seizures and epilepsy syndromes has evolved (Engel, 2006). The major seizure types are classified as *partial* or *generalized*, and the major syndromes are classified as *idiopathic* (primary) epilepsy, *symptomatic* (secondary) epilepsy, and *cryptogenic* epilepsy (presumed symptomatic epilepsy with an unknown etiology). Most recently, a flexible diagnostic scheme was proposed by the ILAE. This new diagnostic scheme relies on five axes that provide a description of the seizures and characteristics of the individual, including Axis 1: Ictal semiology; Axis 2: Epileptic seizure type (e.g., generalized, partial, neonatal, status epilepticus); Axis 3: Syndrome (e.g., idiopathic or symptomatic, focal or generalized); Axis 4: Etiology (when known); and Axis 5: Optional designation of degree of impairment caused by the epileptic condition.

Partial seizures are events in which the first clinical and electrographic changes indicate activation of a system of neurons limited to one part of the cerebral hemisphere. There are two main types of partial seizures: (a) *simple partial* (where consciousness remains intact) and (b) *complex partial* (where consciousness is altered). In addition, some partial seizures start focally but then secondarily generalize. Generalized seizures are those in which the first clinical and electrographic changes indicate involvement of both hemispheres. With these spells, consciousness may be impaired, and the motor and EEG changes are bilateral, at least initially. (See Table 9.1i for ILAE seizure type classification [http://pubs.apa.org/books/sup/parsons].)

C. Syndromes

Epileptic syndromes are a complex of signs and symptoms characterized by a cluster of findings that co-occur, including seizure type, etiology, age at onset of seizures, precipitating factors, cause, severity, electrographic findings, and prognosis. There are 48 epilepsy syndromes listed with onset in childhood or adolescence, such as West syndrome, Dravet syndrome (severe myoclonic epilepsy in infancy), Lennox Gastaut, Landau-Kleffner, benign childhood epilepsy with centrotemporal spikes, Rasmussen's syndrome, and juvenile myoclonic epilepsy, which have varying clinical presentations and cognitive and behavioral correlates. See Besag (2006) and Nordli (2002) for reviews of the cognitive and psychiatric correlates of the major epilepsy syndromes.

1. IDIOPATHIC EPILEPSY

Idiopathic epilepsies are attributed to genetic causes and are often observed in individuals with a family history of epilepsy. The condition typically begins in the first few years of life but not as early as symptomatic epilepsies; intellect is intact, and there are no signs of structural neuronal damage. Seizures are generally self-limited. Idiopathic epileptic syndromes may be localized (e.g., benign centrotemporal lobe epilepsy of childhood) and/or generalized (e.g., childhood absence epilepsy). There is evidence, however, that even these uncomplicated epilepsies are associated with psychiatric, cognitive, and social comorbidities.

2. SYMPTOMATIC EPILEPSY

The symptomatic epilepsies are those that occur as the result of a structural neurologic disease or identifiable metabolic disturbance. Prognosis is typically poor, response to medication is less favorable, and spontaneous remission is less likely than in cases of idiopathic epilepsy. Symptomatic and cryptogenic localization-related epilepsies are the most common type of adult-onset epilepsy. Symptomatic epilepsy syndromes can be generalized (e.g., West syndrome) or focal (e.g., temporal lobe epilepsy).

3. MESIAL TEMPORAL LOBE EPILEPSY SYNDROME

The most common localization-related epilepsy in adults is mesial temporal lobe epilepsy syndrome (MTLE), which has a childhood onset in 67% to 75% of cases (Berg, 2008). Individuals with MTLE often have a family history of epilepsy and a higher incidence of complicated febrile seizures or other precipitating event during the first 5 years of life. Seizures often remit for a period of time and then recur in adolescence or adulthood. Though not present in every MTLE patient, a defining characteristic of this syndrome is hippocampal sclerosis. The clinical presentation generally includes complex partial seizures with automatisms, often preceded by an aura (commonly epigastric or psychic). Compared with other intractable epilepsy syndromes, neuropsychological findings indicate that MTLE is associated with greater impairments in general intellectual functioning, academic achievement, language, visuospatial skills, and modality-specific memory (verbal memory impairment associated with left-sided MTLE; Hermann, Seidenberg, Schoenfeld, & Davies, 1997). MTLE is commonly medically intractable and amenable to treatment by temporal lobe resection. Individuals with MTLE comprise 25% to 50% of the 2,000 epilepsy surgeries performed in the United States each year, and of those, 80% are subsequently free of disabling seizures (Engel, 2001).

II. THE EPILEPSY WORKUP: EEG, NEUROIMAGING, AND FUNCTIONAL MAPPING

A. Multidisciplinary Teams

A multidisciplinary team that includes an epileptologist, neurosurgeon, neuropsychologist, neuroradiologist, neurological nurse, psychiatrist, and social worker is best suited for treating epilepsy. Such individuals use specialized techniques necessary for localization of epileptic foci and evaluation of optimal treatment decisions. Abnormalities associated with seizure foci are detected electrically with EEG, anatomically with structural MRI, neurobehaviorally with neuropsychological testing, and in functional brain activation with fMRI and magnetoencephalography (MEG). Each technique requires a different specialist for its application and interpretation.

For patients with focal seizure disorders that do not respond to pharmacological intervention, surgical resection of the seizure focus may be considered. The surgical work up may include examination of the results of long-term video-EEG monitoring; neuropsychological testing; high-resolution MRI; and brain mapping methods such as fMRI, Wada testing, intracranial EEG, MEG, single photon emission tomography (SPECT), and positron emission tomography (PET). The goal of the presurgical workup is to localize the seizure focus, predict likelihood of seizure freedom, and minimize risk for cognitive morbidity.

B. EEG

Electroencephalography is the most specific (78%–98%) diagnostic test for epilepsy, though the sensitivity of EEG to seizures is far lower (25%–56%). EEG is useful for classifying seizure type, syndrome, and epileptic zone. Various interictal patterns, such as spikes, spike-wave complexes, sharp waves and polyspikes, are considered epileptiform and are rarely seen in individuals without seizures. These epileptiform abnormalities occur in up to 98% of patients with epilepsy (Noachtar & Remi, 2009). In addition, interictal EEG patterns can provide information about epilepsy syndromes. For example, hypsarrhythmia is the hallmark of infantile spasms, and 3 Hz spike and wave complexes are typical of absence epilepsy.

For patients with medically intractable seizures, routine EEG may be inadequate, and ambulatory EEG in an outpatient setting or long-term video-EEG monitoring in an inpatient setting may be needed. Video-EEG monitoring is conducted over days by videotaping the paroxysmal behavior simultaneously with continuous

EEG. Video-EEG monitoring may be necessary to differentiate epileptic from nonepileptic events, to identify the seizure type, and for the purpose of surgical localization.

For patients under surgical consideration for whom the epileptogenic zone has not been identified using routine or video-EEG or for whom more discrete localization is needed within the epileptogenic zone, invasive intracranial recording may be undertaken. Invasive EEG monitoring gives more direct information about the seizure focus by avoiding the filtering that occurs with scalp recordings and by increasing sensitivity to small field potentials. Electrodes can be implanted extradurally (beneath the skull but outside the dura), subdurally (below the dura but overlying the pia), or intracortically (depth electrodes).

C. Structural MRI

High-resolution MRI will identify underlying etiologies of epilepsy, such as malformations of cortical development, neoplastic lesions, focal cortical dysplasias, posttraumatic lesions, vascular malformations (arteriovenous malformations [AVMs], cavernous hemangiomas, venous angiomas, strokes), and mesial temporal lobe sclerosis. Mesial temporal sclerosis is the most common identifiable abnormality on imaging in patients with intractable temporal lobe seizures and is seen in 50% to 70% of patients being considered for neurosurgical intervention. Hippocampal sclerosis and volume loss predict better seizure and cognitive outcome after temporal lobectomy.

D. PET, SPECT

PET with ^{18}F-fluorodeoxyglucose (^{18}FDG) and SPECT are functional imaging techniques that can be used to identify the seizure focus. These techniques operate on the assumption that seizures are associated with increased blood flow or metabolism during the ictus and reduced blood flow or metabolism postictally or interictally. Ictal SPECT shows increased tracer uptake in the location of the onset focus (Richardson, 2010). PET is typically used during the interictal state, at which time the epileptic focus appears hypometabolic. Various PET receptor ligands can be used to identify neurochemical abnormalities in epilepsy. PET imaging plays a role in the presurgical epilepsy evaluation when MRI is unremarkable, when the workup reveals discordant findings, or when improved localization power is needed (Kuzniecky, 2004). For more detail about the imaging techniques, see Chapter 5 in this volume.

E. Wada Testing

The Wada test is used to determine hemispheric representation of language and memory functioning through selective anesthetization of each cerebral hemisphere. The technique was first introduced by Juhn Wada in 1949 (Wada & Rasmussen, 1960) to determine hemispheric representation of language prior to surgical intervention. Amobarbital or another short-acting barbiturate is injected into the internal carotid artery to temporarily anesthetize the hemisphere of surgical interest. This results in a chemically reversible model of the planned resection. During the period of hemianesthesia, language and memory testing of the awake hemisphere is conducted. Memory is typically assessed by exposing the individual during hemianesthesia to information to be encoded, such as real objects, line drawings, or abstract designs. The patient's free recall and recognition for the items encoded during the period when only one hemisphere is "awake" is assessed after the medication effect has resolved. A widely used method for Wada testing was developed at the Medical College of Georgia and has been well described (Loring, 1992). Historically, Wada testing has been used by most epilepsy surgery centers to assess risk for language and memory morbidity following temporal lobectomy. Although less invasive methods for lateralization of language have been developed, Wada testing continues to be used, though with less regularity, prior to surgical intervention (Baxendale, Thompson, & Duncan, 2008). Two methods that are promising replacements for Wada testing are fMRI and MEG. Wada testing has been empirically validated by studies showing that Wada language and memory scores predict naming (Sabsevitz et al., 2003) and memory (e.g., Chiaravalloti & Glosser, 2001) outcomes after dominant anterior temporal lobectomy (ATL) and are related to the functional and pathological status of the hippocampus (Davies, Bell, Dohan, Schweitzer, & Hermann, 1999), seizure onset laterality (e.g., Baxendale et al., 1997), and seizure control postoperatively (e.g., Perrine et al., 1995).

F. fMRI

For patients considering surgical intervention for seizures, fMRI is now considered by some to be a valid replacement for Wada testing for lateralization of function and for predicting cognitive decline (Binder, 2011). fMRI has the advantage of being noninvasive, requiring no exposure to radiation, and providing not only lateralization but also localization data. fMRI detects task-correlated or event-related changes

in blood flow associated with underlying neuronal activity as patients perform various cognitive tasks.

Commonly used tasks for mapping language in epilepsy patients are semantic decision or word generation tasks. The ideal task is active, overt (allowing behavioral monitoring so that performance variables can be examined), and has a perceptual control or contrast task that is matched for difficulty and performance accuracy thereby eliminating all sensory and other (e.g., attentional) processes unrelated to the cognitive function of interest. Laterality indexes (LIs) are calculated based on the number of activated voxels in the left and right hemisphere or region of interest ($V_L - V_R/V_L + V_R$). These LIs have been found to correlate with results of Wada testing and to predict cognitive outcome after temporal lobectomy. There are a number of applications for fMRI in epilepsy, including localization of motor and sensory areas (Bookheimer, 1996), lateralization of seizure of focus (Jokeit, Okujava, & Woermann, 2001), language (Binder et al., 1996; Woermann et al., 2003), and memory (e.g., Binder et al., 2010; Detre et al., 1998). Recent studies have shown that fMRI laterality indexes predict language (Sabsevitz et al., 2003) and memory (e.g., Richardson et al., 2004) outcome after left temporal lobectomy.

G. MEG

Though not widely available, MEG involves noninvasively measuring the magnetic fields generated by brain activity (for a brief review of the method, see Chapter 4 in this volume). MEG provides a direct measure of neural activity with excellent temporal resolution that is superimposed on MRI to create a magnetic source image (Wheless et al., 2004). MEG serves two main purposes in the epilepsy evaluation. It is used for more precise identification of epileptiform abnormalities and for noninvasive functional mapping primarily of language. Because MEG detects magnetic fields induced by intracellular currents and is sensitive to epileptic spikes that may not be seen on surface EEG, it is useful for guiding the placement of intracranial EEG grids and strips (Stefan, Rampp, & Knowlton, 2011).

There is an emerging literature on the role of MEG in localization of language functions in presurgical epilepsy evaluations. The continuous recognition memory paradigm is the most commonly used language task in MEG functional mapping in epilepsy and has a high level of concordance with Wada hemispheric dominance ratings (Papanicolaou et al., 2004). Thus MEG holds promise for both improving localization of seizure foci and noninvasive functional mapping.

III. NEUROPSYCHOLOGICAL EVALUATION

A. Purpose

Neuropsychological testing answers diagnostic questions about the effects of seizures on cognitive and emotional functioning that can help direct treatment (Rausch, Le, & Langfitt, 1998). More specifically, cognitive testing addresses referral issues such as whether cognitive complaints are related to the seizure focus or brain pathology underlying the seizure disorder, a psychological condition, or adverse cognitive side effects associated with antiepileptic drugs (AEDs).

Neuropsychological evaluation is a critical component of the evaluation for patients seeking surgical treatment of epilepsy. Cognitive testing detects lateralized or localized deficits that may correlate with the seizure focus (Stroup & Sherman, 2006). However, the diffuse effects of seizures, functional reorganization, and sensitivity of cognitive tests to other comorbidities can limit the value of neuropsychological testing for localizing seizure foci (Swanson, 2006). In addition, there have been challenges to the material specificity memory model in epilepsy, which postulates that verbal memory deficits occur in association with left temporal lobe seizures and nonverbal memory deficits occur in association with right temporal lobe seizures and temporal lobectomy (Baxendale & Thompson, 2010). Verbal memory and object naming deficits occur with left seizure foci and left temporal lobe surgery with greater regularity than nonverbal memory deficits occur with right seizures and surgery. Moreover, early onset of seizures, including focal seizure disorders, has a negative effect on an array of cognitive functions beyond the seizure focus (Hermann, Lin, Jones, & Seidenberg, 2009). Nevertheless, cognitive test data remains a critical adjunct to other diagnostic measures of seizure localization.

Importantly, neuropsychological data, when combined with age at onset of epilepsy, language lateralization from Wada or fMRI, and results of structural neuroimaging are a powerful predictor of outcome after temporal lobectomy. Risk for cognitive morbidity cannot be predicted without baseline cognitive testing. Comprehensive evaluations that include review of psychosocial functioning and psychiatric state are also imperative for determining if the individual has appropriate expectations with regard to surgery, the social support network for the postoperative period, and the emotional stability to undergo neurosurgical intervention. Preoperative neuropsychological testing is recommended for all epilepsy surgery candidates (Jones-Gotman et al., 2010) given the risk for cognitive morbidity, particularly in object naming and verbal memory that occurs with left ATL.

B. History and Interview

The diagnostic interview for individuals with seizure disorders should include review of seizure variables; demographic information; and social, academic, vocational, and psychiatric history. This information is integrated with the results of EEG, neuroimaging, and cognitive testing to determine the effects of seizures on cognition, psychological functioning, adaptive behavior, and quality of life. Relationships between specific seizure variables (age at onset, seizure frequency, etc.) and cognition have been reported. Review of the individual's experience of their seizures (for those who retain awareness of their events), the video-EEG monitoring, or a collateral report of the semiology are useful for understanding the seizure type. A number of semiological features of seizures have been reported to have lateralizing or localizing value. Neuropsychological testing should not be conducted in the postictal state because this will result in an underestimation of cognitive functioning.

C. Lateralizing Value of Seizure Semiology

Semiology means "the study of signs," which for epilepsy refers to the behavioral or neurologic manifestation of the seizure. The signs and symptoms of the seizures provide clues for lateralization of localization-related partial seizure disorders or the ictal zone, which can be compared with the results of cognitive testing, EEG, and MRI. Among the most common lateralizing signs are automatisms, which are typically seen with the hand ipsilateral to the seizure focus; tonic or clonic movements of face, limbs, or neck muscles, which are contralateral to the seizure focus; and postictal aphasia, which suggests a dominant hemisphere focus. (See Table 9.2i [http://pubs.apa.org/books/supp/parsons] for the lateralizing value semiology.)

D. Effects of Seizure Variables on Cognition

Both seizures and the neuropathology underlying the seizure disorder can cause cognitive impairment in epilepsy. Medically refractory epilepsy is viewed as an evolving condition (Pitkänen & Sutula, 2002), with progressive neuronal loss, reorganization, and kindling that interact with age. Although immature brains have a lower threshold for developing seizures, and early seizures have an adverse long-term effect, seizure-induced damage is less in immature compared with mature brains (Vingerhoets, 2006). Studies of both adults and children followed longitudinally show a relationship between seizures and mental decline (Dodrill, 2004).

Understanding the neuropsychological consequences of epilepsy requires an assessment of the cause of seizures, type of seizure disorder (syndrome or seizure type), seizure variables (duration, frequency, number of seizure types, and age at onset), treatment variables (past surgeries, medications), and complications (episodes of status epilepticus) because all of these factors impact cognitive functioning in epilepsy (Hermann et al., 2009). Volumetric MRI studies have reported abnormalities in dispersed extratemporal regions in those with MTLE (Szabó et al., 2006). Seizures have a pernicious effect on both brain function as seen on cognitive testing and structure as seen in the array of structural imaging abnormalities that have been reported. Exhibit 9.1 describes the effects of seizure variables on cognition.

E. Neuropsychological Evaluation

The diagnostic assessment of epilepsy patients should include a broad battery of tests in order to assess focal and diffuse effects of localization-related or generalized seizure disorders and the networks underlying these conditions. The cognitive domains to be assessed in

Exhibit 9.1. The Effects of Seizure Variables on Cognition

Variables Associated With Poorer Cognitive Functioning

- Earlier age at onset of seizures or first risk for seizures
- Number of antiepileptic drugs
- Longer duration of seizure disorder
- Lifetime total of generalized tonic clonic seizures or partial seizures with secondary generalization are related to lower cognitive and emotional functioning
- Episodes or history of status epilepticus are related to lower IQ
- Frequency of seizures is related to poorer cognitive functioning
- Presence of mesial temporal sclerosis and reduced hippocampal volumes are associated with poorer memory scores
- Seizure frequency correlated with hippocampal volume loss
- Children with refractory seizures have lower IQ

See supplemental material for references: http://pubs.apa.org/books/supp/parsons

patients with epilepsy or those undergoing epilepsy surgery were reviewed by Jones-Gotman et al. (2010). The test battery should include tests or portions of an intelligence test not only because of the lateralizing value of examining the index scores but also because of the known effects of seizures on IQ. Attention and processing speed should be assessed because difficulties in these domains can affect interpretation of other test data, and both are sensitive to the effects of AEDs. Attentional deficits can occur as a result of interictal electrical abnormalities, AEDs, or underlying developmental disorders such as attention-deficit/hyperactivity disorder (ADHD), which are seen with greater frequency in this population (Parisi, Moavero, Verrotti, & Curatolo, 2010).

Comparisons between visual spatial and language tests, such as object naming, auditory responsive naming, and verbal fluency, have lateralizing value. A relationship has been found between visual object naming as measured by the Boston Naming Test and seizure laterality. Visual object naming declines occur in 25% to 60% of patients who undergo left ATL (e.g., Hermann et al., 1999), and thus a naming test should figure prominently in an epilepsy battery. Verbal phonemic and semantic fluency tasks can be included and compared with the Design Fluency test (Jones-Gotman, 1991). Most epilepsy centers administer a measure of premorbid functioning such as the Wide Range Achievement Test—IV Reading or the American National Adult Reading Test. Aside from measuring premorbid level of functioning, such tests help detect reading learning disabilities that may complicate interpretation of the cognitive test data or be secondary to an early onset left hemisphere seizure focus.

Because refractory epilepsy often arises from the anterior temporal lobe, memory testing with measures that assess both verbal and nonverbal memory functions is critical. Although the Wechsler Memory Scale—IV and older versions include verbal and visual modalities, material specific memory deficits have not been consistently demonstrated with the visual reproduction and logical memory subtests in patients with left and right temporal lobe seizures before or after temporal lobe surgery (Lee, Yip, & Jones-Gotman, 2002). At the same time, it is ideal to include verbal and nonverbal memory measures normed on the same population, with stimuli that are less likely to be dually encoded. The Rey Auditory Verbal Learning Test (AVLT) and Buschke Selective Reminding Tests (SRT) have nonverbal analogs. The Warrington Recognition Memory Test has matched tasks using words and faces. Ideally, memory tests will include learning trials, free recall, and recognition trials.

Because significant verbal memory decline has been reported in 30% to 60% of patients who undergo left ATL (e.g., Baxendale, Thompson, Harkness, & Duncan, 2006), all neuropsychological

batteries should contain measures of verbal memory for patients with localization-related epilepsy. Story memory tasks are recommended because much new learning is contextual, but verbal list learning tasks are most sensitive to decline after left ATL. A list learning task such as the Rey AVLT, SRT (Buschke & Fuld, 1974), or California Verbal Learning Test (CVLT) is recommended. The published regression equation for fMRI for predicting memory decline after left ATL employs the SRT (Binder et al., 2008). However, the Rey AVLT is recommended in the Common Data Elements Project (described later in this chapter) for its ease of administration and scoring as well as cost. The SRT and Rey AVLT are both available in the public domain without cost, and the Rey AVLT has a Spanish version.

Motor and sensory examinations are recommended to assess for motor slowing and lateralizing motor and sensory effects of focal seizure disorders. Grooved pegboard and finger tapping will assess lateralized differences in manual dexterity and fine motor speed. Grip strength measured with a dynamometer will detect differences in motor strength related to hemiparesis or more subtle lateralized seizure effects.

The National Institute of Neurological Disorders and Stroke (NINDS) commissioned a group to develop recommendations for neuropsychological testing in epilepsy with the goals of standardizing data collection across investigators, simplifying data aggregation, facilitating development of evidence-based guidelines, and standardizing disease characterization and outcome assessment (Loring et al., 2011). The NINDS Epilepsy Standards, Common Data Elements recommendations, and rationale for neuropsychological test selection for epilepsy, normative data, and vendor are available online (see National Institutes of Health, n.d.). Tests were selected that have been used in previous epilepsy studies and, where possible, are available in the public domain and have a Spanish version. See Table 9.1 for the test list suggested by the Epilepsy Common Data Elements guidelines for adults.

F. Effects of Antiseizure Medications on Cognition

Side effects of AEDs are an important concern for patients with epilepsy. AEDs work by reducing neuronal activity and can lead to undesirable cognitive and behavioral side effects, and thus, the risk–benefit ratio of medications should be considered. Phenobarbital is associated with the greatest cognitive risk, including lower IQ and academic functioning in children prescribed this medication for seizure prophylaxis after a febrile seizure (Farwell et al., 1990). Hyperactivity in children and depression in both children and adults have also been reported in association with phenobarbital (Glauser, 2004).

Table 9.1. Recommended Neuropsychological Tests for Adult Epilepsy Patients Based on the Epilepsy Common Data Elements Project

Domain	Test
IQ or Premorbid Function	American National Adult Reading Test[a]
Formal IQ Testing	WAIS–IV[b]
	WASI (now the WASI–2)
Learning and Memory	
Verbal	Rey AVLT[b]
	Wechsler Memory Scales
	Verbal Paired Associates
	Logical Memory
	California Verbal Learning Test–2
	Selective Reminding Test (less common)
Nonverbal	None
Optional	
	Brief Visual Memory Test
	Rey-Osterrieth Complex Figure
	WMS–VI Visual Reproduction
	Nonverbal Selective Reminding Test
Language	
Naming	Boston Naming Test[b]
Phonemic Fluency	Controlled Oral Word Association Test (FAS)[c]
Semantic Fluency	Animal Naming[b]
Visual Spatial	
Optional Domain	WASI Block Design
	WAIS–IV Perceptual Reasoning
Executive Functioning	
Set Shifting	Trail Making A and B[b]
Attention	WAIS–IV Digit Span[b]
Hypothesis Testing	Wisconsin Card Sorting Test
Speed	
Processing Speed	WAIS–IV Coding and Symbol Search[b]
Motor Speed	Grooved Pegboard[b]

[a]WRAT–4 is commonly used but not in the public domain. [b]Spanish version or Spanish directions are available. [c]Spanish version uses letters PMR

Studies comparing the effects of older AEDs (carbamazepine, phenytoin, and valproate) in healthy adults found modest effects on motor speed, memory and attention but no significant difference between these drugs (Meador et al., 1995).

Few head-to-head studies have been conducted with the newer AEDs developed after the 1990s. In general, fewer cognitive side effects are seen with the newer AEDs relative to the older AEDs. Of the newer AEDs, Topamax has been most associated with cognitive side effects, including changes in language, memory, processing speed, and frontal lobe functioning.

Higher doses, rapid titration, and the additive effect of multiple AEDs increase the likelihood of adverse cognitive side effects (Hermann, Meador, Gaillard, & Cramer, 2010). The most common cognitive side effects are on complex or sustained attention and processing speed. There is a vast literature on this topic, and the reader is referred to comprehensive reviews (Loring, Marino, Meador, 2007; Meador, 2006).

IV. SURGICAL INTERVENTION AND OUTCOME

Surgery is an effective treatment for many patients with epilepsy. In many of the 30% to 40% of epilepsy patients with pharmacoresistant epilepsy, surgery can reduce or eliminate seizures and improve quality of life compared with standard medication treatment. The significant benefits of surgery must be weighed against risks of neurological complications, cognitive decline, and psychiatric symptoms.

A. Seizure Outcome

Approximately 60% to 70% of patients are seizure free in the 1 to 2 years after temporal lobectomy, and 50% are seizure free after neocortical resection (de Tisi et al., 2011). These rates are significantly better than the ≤10% probability of seizure freedom in patients with temporal lobe epilepsy who have failed with two or more anticonvulsant drugs (Wiebe, Blume, Girvin, & Eliasziw, 2001). There are fewer data on long-term seizure outcome following surgery, but a recent study suggested seizure-free rates of 63% at 2 years after surgery, 52% at 5 years, and 47% at 10 years (de Tisi et al., 2011). Higher rates of seizure freedom are associated with location of surgery (ATL and hemispherectomy), age (<50 years), and MRI (abnormal). Approximately 6% of patients experience new neurological deficits after epilepsy surgery, and in half of these patients, deficits resolved within 3 months.

B. Cognitive Outcome

Decline in memory and word-finding are the most common cognitive morbidities associated with ATL. It is estimated that after dominant ATL, 30% to 60% of patients experience substantial episodic memory decline. After left ATL, visual confrontation naming declines an average of 3 to 9 raw score points on the Boston Naming Test, which is significant when compared with control groups (Hermann et al., 1999). A subset of patients experience more striking decline, with up to 42% of left ATL patients declining ≥10 points on the Boston Naming Test after surgery (Sabsevitz et al., 2003).

Side of surgery is the strongest risk factor for memory decline after ATL, with greater risk associated with left resections. Naugle, Chelune, Cheek, Luders, and Awad (1993) found an average auditory memory decline of more than two thirds standard deviation after left ATL, whereas there was no memory decline after right ATL. Preserved functioning or higher preoperative scores is also a strong risk factor for memory decline. Variables predictive of decline after left ATL are listed in Exhibit 9.2 and are described in several excellent reviews (e.g., Bell, Lin, Seidenberg, & Hermann, 2011; Busch & Naugle, 2008).

The relationship between left ATL and verbal memory decline has been a reliable finding across studies, but the relationship between right/nondominant temporal lobectomy and nonverbal memory deficits has been less robust. This may reflect the more distributed network underlying visual compared with verbal memory, the involvement of the left temporal lobe in visual memory, and the variety of methods that have been used to measure visual memory. For example, there is evidence that spatial memory tasks are more sensitive to right ATL than memory for abstract designs and faces (Dulay et al., 2009). Predictors of language decline after surgery are similar to those for memory decline and are listed in Exhibit 9.2.

There is much less research available on cognitive effects of extratemporal surgery. Group studies provide preliminary evidence that frontal lobe surgery causes mild decline in some frontal functions, depending on the location of surgery (e.g., Helmstaedter, Gleibner, Zentner, & Elger, 1998).

C. Psychiatric Outcome

Anxiety and depression tend to decrease after epilepsy surgery, and other disorders (e.g., mania, schizophrenia) may also improve after surgery (Devinsky et al., 2005). Most patients who have psychiatric symptoms after surgery also had symptoms before surgery, although de novo cases of postoperative depression and anxiety occur in

Exhibit 9.2. Univariate Predictors of Decline After Left/Dominant ATL

Variables Predictive of Decline in Episodic Auditory Memory
Wada testing: Lateralization of memory and language function toward the left
fMRI: Lateralization of activation toward the left in semantic decision tasks
Better preoperative verbal memory performance
No/mild left hippocampal sclerosis versus moderate/severe
Older age of recurrent seizure onset
Older age at time of surgery
Endorsement of more depressive symptoms prior to surgery
Male compared with female sex in the presence of MTS

Variables Predictive of Decline in Naming
Wada testing: Lateralization of activation toward the left
fMRI: Lateralization of activation toward the left in semantic decision tasks
Later age of epilepsy onset
Better preoperative naming ability
Presence of mesial temporal sclerosis
Extent of lateral resection

Note. ATL = anterior temporal lobectomy. fMRI = functional magnetic resonance imaging. MTS = mesial temporal sclerosis.

approximately 8% of patients in the year or two following surgery (Devinsky et al., 2005). Patients who experience postictal psychosis and become seizure free will also likely be free of their psychotic episodes. The strongest predictors of postoperative psychiatric symptoms are history of psychiatric symptoms and continued seizures after surgery (Devinsky et al., 2005). When postoperative psychiatric symptoms do occur, it is usually in the first few months after surgery, and symptoms respond well to antidepressant medication (Blumer, Wakhlu, Davies, & Hermann, 1998). Particularly after surgery, patients should be monitored for dysphoric episodes with suicidal ideation.

D. Quality of Life (QOL) Outcome

Patients typically report improved QOL in one or more domains following epilepsy surgery. The best predictor of improved QOL after

surgery is seizure outcome, with the best QOL scores in those who are seizure free. Other determinants include baseline psychological functioning, realistic expectations for surgical results, employment, high patient satisfaction, and ability to drive. Factors associated with decreased postoperative QOL include adverse effects of AEDs, poor psychological function, verbal memory problems, and physical comorbidities (for a review, see Seiam, Dhaliwal, & Wiebe, 2011).

V. PSYCHIATRIC ISSUES IN EPILEPSY

A. Comorbidities

It is well established that epilepsy patients have greater comorbidity of psychiatric disorders than the general population. Population-based research suggests that those with epilepsy have almost twice the lifetime prevalence of mood and anxiety disorders (Tellez-Zenteno, Patten, Jetté, Williams, & Wiebe, 2007). Depression is the most common psychiatric comorbidity and often has an atypical presentation characterized by irritability, anhedonia, hopelessness, fear, and anxiety. This has been termed *interictal dysphoric disorder* and is present in about one third of those on epilepsy monitoring units (Blumer, Montouris, & Hermann, 1995). Suicide is also more common, with lifetime prevalence rate in patients with epilepsy at approximately 12%, compared with 1% in the general population (Jones et al., 2003). Increased prevalence of psychosis (postictal and interictal) and ADHD have also been associated with epilepsy. It used to be thought that there was a common cluster of personality traits in people with temporal lobe seizures (i.e., Geshwind syndrome), but now the general consensus is that depression is the most common interictal psychiatric condition in epilepsy and that there is no specific personality type associated with epilepsy.

Those with temporal lobe epilepsy as well as more severe and chronic epilepsy have a greater likelihood of psychiatric comorbidity. Several factors may be responsible for increased comorbidity in epilepsy, including social and vocational restrictions, psychological factors, AED side effects, genetic predisposition, and underlying neuropathology (Gilliam, 2005). Lin, Mula, and Hermann (2012) provided an excellent review of psychiatric, cognitive, and social comorbidities of epilepsy and how these are affected by neuropathological correlates.

Diagnostic interview is the gold standard for assessing psychiatric symptoms, and screening measures are useful to determine patients at greatest risk. The Center for Epidemiologic Studies Depression Scale (U.S. Department of Health and Human Services, n.d.) and the Beck

Depression Inventory—II (Beck, Steer, & Brown, 1996) are commonly used to screen for depression in epilepsy patients.

Psychiatric symptoms are often effectively treated with similar methods used for patients without epilepsy, including cognitive behavioral therapy and medications. For depression, a recent pilot study demonstrated beneficial effects of group cognitive–behavioral therapy in epilepsy patients (Crail-Meléndez, Herrera-Melo, Martinez-Juarez, & Ramierez-Bermudez, 2012). Although SSRIs are not contraindicated, it is important that the treating provider be mindful about potential interactions with AEDs and effects on seizure threshold.

B. Ictal Aggression

Violent or aggressive behavior is rarely encountered during the ictal period (Marsh & Krauss, 2000). Seizures are characterized by stereotyped, nondirected, and nonpurposeful behavior. The more directed, planned, and organized the behavior, the less likely it is epilepsy (Treiman, 1991). Likewise, one cannot assume that individuals with episodic rage or aggression are having epileptic events even if they have a documented seizure disorder. However, resistive violence when the individual is being restrained during the postictal period or directed violence during postictal psychosis is much more common.

C. Nonepileptic Seizures (NES)

Paroxysmal behavioral events that are not accompanied by abnormal electrical discharges in the brain are considered NES. NES can be divided into two main types of spells: *physiologic* and *psychogenic*. Physiologic NES are episodes of behavioral alteration that have a physical explanation such as syncope, migraine with neurologic signs, sleep disorders such as rapid eye movement behavior disorder or narcolepsy, transient ischemic events, movement disorders (nonepileptic myoclonus), and transient global amnesia (typically not recurrent). Psychogenic NES (PNES) spells superficially resemble epileptic seizures but are initiated by a psychological mechanism. PNES are considered an involuntary response to emotional distress. The most common psychological diagnoses in patients with PNES are somatoform disorders (conversion disorder), posttraumatic stress disorder, panic disorder, dissociative disorders, factitious disorder, and malingering. Behavioral analysis of the spells is useful for determining antecedents, consequences, and environmental reinforcement for the illness behavior. For more complete review of NES, see Gates and Rowan (2000).

Accurate diagnosis of PNES or physiologic NES is critical for directing psychological or medical treatment and avoiding iatrogenic effects of inappropriate treatment. The gold standard for diagnosing NES is long-term video EEG monitoring. However, clinical interview and seizure semiology can also provide adjunctive clues that may point in the direction of PNES. Features more common in, but not definitively diagnostic of, PNES include no response to AEDs, events occurring only in the presence of witnesses, absent or excessive emotional response to the spells, older age at onset of seizures, and history of abuse. PNES spells tend to be longer than epileptic seizures; involve asynchronous motor movements; and are less likely to be associated with falling, injury, incontinence, and postictal confusion. PNES are less likely to occur during sleep but more likely to occur with eyes closed.

Objective personality testing can also be useful in the evaluation of PNES. A set of configural rules were developed to differentiate between NES and epileptic seizure (ES) using the Minnesota Multiphasic Personality Inventory (MMPI) and more recently the Personality Assessment Inventory (PAI). The MMPI decision rules correctly classified 80% to 90% of both epileptic and PNES patients (Wilkus, Dodrill, & Thompson, 1984). These rules are a useful adjunct to psychiatric and neurologic evaluations for differentiating NES and ES but do result in a number of false positive and false negatives.

D. Psychosocial Issues and QOL

Epilepsy has long been associated with adverse QOL. Compared with controls, epilepsy is associated with lower education levels, unemployment, households with low annual incomes, self-perception of fair or poor health, lack of independence in important areas such as driving, and social stigma and isolation (Hermann & Jacoby, 2009). Optimizing QOL for those with epilepsy extends beyond treatment of the seizures and includes recognition and management of more far-reaching factors.

Depression and anxiety are major contributors to QOL, as are seizure-related factors such as seizure severity and frequency (Jehi, Tesar, Obuchowski, Novak, & Najm, 2011). Driving and employment status as well as presence of AED side effects are also important contributors. As with psychiatric and cognitive symptoms, the association between epilepsy and reduced QOL likely reflects neurobiological, seizure-related, and psychological factors (Hermann & Jacoby, 2009). The Quality of Life in Epilepsy (QOLIE) inventory is a commonly used disease-specific self-report measure that assesses various QOL domains. The QOLIE and scoring manuals can be found on the

Rand Health website (http://www.rand.org/health/surveys_tools/qolie.html).

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Chapter 10

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Traumatic Brain Injury and the Postconcussion Syndrome

Traumatic brain injury (TBI) is a significant public health problem facing the United States and other industrialized countries around the world. National estimates of TBI in the United States range anywhere from 1.4 million to 4 million brain injuries per year, depending on the study and methods used to define and include cases (Coronado, Johnson, Faul, & Kegler, 2006; Silver, McAllister, & Yudofsky, 2005). Age-specific rates show a bimodal distribution, with highest risk in young children and older adults. Nearly half a million children in the United States sustain a TBI each year, making TBI the single leading cause of death and disability in the pediatric age group (Keenan & Bratton, 2006; Langlois, Rutland-Brown, & Thomas, 2005).

TBI imposes substantial demands on health care systems in the United States and throughout the world (Coronado, Thomas, Sattin, & Johnson, 2005). Worldwide, at least 10 million TBIs are serious enough to result in death or hospitalization annually (Langlois, Rutland-Brown, & Wald, 2006). In the United States, more than 1 million hospital emergency department visits, 300,000 hospitalizations,

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and 50,000 deaths result from TBI annually (Rutland-Brown, Langlois, Thomas, & Xi, 2006). Because of advances in medical care and other factors, more people are surviving TBI than ever before. Brain injury accounts for more lost productivity at work among Americans than any other form of injury. An estimated 5.3 million Americans are living with significant disabilities resulting from TBI that complicate their return to a full and productive life (Langlois et al., 2006).

This chapter provides an overview of the defining clinical characteristics and pathophysiology of TBI, modern-day diagnostic techniques, and approaches to treatment. Because the incidence of mild TBI (mTBI) is high and neuropsychologists are commonly asked to address issues arising with mTBI, particular emphasis is given in this chapter on a review of the mild end of the TBI severity spectrum.

I. DEFINITION/CLASSIFICATION

Traumatic brain injury is commonly defined as an alteration in brain function or other evidence of brain pathology caused by an external force and characterized by the following: (a) any period of loss or decreased level of consciousness (LOC), (b) any loss of memory for events immediately before (retrograde) or after (posttraumatic) the injury, (c) any neurological deficits, and/or (d) any alteration in mental state at the time of injury (National Institute for Neurologic Disorders and Stroke [NINDS] Common Data Elements [CDE] for TBI; see the NINDS website: http://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards).

Evidence of TBI can include visual, neuroradiologic or laboratory confirmation of damage to the brain, but TBI is more often diagnosed on the basis of acute clinical criteria. Modern structural (e.g., diffusion tensor magnetic resonance imaging [MRI]) and functional imaging (resting state functional MRI) techniques show increasing sensitivity, and it is possible that other sensitive biomarkers may be developed in the future.

A. Mechanisms of TBI

Common mechanisms of TBI include the head being struck by an object, the head striking an object, the brain undergoing an acceleration and/or deceleration movement, a foreign body penetrating the brain, or forces generated from events such as a blast or explosion.

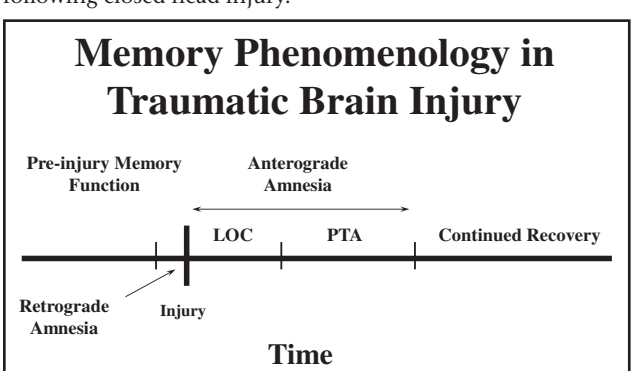
Motor vehicle crashes have consistently been cited as the most common cause of TBI, accounting for 40% to 60% of all TBIs annually (Kraus & Chu, 2005). All forms of transportation, however, are common causes of TBI, including motorcycle crashes, bicycle accidents,

and pedestrian injuries. The other leading causes of TBI are falls, assaults, and sports, with varied frequency across the life span. Certainly, there has been an increased focus on the high frequency of concussion or mTBI encountered by athletes participating in contact and collision sports at all competitive levels as well as the potential short-term effects and long-term risks associated with sport-related concussion. More recently, there have been concerns about risk of head injury in military personnel exposed to blast explosions in the war theater.

B. Classification of TBI Severity

Numerous systems have been developed over the years to define and classify TBI severity along a continuum from mild to moderate to severe. These systems are usually most applicable to closed head injuries, where the dura remains intact, as opposed to penetrating head wounds. In nearly all classification systems, TBI severity is graded based on acute injury characteristics rather than postacute injury status because other factors can intervene to influence functional outcome. Historically, presence and duration of unconsciousness and amnesia have been the main points of distinction along the gradient of TBI severity. Figure 10.1 illustrates the course of mental status changes and amnesia associated with TBI.

Figure 10.1. Timeline of mental status changes and amnesia following closed head injury.



The Glasgow Coma Scale (GCS; Jennett & Teasdale, 1981) is the most recognized and widely used method for grading TBI severity. The GCS provides an indicator of gross neurologic status by assessing motor function, verbal responding, and the patient's ability to open his or her eyes voluntarily or in response to external commands and stimuli (see Table 10.1i at http://pubs.apa.org/books/supp/parsons). The grading is applied to the best response that can be elicited from the patient at the time of assessment, preferably before any paralyzing or sedating medication is administered or the patient is intubated because these interventions confound interpretation of the score. As seen in Table 10.1i, the GCS assessment produces scores ranging from 3 to 15.

Several injury classification systems have been developed to go beyond GCS score or acute injury characteristics and incorporate chief signs and symptoms in defining mTBI. The use of multiple severity indicators is intended to improve the sensitivity in the detection of mTBI while also taking into consideration traditional acute injury characteristics that have been presumed to predict outcome following mild and moderate brain injury. Despite their limited utility in mTBI, loss of consciousness and posttraumatic amnesia (PTA) remain the most common injury characteristics referenced in most classification symptoms. Table 10.1 provides a matrix of criteria for the classification of mild, moderate, and severe TBI based on GCS score and a combination of the total duration of unconsciousness and PTA. The criteria in Table 10.1 have been adopted in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5;* American Psychiatric Association, 2013). In the case of moderate and severe TBI, GCS score and the duration of PTA and LOC can be robust predictors of long-term outcome and morbidity. In cases of mTBI, however, although PTA and LOC are important indicators of acute

Table 10.1. Multiple Severity Indicators of Traumatic Brain Injury

	Severity classification		
Measure	**Mild**	**Moderate**	**Severe**
Glasgow Coma Scale	13–15	9–12	3–8
Loss of consciousness	<30 min	30 min–24 hr	>24 hr
Posttraumatic amnesia	<24 hr	1–7 days	>7 days

injury severity, they are less predictive of eventual recovery time and outcome.

C. Mild TBI

It is estimated that 70% to 90% of all treated TBIs are mild in severity based on traditional case definitions and acute injury characteristic criteria (Cassidy et al., 2004), with most reported estimates in the order of 85% (Bazarian et al., 2005). The World Health Organization (WHO) Collaborating Centre Task Force on Mild Traumatic Brain Injury cited the incidence of hospital-treated mTBI to be 100 to 300 per 100,000 of the population (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). The investigators pointed out, however, that published figures likely underrepresent the true incidence of mTBI because of variable case definitions and heterogeneous methods. Moreover, because a subgroup of individuals with milder brain injuries do not seek medical attention after their injury, epidemiological studies that depend on hospital-based data also underestimate the incidence.

Several operational definitions of mTBI have been developed (see Table 10.2i at http://pubs.apa.org/books/supp/parsons). Perhaps the most popular definition of mTBI was put forth by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM; Kay et al., 1993). The ACRM definition requires a single criterion of unconsciousness, amnesia, or alteration in mental status for the diagnosis of mTBI. Other definitions of mTBI place varied emphasis on acute injury characteristics and other signs and symptoms to establish a diagnosis. For operational definitions of mTBI developed by the ACRM and those from the Centers for Disease Control and Prevention MTBI Work Group, please see Gerberding and Binder (2003), and for those developed by the WHO Collaborating Centre Task Force on MTBI, see Holm, Cassidy, Carroll, and Borg (2005).

D. Sport-Related Concussion

On the basis of its reported prevalence and acute effects and fears over potential long-term neurological consequences, sport-related concussion has become the focus of increasing concern from clinicians, researchers, sporting organizations, and athletes themselves over the past 2 decades (McCrory et al., 2005, 2009, 2013). Concussion is a frequent injury in contact and collision sports (e.g., football, hockey, wrestling) at all levels of participation, including youth sports (Guskiewicz, Weaver, Padua, & Garrett, 2000; Halstead

& Walter, 2010; Powell & Barber-Foss, 1999). A recent study indicated that from 1997 to 2007, emergency department visits for 8- to 13-year-old children affected by concussion in organized team sports doubled and that they increased by more than 200% in the 14- to 19-year-old group (Bakhos, Lockhart, Myers, & Linakis, 2010), which may largely represent improvements in identification rather than actual changes in incidence rates.

Research over the past decade has significantly advanced our scientific understanding of the true natural history of clinical recovery following sport-related concussion. In general, the findings on acute recovery are favorable. A 2003 report was the first to plot the continuous time course of acute recovery within several days after concussion, indicating that more than 90% of athletes reported symptom recovery within 1 week (McCrea et al., 2003, 2005). Several other prospective studies have since demonstrated that the overwhelming majority of athletes achieve a complete recovery in symptoms, cognitive functioning, postural stability, and other functional impairments over a period of 1 to 3 weeks following concussion (Belanger & Vanderploeg, 2005; Broglio & Puetz, 2008; Collins et al., 1999; Guskiewicz et al., 2003; Macciocchi, Barth, Alves, Rimel, & Jane, 1996).

There are frequent anecdotal reports, however, of athletes who remain symptomatic or impaired on functional testing well beyond the window of recovery commonly reported in group studies. The greatest challenge arguably still facing sport medicine clinicians and public health experts is how to most effectively manage and reduce risk in this subset of athletes who do not follow the "typical" course of recovery. The precise frequency of athletes who do not follow the typical course of rapid, spontaneous recovery and instead exhibit prolonged postconcussive symptoms or other functional impairments after concussion remains unclear. There is little empirical evidence regarding which risk factors may be associated with prolonged recovery time or poor outcome in athletes and how these risks can be modified in a clinical setting.

E. Military TBI

TBI during wartime is common. The relative incidence of penetrating head injuries is especially high compared with civilian injuries. Indeed, focal brain injuries from penetrating head injuries during World War I, World War II, and to a lesser extent the Vietnam War have provided a scientific foundation for much of our understanding of brain–behavior relationships. With the advent of modern-day explosive weapons, the incidence of TBI among U.S. military

personnel deployed to Iraq and Afghanistan (Operation Iraqi Freedom and Operation Enduring Freedom [OIF/OEF]) is reportedly the highest of any military conflict in U.S. history (Okie, 2005; Warden, 2006). Official reports from the military indicate that more than 178,000 warfighters in OIF/OEF were formally diagnosed with TBI between 2000 and early 2010 (Armed Forces Health Surveillance Center, 2010). Other reports have indicated that up to 20% of combat veterans meet the criteria for mTBI on postdeployment screening, which translates to as many as 320,000 of the 1.6 million veterans who served in OIF/OEF returning stateside with a history of possible mTBI (Tanielian & Jaycox, 2008).

As in the civilian and sports sectors, the overwhelming majority (>75%) of TBIs in OEF/OIF are categorized as nonpenetrating mTBI (Armed Forces Health Surveillance Center, 2010). Several factors contribute to the unprecedented rate of mTBI in OIF/OEF, the most significant of which are the high frequency of explosive or blast attacks coupled with significant improvements in protective gear to minimize penetrating injuries. The incidence of blast injury and associated blunt trauma in OIF/OEF is significantly higher than in past military conflicts (Warden, 2006).

Blast presents a unique set of mechanisms for TBI in addition to blunt trauma with acceleration/deceleration forces. Blast conveys an initial positive pressure wave that is followed by a negative pressure, both of which have potential to deform brain tissue and create a spike in blood pressure. The magnitude and distribution of these effects are only beginning to be understood. There are also potential secondary effects associated with blast-related injuries, including penetrating wounds from debris or shrapnel, blunt trauma from being thrown into objects, and systemic injuries from burns and inhalation of toxic fumes. Research to learn whether TBI from blast mechanisms has a different outcome than blunt trauma in veterans has proven challenging, in part because blast injuries almost invariably include blunt trauma, too. An additive effect of blast to blunt trauma mechanisms on TBI has not yet been identified in clinical studies of soldiers and veterans; however, methodological obstacles complicate this research. Not surprisingly, the incidence of posttraumatic stress disorder (PTSD) is substantially higher in victims of blast compared with blunt trauma alone. Because many soldiers are exposed to multiple blasts during their deployments, the issues associated with repetitive blast and blast–blunt trauma are present, and the long-term risks associated with blast-related mTBI or repetitive blast exposures and blunt trauma remain unclear.

II. FUNCTIONAL NEUROANATOMY OF TBI

A. Focal Brain Injury

In more severe forms of TBI, structural brain damage after trauma can be categorized based on clinical and neuroradiologic findings. Common forms of focal brain injury include skull fracture, contusions and lacerations, intracranial hematoma, epidural hematoma (EDH), subdural hematoma (SDH), and brain damage due to increased intracranial pressure.

Contusions are the most common brain damage due to TBI and have a characteristic distribution preferentially affecting the pole of the frontal lobe, the inferior aspect of the frontal lobes, the temporal poles, the lateral and inferior aspects of the temporal lobe, and the cortex above and below the operculum of the Sylvian fissures. Less often there can be damage to the undercarriage of the cerebellar hemispheres. Contusions may extend into the white matter, typically comprising a mixture of hemorrhage and necrosis in more severe cases. More severe or larger contusions can be associated with cerebral swelling, which results in subsequent sequelae due to increased intracranial pressure.

Intracranial hematoma is the most common cause of clinical deterioration and death in patients who were initially lucid after TBI, often referred to as the "talk and die" patient group. EDH often occurs from temporal bone fractures that sever the middle meningeal artery. These typically present a neurosurgical emergency because the hemorrhage rate is high from arterial pressure, rapidly creating a potentially life-threatening mass effect. SDH is a common occurrence in TBIs of any severity, especially among older adults, and is often associated with swelling of the ipsilateral cerebral hemisphere and can cause secondary complications from mass effects. SDH typically arises from torn veins in the subarachnoid space, which evolves more slowly than EDH because of the lower pressure in veins. Chronic or slowly developing SDH can occur days or weeks after what appeared to have been a trivial head injury, particularly in older patients. The clinical course is characterized by an accelerated neurologic deterioration some time after a period of apparently normal function following TBI.

B. Diffuse Brain Injury

Acceleration/deceleration and rotational forces often produce effects that are microscopic and distributed widely in the brain. The most common of these, and essentially the signature injury in mTBI,

is traumatic axonal injury (TAI). TAI, which historically has been referred to as *diffuse axonal injury* (DAI), occurs when the brain is deformed from traumatic forces causing axons to be stretched sufficiently to produce at least a transient disruption in neural functioning. If the stretch is mild to moderate (estimated less than 10% of natural length), the neuron will eventually recover function, but recovery time will vary with the degree of stretch. If the stretch is severe (estimated to be greater than 15% of natural length), the axon will be permanently injured, in some cases showing acute disruption of the membrane, referred to as *axonal shearing*. Because most axons are bundled in the white matter of the brain, TAI is largely distributed in subcortical white matter, with greater injury occurring in locations that are vulnerable to stretch (e.g., corpus callosum). Histological appearance of TAI typically involves hemorrhages and tissue tears, axonal swelling, axonal folds, retraction bulbs at sites of membrane disruption, clusters of microglia and macrophages, and Wallerian degeneration. In addition to TAI, diffuse brain injury can also occur from disseminated tears in capillaries causing petechial hemorrhages and from hypoxia.

C. Secondary Brain Injury

Primary traumatic damage to the brain may be further complicated by secondary insults that occur acutely or subacutely. In patients with severe brain injury, hypoxia is considered the most common secondary insult. Other forms of secondary injury may include diffuse (multifocal) vascular injury, focal or widespread cerebral swelling, or disruption of normal brain electrical activity that may cause posttraumatic seizures. Patients with extensive subarachnoid hemorrhage are particularly vulnerable for developing communicating hydrocephalus a month or two after injury.

D. Pathophysiology of mTBI or Concussion

Collectively, the underlying pathophysiological processes of concussion have been eloquently characterized as a "neurometabolic cascade" by Hovda and colleagues (see Giza & Hovda, 2001). The clinical manifestation of concussion signs and symptoms results from sequential neuronal dysfunction due to ionic shifts, altered metabolism, impaired connectivity, or changes in neurotransmission. Contrary to prior thought, concussion or mTBI does not typically result in structural injury to neurons, axons or measureable cell death. Rather, the underlying pathophysiology renders neurons and axons temporarily dysfunctional. The time course of this

physiological disruption is considered to generally parallel that of clinical symptoms and recovery time. Further research is required to more definitively determine the true natural history of physiological recovery or when recovery is fully achieved at a brain level in humans affected by mTBI.

III. NEUROIMAGING OF TBI

Computerized tomography (CT) scanning remains the imaging technique of choice in a critical care setting where the highest neurosurgical priority is to identify acute intracranial hemorrhage requiring intervention. Still, CT has poor sensitivity to markers of TAI in the overwhelming majority of mTBI cases. Conventional MRI sequences are more sensitive than CT in demonstrating structural abnormalities after TBI, particularly in milder forms of injury. Newer MRI pulse sequences and MRI data analysis methods offer promise in enhancing the overall sensitivity of MRI to mTBI by increasing sensitivity to white matter abnormalities, microscopic hemorrhage, and changes in functional connectivity between brain structures.

Still, these newer MRI techniques remain experimental, and for the most part their findings are nonspecific. Although their sensitivity to mTBI is promising, especially in group studies of patients studied during the acute and subacute phases of recovery, there are limited data on their usefulness in individual diagnosis and at postacute intervals. Research is needed to demonstrate the ultimate diagnostic utility of these newer methods, as well as correlating imaging findings with quantitative measures of clinical recovery and outcome following mTBI. There is a particular need for prospective studies of both symptomatic and asymptomatic patients to determine the sensitivity, incremental validity, and functional correlates of newer imaging techniques at the individual case level in mTBI. Table 10.2 provides an overview of imaging techniques for the study of TBI.

IV. NEUROPSYCHOLOGICAL EVALUATION OF TBI

Neuropsychological assessment should begin with an attempt to determine the severity of the TBI because understanding test scores hinges on appreciating the context and time frame in which they occur. Because neuropsychological test abnormalities are not specific to TBI, determination of severity requires an understanding of acute injury markers (e.g., LOC, GCS, PTA, radiological abnormalities). Medical records are the best source of this information, including reports from emergency medical technicians at the scene of injury, emergency department admission notes, and hospital records.

Table 10.2. Common and Promising Neuroimaging Techniques

Method	Advantages	Limitations
Computerized tomography (CT)	Rapid, economical, highly sensitive to acute hemorrhage	Medium resolution, poor sensitivity to microscopic lesions, limited tissue definition
Conventional magnetic resonance imaging (MRI)	Good resolution and tissue definition, medium sensitivity to white matter abnormalities	Slow acquisition, sensitive to subject movement, higher costs than CT, weak sensitivity to microscopic lesions
Diffusion tensor imaging (DTI) and tractography	Technique shown to be sensitive to structural abnormalities in white matter tract bundles	Experimental technique that is not specific to TBI, requires specialized image acquisition, analysis, and interpretation expertise
Susceptibility weighted imaging (SWI)	Highly sensitive to microscopic traces of iron from posttraumatic hemorrhage	Requires specialized acquisition and analysis methods
Magnetic resonance spectroscopy (MRS)	Sensitive, but often nonspecific	Weak association with injury assessment, outcome
Functional MRI (fMRI): Cognitive activation	Reveals normal and abnormal patterns of brain activity, better temporal/spatial resolution than other imaging techniques	Experimental, requires data analysis and interpretation expertise, not specific to TBI, requires active subject participation in task

Caution should be used in accepting mental status ratings as a marker of TBI severity when the patient is intoxicated with alcohol, intentionally sedated or paralyzed to manage care, or heavily treated with narcotic analgesics because all of these have effects on consciousness and memory formation. Use of mental status markers to gauge severity of TBI is most accurate when the effects of these agents can be ruled out as influential factors.

Determination of severity within the spectrum of mild to moderate TBI is often more complicated because frequently one is left to rely on the patient's retrospective report of their mental status to some degree. Determination of PTA is most important here because it has been shown to predict speed of recovery and morbidity better than GCS in this group. In general terms, the longer the interval of PTA, the longer the interval of recovery following mild to moderate TBI.

Technically, PTA refers to the interval of anterograde amnesia that occurs after an individual recovers from unconsciousness until the capacity to form new memories is reliably regained. Without a reliable witness, it is not possible to differentiate amnesia associated with unconsciousness from PTA. In practical terms, at the milder end of the spectrum of TBI it is generally not necessary to separate amnesia from LOC and PTA because the LOC, when it occurs, is typically quite brief relative to the length of the PTA, so lumping them together is not unreasonable when assessing duration of PTA. Other helpful rules for assessing whether a patient is suffering from amnesia, LOC, or PTA include the following:

1. A patient cannot ascertain if he or she had an LOC. Thus, unless there is a witness to verify LOC, a patient's report of LOC most likely represents an interval of amnesia, some portion of which might possibly have been an interval of unconsciousness.
2. The PTA that is a marker of TBI severity begins with the onset of impact of the external forces. Thus, if a patient can describe a personal memory for the injury circumstances, then any brain injury from the event is likely to be trivial or mild at worst. Moreover, if there is delayed onset amnesia, then factors other than primary brain injury are likely mechanisms for the amnesia, for example, evolving EDH, shock form fluid loss, hypoxia from respiratory distress, effects of medication, or emotional distress.
3. The end of PTA is signaled when the individual reliably forms new memories (e.g., recall of numerous details about a scene, retains information that has been expressed to them, or reliably stays oriented to time and place). Having a fleeting and isolated memory of a single event, especially if the event has significant emotional connotations, should

not be used to identify the end of PTA because such "islands of memory" are not uncommon when recovering from the confusional state that exists during PTA.

4. The quality of mental status testing among emergency professionals varies substantially. Thus, "alert and oriented x3" might simply mean that the patient is talking lucidly or is oriented to year, which is an inadequate index of recovery from PTA. Still, multiple consecutive indications of being fully oriented are usually telling.
5. When ascertaining the interval of PTA from retrospective interview, it is important to inform the patient that you are interested in his or her personal memory and not his or her understanding, and then avoid leading questions. Begin by asking what he or she remembers about the injurious event; then carefully probe what was the last memory prior to injury and the first memory after injury, firming up the details of memories (e.g., where it occurred, rough time frame after injury).
6. The presence of an intracranial abnormality typically implies a more prolonged or otherwise complicated recovery course, even in mTBI.

Neuropsychological assessment after TBI is an integral part of care throughout the recovery process, used to characterize cognitive strengths and weaknesses, monitor progress, and facilitate treatment recommendations. The effects of TBI are complex and often include physical, cognitive, behavioral, and emotional sequelae. In addition, recovery may be complicated by the influence of premorbid medical, psychiatric, and psychosocial factors (Ponsford et al., 2000; Ruff, Camenzuli, & Mueller, 1996). Comprehensive neuropsychological assessment takes all of these factors into account, and test selection is guided by the severity of injury, stage in recovery, and specific referral questions. A comprehensive list of TBI outcome measures that are recommended by the NINDS can be found on the National Institutes of Health website (http://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards).

A. Acute Inpatient Assessment

In cases of moderate and severe TBI, the first assessment may occur during the inpatient hospitalization. The goals of inpatient neuropsychological assessment are typically to document severity of injury through determination of neurocognitive status, identify prominent neurobehavioral deficits, track cognitive recovery, evaluate decision-making capacity, and assist with treatment and dispositional planning. Brief repeatable assessments can be used to monitor the

resolution of PTA (e.g., Galveston Orientation and Amnesia Test [Levin, O'Donnell, & Grossman, 1979]) and track general cognitive status (e.g., Mini Mental State Exam [Folstein, Folstein, & McHugh, 1975]; Repeatable Battery for the Assessment of Neuropsychological Status [Randolph, Tierney, Mohr, & Chase, 1998]). As recovery progresses, additional testing may be warranted on an inpatient or outpatient basis (see Table 10.3 for commonly used measures).

B. Brief Neuropsychological Screening

Brief outpatient neuropsychological testing during the subacute phase of recovery (weeks to months after injury) can be used to monitor and potentially enhance recovery. In collaboration with physical medicine and rehabilitation staff, the goal of a brief evaluation (1–2 hours) is to track physical and cognitive recovery; educate patients and families about the normal course of recovery after TBI; and generate referrals as needed to services such as cognitive–speech therapy, physical–vestibular therapy, and psychology–psychiatry. The assessment focuses primarily on attention, memory (particularly new learning and retrieval), and executive functions, which are very sensitive to the effects of TBI (Wilde et al., 2010) and emotional adjustment to TBI (a sample core test battery is shown in Table 10.3). Test results can help guide decision making regarding return to work, school, sports, and driving. Feedback at this time is often a useful intervention, designed to reassure individuals that they are still recovering and have not yet reached their healing plateau as well as to facilitate treatment of secondary issues that may impede cognitive recovery (e.g., sleep disturbance, emotional distress, pain).

C. Comprehensive Neuropsychological Testing

In the postacute phase of recovery, comprehensive outpatient neuropsychological testing is often requested to address a diverse range of issues related to specific accommodations for return to work or school, recommendations for vocational rehabilitation, and determination of neurocognitive residuals for disability application or personal injury litigation. In this setting, test batteries can be tailored to more completely assess the cognitive residuals of focal and/or diffuse injuries, as well as the contribution of emotional symptoms or personality characteristics. In addition, effort testing should be routinely administered because both conscious and unconscious motivational factors (e.g., psychological factors, litigation) have been associated with poor effort and diminished performance on cognitive testing after TBI (Paniak et al., 2002; Silver, 2012). A

Table 10.3. Measures Frequently Used in Neuropsychological Assessment After Traumatic Brain Injury

Domain	Measure	Reference
Cognitive screening	Repeatable Battery for the Assessment of Neuropsychological Status	Randolph et al., 1998
Attention and working memory	Paced Serial Addition Test	Gronwall, 1977
	WAIS–IV Digit Span[a,b]	Wechsler, 2008
	WAIS–IV Arithmetic	Wechsler, 2008
	WAIS–IV Letter Number Sequencing[b]	Wechsler, 2008
	WMS–III Spatial Span	Wechsler, 1997
New learning and retrieval	California Verbal Learning Test—II	Delis, Kramer, Kaplan, & Ober, 2000
	Hopkins Verbal Learning Test—Revised[a]	Benedict, Schretlen, Groninger, & Brandt, 1998
	Rey Auditory Verbal Learning Test[b]	Rey, 1941
	WMS–IV Logical Memory	Wechsler, 2009
	WMS–IV Visual Reproductions	Wechsler, 2009
	Brief Visual Memory Test—Revised[b]	Benedict, 1997
Processing speed	WAIS–IV Processing Speed Index[b]	Wechsler, 2008
	Trail Making Test, Part A[a, b]	Reitan, 1992
	Symbol Digit Modalities Test[a, b]	Smith, 1982
Executive functions	Controlled Oral Word Association[b]	Strauss, Sherman, & Spreen, 2006
	D-KEFS Verbal Fluency Test[a, b]	Delis, Kaplan, & Kramer, 2001
	Trail Making Test, Part B[a, b]	Reitan, 1992
	Wisconsin Card Sorting Test	Heaton, 1981

Table 10.3. Measures Frequently Used in Neuropsychological Assessment After Traumatic Brain Injury *(Continued)*

Domain	Measure	Reference
Psychological symptoms	Beck Depression Inventory—II[a]	Beck, Steer, & Brown, 1996
	Minnesota Multiphasic Personality—2—RF[b]	Ben-Porath & Tellegen, 2008
	PTSD Checklist—Civilian/ Military/Stressor Specific[b]	Blanchard, Jones-Alexander, Buckley, & Forneris, 1996
Effort	Word Memory Test	Green, Allen, & Astner, 2005
	Test of Memory and Malingering	Tombaugh, 1996
Postconcussive symptoms	Rivermead Postconcussive Symptom Questionnaire[b]	Cicerone & Kalmar, 1995
	Neurobehavioral Symptom Inventory[b]	King, Crawford, Wenden, Moss, & Wade, 1995

Note. WAIS–IV = Wechsler Adult Intelligence Scale—Fourth Edition; WMS—III = Wechsler Memory Scale—Third Edition; WMS–IV = Wechsler Memory Scale—Fourth Edition; D-KEFS = Delis–Kaplan Executive Function System; PTSD = posttraumatic stress disorder. [a]Sample battery for brief subacute cognitive screening. [b]National Institutes for the Treatment of Neurologic Disorders and Stroke (NINDS) TBI Common Data Elements measures.

number of commonly used neuropsychological measures are listed in Table 10.3 and can be selected as needed based on specific referral questions. To avoid mental fatigue in the more severely injured, consideration should be given to distributing the administration of longer test batteries over multiple sessions.

In the setting of sport-related concussion, assessment and management are best approached from a multidisciplinary framework, where the neuropsychologist can play a valuable role. Cognitive testing adds useful information from a concussion management standpoint by tracking cognitive recovery and aiding in decision making regarding return to play. The 4th Consensus Statement on Concussion in Sport (McCrory et al., 2013) provides comprehensive recommendations for the assessment and management of

sport-related concussion. A number of measures designed to be used specifically with athletes are among the outcome measures specifically recommended as by the NINDS (http://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards). Computerized testing has been widely used in this setting (see Table 10.4) because these measures are convenient for screening and serial assessment; however, information on test–retest reliability and specificity of the abnormal findings for many of these screening instruments has yet to be well established. Consensus guidelines caution against the use of neuropsychological testing, computerized or conventional, as the stand-alone method for determining when an athlete is fit to return to play after concussion.

V. TBI RESIDUALS, COMORBIDITIES, TREATMENT INTERVENTIONS, AND OTHER ISSUES

A. Postconcussion Syndrome and Neurocognitive Disorders

Within the first few days following mTBI, a collection of symptoms occurs with such regularity that any combination of the symptoms has been referred to as *postconcussion syndrome* (PCS). These symptoms include headache, blurred vision, dizziness and imbalance, concentration problems, forgetfulness, slowed thinking, sleep disturbance, and irritability. PCS as a diagnostic entity with explanatory value only has clinical utility in the acute and subacute window when symptoms are likely related to brain dysfunction. *DSM–5* categorizes presumed residuals from TBI beyond the acute period as mild neurocognitive disorder (NCD) or major NCD depending on whether there are associated impairments in instrumental activities of daily living (IADLs, e.g., ability to pay bills). A diagnosis of mild NCD is made when an individual has neuropsychological test findings in the range of 1 to 2 standard deviations (between the 3rd and 16th percentiles) below appropriate norms and the individual can effectively compensate to manage IADLs. A diagnosis of major NCD is made when neuropsychological test findings are more than 2 standard deviations (<3rd percentile) below appropriate norms and impairments in IADLs are present.

B. Postconcussive Disorder

For the vast majority of individuals with mTBI, the symptoms of PCS subside and resolve within a few weeks of injury. For a subset of individuals with mTBI, complaints of postconcussion symptoms persist beyond the expectation derived from TBI severity markers,

Table 10.4. Commonly Used Computerized Assessments

Measure	Description
Automated Neuropsychological Assessment Metrics (ANAM)	Test development was sponsored primarily by the U.S. Military and includes simple reaction time, code substitution, code substitution-delayed, continuous performance test, mathematical processing, matching to sample, spatial processing, Sternberg memory procedure, and procedural reaction time
Axon Sports Computerized Cognitive Assessment Tool (CCAT)	Tests cognitive domains including processing speed, attention, learning, and working memory
CNS Vital Signs	Consists of seven subtests including verbal memory, visual memory, finger tapping, symbol digit coding, Stroop test, shifting attention test, and continuous performance test
Headminder Concussion Resolution Index	Consists of six tests that measure simple reaction time, complex reaction time, processing speed index, simple reaction time errors, and complex reaction time errors
Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)	Includes six test modules that measure verbal and visual memory, reaction time, processing speed, and impulse control
Sport Concussion Assessment Tool (SCAT–2)	Consists of symptom evaluation, screen of physical signs, Glasgow Coma Scale score, balance examination, and coordination examination as well as a cognitive assessment of orientation, immediate memory, concentration, and delayed recall

Note. Information obtained from the NINDS website (http://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards).

and etiological mechanisms other than brain dysfunction become more likely. The term *postconcussive disorder* (PCD) has been proposed for diagnostic use when symptoms following mTBI, such as neurologic, cognitive, behavioral or somatic complaints, persist beyond the acute and subacute periods and become chronic (Iverson et al., 2007), often operationalized as persisting beyond 3 months. Although the overall risk of developing PCD following mTBI is low, the frequency of mTBI patients who meet criteria for a diagnosis of PCD and present in a clinical setting is believed to be higher.

mTBI patients with PCD frequently present to the outpatient clinics of primary care physicians, physiatrists, or neurologists seeking relief for lingering PCD-related symptoms. Although some patients will have already received an initial medical workup to rule out a more devastating brain injury during the acute phase, such as a neurosurgical emergency, many patients will have had no prior contact with health care specialists (McCrea, 2008). Any medical workup ordered in the outpatient setting for PCD-related complaints is typically unremarkable for any identifiable neurologic cause for the persisting symptoms reported by the patient. Furthermore, there exists no "standard of care" treatment regimen that physicians can rely on to comprehensively address the various symptoms reported by patients with PCD-related symptoms. This can be very frustrating for patients and providers alike. Complicating treatment decision making even more for providers is the fact that it is not at all uncommon for two mTBI patients with very similar injuries (e.g., based on acute injury characteristics) to report very different symptom profiles following injury. While some patients may experience somatic symptoms, other patients may experience subjective cognitive or behavioral changes.

PCD has emerged as one of the more controversial and challenging conditions in the neurosciences to diagnose and treat. Contributing to the controversy is a limited understanding of mTBI among many primary care and specialty professionals who do not routinely provide care to individuals with TBI and the nonspecific nature of the postconcussion symptoms. Such factors can lead to misdiagnosis and misattribution of symptoms. For example, although acute headache following concussion is common and often related to intracranial events (e.g., subarachnoid hemorrhage), chronic headaches following concussion often are related to scalp, neck, and other musculoskeletal injuries that may have occurred at the time of the concussive event but are not from the brain concussion. Still, chronic headaches may precipitate a PCD diagnosis when a whiplash or scalp–nerve injury diagnosis would be more appropriate. Similarly, attention and concentration problems related to the early pathophysiology after mTBI can persist after the brain dysfunction has resolved because of the distracting elements of other persisting symp-

toms, (e.g., chronic pain, dizziness, sleep disturbance). *DSM–5* cautions that when PCS symptom persist beyond expectation and secondary complications (e.g., SDH) have been ruled out, then diagnoses with symptoms that overlap NCD because of TBI should be considered, including somatic symptom disorders, factitious disorder, PTSD, and malingering.

C. Neuropsychological Interventions

A multitude of factors have been shown to contribute to and maintain diverse PCD-related symptoms (Iverson, 2005; McCrea, 2008). McCrea (2008) and Ruff and colleagues (Ruff et al., 1996; Ruff & Richardson, 1999) have highlighted the complexity of the issues associated with PCD by stressing that PCD is not a unidimensional brain-based condition but rather an outcome influenced by cognitive, emotional, medical, psychosocial, and motivational factors, now referred to as the biopsychosocial model of PCD (Iverson, Zasler, & Lange, 2007).

Because of this complexity, treatments targeting PCD-related symptoms need to be equally diverse (e.g., they should follow an integrated model of care). Although emergency medicine and primary care physicians are frequently asked to evaluate, treat, and monitor mTBI patients during the acute and subacute phases of recovery, it is not surprising that these same physicians often feel ill-equipped to manage patients who go on to develop PCD and frequently request the assistance of specialists. For example, patients with daily headaches or migraines following mTBI may be referred for a neurology consultation for expertise related to headache management. PCD patients may be referred to rehabilitation medicine specialists such as physiatry and physical therapy to assist with problems such as neck and back pain, dizziness, and vertigo, which are frequently reported within the context of PCD.

Additionally, patients are frequently referred to behavioral health providers such as neuropsychologists, rehabilitation psychologists, health psychologists, and/or psychiatrists for a variety of reasons but particularly when they are experiencing cognitive, emotional, or behavioral changes that accompany PCD. If a patient with mTBI or PCD reports the following signs or symptoms, a referral to a mental health provider for evaluation and treatment is strongly recommended because their presence can complicate recovery, affect patient quality of life, or interfere with treatment outcome:

- cognitive symptoms;
- emotional and/or behavioral symptoms (e.g., psychiatric disorder, difficulty coping);

- excessive symptoms or worsening symptoms (without underlying medical cause);
- persisting or chronic pain (e.g., headache, neck or back pain);
- substance abuse or dependence;
- functional impairment (e.g., inability to return to work or school); or
- litigation, disability, or workman's compensation claims.

Behavioral health intervention for PCD is not a unitary construct and can be conceptualized in three distinct ways: (a) symptom management (e.g., symptom reduction), (b) cognitive restructuring, or (c) preventative treatment. Treatment for PCD, like many treatments in medicine, is often geared toward symptom management. Treating physicians frequently refer their patients for behavioral intervention when it is apparent that their patients' symptoms are medically intractable. Behavioral health specialists help patients develop a behavioral program to facilitate symptom management (e.g., reduction of pain, improving sleep hygiene, using moderation during daily activities) of persistent symptoms. For example, patients with chronic daily headache or neck pain may benefit from learning progressive muscle relaxation or biofeedback procedures from a qualified health psychologist. Patients with mood disorders (e.g., depression), anxiety disorders (e.g., PTSD), or adjustment reactions may benefit from psychiatric consultation for appropriate medication trials or from time-limited psychotherapy such as cognitive behavioral treatments. Moreover, psychotherapy may increase patients' awareness of factors contributing to psychiatric difficulties, reduce their symptoms, or help them develop appropriate short- and long-term goals postinjury.

Cognitive–behavioral health treatments that focus on cognitive restructuring are like symptom management approaches in that they are delivered to patients that remain symptomatic beyond the window of normal recovery following mTBI (e.g., 3 months postinjury). Patients with well-established PCD frequently develop inaccurate or distorted perceptions of their injury, their recovery, their preserved abilities, and their outcome (Ferguson & Mittenberg, 1996; Iverson et al., 2007). Encouraging patients to remain objective when recovering from their injury includes urging them to consider alternative explanations for symptoms they are experiencing.

Because the symptoms of PCD are nonspecific to PCD, and because they are so prevalent in normal, healthy non-brain-injured persons, we know that some patients with PCD are misattributing symptoms to their injury that are better explained by another source. For example, attention and memory concerns postinjury may be more related to the narcotic pain medication a patient received than

an mTBI. Similarly, attention or memory complaints may be better explained by a posttraumatic stress reaction associated with a motor vehicle collision than an mTBI. Iverson et al. (2007) reviewed cognitive errors or biases exhibited by patients with PCD that can complicate recovery and promote disability.

Psychotherapies focusing on cognitive restructuring work toward dismantling the distorted self-perceptions that frequently accompany PCD and replace them with accurate beliefs and appraisals related to one's injury, recovery, preserved ability and outcome postinjury (Ferguson & Mittenberg, 1996; Miller & Mittenberg, 1998). Ferguson and Mittenberg (1996) developed a six-session structured cognitive–behavioral therapy program that helps patients understand how psychological factors can intensify and maintain PCD-related symptoms and teaches PCD patients cognitive–behavioral techniques to manage stress and cope more effectively with PCD symptoms. Although symptom management and cognitive restructuring approaches are very important for patient health and quality of life, treatment approaches focusing on prevention of PCD are ideal. Early preventative interventions for PCD essentially inoculate patients against a purely neurobiological perspective of concussion, which helps them take personal control over aspects of their recovery that are modifiable and view their injury, recovery, and symptoms as objectively as possible (Ferguson & Mittenberg, 1996; Miller & Mittenberg, 1998; Mittenberg, Canyock, Condit, & Patton, 2001; Mittenberg & Fischera, 1993; Mittenberg, Tremont, Zielinski, Fichera, & Rayls, 1996).

Because psychological and social factors of disease (and PCD) are clearly modifiable variables (e.g., the patient, the provider, and the patient's environment can influence outcome), it should not be surprising that mTBI patients who receive brief behavioral health treatments very early postinjury (hours or days) report fewer and less severe PCD-related symptoms months later relative to control patients with mTBI who do not receive brief behavioral interventions (Borg et al., 2004; Comper, Bisschop, Carnide, & Tricco, 2005; Mittenberg et al., 1996; Paniak, Toller-Lobe, Durand, & Nagy, 1998; Paniak, Toller-Lobe, Reynolds, Melnyk, & Nagy, 2000; Ponsford et al., 1999, 2000, 2001, 2002). In an excellent example of this type of preventive treatment for PCD, mTBI patients who were briefly admitted to a general hospital setting were provided very brief education and cognitive–behavioral training prior to hospital discharge (Mittenberg et al., 1996). Relative to a control group who received standard mTBI discharge instructions by nurses (e.g., mTBI precautions), the patients who received the proactive intervention reported significantly shorter symptom duration, decreased frequency of symptoms, fewer days per week symptomatic, and a lower severity of symptoms.

VI. CONCLUSION

TBI is a major public health problem worldwide that is associated with significant morbidity and mortality. In particular, moderate and severe TBI present the highest risk for serious and permanent disabilities. The overwhelming majority of TBIs are classified as mild in severity. Select populations (e.g., athletes in contact sports, military personnel) may be at heightened risk of mTBI or concussion. Concussion is most often followed by a gradual course of complete cognitive and functional recovery in a matter of days to weeks in the overwhelming majority of cases. A small percentage of mTBI patients report persistent symptoms and functional complaints that prompt diagnostic consideration of possible PCD. Major scientific advances have emerged over the past 2 decades that inform not only the underlying pathophysiology of TBI and concussion but also provide guidance for therapeutic interventions to facilitate recovery, improve outcome, and reduce disability in affected patients. Including neuropsychologists and behavioral health professionals in the treatment of mTBI and PCD is empirically supported by research exploring the efficacy of psychoeducational and cognitive–behavioral treatment paradigms for preventing or reducing PCD-related symptoms.

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Chapter 11

Andrew J. Saykin and Laura A. Rabin

Dementias and Neurodegenerative Diseases

The dementias include a broad range of neurodegenerative disorders with cognitive impairment and often behavioral changes as key features. Alzheimer's disease (AD), the most common underlying disorder, typically presents with amnestic features, with loss of episodic memory for new information as the earliest and most pronounced symptom. The neuropsychologist is called on to determine the presence, severity, and possible etiology of dementia and to comment on its likely course and impact on daily functioning. The neuropsychological evaluation is frequently completed in a multidisciplinary setting in conjunction with other diagnostic studies, such as neuroimaging (computed tomography scan, magnetic resonance imaging [MRI], or positron emission tomography [PET]) and laboratory testing

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on blood and cerebrospinal fluid to determine etiology, devise a treatment plan, and help the patient and family plan for the future.

The field of dementia research and health care is undergoing rapid changes due to new cellular and molecular understanding of disease pathophysiology, genetics, biomarker development, and validation as well as myriad clinical trials. Furthermore, new research and clinical criteria have been proposed and adopted by key professional organizations, and other changes are pending. In particular, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5;* American Psychiatric Association, 2013) was published in May 2013, and the *International Classification of Diseases* (ICD–10; 10th revision; World Health Organization, [WHO] 2013) is due to be adopted in the United States in 2013, with the 11th edition scheduled to be released in 2015 (Mateen et al., 2012). This chapter summarizes general information on dementia and approaches to neuropsychological evaluation and interpretation of test data, placing test results in the broader context of current clinical practices and research directions. For more detailed information the reader is referred to the fourth edition of the *DSM* (*DSM–IV–TR;* American Psychiatric Association, 2000) or the new *DSM–5* and recent systematic reviews and diagnostic guidelines cited throughout this chapter.

I. DEFINITIONS AND DIAGNOSTIC CRITERIA

In the widely used *DSM–IV–TR* framework, the dementias include a group of disorders characterized by memory impairment and one or more additional cognitive deficits. Memory impairment is often prominent as an early symptom. Patients may experience difficulty learning new material or remembering recent conversations or events, and they may misplace valuables, such as keys, or forget to turn off the stove. In more severe dementia, patients also forget previously learned material, including the names of loved ones. Disturbances in spatial abilities, expressive or receptive language, and executive functions (e.g., impaired reasoning ability, poor judgment or insight) are common as well. Examples include underestimating the risks involved in activities (e.g., driving) or exhibiting little or no awareness of memory loss or other cognitive deficits. Patients may also make unrealistic appraisals of their abilities or plan activities that are incongruent with their deficits and prognosis (e.g., preparing to start a new business; American Psychiatric Association, 2002). To receive a diagnosis of dementia, a patient must have cognitive deficits that are sufficiently severe to cause impairment in daily functioning and that represent a change from a previous level of functioning (American Psychiatric Association, 2000). The general

characteristics of dementias, as defined in the *DSM–IV–TR* framework, are the presence of multiple cognitive deficits, including memory impairment (new learning or recall), plus at least one other deficit (aphasia, apraxia, agnosia, or executive dysfunction). The cognitive deficits must be severe enough to significantly impair social or occupational functioning and must represent a significant decline from a previous level of higher functioning. These deficits are not exclusively present during a delirium or better attributed to another Axis I disorder, such as depression or schizophrenia.

DSM–5 employs the framework of Neurocognitive Disorders (NCD), which are classified as Major or Minor to capture severity and by etiological subtype as summarized in Exhibit 11.1. What is presently indicated by the term *dementia* falls under the category of Major NCD in *DSM–5*. The cognitive domains have been expanded to include complex attention, learning and memory, executive ability,

Exhibit 11.1. Neurocognitive Disorder Framework (*DSM–5*) Defined by Major or Mild Severity and Etiological Subtypes

Neurocognitive Disorder due to Alzheimer's Disease
Frontotemporal Neurocognitive Disorder
Neurocognitive Disorder with Lewy Bodies
Vascular Neurocognitive Disorder
Neurocognitive Disorder due to Traumatic Brain Injury
Substance/Medication-Induced Neurocognitive Disorder
Neurocognitive Disorder due to HIV Infection
Neurocognitive Disorder due to Prion Disease
Neurocognitive Disorder due to Parkinson's Disease
Neurocognitive Disorder due to Huntington's Disease
Neurocognitive Disorder due to Another Medical Condition (e.g., structural lesions, immune disorders, metabolic conditions, neurological conditions)
Neurocognitive Disorder due to Multiple Etiologies
Unspecified Neurocognitive Disorder (used in situations in which the precise etiology cannot be determined with certainty)

Note. For the major neurocognitive disorders, one may code for "with behavioral disturbance" (if the cognitive disturbance is accompanied by psychotic symptoms, mood disturbance, agitation, or apathy) or "without behavioral disturbance"; for mild neurocognitive disorders, the behavioral disturbance specifier cannot be coded but should be indicated in writing. For several of the neurocognitive disorders, there are separate criteria for "probable" versus "possible" etiologies (e.g., for mild neurocognitive disorder due to Alzheimer's disease, a probable diagnosis is given only if there is a known genetic predisposition for the disease).

language, visuoconstructional–perceptual ability, and social cognition (Ganguli et al., 2011). Mild NCD are defined to recognize the clinical needs of individuals who have mild deficits in one or more of the same cognitive domains but who function relatively independently (i.e., can carry out complex instrumental activities of daily living, though increased effort or compensatory strategies may be required; American Psychiatric Association, 2013). This parallels the term *mild cognitive impairment* (MCI), used in the setting of prodromal AD and elsewhere, as an important prodromal stage identified as a target for early intervention for secondary prevention to prevent or slow progression. This category may include individuals previously coded as Cognitive Disorder Not Otherwise Specified.

A. Criteria for Mild NCD

1. MODEST COGNITIVE DECLINE

One criterion is evidence of modest cognitive decline from a previous level of performance based on cognitive concerns (self, informant, or clinician) and decline in neurocognitive test performance (typically 1–2 standard deviations below appropriate norms, or 3rd–16th percentile) or equivalent clinical evaluation.

2. INDEPENDENCE IN INSTRUMENTAL ACTIVITIES OF DAILY LIVING

Another criterion is preserved independence in instrumental activities of daily living (IADLs), although greater effort, compensatory strategies, or accommodation may be required to maintain independence (American Psychiatric Association, 2013).

3. ADDITIONAL CRITERIA

As in *DSM–IV–TR*, additional criteria include absence of delirium not primarily attributable to another mental disorder such as major depression or schizophrenia.

B. Criteria for Major NCD

1. SUBSTANTIAL COGNITIVE DECLINE

One criterion is evidence of substantial cognitive decline from a previous level of performance in one or more domains based on cognitive concerns (self, informant, or clinician) as well as decline in neurocognitive test performance (typically 2 or more standard deviations below appropriate norms or below the 3rd percentile) or equivalent clinical evaluation.

2. INTERFERENCE WITH IADLS

Another criterion is that cognitive impairment is sufficient to interfere with independence (IADLs require at least some assistance).

3. ADDITIONAL CRITERIA

The additional criteria are the same as for mild NCD (American Psychiatric Association, 2013). Further details are available at the *DSM–5* website (http://www.dsm5.org). For a thoughtful discussion of the rationale for NCD in *DSM–5*, see Ganguli et al. (2011).

II. ETIOLOGIES AND FUNCTIONAL NEUROANATOMY OF DEMENTIA

There are many etiological subtypes of dementia, and parallel prodromal or minor NCDs, as indicated in Exhibit 11.1. These include AD, Parkinson's disease (PD), Huntington's disease, dementia with Lewy bodies (DLB), vascular cognitive impairment (VCI) and vascular dementia, dementia due to head trauma, and dementia due to HIV disease, among others. The etiology, or probable or possible etiologies, of the dementia or NCD should be specified when the diagnosis is made. In *DSM–5*, following the WHO ICD system, functional impairment is viewed as the consequence of the underlying NCD rather than a diagnostic criteria, hence the greater emphasis on known or presumed etiology. There has been much progress in molecular neuropathology, and most of the conditions leading to dementia have been shown to involve abnormal proteins depositing in the brain by some combination of overproduction, abnormal conformations, failure of clearance, or secondary immune reaction. These "proteinopathies" may involve fibrillar plaque forming amyloid beta (in AD), tau filaments (in AD, frontotemporal dementia [FTD]/Pick's disease), and alpha synuclein (in DLB, PD). Parallel progress in neuroimaging, biomarkers, and genetics make early in vivo diagnosis of many NCDs possible with much greater certainty than in the past, yet in many cases neuropathological diagnosis is still the only way to achieve a definitive diagnosis at a histological and molecular level. The order of onset and relative prominence of the cognitive disturbances and associated symptoms vary with the specific type of dementia, and some have been studied more than others. An exhaustive list of dementia etiologies is beyond the scope of this chapter, but more common or important etiologies are summarized in Exhibit 11.1.

A systematic review of global prevalence rates for dementia (1980–2009) in persons age 60 and above found a rate of 5% to 7%

for most regions (Prince et al., 2013). The authors of this review estimated that 35.6 million people lived with dementia worldwide in 2010 and projected a near doubling every 20 years (Prince et al., 2013). In developed countries, the prevalence of dementia is approximately 1.5% at age 65, then doubling every 4 years to reach approximately 30% at age 80 (Knopman, Boeve, & Petersen, 2003; Ritchie & Lovestone, 2002). AD and vascular dementia are the two most common types of dementia, accounting for approximately 55% and 15% of all incidences, respectively. Less prevalent but not uncommon are dementias caused by conditions such as PD and related disorders (e.g., progressive supranuclear palsy), frontal lobe disease (e.g., Pick's disease and other forms of FTD), normal pressure hydrocephalus, and chronic alcoholism. These conditions occur frequently enough to be routinely considered in differential diagnosis. Far less prevalent are prion diseases. The prevalence rate of Creutzfeldt-Jakob disease (CJD), for example, is about 1 case per million, with about 10% to 15% being familial. Although rare, CJD generates disproportionate interest because of media attention to the bovine spongiform encephalopathy (BSE), or mad cow disease. BSE is believed to be the cause of variant CJD in humans. Overall, it is important to keep in mind that causes of dementia are not mutually exclusive, and several different pathologies often contribute to a patient's clinical symptoms.

A. AD and MCI

AD, the most prevalent neurodegenerative dementing disorder, is characterized by progressive cognitive decline and a broad spectrum of brain pathology, including accumulation of fibrillar amyloid-β protein in plaques and vessels, neurofibrillary tangles, and synaptic and neuronal loss. Although there are variants of AD, a typical presentation involves (a) an insidious onset, (b) initial symptoms of memory impairment (e.g., deficient consolidation, rapid loss of new information), and (c) a gradually progressive course evolving to include other cognitive functions. Much is known about the neuroanatomic basis of AD and MCI in relation to cognitive and biomarker changes. A comprehensive review of this area can be found in Risacher and Saykin (2013).

Genetic factors play a major role in AD. Over 95% of AD is sporadic or late onset AD (LOAD), but mutations in three genes (*APP, PSEN1, PSEN2*) have been shown to cause autosomal dominant or familial early onset AD by up-regulating the production of toxic species of amyloid beta protein. LOAD, by contrast, is associated with the *APOE* gene. There are three alleles of *APOE*, epsilon 2, 3 and 4. Epsilon 4 is the allele associated with increased risk and

earlier age of onset of AD, epsilon 3 is the common version, and epsilon 2 is protective. Although over 60% of AD patients are *APOE4* positive, many patients do not carry this gene and it is clearly not deterministic. Recent large-scale and well-powered genomewide association studies (Hollingworth et al., 2011; Naj et al., 2011) have identified additional genes associated with LOAD, but to date all have small odds ratios and are not useful in predicting who will develop AD or at what age. However, in addition to *APOE*, discovery of a "top 20" hits from genome-wide association studies has pointed to several promising biological pathways (lipid, immune, and endocytic processing) that may prove useful as therapeutic targets.

Amnestic MCI is characterized by relatively isolated memory deficits in the absence of dementia or significant compromise of IADLs (Petersen et al., 1999). As the MCI concept developed, it was recognized that MCI may be single or multidomain, with the latter potentially including deficits in executive, language or spatial functions. Furthermore, non-AD dementias also have a prodromal stage that could be labeled as MCI, and in this case the phenotypes may differ from the classic amnestic presentation (Petersen, 2007). Recently in the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large-scale longitudinal imaging and biomarker study focusing on MCI, groups were defined as early MCI (>1 standard deviation deficit in memory) or late MCI (>1.5 standard deviations deficit). The past decade of research has indicated that individuals meeting criteria for late MCI in a clinical setting convert to AD at a rate of about 12% to 15% per year. Carriers of the epsilon 4 allele of the *APOE* gene are at particularly enhanced risk for progression. Extensive imaging studies have included quantitative structural MRI as well as fluorodeoxyglucose (FDG) PET to measure glucose metabolism and amyloid PET (using the [11C]PiB or [18F]florbetapir tracers). CSF and genomewide association study data were also analyzed. A comprehensive summary of assessments and results from ADNI is available for readers wishing detailed coverage (Weiner et al., 2013). Clifford Jack and colleagues have attempted to build a comprehensive model of the staging of clinical, MRI, and PET imaging and CSF biomarker changes based on ADNI data (Jack et al., 2010, 2013). A similar model based on as yet unaffected mutation carriers from the Dominantly Inherited AD Network (DIAN; Morris et al., 2012) has also been published with striking convergence (Bateman et al., 2012). The ADNI and DIAN models are reviewed in Risacher and Saykin (2013).

B. VCI

The terms *vascular dementia* and *multi-infarct dementia* in *DSM–IV–TR* have now been replaced by *vascular cognitive impairment*, reflecting a

broader concept of NCD as a continuum of cerebrovascular disease (CVD) due to small and large vessel involvement, as endorsed by multiple expert consensus panels (de Haan, Nys, & Van Zandvoort, 2006; Gorelick et al., 2011; Hachinski et al., 2006; Jellinger, 2008; McClure, Salter, Foley, Mahon, & Teasell, 2012; O'Brien et al., 2003; Sahathevan, Brodtmann, & Donnan, 2012; Sorbi et al., 2012). NCD with an abrupt onset (e.g., in the context of a stroke) and a fluctuating or stepwise course as well as more focal or patchy neurological and neuropsychological deficits is much more likely to reflect VCI due to CVD than AD or other neurodegenerative dementias. Early treatment of hypertension, hyperlipidemia, and other features of CVD can help prevent further progression. However, the relationship between AD and VCI is complex, in part because AD and CVD are both common and coexist frequently and because evidence suggests that small strokes or risk factors for vascular disease may lead to increased clinical expression of AD (American Psychiatric Association, 2002). Comorbidity of AD and VCI is especially common in the very old (Kalaria & Ballard, 1999). Enhanced MRI techniques reveal cerebral microbleeds, which are found in up to a quarter of older adults and a third of patients with AD (Loitfelder, Seiler, Schwingenschuh, & Schmidt, 2012). MR perfusion scans can quantitate abnormalities in cerebral blood flow in AD and VCI and help to evaluate the functional integrity of the vasculature (Román & Pascual, 2012; Wolk & Detre, 2012).

DSM–5 criteria for VCI include presence of NCD with clinical features consistent with vascular etiology (onset of the cognitive deficits is temporally related to vascular events; decline is prominent in complex attention, including processing speed, and frontal-executive function; evidence of CVD from history, physical examination and/or neuroimaging). In addition, the NCD is not better explained by another brain disease or systemic disorder.

C. DLB

DLB is ultimately a pathological diagnosis in which there is often a combination of cellular pathologies, including alpha-synuclein and beta-amyloid deposition, as well as dopaminergic denervation (Huang & Halliday, 2013). Consensus guidelines have been developed (McKeith, 2006; McKeith et al., 2005), yet in practice the ability to differentiate DLB from AD clinically and neuropsychologically can be quite challenging and in some cases is not possible (Nelson et al., 2010). Nonetheless, there are some features that provide assistance. Clinically, DLB is characterized by hallucinations and delusions occurring early in the disease process, marked day-to-day

fluctuations in cognition, repeated falls, syncope, transient loss of consciousness, spontaneous parkinsonism, and neuroleptic sensitivity. Pure DLB involves more prominent attention, executive, and visuospatial impairment rather than memory deficits early in its course. Lewy bodies and neurites are composed of clumps of abnormal alpha-synuclein protein that aggregate inside neurons in LBD and PD as well as some regions in AD. As the pathological hallmark of PD, Lewy bodies are usually concentrated in the substantia nigra and also distributed throughout the cortex. The dementia syndrome of DLB is similar to AD, and pathological studies have revealed the presence of Lewy bodies in as many as 20% of AD cases at autopsy. The presence of visual hallucinations and agnosia early in the course of a dementing illness can help distinguish DLB from AD. In addition, as compared with patients with AD, patients with DLB tend to perform better on tests of confrontation naming and verbal memory and worse on tests of executive functioning and visuospatial abilities. Recent biomarker studies suggest that molecular imaging assessment of striatal dopamine transporter activity by [123]I-FP-CIT SPECT and nigrostriatal integrity by [18F]fluorodopa PET may have promise but more studies are needed (Sinha, Firbank, & O'Brien, 2012).

D. FTD

FTD includes a heterogeneous ensemble of neurodegenerative conditions characterized by a spectrum of neuropathological findings (Kövari, 2009; Rohrer et al., 2011). Recent progress in FTD research at many levels is driving a major reevaluation of concepts and methods. The conditions grouped together as FTD are relatively rare compared with AD and tend to be characterized in their early stages by changes in personality, executive dysfunction, deterioration of social skills, emotional blunting, behavioral disinhibition, and language abnormalities. This initial presentation may be mistaken for a psychiatric disorder. Age of onset of frontal dementias is typically much earlier than sporadic AD (often ages 50–60), but FTD can occur among younger or older individuals. Structural brain imaging of patients with FTD typically reveals prominent frontal or temporal atrophy or both, with relative sparing of the parietal and occipital lobes. In the case of Pick's disease, a tauopathy, the diagnosis is confirmed by an autopsy finding of Pick inclusion bodies. A subgroup of patients with disorders that primarily affect *frontal-subcortical* systems (e.g., brain stem, thalamus, basal ganglia, associated frontal regions) often display a constellation of symptoms differing from those seen in other types of dementia. These symptoms include bradyphrenia (i.e., slowing of cognitive processes or psychomotor

retardation); memory retrieval deficits; executive dysfunction; and deficits in sustained or selective attention and visuospatial skills in the absence of aphasia, apraxia, or agnosia. Disorders such as PD, Huntington's disease, and progressive supranuclear palsy may present with this fronto–subcortical profile (Chow et al., 2009).

Typically in FTD, difficulties with memory, apraxia, and additional behavioral disturbances (i.e., apathy or extreme agitation) appear later in the disease course. Although episodic memory was considered relatively preserved until later in the course of FTD, it has recently been suggested that a reappraisal is needed (Hornberger & Piguet, 2012). There has been rapid development of new cognitive and behavioral probe tests that are revealing more nuanced phenotypes of FTD (Chow et al., 2012; Gyurak, Goodkind, Kramer, Miller, & Levenson, 2012; Shany-Ur et al., 2012; Williamson et al., 2010). These subtypes have been correlated with advanced neuroimaging to show involvement of differential brain networks in FTD subtypes (Du et al., 2007; Knopman et al., 2008; Luks et al., 2010; Rohrer et al., 2010, 2011).

Pathologically, FTD can be divided into FTD tauopathies (e.g., Pick's disease, corticobasal degeneration, progressive supranuclear palsy), FTD nontauopathies (lacking distinctive histology), and FTD with ubiquitin–immunoreactive inclusions (+/– motor neuron disease). Very recently the transactivating response (TAR)–binding protein (TDP-43) proteinopathy, and *TDP-43* gene mutations were reported in this subset of FTD and in ALS, and an additional abnormal protein fused-in-sarcoma (FUS) has also been identified (Kövari, 2009; Rohrer et al., 2011). Given the heterogeneity of FTD clinical pathological correlation is challenging. However, pathologically validated case series of increasing size with cognitive, neuroimaging, and other phenotypic correlates have been reported. In a series of 95 FTD cases, 51% had TDP-43 pathology, 44% had tau pathology, and 5% had FUS pathology, and these were differentially related to the cognitive profiles suggesting an interaction of disease-specific and network-specific factors (Rohrer et al., 2011).

E. Idiopathic Normal Pressure Hydrocephalus

Idiopathic normal pressure hydrocephalus (INPH), also known as *nonobstructive* or *communicating hydrocephalus*, is somewhat of a misnomer, falsely suggesting that intracranial pressure is always normal in this condition when in fact there can be elevations in intracranial pressure. Clinical presentation can be varied, making diagnosis challenging. Furthermore, there is also overlap with other disorders of advancing age, including AD (Cabral et al., 2011). Evidence-based consensus guidelines for diagnosis and treatment of INPH have been

developed (Relkin, Marmarou, Klinge, Bergsneider, & Black, 2005) and include symptoms of INPH in combination with neuroimaging demonstrating nonobstructive ventricular enlargement disproportionate to cerebral atrophy. Gait and balance disturbances are the most common presenting findings in INPH and may occur alone or together with cognitive and urinary symptoms (Relkin et al., 2005). Although the disorder is relatively rare, it is important to consider INPH in the diagnostic workup because early detection and treatment may lead to symptomatic improvement through serial lumbar punctures or cerebroventricular shunting (Tsakanikas & Relkin, 2007). Outcome of shunting has been variable (Koivisto et al., 2013; Tisell et al., 2011), but is most likely to be helpful following timely and accurate diagnosis with careful pre- and postoperative planning.

F. Substance-Induced Persisting NCD or Dementia

This type of dementia is most frequently associated with alcohol. This is covered extensively in Chapter 16 in this volume on alcohol-related syndromes and is touched on only briefly here. Ridley, Draper, and Withall (2013) provided an updated evidence-based review of alcohol-related dementia and alcohol-induced persisting amnestic syndrome (Wernicke-Korsakoff syndrome, or WKS) addressing neuropathology, nosology, epidemiology, clinical features, and neuropsychology. Prolonged excessive use of alcohol may lead to nonreversible structural and functional changes, yet the relative contributions of direct neurotoxic effects of alcohol versus thiamine deficiency remain unclear (Vetreno, Hall, & Savage, 2011). Many variables, including associated lifestyle factors, complicate research in this area. It is also unclear what level of exposure creates a significant risk of brain damage and the nature of possible protective effects at lower level exposure. Features associated with alcohol-related dementia are earlier onset; male gender; social isolation; mixed cortical and subcortical pathology; and impairment on visuospatial, memory, and executive tasks. Some partial recovery of brain structure and function is possible with abstinence. Ridley et al. (2013) provided a framework for diagnosis and management.

G. HIV-Associated Neurocognitive Disorder (HAND) and Dementia (HAD)

HAND and HAD include a combination of cognitive, behavioral, and motor dysfunction. The initial symptoms can be subtle and are often overlooked or misdiagnosed as depression. Natural history studies preceding the era of highly active combination antiretroviral therapy (CART) reported typical early changes including (a) reduced

attention and concentration (e.g., losing track of conversations, difficulty tracking the plots of books or films), (b) working and episodic memory problems (e.g., difficulty with retrieval, remembering telephone numbers and appointments, maintaining medication schedules), (c) motor skill deficits (e.g., poor handwriting, unsteady balance or gait, a tendency to drop things easily), (d) changes in personality (e.g., apathy, inertia, irritability), and (e) general slowing of thought processes. This profile was consistent with the concept of a fronto–subcortical dementia distribution. With disease progression, eventually more widespread deficits tended to develop, including a global dementia often accompanied by vacuolar myelopathy and sensory neuropathies. These concepts appear in *DSM–5*, which recognizes both major and mild neurocognitive disorder due to HIV infection. Higher risk of developing HAD is associated with increasing age, decreased CD4 cell count, increased viral load, and in some studies, intravenous drug use. Even in its mild form, cognitive impairment can affect compliance with treatment, functional ability, and survival (McArthur et al., 2003; Price, 2003).

In 2007, the diagnostic nomenclature for HAND originally developed in 1991 by the AIDS Task Force of the American Association of Neurology was reviewed by a joint National Institute of Mental Health/National Institute of Neurological Disorders and Stroke panel to consider the role of CART, definitional criteria, and comorbidities. This panel proposed inclusion of the term *asymptomatic neurocognitive impairment* to categorize individuals with subclinical impairment and provided a diagnostic algorithm to assist in standardized diagnostic classification of HAND (Antinori et al., 2007). Heaton et al. (2010) reported results from the CHARTER Study, a large (1,555 HIV-infected adults) cross-sectional, observational study to examine the frequency, characteristics and comorbidities of HAND using updated criteria in the CART era.

Of the total sample, 52% had cognitive impairment with higher rates in groups with greater comorbidity burden. Prevalence estimates for HAND were 33% for asymptomatic neurocognitive impairment, 12% for mild neurocognitive disorder, and 2% for HAD. Predictors of impairment included degree of suppression of plasma viral loads and nadir CD4 cell count. It still remains to be determined if early disease events trigger chronic CNS changes and whether early CART prevents or reverses these changes (Heaton et al., 2010).

H. Other Disorders

Historically, the term *dementia* referred to a progressive degenerative disorder and loss of previously acquired cognitive functions. However, in *DSM–IV–TR*, diagnosis is based on the pattern of cogni-

tive findings rather than the reversibility or irreversibility of the condition. In *DSM–5*, following the *ICD* framework, the emphasis shifts to underlying etiology either established or presumed. In *DSM–IV–TR*, dementia can technically be diagnosed in young individuals with potential for recovery of function (e.g., after a traumatic brain injury) if they meet the general criteria. Likewise, in *DSM–5*, the term *neurocognitive disorder* may be used to refer to conditions affecting younger individuals, such as impairment secondary to traumatic brain injury or HIV infection (Ganguli et al., 2011). Although the degree and nature of the impairment depend on the location and extent of brain injury, posttraumatic amnesia and persisting memory impairments are common features of dementia due to head trauma. When it occurs in the context of a single injury, dementia due to head trauma is usually nonprogressive. Repeated head injury, however, may lead to a progressive dementia (American Psychiatric Association, 2000). The term *dementia* can also be used to describe the cognitive deficits of individuals with multiple sclerosis (MS) if the symptoms are severe enough to affect daily functioning and patients otherwise meet criteria. However, MS is often associated with relatively mild deficits without pervasive effects on daily functioning, in which case the term *dementia* is not appropriate, although minor NCD may be appropriate. Furthermore, MS patients may show decreased cognitive functioning during an exacerbation that improves during remission. Clinicians and the general public may still associate the term *dementia* with progressive cognitive decline in older adults. The term should therefore be used with caution and with appropriate explanation and context for certain etiologies and the new terminology of "major NCD" would appear advantageous in this context.

III. DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Memory impairment is a hallmark of dementia and is required to make a diagnosis. Dementia is distinguished from amnestic disorder by the involvement of additional cognitive deficits (e.g., language, visuospatial processing, problem solving). Although dementia and delirium both include global cognitive impairment, delirium is characterized by prominent deficits in attention and awareness of the environment, and the symptoms typically develop rapidly and fluctuate in severity (American Psychiatric Association, 2000). Dementia often co-occurs with depression or depressive symptoms, but depression alone can cause significant cognitive impairment that is difficult to distinguish from dementia (see Chapter 10, this volume). Sometimes, the course of the illness can help with this differential. Cognitive deficits that coincide with the onset of a major

depressive episode in a context of previously normal cognition may be more likely due to the depression. In older adults, significant depression-related cognitive impairment can be a harbinger of subsequent dementia. It is therefore important to follow older adults with significant depression-related cognitive impairment even after the depression remits.

Another common differential diagnostic problem is among dementia, MCI, and normal aging. Neuropsychological evaluation can be very helpful in distinguishing MCI from dementia, especially when age- and education-appropriate normative data are available (see Chapter 9, this volume). Standardized criteria for MCI have been developed and are employed in ongoing clinical trials (Stephan et al., 2013). Amnestic MCI is the original and most common form and is typically defined as memory complaints plus a relatively isolated memory deficit on testing with generally intact intellectual functioning and activities of daily living (Petersen, 2007). As mentioned previously, approximately 15% of individuals with amnestic MCI will progress to AD within a year, or up to 40% in 4 years, compared with a 1% to 2% conversion rate in healthy controls. It is therefore important to follow patients with neuropsychological testing to track any changes in cognitive functioning. In addition to the amnestic versus non-amnestic subclassification, other variants of MCI are recognized such as single versus multidomain. Therefore, when making the diagnosis of MCI, neuropsychologists should qualify the term with an appropriate modifier (e.g., amnestic MCI) in order to adequately characterize the condition and address issues related to its likely course and outcome (Petersen, 2007).

Dementia must also be distinguished from age-related cognitive decline, the mild decline in cognitive functioning that may occur with aging (e.g., loss in efficiency of acquiring new information and mild reductions in processing speed, cognitive flexibility, and working memory). This type of decline (see Chapter 9, this volume) is nonprogressive and does not lead to functional impairment. Finally, cognitive complaints are common in aging and may reflect depression. However, increasing attention is being paid to nondepressed older adults with significant memory complaints who perform normally on neuropsychological testing. These individuals with subjective cognitive decline show changes in brain structure and activity similar to those seen in patients with MCI or dementia (Amariglio et al., 2012; Mosconi et al., 2008; Saykin et al., 2006; Scheef et al., 2012; Visser et al., 2009), and they are at an increased risk for future cognitive decline (Jessen et al., 2010; Reisberg, Shulman, Torossian, Leng, & Zhu, 2010; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). Therefore, cognitive complaints in nondemented older adults should be taken seriously, and these indi-

viduals should be followed over time to determine whether deficits emerge.

A. Associated Problems

Changes in functional capacity, mood, personality, and behavior also occur in dementia and are associated with severity of impairment. Anxiety and depression, for example, may be present at the very early stages of dementia, when compromised learning and problem-solving capacities result in difficulty keeping up with the demands of a job. Suicidal behavior may occur, especially in less impaired individuals, who are more likely to gain insight into their deficits and remain capable of formulating and carrying out a plan of action. As memory and executive functioning worsen, problems may develop in areas such as driving a car and managing medication or finances. Patients with dementia may display increased gullibility (rendering them susceptible to fraud and scams), vulnerability, apathy, and disregard for societal norms and expectations (American Psychiatric Association, 2002; Castle et al., 2012). Anxiety is also common at this stage, and some patients manifest overwhelming emotional responses to seemingly minor stressors, such as changes in routine or environment (American Psychiatric Association, 2002).

When recall of recent events becomes severely impaired, relatively benign confabulations may be replaced by delusions of persecution (e.g., the belief that misplaced possessions have been stolen) or infidelity. Agitation may occur when memory loss and perceptual distortions result in incorrect comprehension of one's circumstances (e.g., striking out at a caretaker who is misidentified as an intruder). Threats, combativeness, wandering, and physical violence are also more likely to occur later in the illness and are often associated with frustration, misinterpretations, delusions, or hallucinations. These behaviors pose a particular problem for patients cared for at home, especially by frail spouses, and may necessitate a nursing home or similar long-term care placement. Some patients exhibit a peak period of agitation (or other behavioral disturbance) during the evening hours, referred to as *sundowning*. Dementia can also be accompanied by motor disturbances, including gait difficulties, slurred speech, and a variety of abnormal movements. Other neurological symptoms, such as myoclonus and seizures, may occur. Finally, delirium is sometimes superimposed on dementia because the underlying brain disease increases susceptibility to the effects of medications or concurrent medical conditions (American Psychiatric Association, 2000, 2002).

IV. NEUROPSYCHOLOGICAL EVALUATION OF DEMENTIA

A. Comprehensive Evaluation

A comprehensive evaluation for dementia should include the following:

1. an interview with the patient and a knowledgeable collateral source as well as a review of medical records to obtain patient and family history;
2. a thorough medical examination with diagnostic and laboratory testing by a physician trained in geriatric medicine, behavioral neurology or gero- or neuropsychiatry;
3. a screening examination for primary psychiatric disorders (e.g., depression);
4. a review of the patient's medication regimen by a professional with expertise in geriatric pharmacology (to rule out cognitive deficits owing to medication effects or interactions);
5. an assessment of functional capacities (e.g., by a an occupational therapist or social worker); and
6. comprehensive neuropsychological assessment using tests with appropriate normative data.

Comprehensive neuropsychological testing for dementia covers all cognitive and sensorimotor domains with a focus on memory and other functions required to make the diagnosis, monitor changes in cognition over time, or address issues of everyday functioning. Exhibit 11.2 presents a sample set of instruments used for this type of assessment, and Exhibit 11.3 presents an abbreviated battery. The comprehensive assessment requires approximately 3 to 4 hours of face-to-face contact in addition to the neuropsychological interview and would be appropriate for assessment of MCI and mild dementia. Modifications are made as needed based on the specific referral question and the patient's individual circumstances. An important issue is the selection of norms, which should consider factors such as how the normative sample was selected and how representative the data are with regard to the particular patient (Heaton, Ryan, & Grant, 2009). One should begin the assessment with relatively simple measures, which provide a general sense of the patient's level of functioning and prevent undue frustration, and gradually progress to include more challenging items. More impaired patients may require the replacement of difficult tests with simpler measures (e.g. the nine-item version of the California Verbal Learning Test—II; Delis, Kramer, Kaplan, & Ober, 2000). It is, however, important to use measures that

Exhibit 11.2. Sample Comprehensive Neuropsychological Evaluation

Patient Name_____ Date of Evaluation_____

COMPREHENSIVE EVALUATION: MEMORY DISORDERS/ DEMENTIA CLINIC

____ Word Reading from the Wide Range Achievement Test—Fourth Edition (WRAT–4; Wilkinson & Robertson, 2006)[a]
____ Lateral Dominance Questionnaire
____ Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975)
____ Dementia Rating Scale—2 (DRS–2; Jurica, Leitten, & Mattis, 2001)
____ Logical Memory I from the Wechsler Memory Scale (WMS–IV; Wechsler, 2009)[b]
____ Visual Reproduction I (WMS–IV)
    ____ Sensory-Motor Exam: Finger Tapping Test (Reitan & Wolfson, 1993), Graphesthesia (Lezak, Howieson, Bigler, & Tranel, 2004)
    ____ Delis–Kaplan Executive Function Battery (D-KEFS) Trail Making Test (Delis & Kaplan, 2001) or Trail Making Test Parts A and B (Reitan, 1958)
    ____ Single/Double Simultaneous Stimulation Test (Centofanti & Smith, 1979)
____ Logical Memory II and Recognition (WMS–IV)
____ Visual Reproduction II and Recognition (WMS–IV)
____ Drawings to Command and Copy (e.g., Clock-Drawing Test; Mendez, Ala, & Underwood, 1992)
____ California Verbal Learning Test, Second Edition (CVLT–II)
    ____ Digit Span (WMS–IV)
    ____ Block Design from the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV)
    ____ Coding from the WAIS–IV
____ CVLT–II Long-Delay Free and Cued Recall and Yes/No Recognition
____ Matrix Reasoning (WAIS–IV)
____ CVLT–II Long-Delay Forced-Choice Recognition
____ Vocabulary (WAIS–IV)
____ Similarities (WAIS–IV)
____ Geriatric Depression Scale (Yesavage et al., 1982–1983)
____ Adult Manifest Anxiety Scale—Elderly version (AMAS–E; Reynolds, Richmond, & Lowe, 2003)

(continued)

Exhibit 11.2. Sample Comprehensive Neuropsychological Evaluation *(Continued)*

____ Praxis from the Boston Diagnostic Aphasia Examination—Third Edition (BDAE; Goodglass, Kaplan, & Barresi, 2001)
____ Test of Practical Judgment (TOP-J; Rabin et al., 2007)
____ Boston Naming Test (BDAE)
____ D-KEFS Verbal Fluency or Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989)
____ Comprehension of Complex Ideational Material (BDAE)
____ Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993)
____ Everyday Cognition (ECog; self and informant versions; Farias et al., 2008)
____ Activities of Daily Living Scale (self and collateral; Saykin et al., 1991)
Additional Tests: _____

[a]Comparable measures include the North American Adult Reading Test (NAART), The American National Adult Reading Test (AMNART), and WAIS–IV Test of Pre-Morbid Functioning. A demographic questionnaire or the Barona Index may be more appropriate with individuals who are not native English speakers. [b]Earlier versions of the WAIS and WMS may be preferable, particularly when used in conjunction with large, demographically corrected normative data sets that are co-normed for a variety of neuropsychological tests, for example, Mayo's Older Americans Normative Studies (MOANS) or Heaton norms.

are challenging enough to reveal an early stage of a dementing illness if present. In the later disease stages, when the patient manifests significant cognitive deficits, it is important to include measures simple enough to demonstrate what the patient can still accomplish. Ideally, an occupational therapist or other appropriately trained professional would carry out direct assessment of functional abilities in everyday contexts such as an in-home evaluation. A number of performance-based IADLs have been developed to contribute to functional assessment (Giovannetti et al., 2008; Goldberg et al., 2010; Reuben, Valle, Hays, & Siu, 1995; Schmitter-Edgecombe, McAlister, & Weakley, 2012; Suchy, Kraybill, & Franchow, 2011). Minimally, everyday functioning should be covered in the interview and through the use of self- and collateral-report questionnaires (Desai, Grossberg, & Sheth, 2004; Gold, 2012; Sikkes, de Lange-de Klerk, Pijnenburg, Scheltens, & Uitdehaag, 2009).

Exhibit 11.3. Sample Brief Neuropsychological Screening Battery

Patient Name_____ Date of Evaluation_____

SCREENING EVALUATION: MEMORY DISORDERS/ DEMENTIA CLINIC

____ Mini-Mental State Examination or Dementia Rating Scale—2
____ Visual Reproduction I (Wechsler Memory Scale [WMS–IV] or previous version; Wechsler, 2009)
____ California Verbal Learning Test, Second Edition (CVLT–II; standard or nine-item version)
____ Sensory-Motor Exam (Finger Tapping Test, Graphesthesia)
____ Digit Span (Wechsler Adult Intelligence Scale—Fourth Edition [WAIS–IV] or previous version)
____ CVLT–II Long-Delay Free and Cued Recall and Yes/No Recognition
____ Visual Reproduction II and Recognition (WMS–IV or previous version)
____ CVLT–II Long-Delay Forced-Choice Recognition
____ Vocabulary (WAIS–IV or previous version)
____ Matrix Reasoning (WAIS–IV or previous version)
____ Delis–Kaplan Executive Function Battery Trail Making Test
____ Praxis Screen (Boston Diagnostic Aphasia Examination—Third Edition [BDAE])
____ Drawings to Command and Copy (Including Clock Drawing Test)
____ Test of Practical Judgment (TOP-J; Rabin et al., 2007)
____ Boston Naming Test (BDAE)
____ Sentence Comprehension (BDAE)
____ Wisconsin Card Sorting Test (Abbreviated)
____ Geriatric Depression Scale or Hamilton Depression Rating Scale
____ Activities of Daily Living Scale (Self and Informant)

Additional Tests: _____

Studies have examined use of self- and informant reports of everyday cognitive functioning in dementia and prodromal conditions such as MCI and subjective cognitive decline and in some cases have related these results to neuroimaging or other biomarkers (Amariglio et al., 2012; Farias et al., 2008, 2013; Saykin et al., 2006). The informant or collateral should be someone who has known the patient long enough to have witnessed decline over time, if present. The collateral should also have firsthand knowledge of the patient's current daily functioning in a variety of contexts. Children who live at a distance may not be able to provide sufficient firsthand information, and it may be necessary to access other local sources of information. Often it is very informative to interview the collateral separately from the patient (with the patient's permission) to enable a more open expression of concerns. It is also important to note that self, interviewer, and performance-based assessments often yield different results (Reuben et al., 1995), requiring the clinician to reconcile the data. Ultimately, experienced clinical judgment remains critical for strategically assembling information, integrating and interpreting data, and appropriately communicating results of the assessment including recommendations for appropriate follow-up.

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Chapter 12

Alexander I. Tröster and Sonia Packwood

Movement Disorders and Deep Brain Stimulation

There are a considerable number of movement disorders. Whereas some of these disorders (e.g., Parkinson's disease [PD], Huntington's disease [HD]) commonly have cognitive and emotional features, others (e.g., dystonia) appear to involve milder and less frequent neuropsychological impairments. Given that it is one of the most common movement disorders, PD is the focus of this chapter. Other movement disorders are mentioned briefly. Because deep brain stimulation (DBS) has become a commonplace treatment for movement disorders, this treatment is given attention.

I. DEFINITIONS AND DESCRIPTIONS OF DISORDERS

A. Classification and Definitions of Abnormal Movements

Extrapyramidal movement disorders (invariably affecting the basal ganglia) are of two broad types: *akinetic* (involving paucity of

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voluntary movement) and *hyperkinetic* (involving excessive, involuntary movements). Terms pertaining to *paucity of movement* include

- *akinesia:* loss or reduction of voluntary movement,
- *hypokinesia:* slowing in the *initiation* of movements, and
- *bradykinesia:* slowing in the *execution* of movements.

Abnormalities involving *excessive movements* include the following:

- *Tremor:* rhythmic, repetitive, oscillating movements of a body part. *Resting tremor* is one occurring at rest; *action (kinetic or intention) tremor* occurs during movement; *postural tremor* is observed when the affected body part is voluntarily held against gravity.
- *Chorea:* asynchronous, irregular, and appear to semipurposively move from one body part to another.
- *Ballismus:* an irregular, unilateral, choreiform movement, typically affecting an upper limb. The limb appears to move in a "flinging" fashion.
- *Dystonia:* characterized by prolonged muscle contraction, often painful, causing abnormal posture, twisting, or repetitive movements.
- *Tic:* repetitive, sudden, transient, stereotyped movements, with a limited distribution. When prolonged, tics are described as *dystonic*.
- *Athetosis:* peripheral dystonic movements that look like "writhing" movements, typically iatrogenic in origin.
- *Dyskinesia:* strictly referring to any involuntary movement, *dyskinesia* is most often used to describe complex, choreiform, dystonic movements of iatrogenic origin. Not only seen after chronic neuroleptic treatment, dyskinesias can develop as a side effect of dopaminergic treatment for parkinsonism.
- *Myoclonus:* brief, repetitive, shocklike muscle contractions of central nervous system origin, typically affecting the same muscles. It can be of cortical or subcortical origin. When of subcortical origin, myoclonic movement is generalized; when of cortical origin, myoclonus is typically focal or multifocal.
- *Fasciculation:* visible as "twitches" beneath the skin, fasciculations are due to random, repetitive contractions of groups of muscle fibers.
- *Parkinsonism:* a syndrome consisting of four motor signs: tremor, rigidity, akinesia, and postural abnormalities. Note that parkinsonism and PD are not synonymous. Parkinsonism is seen in PD but can also be a manifestation of numerous other conditions, including neurodegenerative, vascular, metabolic, toxic, infectious, and even psychogenic.

B. Parkinson's Disease

Age-adjusted prevalence estimates range from 98 to 175 per 100,000, and annual incidence is estimated at 11 per 100,000, reaching a peak of 93 per 100,000 among those ages 70 to 79 years. Cognitive declines may be obvious on testing at or near time of diagnosis in 25% to 35% of those with PD (see suggested readings). Early in PD, cognitive abnormalities are ascribed to a dysexecutive syndrome attributable to frontostriatal and dopaminergic systems dysfunction, whereas later impairments in memory and visuoperceptual and verbal fluency deficits are thought to relate to changes in other neurotransmitter systems (Kehagia, Barker, & Robbins, 2010). Recently, criteria have been proposed for mild cognitive impairment (MCI) in PD (Litvan et al., 2012; Tröster, 2011). MCI is estimated to affect 25% to 30% of persons with PD. Although nonamnestic MCI is the most common, there is heterogeneity, and some persons have amnestic MCI.

Cross-sectional dementia prevalence estimates fall into the 20% to 50% range. Though heterogeneous, and probably better referred to as the "dementias of Parkinson's disease," the dementia is often of the frontal–subcortical type and characterized by predominant impairments in processing speed, attention and executive functions, visuospatial abilities, and memory. Language and praxis are typically relatively preserved until the disease is more advanced. Dementia criteria specific to PD, avoiding *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) pitfalls in PD dementia diagnosis, have been published (Emre et al., 2007).

C. Other Parkinsonian Syndromes and Movement Disorders

The conditions from which PD is most difficult to differentiate are disorders known as *Parkinson-plus syndrome* or *atypical Parkinsonian syndrome*s. Atypical syndromes include progressive supranuclear palsy (PSP; also known as *Steele-Richardson-Olszewski syndrome*), the *multiple system atrophies* (previously called *olivopontocerebellar atrophy* [OPCA], striatonigral degeneration [SND], and Shy-Drager syndrome but more recently referred to as *multiple system atrophy of the parkinsonian* [MSA-P] and *cerebellar* [MSA-C] types), and corticobasal degeneration (CBD). The key neuropsychological features of PD, PD with dementia (PDD), dementia with Lewy bodies (DLB), CBD, and Alzheimer's disease (AD) are compared in Table 12.1.

1. PSP (STEELE-RICHARDSON-OLSZEWSKI SYNDROME)

Age-adjusted prevalence is about five per 100,000. Two phenotypes of PSP have been identified (Williams et al., 2005).

Table 12.1. Patterns of Cognitive Impairments in Parkinson's Disease (PD), Parkinson's Disease With Dementia (PDD), Dementia With Lewy Bodies (DLB), Corticobasal Degeneration (CBD), and Alzheimer's Disease (AD)

Area of impairment	PD	PDD	DLB	CBD	AD
Attention	0/–	–/—	—	–/—	—
Problem-solving/ conceptualization/ cognitive flexibility	—	—	–/—	—	–/—
Speech (e.g., dysarthria)	—	—	0/–	—	0
Language					
Visual confrontation naming	0/–	—	–/—	—	—
Letter fluency	0/–	—	–/—	–/—	—
Category fluency	—	—	–/—	–/—	—
Word knowledge	0/–	0/–	?	0	—
Anterograde memory					
Encoding	0/–	—	—	0/–	–/—
Storage	0	0/–	—	0/–	—
Retrieval	—	—	—	–/—	0/–
Proactive interference	0	—	0/–	?	—
Retrograde memory	0	—	?	0/–?	—
Praxis	—	–/–	—	—	—
Alien-hand sign	0	0	0	—	0
Visuoperceptual functions	—	–/—	—	0/–?	—
Visuoconstructional functions	0/–	—	—	?	–/—

Note. 0 = unimpaired; – = mild-to-moderate impairment; — = moderate-severe impairment; ? = unknown or to-be-confirmed.

Approximately half (54%) of cases had the traditional Richardson syndrome characterized by early gait instability and falls, cognitive (especially frontal) deficits, vertical gaze palsy, and an akinetic-rigid syndrome unresponsive to levodopa. Approximately one third (32%) of cases had a syndrome readily confused with PD and were referred to as having PSP-parkinsonism. These patients had asymmetric symptom onset and tremor, were initially responsive to levodopa, and had minimal if any cognitive dysfunction. The typical onset, as in PD, is in the 6th decade of life. Progression of the disease is more rapid than in PD. Research criteria (Litvan, Agid, et al., 1996) are specific but lack sensitivity. Some have suggested that cognition is unaffected in PSP and overdiagnosis of dementia is attributable to patients' bradyphrenia, emotional changes, and visual dysfunction. Others have observed that dementia occurs in 50% to 80% of cases and that it involves pronounced executive dysfunction (Grafman, Litvan, & Stark, 1995). Episodic memory impairment may be comparable to that in PD, but executive and attentional deficits may be present earlier and progress more rapidly in PSP than PD. The executive behavioral deficits have been linked to magnetic resonance imaging–visualized frontal lobe pathology.

2. MULTIPLE SYSTEM ATROPHIES

MSA refers to progressive neurodegenerative conditions that involve a variable combination of extrapyramidal (parkinsonian) and pyramidal motor signs, cerebellar ataxia, and autonomic dysfunction. MSA is increasingly recognized as primarily an oligodendrogliopathy Diagnostic accuracy is poor (25%–50%), and probabilistic diagnostic criteria remain to be prospectively evaluated. Two predominant motor presentations are recognized: MSA-P (80% of cases) and MSA-C (20%), probably corresponding closely to SND and OPCA, and respectively characterized by parkinsonism and ataxia. Prevalence estimates range from two to five per 100,000, and incidence is estimated at three per 100,000 among persons ages 50 to 99 years. Cognitive impairments include deficits in attention, executive function, verbal fluency, and memory (Dujardin, Defebvre, Krystkowiak, Degreef, & Destee, 2003). Though similarities in the cognitive profiles of PD and MSA outweigh differences, attention and verbal fluency may be more impaired in MSA than PD when the groups are equated for overall severity of cognitive deficits.

3. CORTICOBASAL DEGENERATION

The clinical features of CBD can be produced by conditions other than CBD (e.g., PSP, AD), and pathologically confirmed CBD

can have heterogeneous clinical presentations (Wenning, Litvan & Tolosa, 2011). Consequently, *corticobasal syndrome* (CBS) is the term applied to conditions characterized by the core motor and cortical features of CBD regardless of etiology, whereas CBD is reserved for neuropathologically confined CBD.

CBS has an insidious onset late in adulthood and is slowly progressive. There is poor diagnostic accuracy and lack of concordance among different criteria (Mathew, Bak, & Hodges, 2012). The patient's most typical initial complaint involves clumsiness, stiffness, and jerkiness of an arm and, less frequently, clumsiness of a leg. The most common early movement problems are akinesia and rigidity (and the "classic" alien limb and myoclonus may not emerge until later in the disease). The initial presentation is typically asymmetric, and both cortical and subcortical deficits (of which unilateral apraxia is a frequent cortical feature) are evident. Typical cognitive deficits in addition to apraxia include phonological rather than semantic deficits, poor episodic memory, and executive dysfunction. CBD can present resembling the behavioral variant of frontotemporal dementia and nonfluent primary progressive aphasia.

4. HUNTINGTON'S DISEASE

A disorder inherited in autosomal dominant manner, HD symptoms typically emerge in the mid-30s to mid-40s. Initial manifestations of HD include personality change, adventitious movements, and the gradual emergence of chorea and cognitive impairment progressing to dementia. In the juvenile form (onset before age 20), resting tremor and rigidity may predominate. Prevalence is estimated at five to seven per 100,000. The course of the disease spans 10 to 30 years, and death is usually attributable to complications of HD (e.g., pneumonia). The characteristic subcortical dementia associated with HD has been well characterized. Commonly, deficits are observed in memory (encoding and retrieval), working memory and complex (divided and selective) attention, executive functions, and aspects of visuoconstructional performance. There is a slowness of thought and word retrieval, though aphasia and apraxia are not evident. Cognitive and behavioral measures have been helpful in predicting functional capacity, especially in instrumental activities of daily living (i.e., in those skills required to remain independent within the community). Cognitive alterations can precede the motor features required for diagnosis by 15 years, and cognitive and behavioral manifestations of HD are more important than motor features in caregiver burden, functional decline, and institutionalization (Paulsen, 2011).

II. NEUROPSYCHOLOGICAL EVALUATION

A. General Considerations

There is no single "diagnostic" test (neuropsychological or otherwise) for the conditions outlined in this chapter, and neuropsychologists are rarely asked to make differential diagnoses among movement disorders. An understanding of the neuroanatomical pathways (and their derangements) that underlie these disorders is critical for the neuropsychologist evaluating them (consult the online resources at http://pubs.apa.org/books/supp/parsons for a more extensive discussion of the neuroanatomy and Figure 12.1i for a diagram of the circuitry). It is advisable to report whether neuropsychological evaluation results are or are not consistent with a particular condition. Neuropsychologists are, however, asked to assist in differential diagnosis when there is a suspicion of a psychogenic movement disorder or, in individuals with dementia, whether the dementia is associated with the movement disorder, depression, or some other neurological condition such as AD. Referrals also are often made to obtain a baseline neuropsychological evaluation, enabling one with repeat evaluation to determine if a dementia is evolving, if a particular drug or surgical (e.g., DBS) treatment is associated with cognitive and behavioral change, or if an individual is likely to require assistance with activities of daily living.

Clinicians administering lengthy, fixed test batteries need to be particularly cognizant of fatigue effects common in PD as well as the fluctuation of symptoms (on–off phenomenon) to which some PD patients are prone. Test selection should consider the patient's condition or the differential diagnosis, the referral question(s), 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, the potential impact of various symptoms (e.g., motor fluctuations, sleep disturbance and daytime sleepiness, choreiform and dystonic dyskinesias, gaze palsy, apraxia, dysarthria) on test performance should be monitored.

Standard test administration methods may need to be modified. Downward gaze palsy in PSP makes it difficult for patients to look down at test forms. Thus, stimuli may be held up for the patient to see at eye level. 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. Patients with tremor, dyskinesia, dystonia, or apraxia may require help from the examiner when completing

questionnaires. On some tasks, such as card sorting or tower tests, the examiner may need to hold and move the cards, blocks, or 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 significant movement limitations. Many persons with movement disorders whose symptoms are well controlled by medicines, however, can adequately complete these tasks, and the tasks should not be excluded from a test battery a priori simply on the basis of diagnosis.

For patients with somnolence, fatigue, severe motor "off" periods, or frequent fluctuations, breaks will need to be taken. It is recommended that patients with PD be tested while on their antiparkinsonian medications (though anticholinergics are best discontinued and tapered prior to evaluation). Testing during the off state can be challenging to patient and examiner, not just for motor reasons but because the patient may experience dysphoria and anxiety, thereby further complicating test interpretation.

The best way to ensure a smooth and informative evaluation is to plan ahead. The neuropsychologist may wish to speak with the patient before the appointment to determine whether some of the factors outlined above will require test modifications. Knowledge of when the patient is functioning optimally (minimal motor symptoms or fluctuations and fatigue or attention variation) helps one determine when best to test the patient. Knowledge of age at onset of various symptoms can facilitate differential diagnosis (e.g., cognitive decline before or within the 1st year of motor symptom onset might suggest Lewy body dementia rather than PD). Consideration of motor symptom asymmetry and the nature of motor symptoms can be helpful in diagnosis, planning accommodations, and interpreting cognitive findings in light of the greater compromise of one hemisphere or brain region than another. As in many neurologic conditions, the neuropsychologist should be aware of prior evaluations and neurosurgical treatments the patient might have had as well as the medications the patient is taking and their possible neurobehavioral side effects.

B. Screening Examinations

Although a cognitive screening examination might not yield useful information early in the course of diseases, it is worthwhile obtaining a baseline on a screening measure: This will facilitate monitoring of cognitive function once the patient can no longer cooperate with a lengthy neuropsychological test battery. Two commonly used screening instruments not specifically designed for PDD and DLB are the Mini-Mental State Exam (MMSE; Folstein, Folstein, & Fanjiang, 2001)

and the Dementia Rating Scale (DRS; Mattis, 2001). More recently, the Montreal Cognitive Assessment (MOCA; http://www.mocatest.org) has been used in PD (Nasreddine et al., 2005). Although an MMSE score of 23 and below has good sensitivity (98%) and adequate specificity (77%) in detecting dementia among PD patients with *DSM*-diagnosed dementia, it is not sensitive to milder cognitive impairment. The MMSE also appears to be less sensitive than the DRS and the MOCA in detecting cognitive deficits in atypical parkinsonian syndromes (Bak et al., 2005; Hoops et al., 2009). Alternative instruments specifically for use with PD have been developed but remain to be adequately evaluated in large, independent studies. The instruments include: the Mini-Mental Parkinson, the Scales for Outcomes of Parkinson's Disease—Cognition (SCOPA-COG), the Parkinson Neuropsychometric Dementia Assessment, and the Parkinson's Disease Cognitive Rating Scale (PD–CRS; see suggested readings). The MOCA, PD–CRS, SCOPA-COG, and DRS have been suggested as reasonable tests when screening for MCI in PD (Litvan et al., 2012), and the MOCA has been suggested for inclusion as a brief instrument in clinical trials (Chou et al., 2010).

C. Assessment of MCI in Parkinson's Disease

Recent studies reported heterogeneous cognitive changes in approximately 30% of persons with PD near or at the time of diagnosis (Foltynie, Brayne, Robbins, & Barker, 2004; Muslimovic, Post, Speelman, & Schmand, 2005). A slow progression of impairment in attention and executive functions, likely related to dopaminergic abnormalities, appears to be the most common course. The emergence of "posterior" cognitive deficits (visuoperceptual, semantic fluency, and memory) may herald dementia, although poor performance on tests of frontal function have also been shown to be predictors of dementia (Tröster, 2008).

Deficits of mild magnitude insufficient to significantly compromise functioning (but noticeable to patient, care partner, or health care provider) are referred to as MCI, and research and clinical criteria for MCI in PD have recently been proposed (Litvan et al., 2012; Tröster, 2011). The latest diagnostic criteria use a two-level schema (depending whether abbreviated or comprehensive assessment was undertaken to establish the diagnosis of MCI) and thus allow different levels of diagnostic certainty (see Exhibit 12.1). Exemplar tests for use in the detection of PD–MCI were also listed by Litvan et al. (2012) and cover five domains: attention/working memory, executive functions, language, memory, and visuospatial functions.

The nonamnestic, single-domain MCI subtype is the most commonly observed in PD. The amnestic single-domain and

Exhibit 12.1. Parkinson's Disease (PD)–Mild Cognitive Impairment (MCI) Criteria Based on Movement Disorder Society Task Force Guidelines

Inclusion Criteria	**Exclusion Criteria**
■ Diagnosis of PD (UK PD Brain Bank Criteria) ■ Gradual cognitive decline according to the patient, informant, or observed by clinician ■ Cognitive decline on neuropsychological testing and/or global cognitive ability scale ■ Decline does not significantly interfere with functional independence	■ Diagnosis of PD dementia ■ Other explanation (delirium, depression, metabolic factors, etc.) ■ Comorbidities affecting testing (e.g., motor impairment, fatigue, psychosis)
Level I: Abbreviated assessment	**Level II: Comprehensive assessment**
■ Impairment on PD-appropriate global cognitive ability scale or ■ Impairment on at least two tests when limited battery is used (fewer than two tests per domain or fewer than five domains assessed)	■ Neuropsychological testing includes two tests per domain (attention and working memory, executive functions, language, memory, and visuospatial skills) ■ Impairment on two tests in one domain or impairment on one test in two different domains ■ Impairment = score 1 to 2 standard deviations below norms, or significant declines on either serial testing or from estimated premorbid functioning
PD–MCI Subtype classification (comprehensive assessment requested)	
■ Single-domain: Impairment on two tests in one domain ■ Multiple-domain: Impairment on at least one test in two or more domains	

multiple-domain subtypes are also of importance and may occur in approximately 5% and 9% of persons with PD, respectively (Aarsland et al., 2010).

D. Assessment of Lewy Body Dementias

PDD and DLB are Lewy body dementias (LBD) whose differential diagnosis rests largely on the temporal pattern with which motor and neurobehavioral symptoms emerge. PDD criteria require that neurobehavioral features emerge more than 1 year after motor symptoms.

A longitudinal study (Halliday & McCann, 2010) identified three cognitive phenotypes of dementia in PD: (a) an early onset of prominent dementia and akinetic-rigid PD, corresponding clinically to DLB; (b) a late onset dementia (> 70 years old) developing within 3 to 10 years following the onset of PD, corresponding clinically to PDD; and (c) dementia occurring 10 to 15 years following the onset of PD, during which time cognitive functioning was relatively intact.

Regardless of the type of movement disorder, the neuropsychological profile will often resemble one that might be expected from frontosubcortical dysfunction, at least early on. DLB, however, can present with visuoperceptual and attention disturbances. As the condition progresses, the memory impairment may more closely resemble that seen in AD. An assessment of LBD thus should be comprehensive and include measures of dementia severity, premorbid function, fluency and naming (comprehension if clinically indicated), visuoperceptual functions, complex attention, executive function, and recall and recognition. Given psychiatric comorbidity, rating scales or interview should address sleep disturbance, attention and arousal fluctuations, hallucinations, depression, and anxiety. Questions regarding obsessive and impulse control disorders should be posed, especially to persons treated with dopamine agonists. Relatively briefer and longer evaluation paradigms have been described for PDD (Dubois et al., 2007).

E. Neuropsychological Measures Helpful in Differential Diagnosis

Neuropsychological measures are less likely to be helpful in differential diagnosis among movement disorders, but they are helpful in differentiating between PDD and AD on the one hand, and CBD and AD on the other hand. In particular, measures of language (fluency and visual confrontation naming), praxis, attention, and memory are helpful in this regard. It is emphasized that the sensitivity and specificity of different patterns of performance among these patient groups remains to be empirically demonstrated.

With respect to verbal fluency, letter fluency (e.g., Controlled Oral Word Association Test) and semantic category fluency (e.g., the Animal Naming Test from the Boston Diagnostic Aphasia Examination) tasks are helpful. Verbal fluency may be preserved early in PD. Patients with movement disorders and dementia are likely to perform particularly poorly on letter fluency tasks, whereas patients with AD perform especially poorly on semantic fluency. The patient with PD has only mild if any difficulty with visual confrontation naming (e.g., Boston Naming Test), and even PDD and HD involve lesser deficits than does AD.

Among attention tests, the Trail Making and Stroop tests may be helpful in differentiating AD, PDD, and DLB, with DLB demonstrating greater impairment. For executive function, the most commonly used tests are variants of the Tower test and short forms of the Wisconsin Card Sorting Test that have been found to be sensitive to AD, HD, and/or PD with and without dementia. Regarding visuospatial functions, a recent study demonstrated that patients with DLB performed worse on a measure of visuospatial skills (i.e., the five-item Rosen Drawing Test) compared with patients with AD, whereas patients with AD showed greater impairment in memory retrieval (as measured by Selective Reminding Test) relative to a DLB group (Yoshizawa, Vonsattel, & Honig, 2013).

Subgroups of PD patients demonstrated patterns of cortical and subcortical dementia on the California Verbal Learning Test (CVLT), but the PD patient without dementia is likely to demonstrate mild impairment on recall and perform fairly normally on recognition, although recognition should not be presumed to be intact (Brønnick, Alves, Aarsland, Tysnes, & Larsen, 2011). Although semantic encoding is diminished, serial encoding is preserved, and normal serial position effects are seen. A similar pattern is seen in HD. The patient with AD, however, is likely to demonstrate equally impaired recall and recognition and to make many intrusion and perseveration errors. Clinicians using the Auditory Verbal Learning Test will similarly find that PD is associated with preserved recognition.

In terms of apraxia, PD and PDD patients are likely to perform normally. AD and CBD both will show impairments, but CBD patients especially so and already early in the disease. One test useful for apraxia screening is the apraxia test from the Western Aphasia Battery.

Care needs to be taken in assessing mood state. Because symptoms of depression and anxiety overlap those of PD and to some extent HD, depression and anxiety disorders may be overestimated using traditional cutoffs on self-report scales such as the Beck Depression Inventory and the Beck Anxiety Inventory, although these scales can still be validly used with PD patients. Table 12.2 provides empirically validated cutoffs for some depression scales commonly used in PD.

Table 12.2. Self-Report and Rating Scales With Empirically Modified Cutoff Scores to Detect Depression in Parkinson's Disease (PD)

Scale (reference)	No. of items; max score; traditional cutoff	Cutoffs		
		For depression in PD (sensitivity/specificity)	Screening (sensitivity/specificity)	Diagnostic (sensitivity/specificity)
Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)	21 items max = 63 10 = mild; 12 = mod; 30 = severe	13/14 (0.67/0.88)[a]	8/9 (0.92/0.59)[a]	16/17 (0.42/0.98)[a]
Hamilton Rating Scale for Depression (17-item; Hamilton, 1960)	17 items max = 50 8 = mild; 14 = mod;19 = sev; 23 = vsev	13/14 (0.88/0.89)[b]	11/12(0.94/0.75)[b]	16/17 (0.75/0.98)[b]
Hamilton Rating Scale for Depression (24-item; Hamilton, 1960)	24 items	12/13 (0.80/0.92)[c] 12/13 (0.89/0.93)[d] 9/10 (0.88/0.78)[e]	9/10 (0.95/0.98)[c] NA[d] NA[e]	15/16 (0.99/0.93)[c] 18/19 (1.00/0.99)[d] NA[e]
Hamilton Depression Inventory (Reynolds & Kobak, 1995)	17 items; maximum = 52	13.5/14 (0.78/0.90)[d]	NA[d]	15.5/16 (0.89/0.93)[d]

Geriatric Depression Scale (Yesavage & Sheikh, 1986)	15 items; maximum = 15	4/5 (0.88/0.85)[e] 6/7 (0.89/0.87)[d]	NA[e] NA[d]	NA[e] 8/9 (0.89/0.87)[d]
Geriatric Depression Scale (Yesavage et al., 1982–1983)	30 items max = 30 10 = mild; 20 = sev	10/11 (1.00/0.76)[f]	10/11 (1.00/0.76)[f]	12/13 (0.80/0.85)[f]
Montgomery-Åsberg Depression Rating Scale (Montgomery & Åsberg, 1979)	10 items max = 60 15 = mild; 25 = mod; 31 = sev; 44 = vsev	14/15 (0.88/0.89)[b]	14/15 (0.88/0.89)[b]	17/18 (0.63/0.94)[b]
Hospital Anxiety & Depression Scale (Zigmond & Snaith, 1983)	7 items max = 21 8 = mild;11= sev	10/11 (1.00/0.95)[f]	10/11 (1.00/0.95)[f]	11/12 (0.80/0.98)[f]

Note. Lettered footnotes indicate which researchers recommended the indicated PD cutoffs. max = maximum; mod = moderate; sev = severe; vsev = very severe.
[a]Leentjens, Verhey, Luijckx, & Troost, 2000. [b]Leentjens, Verhey, Lousberg, Spitsbergen, & Wilmink, 2000. [c]Naarding, Leentjens, Van Kooten, & Verhey, 2002. [d]Dissanayaka et al., 2007. [e]Weintraub, Oehlberg, Katz, & Stern, 2006. [f]Mondolo et al., 2006.

III. TREATMENT, COMORBIDITY, AND OTHER ISSUES

A. Psychiatric Morbidity in Movement Disorders

Depression, apathy, anxiety disorders, psychosis, and impulse control disorders occur with noteworthy frequency in movement disorders. Depression is common among individuals with HD and PD. In HD, about 30% of individuals experience major depressive episodes, 5% experience dysthymia, and many more experience episodes of dysphoria. Suicide prevalence is increased fourfold to sixfold in patients with HD compared with the general population. Individuals with HD and depression and those with HD over age 50 years appear especially vulnerable. Other psychiatric morbidity in HD includes personality changes, which frequently are evident many years before diagnosis. Such changes might include irritability, lability, social disinhibition, and apathy. HD patients with intermittent explosive disorder and antisocial personality disorder appear more prone to aggressive outbursts. Estimates of psychosis range from about 5% to 25%. The psychosis often resembles that observed in schizophrenia.

Estimates of the prevalence of depression in PD vary greatly, but the preponderance of estimates is 30% to 40%. A recent study reported weighted prevalences of 17% for major depression, 22% for minor depression, and 13% for dysthymia (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Anxiety symptoms are a prominent feature among PD patients with depression. Diagnosis of depression in PD is difficult, given that symptoms such as fatigue, psychomotor slowing, and appetite changes occur in PD without depression. Table 12.2 identifies depression rating scales and modified cutoffs for use in PD. Depression may also occur in about 70% of CBD patients, though in CBD there is also a notable prevalence of apathy, irritability, and agitation.

Apathy is most common in PSP, with prevalence estimates up to 90% (Litvan, Cummings, & Mega, 1998; Litvan, Mega, Cummings, & Fairbanks, 1996). This condition has also received increasing attention in PD recently, in which apathy often coexists with depression but also occurs in the absence of depression.

Psychosis characterized by paranoid delusions, hallucinations, and confusion is estimated to occur in 20% to 30% of persons with PD. Psychosis often relates to treatment with dopamimetics. Although anticholinergics on their own rarely produce acute confusional states, elderly PD patients are particularly vulnerable to acute confusional states when treated with a combination of anticholinergics and dopaminomimetics. Patients with DLB in particular appear sensitive to neuroleptic-induced hallucinations. Overall it appears that depression and hallucinations are more common in DLB than AD, but delusions are more common in AD.

B. Treatment

Symptomatic treatments (dopaminergic agents and surgical interventions such as ablation and DBS) are available for PD. CBD, PSP, and MSA respond poorly to dopaminergic medications. In HD, dopamine-depleting agents and neuroleptics, which lessen choreiform movements but do not improve other symptoms, are usually only used in persons with the most severe and disabling movement disorder due to their side effects. For a description of the more common medications and surgical interventions used in PD along with their cognitive and behavioral effects, the reader is encouraged to consult Tables 12.1i and 12.2i (http://pubs.apa.org/books/supp/parsons).

C. Neurosurgical Treatment and Deep Brain Stimulation for PD

Thalamotomy and pallidotomy for PD symptom amelioration have increasingly been replaced by less invasive surgical procedures, including DBS. Targets of DBS include the subthalamic nuclei (STN) and internal globus pallidus (GPi), far less commonly now the ventral intermediate nucleus of the thalamus, and occasionally the pudunculopontine nucleus (an experimental target). The physiological mechanisms underlying DBS's effects are largely unknown, but DBS has been found to decrease motor symptoms of PD, including tremor, rigidity, akinesia, on–off motor fluctuations, dystonias, and dyskinesias.

Overall, the largest randomized trials of DBS show it to be neuropsychologically safe in carefully selected patients (Okun et al., 2012; Weaver et al., 2009). STN DBS seems to allow a greater reduction in dopaminergic medications than GPi DBS but also appears related to more frequent mood and cognitive disturbances (Volkmann et al., 2001). Psychiatric problems after STN DBS include apathy, emotional reactivity, depression, and hypomania (Voon, Kubu, Krack, Houeto, & Troster, 2006). A few studies have shown decline in verbal and visuospatial memory, processing speed, and executive functions following STN DBS. However, the most consistent finding appears to be a decline in word fluency (Parsons, Rogers, Braaten, Woods, & Troster, 2006). Although there is no universal agreement regarding the inclusion–exclusion criteria for DBS, the following selection criteria are commonly proposed. The patient should free of severe cognitive impairment, prior head injury or other neurodegenerative condition. It has been found that poor preoperative attention and poorer response to levodopa may predispose to postoperative cognitive decline, but this finding needs replication. History of psychiatric conditions such major depression, psychosis, bipolar disorder, impulse control disorder (e.g., history of excessive gambling), or obsessive–compulsive disorder, as well as language impairment (e.g.,

severe dysarthria), and age (over 69 years old) are considered vulnerabilities increasing the risk of adverse outcomes after DBS.

The Movement Disorder Society recommended a neuropsychological assessment as part of the presurgical workup (Lang et al., 2006). The assessment should typically include evaluation of memory, attention and working memory, executive function (abstraction, reasoning, and planning), visuoperceptual skills, and language (see Table 12.3i at http://pubs.apa.org/books/supp/parsons). It should also include an assessment of current and prior depression, anxiety, apathy, psychotic symptoms (e.g., hallucinations), hypomanic–manic symptoms, and obsessive–compulsive and impulse control disorder symptoms. The assessment should help rule out any evidence of ongoing neurodegenerative conditions, such as dementia, and psychiatric conditions that could potentially worsen following the surgery. The assessment should aim to clarify the risks and benefits of surgery and therefore help the patient give an informed consent. Finally, the assessment may serve as a presurgical baseline against which postsurgical evaluation can be compared.

Fetal tissue transplantation and gene transfer are experimental treatments. The former has yielded disappointing results, and limited data are available on the cognitive safety of gene transfer.

IV. CONCLUSION

Movement disorders involving paucity or excess of movements represent a challenge to neuropsychologists. The best assessments are carefully planned to account for the phenomenology of motor symptoms and the patient's cognitive and emotional status. Accommodations may need to be made in test administration. Neuropsychological evaluation is helpful in differential diagnosis of the cause of cognitive and emotional issues, in treatment selection, and in evaluation of pharmacologic and surgical treatments.

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Chapter 13

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Multiple Sclerosis and Demyelinating Disorders

The pathophysiologies, signs, and symptoms of multiple sclerosis (MS) and other demyelinating disorders are distinct. However, there is no "diagnostic" test (neuropsychological or otherwise) for MS or any of the other demyelinating conditions outlined in this chapter. Neuropsychologists are rarely asked to make differential diagnoses in regards to MS or other demyelinating disorders. Many differences in neuropsychological profiles associated with various disorders are based on group studies that do not reveal the diagnostic sensitivity and specificity of neuropsychological test profiles. Consequently, it is advisable to report whether neuropsychological evaluation results are or are not consistent with a particular condition. Neuropsychologists are, however, often asked to conduct neuropsychological evaluations of MS patients and other demyelinating disorders to determine whether cognitive deficits exist and then to evaluate the extent to which such deficits might be related to functional disabilities patients may be experiencing. Additionally, baseline neuropsychological evaluations are often conducted, making it possible with repeat evaluation

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to determine if a cognitive disorder is evolving, if a particular drug treatment or treatment of some secondary influence on cognitive functioning (e.g., depression, anxiety, fatigue) is associated with cognitive and behavioral change, or if an individual is likely to require assistance with activities of daily living.

I. DEFINITIONS AND DESCRIPTIONS OF THE DISORDERS

A. Description of Disorders and Evolution of Disease States

Demyelinating conditions include MS, *concentric sclerosis* (or *Balo's disease*, a variant of MS, characterized by rings of demyelination in cerebral white matter), *Schilder's disease* (a variant of MS involving diffuse sclerosis characterized by a monophasic course, affecting younger patients), *Devic's disease* (a variant of MS, characterized by a single spinal, typically cervical, demyelinating lesion, accompanied by signs of demyelination in the optic pathway), *central pontine myelinolysis*, and *Marchiafava-Bignami disease* (which involves primary degeneration of the corpus callosum). Other, very rare, conditions include *acute disseminated encephalomyelitis* (usually occurring in relation to acute hemorrhagic leukoencephalitis) and *acute hemorrhagic leukoencephalitis*, which is characterized by sudden onset of severe neurologic disturbance, rapid progression, and frequently death. MS is by far the most common among these conditions and the only condition that has been adequately studied from a neuropsychological perspective. Consequently this review focuses primarily on MS.

The incidence and prevalence of MS varies geographically, with few cases near the equator and larger numbers of cases in northern and southern latitudes (from about 60 to 300 per 100,000). There are estimated to be about 400,000 persons with MS in the United States and 2.5 million people worldwide (National Multiple Sclerosis Society, n.d.). MS affects females about 2.5 times as often as males, with a peak onset around 30 years of age (Chitnis et al., 2011). Recent studies suggest that the higher prevalence in women is increasing (Koch-Henriksen & Sørensen, 2010). Residents north of latitude 40 degrees north are about 3 times as likely to have MS as are residents of southern regions of the U.S. This differential geographic pattern suggests an environmental contribution to the disease. A significant genetic contribution to MS is suggested by the 30% to 40% concordance in identical twins but only 1% to 13% in fraternal twins.

It is likely that MS is acquired before puberty, but actual disease onset occurs in most (70%) of patients between the ages of 20 and 40 (Compston et al., 2005). Late onset after age 40 is often characterized by quicker progression and greater morbidity. Average life expectancy following disease onset is estimated at 30+ years, but variability is great. Typically, MS runs its course over one or more decades; very rarely does death from MS-related complications ensue within months of disease onset.

Two severity outcome definitions of MS have been identified. About 33% of patients have a "benign" outcome where the disease is minimally disabling, even after 20 years or more (Forn et al., 2006). About 10% of patients have a "malignant" outcome, which is usually defined as reaching significant disability (Expanded Disability Status Scale [EDSS] score of at least 6) within 5 years of disease onset (Smith et al., 2012). Most patients fall in between these two extremes. Patients likely to have a malignant course are those who, at onset, are older, have motor symptoms, and have a progressive disease course. Patients with a malignant versus benign course differ in terms of clinical course, response to treatment, and genetics (Smith et al., 2012).

Initial symptoms vary greatly, but the most common symptoms at MS onset are muscle weakness, paresthesias (usually numbness and tingling in the limbs, trunk, or face), gait and balance problems, and visual disturbances. Visual anomalies are characterized by diplopia, loss of visual acuity, blurry vision, and visual field defects. Other common symptoms include urinary disturbance and fatigue. Significant cognitive difficulties and problems with depression are very common symptoms as well. The mode of symptom onset in MS is typically acute or subacute. Many MS symptoms are transient and unpredictable. For example, visual disturbances and paresthesias may last for seconds or hours. Because of the short-lived and sometimes bizarre nature of the symptoms, it is not uncommon for patients to be labeled with hysteric or somatization disorders before formal diagnosis.

The diagnosis of MS was typically based on Poser and colleagues' criteria (Poser et al., 1983) until the publication of updated guidelines (McDonald et al., 2001), which were then subsequently revised in 2005 (Polman et al., 2005), and 2010 (Polman et al., 2011). A key advance over the Poser criteria is that the McDonald (2001) and Polman et al. (2005, 2011) criteria involve systematic integration of magnetic resonance imaging (MRI) data with clinical and paraclinical diagnostic methods. Still, even with the most recently updated system, a definite MS diagnosis can be made based exclusively on clinical criteria. Another key addition is that the revised criteria provide guidelines for diagnosing MS presentations involving an insidious progression where clear attacks and remissions are

absent, as in the case of primary progressive MS. The revision by Polman and colleagues in 2010 was the result of a consensus panel designed to simplify the criteria. Outcomes in this new diagnostic system include "MS," "not MS," and "possible MS."

Key factors in making an MS diagnosis in Polman et al.'s (2011) revised McDonald criteria include the consideration of clinical and paraclinical (e.g., the presence of oligoclonal bands in the cerebral spinal fluid [CSF]) assessments, evidence that lesions are disseminated in space (DIS) and time (DIT), and disease attacks that last at least 24 hours. DIS is demonstrated by the presence of at least one T2 lesion in at least two of four MS-typical regions of the central nervous system (CNS; periventricular, juxtacortical, infratentorial, or spinal cord) or by a further clinical attack that implicates a different CNS site. DIT is demonstrated when a new T2 and/or gadolinium-enhancing lesion or lesions appear on follow-up MRI after a baseline scan has been conducted or by the simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions. There are four ways to meet these criteria spelled out by Polman et al. (2011): (a) evidence of at least two attacks, combined with objective clinical evidence of at least two lesions *or* objective clinical evidence of one lesion combined with reasonable historical evidence of a previous attack; (b) at least two attacks with objective clinical evidence of one lesion, combined with evidence for DIS; (c) one attack combined with objective clinical evidence of at least two lesions as well as DIT; or (d) one attack combined with objective clinical evidence of one lesion as well as DIS and DIT.

When the presentation of MS involves insidious progression (primary progressive MS), there must be evidence of at least 1 year of disease progression combined with at least two of the following: (a) evidence for DIS in the brain, (b) evidence for DIS in the spinal cord based on the presence of at least two T2 spinal cord lesions, or (c) positive CSF findings (isoelectric evidence of oligoclonal bands and/or elevated IgG index). Polman et al. (2011) underscored the necessity of validating the McDonald criteria in Asian and Latin American populations, something that has not yet been done.

Clinically isolated syndrome (CIS) is the term used to describe the first clinical episode suggestive of MS, typically affecting the optic nerve, brainstem, or spinal cord. The word *isolated* implies that the event (and related lesion) is isolated in time and space; though some individuals meet criteria for dissemination in space, the event is still isolated in time. Thus, the criteria for CIS include an episode with an acute or subacute onset lasting for at least 24 hours and peaking within 2 to 3 weeks in the absence of encephalopathy and fever. Approximately 70% of cases of CIS occur between the ages of 20 and 40. Although a harbinger of MS, it is estimated that the risk for conversion from CIS to definite MS is 20% among individuals whose

brain imaging is normal at baseline (with the exception of the symptomatic lesion) and 60% to 80% among those whose brain imaging revealed the presence of other lesions. With regard to cognitive functioning, individuals with CIS have been shown to demonstrate some degree of cognitive impairment even early on, with subtle impairments in information processing speed, memory, attention, and executive functioning. Recent studies suggest this occurs in approximately 25% of CIS patients (Reuter et al., 2011).

Attacks, relapses, or exacerbations that imply new disease activity are common. Previously, MS was classified by two major disease-course types: *relapsing-remitting* and *chronic progressive*. However, this system has been updated (Lublin & Reingold, 1996) and now includes four course types. Relapsing-remitting is the most common type, affecting more than half of all patients, and is characterized by clearly defined disease relapses. Recovery can be complete or with sequelae and residual deficit. A defining feature of the relapsing-remitting type is that there is no progression of disease between relapses. The next most common type of MS is secondary progressive. This disease type is first characterized by a relapsing-remitting course and then a more significant progression. If there are relapses once the disease evolves to secondary progressive, this progression is evident even between relapses. However, relapses and remissions may or may not occur. Next most common is the primary progressive type, and this involves an unremitting disease progression from disease onset for most patients. However, there is occasional stabilization and even improvement in functioning for others, but no clear relapses. Finally, progressive relapsing is the least common type of MS and involves disease progression from onset that is punctuated by acute relapses from which patients may or may not fully recover. The term *chronic-progressive* formerly encompassed all progressive types.

After the first episode of symptoms for the relapsing-remitting type of MS, complete remission typically ensues. Subsequent episodes are unpredictable, occurring weeks to years later, and symptoms associated with them remit less completely or not at all. Relapses themselves may last days to weeks, more rarely hours or months. The median time to conversion from relapsing-remitting to secondary progressive course is 15 to 20 years (Loitfelder et al., 2011).

Approximately 45% to 65% of persons with MS experience cognitive impairment, but most (about 80%) patients with deficits are relatively mildly affected. However, even mild cognitive problems in MS have been shown to relate to everyday activities (e.g., work, homemaking, personal care activities, social activities; Higginson, Arnett, & Voss, 2000). About 20% to 30% of MS patients experience cognitive impairment severe and extensive enough to qualify for the diagnosis of dementia. Dementia in MS is characterized by a "subcortical

dementia" pattern of cognitive impairments, at least if one looks at groups of patients. As Beatty (1996) pointed out, there is, however, considerable heterogeneity among individuals' cognitive impairments, and only 10% to 15% of persons with MS might exhibit all of the cognitive deficits associated with subcortical dementia.

Although commonly assumed to be an adult disorder, the incidence and awareness of pediatric MS has increased over the past few years. In particular, approximately 20,000 children are known to suffer from MS in the United States (MacAllister, Christodoulou, Milazzo, & Krupp, 2007). The frequency is about 1.35 to 2.5 per 100,000 (Gadoth, 2003), with a mean age of onset between 8 and 14 years, with onset prior to 10 years of age being least common and indicative of a poor prognosis. Although the gender distribution is similar to adult MS, the ethnic distribution is different, with more African American and Latino children being susceptible. Comparable to adult MS, children initially present with symptoms of sensory disturbances, optic neuritis, brainstem related symptoms, motor deficits, and gait disorders (Patel, Bhise, & Krupp, 2009). Optic neuritis is the most common symptom at onset, followed by sensory disturbances. Transverse myelitis is also more common among children than adults. It is estimated that approximately 90% or more of children suffer from a relapsing-remitting course, with 2.3% to 7% experiencing a primary progressive course (Ness et al., 2007). The time for conversion to a secondary progressive course is also longer in children than adults, and children typically have a less progressive course. Indicators of a poor prognosis include a short (less than 1 year) interval before the first and second attack, incomplete recovery after the first attack, and a secondary progressive course, which is more common following a greater number of attacks in the first 2 to 5 years (Ness et al., 2007). Similar to adult MS, fatigue and psychiatric issues are a frequent concern. Rates of fatigue have been reported to be as high as 73%, and upwards of 48% of children report experiencing some sort of affective disorder (Chitnis et al., 2011). Finally, cognitive disturbances are estimated to occur in upwards of 77% of children and include difficulties in complex attention, working memory, processing speed, language (confrontation naming and receptive functions), visuomotor integration, and executive functioning (Chitnis et al., 2011; Patel et al., 2009; MacAllister et al., 2005). Taken together, these factors are known to have a substantial impact on a child's academic achievement, psychosocial adjustment, and overall quality of life.

B. Neuropathologic Correlates

MS is a demyelinating disease of the CNS presumed to be caused by an autoimmune process, a slow-acting virus, or a delayed reaction to

a common virus (Brassington & Marsh, 1998). Demyelination occurs in the form of multiple discrete plaques at demyelinated sites that are formed, in part, by proliferating astrocytes. The plaques appear as ill-defined, pale, pink-yellow lesions in the unfixed brain and consist of demyelination, inflammation, gliosis and axonal injury. Myelin sheaths within plaques are either destroyed or swollen and fragmented. Neural conduction is facilitated by myelin because an intact nerve is enclosed in myelin sheaths separated by gaps from which the nerve impulse jumps. Affected areas thus interfere with or block neural transmission by limiting this saltatory conduction process. Axons and cell bodies of neurons often remain intact. The size of plaques varies from about 1.0 mm to several centimeters, and their shape is typically round or ovoid. Lesions are usually not punctuate and are found in a random or asymmetrical pattern in the periventricular, juxtacortical, and infratentorial regions.

Symptoms from demyelination in MS often reflect functions associated with affected areas. Plaques can occur in the brain or spinal cord. The location of plaques is highly variable between patients. Within the cerebrum, plaques near the lateral and third ventricles and so-called periventricular region are most common. The frontal lobes are the next most commonly affected, even when the size of the frontal lobes relative to rest of the brain is taken into account. Plaques in other major lobes of the brain are also frequently observed. Additionally, plaques are commonly seen in the optic nerves, chiasm, or tracts as well as the corpus callosum, brain stem, and cerebellum. Plaques are also found in white matter regions of the thalamus, hypothalamus, and basal ganglia.

Although MS has primarily been considered a white matter disease, advances in the past decade or so have suggested a greater involvement of gray matter, even early on in the disease (Zivadinov & Pirko, 2012). The most affected regions are the cingulate areas, thalamus, basal ganglia, hypothalamus, cerebellum, hippocampus, and frontal and temporal lobes (Horakova, Kalincik, Dusankova, & Dolezal, 2012). Such cortical demyelination occurs more frequently in primary and secondary progressive MS and has been suggested as a marker of disease progression and potential irreversible disability (Popescu & Lucchinetti, 2012).

Historically, postcontrast T1-weighted (T1W), T2-weighted (T2W), and fluid-attenuated inversion recovery (FLAIR) imaging have been used to diagnose and monitor disease progression. On T1W images, lesions appear as hypointensities. In the acute phase, these hypointensities likely reflect marked edema and demyelination and may completely disappear as the inflammation subsides (Filippi et al., 2012). However, chronic hypointensities are indicative of areas with severe destruction, so-called black holes. On T2W images,

lesions present as hyperintense areas and are visualized as bright, white objects. Conventional MRI can also assist in distinguishing acute or active lesions from chronic or nonactive lesions through contrast enhancement (gadolinium). Gadolinium enhancement is indicative of a breakdown of the blood–brain barrier and inflammation that can last as long as 6 weeks. Lesions are defined as early active, late active, inactive, early remyelinated, and late remyelinated (Brück et al., 1995). Finally, newer imaging techniques have been capable of identifying pathological processes that were neglected in the past (e.g., iron deposition).

More recent advances in imaging, such as magnetic resonance spectroscopy (MRS), magnetization transfer imaging (MTI), and diffusion tensor imaging (DTI) have shed light on the microscopic changes in the "normal-appearing" white matter and gray matter. More specifically, MRS allows for an examination of disease involvement (active inflammation, demyelination, and axonal/neuronal injury) while MTI and DTI provide a measure of the integrity (or destruction) of the myelin and other cell membranes. These more unconventional techniques have greatly advanced our current understanding of the pathological substrate underlying MS.

II. FUNCTIONAL NEUROANATOMY

Because lesion size and distribution are highly variable in MS, there is no one pattern of cognitive dysfunction that might be considered "typical." Early in the course of MS (when it is suspected but unconfirmed), neurobehavioral deficits might be a manifestation of a single lesion (and cognitive deficits will depend on the lesion's location). Early on in confirmed or definite MS, the neurobehavioral deficit pattern is often consistent with multifocal lesions. Deficits consistent with diffuse pathology (e.g., a subcortical dementia) typically develop later in the disease, although such a pattern of deficits may be present early in some cases. Conversely, an individual with a long disease course may be quite intact cognitively.

Generally, cognitive deficits tend to be proportional to MRI-visualized total lesion load on T2 sequences (Bagert, Camplair, & Bourdette, 2002). Regional lesion burden has also been shown to correlate with cognitive functioning. Namely, frontal and parietal region lesion load has been shown to correlate with observed deficits in processing speed and memory (Sperling et al., 2001). Some studies have also reported an association between specific locations of lesions on MRI and particular patterns of dysfunction, such as primarily frontal lesion patterns associated with executive task dysfunction.

Although total and regional lesion load are commonly examined in MS, recent investigations suggest more robust correlations between disability and cognitive impairment with measures of brain atrophy (Zivadinov et al., 2000). In particular, atrophy measures such as bicaudate ratio, third ventricular width, and brain parenchymal fraction have all been shown to be significantly related to neuropsychological performance and account for a significant amount of the variance in predicting cognitive impairment in MS (Tekok-Kilic et al., 2007). Regional brain atrophy has also been shown to be related to specific cognitive deficits. Namely, regional frontal volume has been shown to be correlated with performance on measures assessing executive function, attention, and processing speed, while atrophy in the left temporal region has been shown to be predictive of poor verbal memory and both left and right temporal atrophy associated with visual memory performance (see Tekok-Kilic, 2006).

As stated earlier, recent advances in imaging have significantly improved our understanding of the pathology of MS and related cognitive impairment. In fact, Filippi et al. (2000) revealed that cognitively impaired individuals with MS had significantly more abnormalities in normal-appearing white matter than cognitively intact individuals. Moreover, they found that the magnetization transfer ratio correlated significantly with the severity of cognitive impairment, whereas T1 and T2 lesion burden did not (Bagert et al., 2002). Thus, some of the damage associated with cognitive impairment in MS may go undetected by conventional MRI.

An increasing number of functional MRI (fMRI) studies on cognitive functioning in MS have been conducted in the past 10 years or so. Initial studies suggested that contrary to most expectations, MS patients displayed *greater* increases in brain activation relative to non-MS controls when performing complex cognitive tasks (Forn et al., 2006; Hillary et al., 2003). More recently, Loitfelder et al. (2011) examined fMRI activation patterns during a go/no-go discrimination task in CIS, relapsing-remitting, and secondary progressive MS patients compared with controls. Although they found that CIS patients did not differ from controls, relapsing-remitting and secondary progressive patients showed characteristically greater activation increases during task performance. Interestingly, the patterns of increased activation were more pronounced in the secondary progressive patients who showed more widespread activation, and also less deactivation. More recent work has generally supported such initial findings; however, consistent increases across all brain areas have often not been found. For example, Smith et al. (2012) compared differences in fMRI activation patterns in MS patients and controls on the Computerized Test of Information Processing. They found that compared with controls, MS patients displayed a significant increase in activation in the

prefrontal cortex and right temporal gyri but decreased activation in areas of the left temporal gyrus. Of note, patients showed longer reaction times (RTs) for the choice RT condition of the task compared with controls, but the accuracy of the groups was comparable. Studies such as those by Smith et al. show that the initial findings of broadly greater task activation in MS patients versus controls may be more complex than initially appreciated. Further work will be necessary to more accurately characterize the conditions under which increased versus decreased activation occur in MS during task performance. Attention to issues such as disease type, disease severity, and task demands will be critical.

III. AREAS OF EMPHASIS WITHIN THE NEUROPSYCHOLOGICAL EVALUATION

A. Nature of Cognitive Impairment in MS

The most informative investigation regarding typical patterns of cognitive impairment in MS remains Rao and colleagues' seminal study (Rao, Leo, Bernardin, & Unverzagt, 1991) comparing 100 community-based MS patients with 100 matched healthy controls on an extensive neuropsychological battery. It was suggested at that time that individuals with MS "were more frequently impaired on measures of recent memory, sustained attention, verbal fluency, conceptual reasoning, and visuospatial perception, and less frequently impaired on measures of language and immediate and remote memory" (Rao et al., 1991, p. 685). Subsequent studies have generally supported their findings and suggest that complex attention–speeded information processing and memory are the cognitive domains most affected in MS (Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2009).

Difficulties with tasks involving complex attention (e.g., divided, selective) and speeded information processing are perhaps the most common in MS. Together, these two domains may serve as a sensitive indicator of MS-related cognitive problems (Amato, Zipoli, & Portaccio, 2008; DeLoire et al., 2006). It can be difficult to separate speeded information processing from attentional functioning because the latter is necessary for performing any speeded cognitive task. MS patients typically show their greatest difficulty on tasks requiring rapid and complex information processing, such as those requiring swift application of working memory operations, attentional switching, or rapid visual scanning. About 20% to 25% of MS patients have substantial difficulty in this cognitive domain. Simple attention span is usually intact, but mild impairments are sometimes found. Individuals may also demonstrate a decline in performance during

sustained attention tasks, so-called "cognitive fatigue" (Amato et al., 2008). Clinically, complex attention–speeded information processing problems are commonly manifested as difficulty tracking and keeping up with and focusing on details of conversations, work tasks, television programs, and so on. Some contend that slowed information processing is the most fundamental deficit because it impacts new learning and the ability to perform higher order cognitive functions (Chiaravalloti & DeLuca, 2009). In clinical evaluations it is also important to be cognizant of the possibility that memory problems in MS may, in part, be a function of deficits in these domains.

Regarding memory, difficulties in encoding and/or retrieving both verbal and visual information are most common among individuals with MS. These are typically manifested as immediate and delayed recall memory deficits on neuropsychological testing. About 30% of patients have substantial problems, another 30% have moderate problems, and the remaining 40% have mild or no problems with this type of memory (Brassington & Marsh, 1998). Delayed recall deficits are usually a function of deficient immediate recall, not forgetting. The learning curve across repeated trials is similar in slope in MS compared with controls but is lower in magnitude. Percent retention, recognition, incidental memory following a delay, and remote memory are usually intact in MS. Clinically, memory problems are often manifested as complaints of difficulty remembering conversations, appointments, work tasks, and so on. Working memory, the ability to maintain and manipulate information "on-line," is also commonly impaired in MS. In contrast, semantic and implicit memory are fairly preserved.

The next most common cognitive domain typically affected in MS is executive functioning. Deficits in cognitive flexibility, concept formation, verbal abstraction, problem solving, and planning are commonly found. An estimated 15% to 20% of individuals with MS show substantial difficulties in this cognitive domain. These problems may manifest clinically as difficulty planning day-to-day activities (e.g., job tasks, meals, grocery shopping), verbal disinhibition, and tangential speech as well as problems organizing ideas and shifting appropriately from one topic to another in conversation.

Verbal and linguistic skills are variably affected in MS. Aphasias are rarely seen in MS, but mild confrontation naming difficulties are more common. Similarly, alexia, agraphia, and apraxia are very rare. In contrast, speech abnormalities such as dysarthria and hypophonia are common in MS (Arnett, Vargas, Ukueberuwa, & Rabinowitz, 2013). Also, deficits in verbal fluency are common, with approximately 20% to 25% of individuals having substantial problems on verbal fluency tasks. Evidence suggests that impairments in verbal fluency may be as great as impairments in speeded information processing (Henry &

Beatty, 2006). It can be important in clinical evaluations to determine whether deficits in verbal fluency are associated with memory retrieval difficulties that are common to MS (Fischer et al., 1994). Because fluency tasks require rapid production of information, patients' poor performance on them may also be related to their speeded information processing deficits. Additionally, the slowed speech common to MS should be considered as a possible contributor to patients' verbal fluency (Arnett et al., 2013). Fluency problems may manifest clinically as word-finding problems that impair the flow of patients' conversations.

Visuospatial deficits occur with reasonable frequency in MS, with 10% to 20% of patients showing substantial difficulty with higher order visual–spatial skills involving angle matching or face recognition. It is unclear whether higher order visual deficits are a function of primary visual disturbances involving blurred vision and diplopia (Rao et al., 1991). Clinical manifestations may involve accounts of running into things frequently while walking (e.g., doorways) or driving (e.g., hitting curbs) because of visual miscalculations.

Although intellectual functioning is significantly affected in about 20% of MS patients relative to healthy controls, most patients score within the broad normal range on general measures of intelligence, with greater verbal than nonverbal scores. Little systematic research on changes in academic skills in MS has been conducted, but these are assumed to be intact in most patients.

Cognitive impairment occurs during all stages of the illness and across all disease courses. Deficits are noted to occur early on in the disease, with 45% to 49% of individuals with early MS or CIS demonstrating impairment on at least one measure (Glanz et al., 2010). There is evidence to suggest that patients with cognitive deficits are at greater risk for cognitive decline over time than patients with minimal cognitive difficulties on initial testing (Kujala, Portin, & Ruutiainen, 1997). Longitudinal investigations spanning 3 to 5 years suggest a slow and somewhat inconsistent deterioration of cognitive abilities, predominantly in information processing speed, verbal learning and memory, visual memory, and attention–working memory (Amato et al., 2010; Denney, Lynch, & Parmenter, 2008; Kujala et al., 1997). Changes in verbal skills and executive functions are also noted to occur (Amato et al., 2010; Reuter et al., 2011). Longitudinal investigations spanning a longer term follow-up period (approximately 7 to 10 years) suggest notable declines in long-term verbal memory (Piras et al., 2003), information processing speed, motor speed, RT, visuospatial ability, and visual short-term memory (Bergendal, Fredrikson, & Almkvist, 2007). In one of the most extensive longitudinal studies (10 years), individuals with early onset MS demonstrated difficulties on measures of concentration, verbal memory, and abstract reasoning at study entry but

developed additional impairments in verbal fluency, verbal comprehension, and short-term verbal and spatial memory–attention (Amato, Ponziani, Siracusa, & Sorbi, 2001). Over the 10-year period, the rate of cognitive impairment increased from 26% at entry to 56% at follow-up, a twofold increase.

With regard to disease course, the general consensus is that individuals with a relapsing-remitting course type exhibit less severe cognitive impairment than those with progressive courses. A large meta-analysis suggested that individuals with a chronic progressive course (as noted, an old diagnostic term encompassing all progressive types of MS) are more likely to present with frontal–executive impairment, whereas memory-related impairments are more common among individuals with a relapsing-remitting course (Zakzanis, 2000).

B. Measuring Cognitive Functioning in MS

Because MS is characterized by heterogeneous cognitive findings, a test battery sampling multiple areas of cognitive functions is critical. Any battery administered should ideally be kept relatively brief (2–3 hours) given the fatiguability of individuals with MS, especially in light of recent data suggesting that patients' performance deteriorates more significantly than non-MS patients over the course of a demanding neuropsychological evaluation (Krupp & Elkins, 2000). Some research has also shown that MS patients' performance can decline more sharply than healthy controls over the course of standard neuropsychological tasks such as the PASAT (3s version; Walker, Berard, Berrigan, Rees, & Freedman, 2012).

An efficient way of approaching neuropsychological testing in MS is to conduct a brief screening evaluation to determine if further testing is warranted. MS patients impaired in one domain of cognitive functioning are not necessarily impaired in others (Rao et al., 1991). Thus, neuropsychological assessments that evaluate major areas of cognitive functioning typically impaired in MS are critical because performance on a test in one domain provides little information about the likelihood of deficits in other domains. The Brief Repeatable Battery (BRB; Rao, 1990) comprises tests most sensitive to cognitive impairments typically seen in MS; most tests also include 15 alternate forms to allow for repeat testing (see Exhibit 13.1). The BRB is available through the National MS Society, and it takes about 20 to 30 minutes to administer.

A more extensive consensus battery was suggested in 2002 that includes most of the BRB tests in addition to measures of emotional functioning and fatigue. This battery, known as the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002), is designed to take approximately 90 minutes (See Exhibit 13.1).

Exhibit 13.1. Recommended Brief and Comprehensive Batteries for Assessing Multiple Sclerosis Patients

Brief Screening Battery (about 30 minutes)—Mostly BRB (Rao, 1990) Tests
Premorbid Intellectual Functioning: Wechsler Test of Adult Reading (WTAR) ***Memory:*** Verbal Selective Reminding Test (6-Trial Version) with delayed recall and recognition,[a] 10/36 Spatial Recall with delayed recall and copy[a] ***Attention and Concentration/Processing Speed:*** Symbol Digit Modalities Test (SDMT), Oral Version;[a] Paced Auditory Serial Addition Test (PASAT), 2s and 3s versions[a] ***Verbal-Linguistic:*** Controlled Oral Word Association Test (COWAT)[a] ***Affective/Emotional, Fatigue:*** Chicago Multiscale Depression Inventory (CMDI),[b] Beck Depression Inventory (BDI)—Fast Screen,[b] Fatigue Severity Scale
Mid-Length Battery (about 90 minutes)—Mostly MACFIMS (Benedict et al., 2002) Tests
Premorbid Intellectual Functioning: North American Adult Reading Test (NAART)[b] ***Memory:*** California Verbal Learning Test (2nd ed.; CVLT-II),[b] Brief Visuospatial Memory Test—Revised (BVMT–R)[b] ***Attention & Concentration/Processing Speed:*** SDMT (Oral Version),[b] PASAT (2s & 3s)[b] ***Verbal-Linguistic:*** COWAT[b] ***Executive:*** D-KEFS Sorting Test[b] ***Visuospatial:*** Judgment of Line Orientation (JLO)[b] ***Affective/Emotional, Fatigue:*** CMDI or BDI—Fast Screen,[b] Fatigue Impact Scale (FIS)[b] ***Sensorimotor:*** 9-Hole Peg Test[b] (9HPT), Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC),[b] Rosenbaum Pocket Vision Screener[b]
MS Plus: Standard Comprehensive Battery (about 3 hours; Arnett & Rabinowitz, 2010)
Orientation: Information/Orientation from Wechsler Memory Scale, 3rd Edition (WMS-III)[c] ***Intellectual:*** Four-subtest form: Wechsler Abbreviated Scale of Intelligence (WASI)[c]

Exhibit 13.1. Recommended Brief and Comprehensive Batteries for Assessing Multiple Sclerosis Patients *(Continued)*

Academic: Wide Range Achievement Test—IV (WRAT–4)
Memory: California Verbal Learning Test—2nd Edition (CVLT–II);[c] Brief Visuospatial Memory Test—Revised (BVMT–R);[c] 10/36 Spatial Recall (delayed recall & copy);[c] Logical Memory from WMS–III;[c] Information from Wechsler Adult Intelligence Scale, 4th Edition (WAIS–IV)[c]
Attention & Concentration/Processing Speed: SDMT Oral Version;[c] PASAT 2s and 3s versions;[c] *Digit Span from WAIS–IV;[c] Letter-Number Sequencing (WAIS-IV)[c]
Verbal-Linguistic: COWAT;[c] Boston Naming Test[c]
Executive: D-KEFS[c] Tower & Sorting (free-sorting condition only);[c] *Similarities (WAIS–IV)[c]
Visuospatial: Judgment of Line Orientation (JLO)[c]
Affective/Emotional, Fatigue: CMDI or BDI—Fast Screen;[c] Hospital Anxiety and Depression Scale (HADS);[c] Fatigue Impact Scale (FIS)[c]
Sensorimotor: 9-HPT;[c] MRRSMC;[c] Rosenbaum Pocket Vision Screener[c]
Disability: Multiple Sclerosis Functional Composite (MSFC)

Note. BRB = Brief Repeatable Battery; MACFIMS = Minimal Assessment of Cognitive Functioning in MS (Benedict et al., 2002). From "The Neurological Presentation and Treatment of Demyelinating Disorders" (pp. 593–594), by P. A. Arnett and A. R. Rabinowitz, 2010, New York, NY: Oxford University Press. Copyright 2010 by Oxford University Press. Adapted with permission.
[a]Included in BRB. [b]Included in MACFIMS. [c]Included in Arnett and Rabinowitz (2010).
*WAIS–IV recommended now, previously WAIS–III.

In addition to neurocognitive tests, the battery includes optional measures designed to assess depression and fatigue in addition to premorbid functioning. Measurement of depression is important because depression is common in MS and because some research has shown an association between depression and cognitive dysfunction in MS (Arnett, Barwick, & Beeney, 2008).

A recent comparison of the BRB and the MACFIMS (Strober et al., 2009) suggests that the BRB and MACFIMS have comparable sensitivity, with the Symbol Digit Modalities Test (SDMT) reigning as the most significant predictor of MS status and performance on verbal fluency and verbal memory also contributing. One problem with the SDMT is that although it appears very sensitive to cognitive

problems in MS, performance on it can be compromised by the slowed speech that is common in MS (Arnett et al., 2013) as well as relatively minor rudimentary visual problems (Bruce, Bruce, & Arnett, 2007). With regard to the differing verbal and visual learning and memory tasks employed in the batteries, comparisons of the Selective Reminding Test and 10/36 in the BRB and California Verbal Learning Test (2nd ed.; CVLT–II) and Brief Visuospatial Memory Test—Revised (BVMT–R) in the MACFIMS suggest that the SRT and CVLT–II are comparable whereas the BVMT–R is superior to the 10/36.

A comprehensive neuropsychological battery was also suggested by Arnett and Rabinowitz (2010), referred to in Exhibit 13.1 as the MS Plus Battery. This approach recommends many of the same tests suggested in the BRB and the MACFIMS but simply expands on them. Measures of global intelligence, academic functioning, confrontation naming, and working memory are added in addition to a slightly more extensive evaluation of long-term memory and executive functioning.

All of these suggested approaches to neuropsychological assessment in MS survey the major domains of cognitive functioning typically affected in the disease and differ primarily in their comprehensiveness. Selection of one battery versus another depends on the goals for the evaluation in addition to the setting in which the evaluation takes place.

C. Neuropsychological Measures Helpful in Differential Diagnosis

Differential diagnosis is rarely requested in cases of MS. Rather, characterization of cognitive deficits, their potential impact on social and occupational functioning, and the assessment of change over time are common reasons for neuropsychological referral. Neurologists experienced in MS make very judicious, appropriate use of neuropsychology, requesting evaluations when clinical examination or cognitive screening indicates probable cognitive dysfunction. It is also appropriate to refer patients who appear to be functioning well cognitively in the interest of getting a baseline evaluation for comparison with later disease progression.

Determining the influence of other factors on cognition and perception of cognitive complaints is vital to the assessment of individual with MS. For instance, depression has been shown to be correlated with poor performance on measures of processing speed, working memory, and executive functioning (Arnett et al., 2008; Rabinowitz & Arnett, 2009; Siegert & Abernethy, 2005). Deciphering the contribution of disease processes and depression to the deficits

seen in these domains is important because the latter etiology can result in reversible deficits with appropriate treatment of depression. The Beck Depression Inventory (BDI)—Fast Screen and the Mood subscale of the Chicago Multiscale Depression Inventory have been shown to be valid screening tools for depression in MS (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Nyenhuis et al., 1995; Strober & Arnett, 2009).

IV. PSYCHIATRIC COMORBIDITY IN MULTIPLE SCLEROSIS

Although anxiety and depression symptoms are common among MS patients, careful interview is needed to clarify whether the symptoms reflect a mood disturbance or a somatic manifestation of MS. Raising the screening cutoff on the BDI has also been suggested to account for inflation of scores that can occur because of neurovegetative symptoms of depression that overlap with MS symptoms. MS patients have an approximately 50% lifetime risk for depression (Arnett et al., 2008; Chwastiak et al., 2002; Sadovnick et al., 1996). This lifetime risk is much higher than in the general population, where lifetime prevalence rates are at about 8%, but also compared with many other neurological disorders and chronic illnesses. One study has reported a suicide rate 7.5 times higher in MS than the general population, but this elevated figure requires replication.

Depression has been shown to be treatable through brief and even telephone-based cognitive–behavioral therapy (Mohr et al., 2000, 2005) as well as group therapy. Also, cognitive–behavioral stress management training has been shown to reduce emotional distress in MS (Fischer et al., 1994). Nonetheless, depression has historically been undertreated in MS despite the fact that it is unlikely to remit spontaneously. Successful treatment of depression is associated with greater adherence to immunotherapy.

Unfortunately, even the most promising interventions for depression are effective in only about 50% of MS patients (Ehde et al., 2008; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). Depression in MS negatively affects quality of life, adaptive functioning and well-being (Vargas & Arnett, 2010), interferes with medication adherence (Bruce, Hancock, Arnett, & Lynch, 2010), and may increase mortality (Feinstein, O'Conner, & Feinstein, 2002). There is a need for developing models with greater explanatory power that could result in the development of better treatments to reduce depression in MS.

There is no consensus regarding the nature of depression in MS. Some investigators have suggested that neurovegetative symptoms

of depression are not valid indicators of depression because of their overlap with MS symptoms (e.g., sleep disturbance, fatigue, sexual dysfunction; Rabinowitz, Fisher, & Arnett, 2011), whereas others have provided evidence to the contrary (Moran & Mohr, 2005). This debate suggests that caution is warranted in interpreting neurovegetative symptoms of depression as depression symptoms in any individual MS patient. Still, as noted earlier, both the BDI—Fast Screen and the Mood subscale of the Chicago Multiscale Depression Inventory have been shown to be valid screening tools for depression in MS (Benedict et al., 2003; Nyenhuis et al., 1995; Strober & Arnett, 2009).

The cause of depression in MS is unknown, but high levels of perceived stress, low levels of social support, and disease exacerbation–pharmacological treatment have been shown to be associated with increased depression and emotional distress. A genetic interpretation of the relationship between depression and MS has been ruled out because of studies showing that unipolar major depression is not more common in first-degree relatives of depressed MS patients compared with first-degree relatives of nondepressed MS patients. Nonetheless, a biological contribution to depression in MS has been suggested by emerging evidence of an association between depression and both neuroanatomical and functional neuroimaging parameters.

Neuropathology has consistently been found to be associated with depression in MS (Feinstein, 2004). The combination of lesion load, brain atrophy, and white matter fiber tract integrity have been shown to account for up to 43% of depression variance in MS (Bakshi et al., 2000; Feinstein et al., 2010). Although temporal and frontal brain regions are often implicated in these studies (Arnett et al., 2008; Feinstein et al., 2010), the mechanism by which structural brain damage leads to depression in MS is unknown. It may be that such structural changes lead to characteristic functional brain changes that in turn predict depression in MS.

Functional brain variables in relation to emotional functioning in MS have been examined in only a limited way in one study. Although not examining depression, per se, Passamonti et al. (2009) explored emotional processing in a small group ($n = 12$) of relapsing-remitting MS participants. They found that compared with controls, MS participants showed a lack of functional connectivity between the amygdala and the prefrontal cortex during an emotional processing task involving the matching of affective faces. Although the MS participants in the study were not clinically depressed, they reported significantly higher scores on depression measures than controls. These authors suggested that reduced functional connectivity could reflect a disruption in an important affective processing system in the brain of MS patients early in the disease process that might ultimately put them at risk for emotional difficulties such as depression.

Depression is associated with reduced quality of life and the employment of generally less effective (emotion-focused or avoidant-focused) coping strategies in MS (Arnett, Higginson, Voss, & Randolph, 2002; Rabinowitz & Arnett, 2009). Patients with a history of depression, either before or after MS onset, appear to be at increased risk for future depressive and manic states. Although it was initially assumed that there was no relationship between depression and greater cognitive impairment in MS, more recent work has suggested an association. In particular, some studies have found that complex attention and information processing speed, and perhaps executive deficits, are associated with depression in MS (Arnett et al., 2008). These associations are most likely to be seen when depression symptoms uncontaminated by MS symptomatology (e.g., neurovegetative symptoms) are excluded from the measurement of depression and the focus is on mood and negative evaluative depression symptoms (Arnett, Higginson, & Randolph, 2001). Considering coping as a moderator has also resulted in clearer cut findings, with cognitive deficits most likely to be predictive of depression in the context of patients who favor avoidant coping or minimally use active coping (Arnett et al., 2002; Rabinowitz & Arnett, 2009). Surprisingly, the severity of neurologic disability has typically not been found to be associated with depression in MS.

Anxiety is possibly more common than depression in MS, but has been infrequently studied. Data are limited, but the point prevalence of clinically significant anxiety is thought to be about 25%; the lifetime prevalence is unknown. The cause of anxiety in MS is unknown, but it is prominent in the early stages of the disease when the diagnosis and prognosis are most uncertain. Decline in distress is associated with more definitive diagnostic statements by treatment professionals. There are no published studies treating specific anxiety disorders in MS. Comorbidity of anxiety and depression in MS is more associated with thoughts of self-harm, social dysfunction, and somatic complaints than either alone (Feinstein, O'Connor, Gray, & Feinstein, 1999). The only other emotional disorder occurring with any significant frequency in MS is bipolar disorder. Point prevalence is estimated at 0% to 2% and lifetime prevalence 13% to 16%. There are no published treatment studies of bipolar disorder in MS. Its cause is unknown.

V. CONCLUSION

MS is a complex neurological disorder with a varied symptom presentation depending on the stage of the disease, clinical course type, and comorbidities. Such variation in clinical presentation and associated comorbidities makes neuropsychological assessment challenging in

MS. In this chapter, we have attempted to lay out some of the complexities associated with the diagnosis of MS, in addition to practical suggestions for neuropsychological assessment. A valid neuropsychological assessment of MS patients can be conducted in about 1.5 to 2 hours on the basis of existing consensus batteries and available clinical tools. Clinical neuropsychologists are encouraged to employ batteries that have been shown to be sensitive to cognitive impairment in MS (e.g., BRB, MACFIMS, MS Plus) but involve a reasonably limited amount of time so that factors such as patients' susceptibility to fatigue are less likely to impact neurocognitive performance. Consideration of secondary factors that can impact neuropsychological test performance (e.g., depression, anxiety, fatigue, oral motor problems) is important so that clear test interpretation can be made. Such clarity in interpretation is critical so that neuropsychologists can direct resources toward targeting the source of the neurocognitive problem. Accuracy in neuropsychological test interpretation will certainly result in better clinical care of patients suffering from this debilitating neurological condition.

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Chapter 14

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The Neuropsychology of Oncology

With advances in cancer management and increasing numbers of long-term survivors, cognitive functioning and quality of life are increasingly recognized as important issues that should be integrated into traditional oncologic care. Additionally, cognitive function has proven to be a viable clinical trial endpoint that can and should be assessed as an adjunct to traditional measures of treatment outcome, such as survival time and tumor response. This chapter presents evidence regarding the presence and nature of cancer- and treatment-related cognitive sequelae in adult cancer patients, as well as information regarding the neuropsychological assessment of and interventions for those side effects.

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I. DEFINITION/CLASSIFICATION: EFFECTS OF CANCER AND CANCER TREATMENT ON COGNITION

Across cancer types, grading systems vary based on histological characteristics; although the factors used to determine tumor grade vary with each type of cancer, in general, a lower grade tends to be associated with better prognosis. Other factors, such as the site, size, and number of tumors, as well as the presence or absence of metastases, may also affect prognosis and treatment planning. In addition, although there is heterogeneity among both central nervous system (CNS) and non-CNS cancers, there is an increased recognition of molecular genetic subtypes that may lead to increased "personalization" of treatment approaches and different outcomes within tumor types. To date, the relationship between the genetic alterations of tumor types on cognitive function remains largely unknown.

A. Cancer-Related Cognitive Impairment

The potential impact of cancer therapies on cognitive function must be understood in the context of pretreatment cognitive symptoms. The presence and pattern of cognitive impairment in patients with brain tumors may vary in association with lesion location and lesion momentum, or the rate at which tumors grow, as tumors destroy, crowd, displace, and infiltrate brain tissue. It has been estimated that 60% to 100% of patients with supratentorial primary brain tumors exhibit some degree of cognitive dysfunction; variability in estimates are dependent on the sensitivity of the test used to measure cognitive functioning and the relative "eloquence" of the lesion location. It is also noted that in general, patients with high-grade gliomas often demonstrate greater cognitive impairment compared with those with low-grade gliomas (Wefel, Patwardhan, & Strange, 2010). In patients with brain metastases, up to 90% exhibit at least some cognitive impairment before treatment; the degree of impairment is correlated with total lesion volume, as opposed to number of metastatic lesions (Meyers et al., 2004).

Cancer-related cognitive dysfunction is not limited to CNS cancers; rather, evidence of cognitive impairment secondary to cancer has been documented in numerous non-CNS cancers, most often in the domain of learning and memory. For example, pretreatment impairments have been identified in patients with acute myelogenous leukemia and myelodysplastic syndrome, with impairments noted in learning and memory (41%–44%), cognitive processing speed (28%), aspects of executive dysfunction (29%), and upper

extremity fine motor dexterity (37%; Meyers, Albitar, & Estey, 2005). A similar pattern of impairment in verbal learning, psychomotor speed, and executive function was observed in 39% of patients scheduled to undergo hematopoietic stem cell transplantation (Friedman et al., 2009). In patients with small cell lung cancer, pretreatment impairments were noted in memory (70%–80%), executive functions (38%), and motor coordination (33%; Meyers, Byrne, & Komaki, 1995). In men with newly diagnosed testicular cancer, one study found that approximately 46% demonstrated cognitive impairment after orchiectomy but before adjuvant chemotherapy, with impairments in motor function, verbal learning, and executive function most commonly noted (Wefel, Vidrine, et al., 2011). Pretreatment cognitive impairment has also been demonstrated in at least a subgroup of women with breast cancer, with estimates ranging from 11% to 35% of patients (Hurria et al., 2006; Wefel, Lenzi, et al., 2004), with particularly frequent difficulties (18%–25%) on measures assessing learning and memory (Wefel, Lenzi, et al., 2004).

B. Treatment-Related Cognitive Impairment

In addition to cognitive impairment associated with cancer itself, patients with cancer are also at risk for experiencing cognitive changes secondary to the treatments used against their disease, including surgery, radiation, chemotherapy, biological response modifiers, and hormonal therapy. In addition, supportive therapies used to palliate symptoms that may emerge in conjunction with cancer may have an untoward impact on cognitive functioning. Antiepileptic therapy has been associated with worse cognitive performance in glioma patients, even after controlling for seizure frequency (Klein et al., 2003). Use of corticosteroids also has the potential to disrupt cognitive functioning, particularly memory (Keenan et al., 1996), and may also be associated with mood disturbance. However, the resolution of edema achieved via treatment with corticosteroids may also lead to improvements in cognitive functioning (Klein, Taphoorn, & Heimans, 2001).

1. SURGERY

We are not aware of any data to suggest that the surgical resection of non-CNS cancers carries any greater risk with regard to cognition than other non-CNS surgeries for nononcologic purposes. However, in patients with brain tumors, surgery may result in damage to normal tissue that surrounds the tumor. This can engender relatively focal cognitive impairments or more diffuse impairments secondary to disconnection of subcortical networks. Often, cognitive

and neurological declines observed in the immediate postoperative period are transient, but permanent declines are possible in the event that resection results in injury to functional brain surrounding or interdigitated within the lesion. In patients with newly diagnosed glioblastoma, greater postoperative cognitive impairment has been associated with poorer prognosis; executive functioning and attention were the cognitive domains most closely associated with prognosis (Johnson, Sawyer, Meyers, O'Neill, & Wefel, 2012). Recently it was reported that patients with better preoperative memory and language function are at greater risk for postoperative memory and language decline (Gehring, Sawyer, Etzel, Lang, & Wefel, 2011a, 2011b).

2. CHEMOTHERAPY

The term "chemobrain," which was initially created by patients, has entered the popular vernacular to describe postchemotherapy cognitive difficulty. It must be acknowledged that postchemotherapy changes may be multifactorial. However, there is evidence that chemotherapy alone can directly and/or indirectly produce neurotoxicity that accounts for the neurobiological changes seen in animal models and imaging studies, as well as for the findings of observational human studies. The risk of developing chemotherapy-associated neurotoxicity appears to be increased in association with several factions, including exposure to higher doses (Shah, 2005). Additive or synergistic effects of multiagent chemotherapy can also increase risk, as can the additive or synergistic effects of administration of chemotherapy either concurrent or subsequent to cerebral radiation. In addition, administration of chemotherapy via intra-arterial or intrathecal methods can be associated with increased risk (Keime-Guibert, Napolitano, & Delattre, 1998; Sul & DeAngelis, 2006).

The majority of research regarding chemotherapy-related side effects has been conducted in patients with breast cancer; recent longitudinal studies have revealed evidence of treatment-related cognitive decline of varying degrees of severity, most commonly reflecting a frontal-subcortical profile, including deficits in learning and memory, processing speed, and executive function, with incidence estimates ranging from 19% to 78% across studies (see Wefel & Schagen, 2012, for a complete review). Although many patients will experience relief from side effects over time after treatment cessation (Schagen et al., 2002), others will experience ongoing problems; of particular concern is the finding that a subset of women may exhibit ongoing, progressive cognitive decline after completion of chemotherapy (Wefel, Saleeba, Buzdar, & Meyers, 2010).

Cognitive and emotional dysfunction associated with hematopoietic stem cell transplant (HSCT) has also been reported; this is believed to be secondary to the intense treatment regimen used dur-

ing pretransplant conditioning, which generally involves high-dose chemotherapy and/or radiation (Meyers et al., 1994). Although much of the data in this patient population is limited by small sample size and cross-sectional designs, available findings suggest decline in executive function (Ahles et al., 1996) and memory (Friedman et al., 2009; Meyers et al., 1994) following HSCT.

Clinical trials investigating surgery, radiation, and chemotherapy for patients with CNS cancers have recently begun to include cognitive functioning as an outcome measure. For example, in a large Phase III trial in patients with glioblastoma, up to 30% of clinically and radiographically stable brain tumor patients treated with either standard-dose or dose-dense temozolomide after chemoradiation evidenced cognitive declines. Both baseline cognitive functioning and cognitive decline after concurrent chemoradiation and before adjuvant chemotherapy were prognostic for overall and progression-free survival (Wefel, Armstrong, et al., 2011). A Phase II noncomparative trial investigating bevacizumab as a treatment for recurrent or progressive glioblastoma revealed a positive relationship between radiographic findings of disease stability and stable to improved cognitive functioning (Wefel, Cloughesy, et al., 2011), whereas cognitive function was found to decline at the time of disease progression. However, results of a randomized double blind placebo controlled trial of bevacizumab in newly diagnosed glioblastoma patients reported decreased processing speed and executive function, but not learning and memory, as well as decreased quality of life and increased symptom burden in patients who were progression free and treated with bevacizumab (Wefel et al., 2013). Interestingly, research with patients who are diagnosed with primary CNS lymphoma suggests that although they frequently present with cognitive impairments, they often evidence improvements in executive functioning and verbal memory after undergoing treatment with chemotherapy. This is likely secondary to the excellent response rates that can be achieved in this disease resulting in reduced tumor burden and discontinuation of supportive medications such as steroids and antiepileptic medications (Correa et al., 2009).

3. RADIATION

During radiation treatment to the brain (the acute phase), patients experience transient symptoms of headache, fatigue, and nausea, as well as exacerbation of preexisting neurologic deficits. These signs and symptoms are often related to edema and frequently respond well to treatment with corticosteroids. Subacute toxicity typically develops 1 to 6 months after completion of radiotherapy and has been associated with declines in information processing speed, attention, word and memory retrieval, executive functioning,

and fine motor dexterity. Changes in white matter integrity are commonly associated with these declines. Recovery in white matter may occur, resulting in improvements in cognition over time. Frank dementia is atypical during this period. However, late-delayed toxicity can occur months to years after completion of radiation therapy and can include severe memory loss and/or progressive dementia; unlike acute and subacute effects, late-delayed toxicity tends to be irreversible (Sheline, Wara, & Smith, 1980). Thus, as the most profound effects of radiation may not be evident immediately after treatment, careful monitoring of cognitive function over time remains necessary.

Numerous risk factors for developing radiation-induced cognitive dysfunction and necrosis after radiation have been identified and include age under 5 years or more than 60 years, greater than 2-Gy dose per fraction, higher total dose, hyperfractionated schedules, shorter overall treatment time, the presence of comorbid vascular risk factors, concomitant or subsequent treatment with chemotherapy, and greater total volume of brain irradiated (Crossen, Garwood, Glatstein, & Neuwelt, 1994; Merchant, Conklin, Wu, Lustig, & Xiong, 2009). Gondi, Hermann, Mehta, and Tomé (2012) recently examined the relationship between radiation dose, volume of brain treated, and cognitive function and demonstrated that increased exposure to the bilateral hippocampi was associated with long-term impairment in memory. Specific dose volume histogram parameters were reported; they suggest that future studies using currently available treatment modalities, such as intensity-modulated radiation therapy, that allow for conformal avoidance of the hippocampus should be used to spare as much healthy brain tissue as possible and avoid these untoward effects. In the treatment of patients with brain metastases, there is debate regarding the risks and benefits of whole brain versus focal radiation, with one study showing that for patients with one to three newly diagnosed brain metastases treated, adding whole brain radiation to stereotactic radiosurgery increased the risk of significant declines in learning and memory at 4 months after treatment compared with those treated with stereotactic radiosurgery alone (Chang et al., 2009).

4. 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. These treatments include cytokines, vaccines, monoclonal antibodies, thymic factors, and colony-stimulating factors. BRMs may directly or indirectly augment the patient's immunological defenses, modify tumor cells such that the patient's immunologic response is increased, or bolster the patient's ability to manage toxicities secondary to other cancer treatments (Mihich, 2000). Given the number of mechanisms by

which BRMs act, their impact on cognition is variable. Some BRMs, such as colony-stimulating factors, may have a beneficial effect on quality of life and cognitive functioning secondary to alleviation of treatment-related anemia (Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006). In contrast, the cytokine interferon-alpha (IFN-α) can adversely affect quality of life and cognitive functioning. It is estimated that between 70% and 100% of patients undergoing IFN treatment experience fatigue, with 10% to 40% requiring dose reduction (Malik, Makower, & Wadler, 2001). Psychiatric symptoms, usually increased depression, are also reported in 15% to 50% of patients receiving IFN treatment (Valentine & Meyers, 2005), although the clinical picture may vary to include mania. Cognitive impairment may also arise, though findings have been mixed; for example, although some studies have documented posttreatment impairments on measures of verbal memory, psychomotor speed, and executive functioning, especially when used in combination with chemotherapy (Scheibel, Valentine, O'Brien, & Meyers, 2004), others have found no evidence of cognitive decline following treatment (Bender et al., 2000).

5. HORMONE THERAPY

Treatments affecting estrogen and testosterone are commonly used in the treatment of patients with breast and prostate cancers; both of these hormones have been found to affect cognitive functioning (Maki & Sundermann, 2009; Nelson, Lee, Gamboa, & Roth, 2008). Although results have been somewhat mixed, results to date do raise concern that hormone therapies may have an untoward impact on cognition for some patients. Breast cancer patients who received the selective estrogen receptor modulator tamoxifen (TAM), the aromatase inhibitor (AI) anastrozole, or a combination of those therapies performed more poorly than noncancer controls on measures of memory and processing speed (Ahles et al., 1996). In another study, 1 year of treatment with TAM was associated with declines in memory and executive functioning, whereas no such decline was observed in patients treated with the AI exemestane (Schilder et al., 2010). In patients with prostate cancer, group analyses of mean change have often failed to demonstrate a statistically significant effect when comparing men treated with a luteinizing hormone-releasing hormone (LHRH) agonist such as leuprolide and goserelin to untreated controls. However, analyses using reliable change indices demonstrated cognitive decline in up to 50% of treated men (Green et al., 2002). LHRH agonists have been associated with declines in visuospatial processing, including visual memory, as well as with declines in executive functioning; findings with regard to the effect of LHRH agonists on verbal memory have been mixed (Nelson et al., 2008).

II. FUNCTIONAL NEUROANATOMY

A. Tumor and Surgery

The majority of adult brain tumors are supratentorial and distributed in the frontal, parietal, temporal, and occipital lobes, in descending order of frequency (Berger, Leibel, Bruner, Finlay, & Levin, 2002). Deficits associated with brain tumors can be specific to lesion location; for example, frontal lobe tumors may result in personality changes, executive dysfunction, and expressive aphasia; parietal tumors may cause neglect or alexia; temporal lobe tumors may result in fluent aphasia or memory loss; occipital tumors can cause contralateral homonymous hemianopsia. It is noted, however, that such findings are often superimposed on a more diffuse frontal-subcortical pattern of cognitive deficits; in general, the nature and degree of cognitive impairment due to brain tumors tends to be more variable than that associated with rapid-onset lesions such as strokes (Anderson et al., 1990). This can be attributed to several factors, including the infiltrative nature of many tumors that destroy or displace healthy tissue, mass effect, disconnection, diaschisis, edema, hemorrhage, and seizure.

B. Chemotherapy

It is noted that the pattern of treatment-related cognitive decline in CNS and non-CNS cancers is also often suggestive of frontal-subcortical dysfunction. Neuroimaging and neurophysiologic correlates of treatment-related cognitive dysfunction shed light on this tendency (Scherling & Smith, 2013). Both brain atrophy and white matter pathology have been observed after chemotherapy in patients with breast cancer. Evidence of reduced white matter integrity, believed to reflect axonal degeneration and demyelination, has been demonstrated using diffusion tensor imaging. Reductions in gray matter have also been noted (de Ruiter et al., 2012; Koppelmans et al., 2012). In breast cancer survivors of more than 20 years, these changes in gray matter volume were equivalent to 4 additional years of aging (Koppelmans et al., 2012). Results of functional imaging studies performed to date have been less consistent, but both hypo- and hyperactivation have been noted, particularly in the frontal and prefrontal areas. Hypoactivation in the prefrontal cortex has been observed during memory encoding and executive function tasks in chemotherapy-treated breast cancer patients (Kesler, Bennett, Mahaffery, & Spiegel, 2009). A positron emission tomography study revealed higher activation in the prefrontal cortex during a short-term

memory recall task in chemotherapy-treated breast cancer patients compared with untreated controls (Silverman et al., 2007). A recent prospective, longitudinal study with breast cancer patients tracked alterations in frontal activation during a working memory task, with evidence of hyperactivation at baseline, a decrease 1 month after completion of chemotherapy, and a return of hyperactivation after 1 year. The authors suggested that the observed hyperactivation reflects compensatory recruitment of neural circuitry to support working memory function and that patients may not be able to sustain this recruitment after chemotherapy due to the untoward effect of treatment on brain functioning (McDonald, Conroy, Ahles, West, & Saykin, 2012). Altered resting-state functional brain network topology, characterized by disrupted frontal, striatal, and temporal areas, as well as reduced global clustering, has also been observed in women treated with chemotherapy for breast cancer compared with healthy controls (Bruno, Hadi Hosseini, & Kesler, 2012; Hosseini, Koovakkattu, & Kesler, 2012). One such resting state network, the default mode network (DMN), is known to exhibit reduced connectively with age, and especially with pathological aging. Patterns of disrupted DMN connectivity were able to correctly classify breast cancer patients treated with chemotherapy from breast cancer patients who did not receive chemotherapy as well as healthy controls. Moreover, alterations in DMN connectivity were associated with patient-reported memory disturbance (Kesler, Wefel, et al., 2013). In addition, magnetic resonance spectroscopy has revealed alterations in brain metabolites in breast cancer survivors treated with chemotherapy compared with controls, in a pattern similar to that observed in normal and pathological aging. Specifically, Kesler, Watson, et al. (2013) reported increased choline (Cho) and myo-inositol (mI) along with corresponding decreases in *n*-acetylaspartate (NAA)/Cho and NAA/mI ratios, whereas others have reported decreased NAA/creatine (Cr; Brown et al., 1998; de Ruiter et al., 2012) and decreased Cho/Cr (Brown et al., 1998).

Animal and preclinical cellular neurobiology studies provide additional insight into the mechanisms underlying the cognitive and imaging abnormalities seen in some patients exposed to chemotherapeutic treatments. A thorough review of these data is beyond the scope of this chapter; interested readers are referred to Seigers and Fardell (2011) and Dietrich et al. (2008) for reviews of recent literature regarding the impact of cytotoxic agents on neurobiology and behavior. Reviewed evidence of neurotoxicity includes data regarding increased cell death and decreased cell division in brain areas important to neurogenesis, oxidative stress after treatment, degeneration of white matter, activation of the immune system via cytokine release, and alterations in blood flow.

C. Radiation

Historically, models of radiation-induced injury have focused on either vascular damage resulting in ischemia with secondary white matter necrosis or on the loss of oligodendrocytes required for the formation of myelin. A more contemporary model suggests that radiation-induced CNS damage is a complex process, occurring via acute cell death as well as via specific cytokines and secondary processes involving chronic reactive oxidative stress/inflammation; these changes are associated with decreased neurogenesis and neuronal function, vascular injury, and gliosis (Tofilon & Fike, 2000). Animal models have demonstrated that radiation to the hippocampus results in dose-dependent reductions in neurogenesis (Monje, Mizumatsu, Fike, & Palmer, 2002). In addition, sustained activation of microglia following radiation is believed to contribute to chronic neuroinflammation (Zhao, Diz, & Robbins, 2007).

D. Hormone Therapy

Hormone therapies appear to act on the estrogen and androgen receptors in the hippocampus and cerebral cortex. TAM may have estrogen antagonistic effects in at least some brain regions; imaging studies have revealed that women being treated with TAM had smaller hippocampal volumes and lower frontal lobe glucose metabolism compared with controls and especially compared with women taking estrogen (Eberling, Wu, Tong-Turnbeaugh, & Jagust, 2004). In addition to its involvement with the estrogen system, TAM appears to affect several neurotransmitter (e.g., serotonin, dopamine) and cytokine (e.g., interleukin [IL]-1β, IL-6, IFN-γ, and tumor necrosis factor [TNF]) systems that are implicated in cognitive functioning. Repeated administration of TAM impaired acquisition and retention of learned responses in mice (Walker, Foley, Clark-Vetri, & Raffa, 2011). Androgen deprivation has also been shown to impair performance on hippocampally mediated memory measures in rodents (Kritzer, McLaughlin, Smirlis, & Robinson, 2001), suggesting a potential mechanism of action to explain memory loss in men treated with hormone therapy for prostate cancer.

E. Biological Response Modifiers

Although it remains unclear exactly how BRMs such as IFN exert an effect on cognitive functioning, several possible mechanisms have been identified. IFN may alter the endocrine system by stimulating the release of cortisol (Menzies et al., 1996). This has been associated with disruptions in the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–thyroid (HPT) axes and may therefore con-

tribute to mood and cognitive disturbances (Valentine, Meyers, Kling, Richelson, & Hauser, 1998). An additional potential mechanism of action involves dysregulation of neurotransmitters; IFN interacts directly with the opioid receptor system (Blalock & Stanton, 1980) and may interact indirectly with other neurotransmitter systems (Schefer, Schwiger, Pich, Lieb, & Heinz, 2003). IFN may also activate secondary cytokine pathways, such as IL-1, IL-2, IL-6, and tumor necrosis factor (TNF; Taylor & Grossberg, 1998), which are known to be involved in the regulation of the HPA and HPT (Zaloga, Bhatt, & Marik, 2001).

III. NEUROPSYCHOLOGICAL EVALUATION

As noted above, longitudinal studies that have used pretreatment baseline evaluations have clarified the nature and incidence of treatment-related cognitive dysfunction. When available, baseline data ensures that posttreatment cognitive impairments are not erroneously attributed to a specific treatment, when they may in fact by secondary to the cancer itself. Alternatively, baseline data may allow for identification of relatively subtle treatment-related neurotoxicities and can prevent misclassification of a patient who exhibits a meaningful posttreatment decline but continues to perform in the nonimpaired range relative to normative expectations, as elucidated in a prospective, longitudinal study by Wefel, Lenzi, et al. (2004).

Although baseline cognitive evaluation is critical for research, the reality for the majority of clinicians is that such information is rarely available as a point of comparison. In clinical practice, neuropsychologists are generally presented with referral questions in the absence of baseline data and in the aftermath of cancer and cancer treatment. Thus, as with any evaluation, it falls to the assessing neuropsychologist to estimate a patient's premorbid level of functioning using information regarding educational and occupational attainment and any developmentally based weaknesses, as well from neuropsychological tests that are robust to neurologic insult.

During the clinical interview and/or record review, efforts should be made to gather information regarding the onset and course of cognitive symptoms and how that timeline relates to the patient's cancer diagnosis and treatment. Information regarding medical comorbidities and the type of cancer treatment received should also be obtained; this may be of particular importance in interpreting neuropsychological test results should the obtained cognitive profile and clinical correlates, such as imaging studies, 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; both might be accounted for either by cerebrovascular disease or by leukoencepholopathy secondary to treatment with specific chemotherapeutic agents. Given this etiologically

nonspecific picture, knowledge regarding the presence or absence of risk factors for cerebrovascular disease and the type of cancer therapy used may clarify the potential etiologies underlying the observed cognitive profile.

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; when possible, the use of alternate forms is recommended. This may be particularly important if patients are being tracked throughout the course of their treatment and are therefore undergoing more frequent assessment. In brain tumor patients, decline on formal cognitive assessment has been shown to occur in advance of radiographic progression (Meyers & Hess, 2003) and be prognostic for overall and progression-free survival (Wefel, Armstrong, et al., 2011), demonstrating the beneficial additive information such evaluation can provide in this patient population. In patients with brain tumors and in patients with non-CNS cancers, there is often a heavy emphasis on tests assessing frontal-subcortical network functioning. 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 (Wefel, Kayl, & Meyers, 2004). Patients may present with complaints of difficulty with short-term memory, such as forgetting the details of recent conversations and events or misplacing possessions and may also describe problems with concentration, organization, and multitasking.

Selection of additional appropriate neuropsychological measures may vary in association with a patient's specific cancer diagnosis; for example, tests of visuospatial functioning may be critical in 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; as noted above, focal deficits related to the site of the tumor may be superimposed on more a more diffuse frontal-subcortical pattern. It is noted that in non-CNS cancers, it is rare to observe distinct syndromes suggestive of cortical dysfunction, such as aphasia, agnosia, or apraxia.

It is important to regard the physical well-being and stamina of patients being assessed, and consideration of overall prognosis is also warranted. For example, if one hopes to follow patients with short estimated survival time throughout their treatment, an extensive battery spanning numerous hours is neither warranted nor recommended. Rather, careful selection of tests tapping critical domains is more important; as reevaluation may occur within a relatively shorter time interval than is typical with other patient populations, use of measures with alternate forms, when possible, is ideal to reduce practice effects.

Fatigue and affective distress should also be assessed in a thorough neuropsychological examination of the cancer patient, as both have the potential to 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 (Schagen et al., 2008). Thus, reliance on self-report alone is insufficient to determine whether perceived difficulties are secondary to cancer- and treatment-related cognitive dysfunction and/or affective distress and fatigue.

Clearly, test selection will vary according to a variety of factors, and no standard test battery will be appropriate for every cancer patient. Efforts have been made, however, to identify a very brief (e.g., 20-minute) core set of measures that are appropriate for use with both CNS and non-CNS cancer patients; these measures meet the criteria described above (e.g., adequate psychometric properties, alternate forms where possible) and have been used in clinical trials (van den Bent et al., 2011; Wefel, Vardy, Ahles, & Schagen, 2011). Clinicians are encouraged to supplement with additional measures, as described above, on a case-by-case basis.

The degree of neuropsychological involvement with any given patient over time will vary depending on the patient's diagnosis, treatment, functional status, and goals. It is ideal to obtain a pretreatment baseline evaluation when possible. Evaluation shortly after postoperative recovery provides opportunity to offer recommendations for rehabilitation planning and/or supervision needs. Timing surveillance evaluations with awareness of when disease progression is most likely, critical points in the patient's treatment plan, common times when treatment toxicities manifest, and in association with individual goals and activities (e.g., return to work evaluation) ensures neuropsychological care is available at times of greatest need for the patient. Patients with non-CNS cancers may require less intensive surveillance, but again, attention to changes in disease and functional status will help guide follow-up planning.

IV. TREATMENT, INTEGRATION, COMORBIDITY, AND OTHER ISSUES

A. Prevention

Select factors that place patients at increased risk for treatment-related cognitive dysfunction, such as the dose, type of agent, and schedule and route of administration, may be able to be adjusted to

reduce neurotoxicity while still maintaining adequate disease control (Keime-Guibert et al., 1998). Inclusion of cognitive endpoints into clinical trials will help identify which treatments most effectively achieve disease control with the least neurotoxic side effects. For brain tumor patients undergoing surgical resection, preoperative functional imaging and intraoperative language mapping can provide important information regarding distribution of eloquent brain areas, allowing maximal resection with minimal neurological consequences; multistage surgeries may also allow for preservation of brain function (Duffau, 2012).

B. Pharmacotherapy

Other neurotoxic side effects can be managed with pharmacologic interventions; for example, psychostimulant medications have been shown to be effective in addressing fatigue and cognitive dysfunction in cancer patients. Methylphenidate has been demonstrated to reduce fatigue in non-CNS cancer patients (Bruera et al., 2006) and has been associated with improvements in frontal-subcortically mediated functions such as memory, psychomotor speed, visual-motor function, executive function, and fine motor speed in patients with primary brain tumors (Meyers, Weitzner, Valentine, & Levin, 1998). A more recent study with brain tumor patients revealed improvements in divided attention for patients treated with psychostimulants (methylphenidate or modafinil); gains were especially notable for those patients with greater impairment at baseline. In addition, benefits were noted on self-report of fatigue, mood, and quality of life (Gehring et al., 2012). Donepezil has also been used to combat difficulties with cancer-related fatigue, attention, and memory (Shaw et al., 2006). In patients with nasopharyngeal carcinoma who had imaging evidence of temporal lobe necrosis, those who were treated with high-dose vitamin E demonstrated greater improvement on measures of learning, memory, and cognitive flexibility than nontreated controls (Chan, Cheung, Law, & Chan, 2004). A recent study demonstrated delayed time to cognitive decline in patients with brain metastases undergoing whole brain radiation who received memantine compared with placebo (Wefel et al., 2012).

Additional potential pharmacologic interventions are being identified in animal studies. For example, it has been found that supplementation with an antioxidant, *N*-acetyl cysteine, can prevent the severe memory impairment observed in rats treated with chemotherapy (Konat, Kraszpulski, James, Zhang, & Abraham, 2008). Similarly, administration of the peroxisomal proliferator-activated receptor γ agonist pioglitazone prevented memory disturbance associ-

ated with whole brain irradiation in rats (Zhao, Payne, et al., 2007). Targeting specific neurotransmitters may also be of benefit; coadministration of the chemotherapy 5-fluorouracil with the selective serotonin reuptake inhibitor fluoxetine was associated with improvements in chemotherapy-related impairments in object location recognition and eliminated the reduction of proliferating cells within the dentate gyrus (ElBeltagy et al., 2010). Radiation-induced memory loss was also attenuated via transplantation of human embryonic stem cells into the rat hippocampus (Acharya et al., 2009).

C. Behavioral Intervention

In addition to adjusting primary treatments and using pharmacological interventions to combat cognitive inefficiencies and fatigue, goal-focused compensatory interventions and behavioral strategies can be used to minimize the effect of neurobehavioral disorders and maximize daily functioning in patients with cancer. The evidence-based techniques derived from traditional rehabilitation disciplines treating survivors of traumatic brain injury or stroke can also be applied to patients with cancer-related cognitive dysfunction. These multidisciplinary interventions, delivered by a team of psychologists, speech/language pathologists, occupational therapists, and vocational specialists, have been associated with improved community independence and employment outcomes in brain tumor patients; these gains were achieved 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 (Sherer, Meyers, & Bergloff, 1997). Attention retraining and instruction in the use of compensatory strategies have also shown promise in addressing both cognitive complaints and mental fatigue (Gehring et al., 2009). Compensatory tools often include external memory aids such as memory notebooks, user-programmable paging systems, and medication reminder systems to facilitate recall of important information.

Physical exercise has been associated with improvements in patient self-reported quality of life, including cognition, in cancer patients (Korstjens, Mesters, van der Peet, Gijsen, & van den Borne, 2006). Animal studies provide support for exercise as a protective factor against cancer treatment-related side effects; daily running after whole brain radiation prevented declines in spatial memory in mice (Wong-Goodrich et al., 2010). In human cancer patients, one small study involving patients with melanoma revealed a correlation between improvements in the 12-minute walk test and improvements in performance on the Trail Making Test (Schwartz, Thompson, & Masood, 2002). Larger scale studies are currently underway to investigate the potential benefit of exercise on cognitive function.

D. Psychological Intervention

It has been recommended that providers screen for symptoms of depression at the time of cancer diagnosis and any time a new treatment is initiated, as well at the time of disease progression (Dy et al., 2008). Despite a desire to discuss their psychosocial needs, cancer patient may be reluctant to initiate discussion regarding their mood state (Vodermaier, Linden, & Siu, 2009). Symptoms of depression may not be overtly obvious to physicians; in a study investigating the incidence of depression in patients undergoing surgery for high-grade glioma, physicians reported depression in 15% of patients in the early postoperative period, whereas 93% of patients self-reported symptoms consistent with depression in that same time period (Litofsky et al., 2004). These data highlight the need for providers to initiate discussion regarding these symptoms in order to recognize affective distress and begin intervention, as appropriate.

V. CONCLUSION

Cancer is becoming a chronic illness with an increasing number of long-term survivors and therefore requires ongoing symptom assessment and intervention. Studies to date have revealed that cognitive decline is most commonly observed in the domains of learning and memory, processing speed, and executive functioning. The potential cognitive side effects of cancer treatments must be weighed against the overall health benefit they provide, as these therapies remain a critical component in the management and eradication of many cancers. Continued research into the mechanisms of treatment-related cognitive dysfunction may afford opportunities for the development of neuroprotective therapies, effective adjuvant supportive pharmacotherapies, or the personalization of primary treatments, and understanding of the cognitive functioning of cancer patients may inform prognosis. Advances in behavioral interventions will help minimize the impact of cancer and cancer therapy on cognitive function, mood, quality of life, and functional abilities.

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Chapter 15

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Neurotoxicology

This chapter addresses the clinical evaluation of the neuropsychological effects of exposure to neurotoxic substances in adults. The focus here is on environmental and occupational exposures to industrial toxicants. Because the literature on these substances is vast and the structural and functional effects of exposure to different chemicals are often quite distinct, we pay close attention to four kinds of exposures: carbon monoxide, metals (lead, mercury), pesticides, and organic solvents. Organic and inorganic mercury effects are summarized separately.

It is quite important to note that we will mostly talk about exposures in adulthood. The central nervous system (CNS) effects of the toxicants under consideration are often different in childhood, when diffuse rather than focal structural effects often occur. We briefly consider childhood exposures with regard to differential diagnoses and comorbidities later in the chapter. However, the reader should note at the outset that if an adult is referred for evaluation of effects of an exposure occurring in childhood, the

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neuropsychological consequences will be distinct from those generally described in this chapter (White, Diamond, Proctor, Morey, & Hu, 1993; White & Janulewicz, 2009).

I. DEFINITION/CLASSIFICATION

What is a *toxicant*, and how are neurotoxicants identified? Although often referred to in the literature and popular press as *toxins*, the industrial chemicals that we consider here are more accurately referred to as toxicants: that is, they are exogenous substances that are not biologically produced. Both toxins and toxicants can be poisonous or cause intoxication.

Neurotoxicants are substances that are poisonous to the nervous system. The substances or exposures that are the topic of this chapter have been intensively studied, and there is convergent evidence using multiple research approaches that they are neurotoxic. Some chemicals, such as many pesticides and nerve gas agents, were designed to act by attacking the nervous system (to kill pests or enemy combatants). However, there are hundreds of thousands of naturally occurring and manmade chemicals that might potentially be neurotoxic. How do we know which ones actually are? The potential for neurotoxicity of individual chemicals is often identified in the laboratory through animal models or tissue systems. In humans, a few studies have been conducted in which subjects are exposed to chemicals at various dosages in experimental exposure chambers, and there is a large epidemiological literature that links exposures to various chemicals to CNS outcomes. When reviewing research that uses any of these methodologies, it is important to consider the animal system, the form of the chemical (e.g., organic vs. inorganic mercury), the dosage and route of exposure, and whether the exposure was chronic or acute. We consider each of these sources of scientific evidence on neurotoxicity and their value to the clinician when assessing a patient who has experienced an exposure that may or may not be neurotoxic.

In vivo studies using models in which animals are exposed to chemicals are commonly encountered in the literature, as are in vitro laboratory experiments that assess the effects of chemical exposures on neural tissue cultures. These kinds of research provide evidence that a chemical can be neurotoxic at least in some animal systems, at the doses and under the conditions imposed in the laboratory. They raise the likelihood that the chemical(s) investigated will be neurotoxic in humans as well. The important questions of dose and route of exposure (dermal, respiratory, dietary, nervous system injection) must be considered when reviewing these kinds of research. An extremely high-dose exposure can be toxic to an animal but irrelevant

to most human situations, whereas effects of acute exposure in an animal model can underestimate those that would be seen in a human with chronic, long-term, low-dose exposure. Human laboratory studies using exposure chambers must be considered with caution because the exposures utilized are often both acute and low-dose (otherwise they would not pass institutional review board approval, at least today).

Case reports of patients with specific kinds of exposures and negative CNS outcomes abound in the literature and are an important source of information on the potential neurotoxicity of specific chemicals. Such reports often then lead to animal or epidemiological studies to explore the issue scientifically in a more controlled setting. They are also the source of information on the key clinical manifestations of exposure. Absent such literature, we would not know many clinical features of intoxication. Examples include white matter and globus pallidus lesions as magnetic resonance imaging (MRI) manifestations (Devine, Kirkley, Palumbo, & White, 2002) and delayed onset of symptoms, including loss of consciousness, following carbon monoxide (CO) exposure or the extreme neurotoxicity of certain forms of organic mercury.

Epidemiological studies linking exposures to nervous system outcomes can be an important source of evidence and are often easier for clinicians to understand than animal models. Again, it is important to consider dosages, routes, and acute versus chronic exposure scenarios. (For example, early in her career one of the authors [RFW] evaluated a group of individuals with chronic low-dose environmental exposure over decades to trichloroethylene, a degreasing solvent. She was extremely surprised to find evidence on cognitive assessments of neurotoxicity at the very low dosages reported in the patients, finally realizing that she had been relying on data from relatively short-term occupationally exposed groups with higher exposures as her benchmark for dosages at which effects would appear.) Another important consideration when referencing epidemiological research is how the exposure was evaluated. Quantitative measures such as biomarkers (levels of a chemical or its metabolites in blood, urine, hair, fat, teeth) and environmental assessments (measures of contaminants in air, water) are generally strong indicators of exposure. Was a dose–effect relationship between exposure dosage and outcome identified (i.e., higher exposure is associated with worse outcomes)? Dose–effect relationships are the gold standard for identifying exposure effects. They provide stronger evidence to conclude that a substance is neurotoxic than do methods such as comparing exposed individuals versus unexposed controls. It is also critical to think about any inherent biases or confounding in the research. If a control group is different in some critical way from the exposed

group, confounding can explain the entire findings. For example, if the outcome measure is score on the vocabulary subtest of an omnibus intelligence test, it is critical to know whether the controls showed other evidence of higher premorbid IQ (e.g., better Wide Range Achievement Test [WRAT] reading scores) or greater education and whether any attempt was made to control for these differences in the data analysis. On the other hand, if the control group had lower WRAT scores and less education, a bias toward negative outcomes could occur. Biases can be also be introduced by age, methods of subject selection, and other subject characteristics or study design.

The epidemiological literature can be highly informative to the clinician because outcomes used in research may be similar to those used in the clinic, providing clues on which cognitive domains or which test outcomes may be especially informative with regard to adverse effects of exposure. Certainly, this makes looking at this literature worthwhile. One important factor that the clinician should bear in mind is that epidemiological methods rely on different definitions of significance when evaluating outcomes. Clinical evaluations require that the patient perform 1 to 2 standard deviations below expectation on a test to be "clinically significant." However, in an epidemiological study, a statistically significant relationship between exposure dosage and outcome is important, and such dose–effect relationships can be seen anywhere on the normal curve of scores, including within the normal range. Thus, epidemiological methods can detect "subclinical" manifestations of CNS dysfunction in exposed populations. This indicates neurotoxicity and often identifies functional changes that subjects report noticing, but it would not meet the standard of clinical significance. As an example from the lead literature, meta-analyses of research on childhood lead exposure show that lead levels in the 3-to-10 μg/dl range are associated with a 3-point decrement in IQ scores (Bellinger & Bellinger, 2006; Lanphear, Dietrich, Auinger, & Cox, 2000), meaning that a population of children with exposures in this range would have a downward shift of average IQ to 97. However, a child evaluated with a history of lead levels in the 3-to-10 range who has a Wechsler Intelligence Scale for Children IQ of 97 would not be considered to have clinical evidence of lead neurotoxicity, unless estimated potential in the absence of exposure was quite a bit higher than 100. For the clinician evaluating patients, the issue of subtle, subclinical dysfunction following exposures can be a challenging one, and the role of such dysfunction in neuropsychological diagnostic and treatment assessments is considered in Section III of this chapter.

Toxicants belonging to metallic, gas, pesticide, and solvent groups are listed in Table 15.1. Sources of environmental and

Table 15.1. Toxicant Types

Gases	Metals	Organic solvents	Pesticides and organophosphates
Carbon monoxide	Alkytins	Acetone	Aldrin
Ethylene oxide	Aluminum	Carbon disulfate	Carbamates
Nitrous oxide	Arsenic	Ethyl benzene	Chlorinated hydrocarbons
Methyl chloride	Lead	methanol	Lindane
	Manganese	Methyl chloroform	Methyl bromide
	Mercury	Methyl *n*-butyl ketone	Organophosphates
	Thallium	Methyl ethyl ketone	Pyrethroids
		Methylene chloride	Sarin
		n-Hexane	
		Perchloroethylene	
		Solvent mixtures	
		Styrene	
		Toluene	
		Trichloroethylene	
		Xylene	

occupational exposure to CO, organic mercury (methylmercury [MeHg]), inorganic mercury (Hg), lead (Pb), pesticides, and solvents are listed in Table 15.2.

In general, the diagnosis associated with a toxicant exposure is identified using the name of the toxicant in question. Brain damage associated with lead intoxication (sometimes called *plumbism*) is referred to as *lead encephalopathy*, that associated with solvents is *solvent encephalopathy*, and so on. Baker and White (1985) developed a diagnostic system for solvent encephalopathy that incorporated the notion of acute short-term and chronic exposures with the severity of signs/symptoms and clinical course. Diagnoses associated with acute exposure to solvents were referred to as *acute organic mental disorders* and included acute intoxication and acute encephalopathy. Those associated with chronic exposures (with insidious onset of symptoms) were referred to as *chronic organic mental disorders* and included organic affective syndrome, mild encephalopathy, and severe encephalopathy (White & Proctor, 1997). This system has

Table 15.2. Occupational and Environmental Exposures

Neurotoxicant	Occupational exposure	Environmental exposure
Carbon monoxide (CO)	Blast furnaces at iron foundries, firefighters, propane-fueled engines, automotive repair workers, parking garage attendants, methylene chloride paint remover	Incomplete combustion of wood, tobacco and petroleum, charcoal briquettes, fire victims, improperly installed stoves, exhaust fumes
Lead (Pb)	Insecticides, welding, battery manufacturing, foundries, miners, lead-based paint, construction, autobody work	Paint, water, soil, glazed ceramics, firearms, imported candy
Methylmercury (organic mercury) (MeHg)	Battery factories, electrical equipment, photography	Fish consumption
Inorganic or elemental mercury (Hg)	Manufacture of scientific instruments, dental personnel, gold mining	Thermometers, bulbs, batteries, cosmetics, fuel combustion, autobody refinishing, dental amalgams
Pesticides (organophosphates, organochlorides, carbamates, DDT)	Agricultural industry, manufacturing and application	Home and lawn care pesticides, nonorganic fruits and vegetables
Solvents (acetone, carbon disulfide, methylene chloride, *n*-hexane, perchloroethylene, toluene, TCE)	Dry cleaning industry, textiles, cleaning agents, glues, paints, gasoline, salon workers	Household cleaning products, cosmetics, paints

Note. TCE = trichloroethylene.

been adapted by White (2011; White, Feldman, & Proctor, 1992) to include organic affective and encephalopathic outcomes associated with toxicants in general (see Exhibit 15.1).

In addition, other neurological syndromes have been identified in connection with exposure. These include parkinsonism associated with exposure to carbon disulfide (Peters, Levine, Matthews, & Chapman, 1988), mixed solvents (Feldman, 1999), and pesticides (Research Advisory Committee on Gulf War Veterans' Illnesses [RAC], 2008), and leukoaraiosis associated with exposure to Hg and toluene (Filley, 2012). In addition, several neurological disorders have been linked to chemical exposures in the epidemiological literature, including brain tumors (RAC, 2008), multiple sclerosis (White, Feldman, Moss, & Proctor, 1993), and amyotrophic lateral sclerosis (Beal, 1992; Garruto, Swyt, Fiori, Yanagihara, & Gajdusek, 1985). Filley (2012) hypothesized that exposure-related changes in blood pressure and heart rate variability increase the likelihood of development of cerebrovascular and cardiovascular diseases.

II. FUNCTIONAL NEUROANATOMY OF NEUROTOXICANT EXPOSURE

Adult exposures to neurotoxicants can result in highly focal structural and cellular brain damage and/or diffuse effects, depending on the toxicant and dose. Brain structures that have been identified as vulnerable to CO, Pb, MeHg, Hg, solvents, and pesticides are summarized in Table 15.3.

In the authors' clinical experience, MRI evidence of structural damage is seen in the white matter and globus pallidus of patients with both acute and chronic CO exposure. Interestingly, the globus pallidus lesions are sometimes unilateral. White matter lesions on MRI are associated with exposure to Hg (White, Feldman, et al., 1993), to solvents (Filley, 2012), to lead (Weisskopf et al., 2004), and to total white matter volume in sarin-exposed Gulf War veterans (sarin is a nerve gas agent in the organophosphate class; Chou, Abadjian, Hlavin, Meyerhoff, & Weiner, 2011; Heaton et al., 2007). Neuropsychological findings of poor memory retention that are highly suggestive of hippocampal involvement are often seen in patients and exposed populations with exposures to CO, Pb, and solvents but are not commonly seen in inorganic Hg exposure.

Knowledge about the neuropathological underpinnings of the neurotoxic effects of exposure to many chemicals is rudimentary. According to the animal and human clinical literature, some candidate mechanisms include cell death, transneuronal degeneration, demyelination, dying-back syndromes in the peripheral nervous

Exhibit 15.1. Diagnostic System: Toxicant-Induced Encephalopathy

I. Acute organic mental disorders
  A. Acute intoxication
    1. Duration: minutes to hours
    2. Residua: none
    3. Symptoms: CNS depression, psychomotor or attentional deficits
  B. Acute toxicant-induced encephalopathy
    1. Symptoms: confusion, coma, seizures
    2. Pathophysiology: cerebral edema, CNS capillary damage, hypoxia
    3. Residua: permanent cognitive deficit my occur

II. Chronic organic mental disorders
  A. Organic affective syndrome
    1. Symptoms: mood disturbance (depression, irritability, fatigue anxiety)
    2. Duration: days to weeks
    3. Residua: none
  B. Mild chronic toxicant-induced encephalopathy
    1. Symptoms: fatigue, mood disturbance, cognitive complaints
    2. Course: onset may be insidious, duration: weeks
    3. Cognitive deficits: may include attentional impairment, motor slowing or incoordination, visuospatial deficits, short-term memory loss
    4. Residua: improvement may occur in absence of exposure but permanent mild cognitive deficits can persist
  C. Severe chronic toxicant-induced encephalopathy
    1. Symptoms: cognitive and affective change sufficient to interfere with daily living
    2. Cognitive deficits: same as in mild chronic toxic encephalopathy but more severe
    3. Neurologic deficits: abnormalities seen on some neurophysiologic or neuro-radiologic measures (e.g., CT, EMG, MRI, EEG)
    4. Course: onset may be insidious, irreversible
    5. Residua: permanent cognitive dysfunction

Note. CNS = central nervous system; CT = computed tomography; EMG = electromyography; MRI = magnetic resonance imaging; EEG = electroencephalography.

Table 15.3. Toxicants and Affected Brain Areas

Neurotoxicant	Brain areas and cell types affected
Carbon monoxide (CO)	Hippocampus, cerebellum, globus pallidus, putamen, basal ganglia, internal capsule, centrum semiovale, patchy white matter lesions in cortex, corpus callosum, diffuse demyelination in higher cortical areas
Lead (Pb)	Spinal cord, medulla, pons, cerebellum, basal ganglia, hippocampus, insula, demyelination, flattened gyri, narrowed sulci, collapsed ventricles
Methylmercury (MeHg) (organic mercury)	Purkinjie cell loss in cerebellum, cerebral cortex (calcarine/visual, pre- and postcentral areas), deep sulci of visual cortex, spongiform degeneration, hippocampus, gliosis
Inorganic mercury (Hg)	Mild central and cortical atrophy, and lesions in the precentral gyri, subcortical white matter, and white matter of the gyri
Pesticides	Vestibular nuclei, trigeminal nerve, brainstem, muscle fiber necrosis, demyelination, axonal degeneration, changes to corticospinal tracts at lumbar levels and fasciculus gracilis
Solvents	Demyelination; changes to axonal diameters, gliosis, brainstem, superior olivary nuclei, Purkinjie cells in cerebellum, brainstem, globus pallidus, putamen, caudate nucleus, hippocampus, cortical and cerebellar atrophy, basal ganglia, corpus callosum, substantia nigra, centrum semiovale, ventricular changes, thalamus

Note. All references for this table are on the suggested readings list at http://pubs.apa.org/books/supp/parsons

system, hypoxia, and neurotransmitter disruptions (Feldman, 1999). Exposure to substances that are not toxic to the brain itself can result in brain damage due to downstream physiological changes. For example, some toxicants can cause respiratory arrest, resulting in primary hypoxia, at which time the associated brain damage would be considered to be hypoxic in origin. Others affect specific organ systems such as the kidney or immune system, resulting in nervous system damage (Feldman, 1999; White et al., 1992).

III. NEUROPSYCHOLOGICAL EVALUATION

Virtually all referrals for neuropsychological evaluation of persons with known or suspected neurotoxicant exposures involve identification of exposure-related dysfunction and differential diagnosis of etiology of any cognitive deficits or affective complaints identified in the assessment. The approach described in this chapter has evolved over 30+ years' experience evaluating patients with occupational and environmental exposures, including those from military populations. In her initial years working with patients with these kinds of exposures, the senior author (RFW) saw many patients who had experienced quite high levels of exposure with frank symptoms and obvious exposure-related neuropsychological deficits. Some of these patients recovered all or much function, whereas others were left with permanent amnestic syndromes or other severe dysfunction. Many were described in case reports (Devine et al., 2002; White, Feldman, et al., 1993). Thankfully, occupational standards for exposure to the chemicals described in this chapter have led to much lower exposures among patients, due at least in part to burgeoning of the field of behavioral toxicology over the past 40 years (Feldman, 1999). When patients are seen today, exposures are likely to be much lower and findings more subtle, which creates a special challenge to the clinical neuropsychologist. The cognitive and behavioral domains most affected in adult exposures to neurotoxicants remain the same, but differential diagnosis can be more difficult.

As in all consultations requesting detailed neuropsychological assessment, differential diagnosis and treatment recommendations, a careful, comprehensive approach is required. The evaluation of exposed patients ideally includes a detailed understanding of the known or suspected exposure to neurotoxicants as well as the usual elements of a complete neuropsychological examination—medical chart reviews, school records review, clinical interview of the patient, interviews of significant others who have independent knowledge of the patient's clinical course and function, and neuropsychological testing covering all functional domains. Psychiatric assessment and

consideration of developmental disorders are also often appropriate (including school record reviews).

A. Interview and Exposure Assessment

A standard, detailed clinical interview (see suggested readings) should be completed with the patient to understand exposure as well as comorbidities and other factors essential to interpreting the results of the neuropsychological assessment. We have repeatedly found the interview to be key to understanding patient presentation and routinely ask about issues that were covered in the medical chart. Often we obtain more detailed or new information from the patient (e.g., in areas such as family medical history, substance abuse). Understanding the exposure itself can be quite challenging. However, it is important to collect as many details from the patient as possible about exposures, especially any that prompted referral, as well as information about other kinds of exposure. In patients who have significant cognitive or affective changes associated with exposure, interviews with family members can be key to understanding changes following exposures.

Review of the medical chart(s) of the patient is critical in any neuropsychological evaluation. In the case of toxicant exposure, it can provide data on emergency department and other exposure-related medical visits and evaluations as well as any biomarker data that have been collected (levels of a toxicant or its metabolites in blood, urine). If prior neuropsychological testing was carried out, whether pre- or postexposure, the report and, if possible, data and test scores should be obtained to inform the assessment.

Material safety data sheets (MSDS) contain information on the chemical components of substances used at work. They also have information on known health effects of exposure to these chemicals. MSDS should be obtained and reviewed, if possible. They are often available to patients with occupational exposures. Finally, in some cases an exposure event is evaluated collaboratively with an industrial hygienist who can model the exposure or estimate likely chemical exposures, dosages, and timing.

When available, school records can be quite helpful in determining patterns of premorbid skills and intellectual function and in identifying developmental disorders of cognition or behavior. Data that can be useful include grades the patient has earned over time in specific subject areas, standardized test scores over time, IQ and academic achievement data, and records of Individual Education Plans and associated diagnoses. In one patient seen after long-term environmental exposure to inorganic mercury, school records were essential in documenting the deterioration in specific cognitive areas leading

to the motor, intellectual, and behavioral dysfunction observed during the assessment carried out when he was 20 (see suggested readings). School reviews have helped to rule out preexisting problems with attention or nonverbal skills in patients who develop them postexposure.

B. Neuropsychological Tests

Table 15.4 lists a sample neuropsychological test battery, with optional ancillary tests. The battery is designed to allow the clinician to model likely premorbid (or preexposure) intellectual patterns of ability, facilitate differential diagnosis by broad coverage of skills and behaviors, identify functional consequences of cognitive impairment, and test limits (i.e., include a wide range of difficulty levels so that subtle as well as obvious dysfunction can be detected and that can challenge individuals at the upper end of intellectual function when appropriate). The table incorporates tasks that we routinely use, though our general clinical approach is to flexibly apply tests, depending on the patient and referral question.

The tasks that are most useful in identifying exposure-related dysfunction are in the domains of attention, working memory/executive function, fine motor abilities, visuospatial skills, short-term memory, and mood/affect. This reflects the structural consequences of such exposures noted in Part II. Common sites of action of neurotoxicants include white matter, cerebellum, frontal lobes, and hippocampus, with important implications for frontal system function, fine manual motor coordination and speed, memory, and visuospatial skills. Certain toxicants—such as MeHg—affect posterior brain structures and premotor cortex, whereas others, such as the solvent perchloroethylene (PCE; dry cleaning fluid) have been shown to disproportionately affect visuospatial skills (Echeverria, White, & Sampaio, 1995).

At the outset, it is important to note that tests assessing response effort must be included. This is especially true when occupational or environmental exposures lead to applications for disability, financial settlement, or other benefits. See Chapter 4 for a detailed discussion of methods of symptom validity testing. If the patient scores poorly on effort tasks such as the Test of Memory Malingering, we talk to him or her about the fact that we know he or she does not seem to be giving full effort to the tests and that the evaluation will not be useful if consistent effort cannot be applied. If the patient agrees to cooperate, we administer some other tasks (e.g., Mini-Mental Status Examination, some other simple tests such as Finger Tapping that can also pick up minimal response effort). If the patient's performance appears to remain invalid, we often stop testing or administer

Table 15.4. Suggested Neuropsychological Tests

Domain/test	Rationale for inclusion
General intelligence	
WAIS–IV Information	Premorbid verbal
WAIS–IV Picture Completion	Premorbid nonverbal
Academic skills	
WRAT–4 Reading, Arithmetic, Spelling	Premorbid hold tests (verbal and nonverbal), Motor, spelling qualitative
Language	
BNT	Hold test, premorbid verbal
Cookie theft writing	Assess premorbid spelling, verbal
Motor	
Finger-tapping test	Dominance, simple motor speed; effort
Grooved pegboard*	Dominance, complex motor speed, and coordination
Attention	
Conner's CPT*	Reaction speed and accuracy; variability; ADHD
Digit/visual span forward	Control for memory and backwards span
TMT A*	Check for tremor, control for TMT B
Working memory/executive function	
Digit span backward*	Compare to forward digit and to visual span backward
Visual span backward*	Compare to forward and to verbal (digit) span backward
TMT B*	Compare to TMT A; assess errors; check for tremor
Recurrent motor programs*	Assess errors, perseveration type
WCST	Cognitive flexibility; error types
Categories test*	Errors, flexibility; use as adjunct to WCST

Table 15.4. Suggested Neuropsychological Tests *(Continued)*

Domain/test	Rationale for inclusion
Visuospatial	
WAIS–IV BD*	Visuomotor integration skills
ROCT*	Complex visual organization and fine motor: limits testing; strategy
Hooper Visual Organization Test	Visuospatial skills w/no motor element
Boston Visual Quantitative Battery	Qualitative aspects of visuo-integration and perception
Learning/memory	
Wechsler Logical Memory*	Learning, spontaneous recall, retention, recognition
CVLT–II*	Strategy, learning, Trial 1 learning, sensitivity to interference, retention, spontaneous recall, recognition
Wechsler Visual Reproduction*	Learning, retention, compare to verbal
ROCT-IR*	Compare to copy, retention
ROCT-DR*	Retention, consolidation
Response effort	
Test of memory malingering	Assess validity of results
16-item test	Assess validity of results
Affect	
POMS*	Assess several aspects of affect (fatigue, irritability, confusion, anxiety, sadness) + positive response bias
MMPI–3	Validity scales, content scales, screen
Ancillary instruments	
Mini-Mental Status Examination	Cursory measure of general cognitive function
Diagnostic Interview Schedule	Role of major psychiatric disorder

(continued)

Table 15.4. Suggested Neuropsychological Tests *(Continued)*

Domain/test	Rationale for inclusion
PTSD checklist	Role of PTSD
Conners ADHD checklist	Role of ADHD
LD tests	Role of LD

Note. Asterisks (*) indicate tests that are often used in identifying exposure-related dysfunction. WAIS–IV = Wechsler Adult Intelligence Scale—Fourth Edition; WRAT–4 = Wide Range Achievement Test—Fourth Edition; BNT = Boston Naming Test; CPT = Continuous Performance Test; ADHD = attention-deficit/hyperactivity disorder; TMT = Trail-Making Test; WCST = Wisconsin Card Sorting Test; WAIS–IV BD = WAIS–IV Block Design; ROCT = Rey-Osterrieth Complex Figure Test; CVLT–II = California Verbal Learning Test; IR = Immediate Recall; DR = Direct Recall; POMS = Profile of Mood States; MMPI–III = Minnesota Multiphasic Personality Inventory—3; PTSD = posttraumatic stress disorder; LD = learning disorder.

a Minnesota Multiphasic Personality Inventory (MMPI) and then stop testing, depending on the referral source or question.

To identify newly acquired brain dysfunction, it is important to model premorbid verbal and nonverbal skills using tasks that are generally not affected by exposure to neurotoxicants ("hold" tests). Test-based clues about verbal skills can be derived from performance on tasks that assess store of information (Wechsler Adult Intelligence Scale—Fourth Edition [WAIS–IV]), single-word reading (Wide Range Achievement Test—Fourth Edition [WRAT–4]), and confrontation naming (Boston Naming Test). WAIS–IV Picture Completion and WRAT–4 Arithmetic provide clues to premorbid nonverbal or visuospatial skill levels. Spelling can be affected by developmentally based dysfunction in either domain. It should be noted that exposure can result in slowing on timed tasks such as arithmetic, affect motor dexterity on writing, or lead to slurring during confrontation naming. These qualitative findings should be considered when interpreting the data.

Assessment of attention is important to interpreting the neuropsychological test results and can provide evidence of exposure-related dysfunction. Because reaction times are often slowed or variable following neurotoxicant exposures, the Conners' Continuous Performance Test can be a valuable assessment tool; in fact, it is often used in epidemiological research for this reason. Digit span forward is generally minimally affected by exposures and allows the clinician to assess span of apprehension to use in interpreting data from verbal memory tests. Visual spans forward are somewhat more fragile

following exposures and may be significantly lower than verbal spans. Trail-making Test (TMT) A performance can be slowed following exposure, though the A condition is most important for interpreting performance on TMT B.

Working memory and executive function are often disrupted following toxicant exposures, especially as tasks increase in difficulty. Tests can be used to assess this domain at varying levels of difficulty (backward spans, recurrent motor programs, Wisconsin Card Sorting Test, Categories, Rey-Osterrieth Complex Figure [ROCF] strategy/organization).

Given that toxicants can affect white matter, cerebellum, basal ganglia, and/or premotor cortex, it is not surprising that manual motor slowing and tremulousness are often observed. In general, performance on challenging tasks such as pegboards will be significantly worse than that seen on finger tapping, which may be normal or slightly slowed. Tremulousness can also be seen qualitatively on writing or drawing tasks.

Visuospatial functioning is frequently disrupted in adult neurotoxicant exposure and inclusion of tests to assess this domain is critical. The Hooper Visual Orientation Test is included in the battery to allow assessment of visuospatial organization without complication from the task-related motor demands associated with other visuospatial tests. Performance on the Wechsler Block Design subtest has been shown to be negatively affected by a number of exposures, including lead, pesticides, and solvents (White et al., 1992). Performance on the ROCF Test can also be informative, because it is a multidetermined task involving visuospatial, motor, and executive demands.

Given toxicant effects on white matter and hippocampus, it is not surprising that exposures affect learning and memory. The battery includes a task assessing learning and memory for material that is already structured (Wechsler Logical Memory), which allows for assessment of learning and retention in the context of low strategy/executive demands. The California Verbal Learning Test allows assessment of learning, strategies, and short-term and longer term retention all in the same test; however, the recognition condition is not especially informative, and we have adopted a larger forced-choice, visually presented list that allows us to look at recognition versus recall more accurately. Simpler (Wechsler Visual Reproduction) and more difficult (ROCF) tests allow assessment of visual memory and comparison to verbal memory capacity. Some toxicants (e.g., PCE) appear to affect visual memory to a greater extent than verbal memory.

Subjective changes in affect and energy are common complaints in patients with toxicant exposures. Dose–effect relationships between exposure to lead, solvents, and other neurotoxicants and reports of

fatigue, confusion, irritability, and other dysphoric symptoms have been demonstrated repeatedly in the epidemiological literature. The affective changes sometimes seen in research findings and in clinical patients with neurotoxicant exposure generally do not reflect psychiatric disorders of the type that appear in the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (American Psychiatric Association, 2013). Rather, they appear to result from exposure-related limbic system dysfunction. Often they are among the first symptoms to remit following removal from exposure and recovery from exposure effects. For these reasons, we often administer the Profile of Mood States (POMS) to detect subjective complaints of dysphoria. In some cases the affective and behavioral effects of exposure can be severe, including paranoid ideation and hallucinations following high-level exposure to Hg and suicidal and homicidal ideation following high-level solvent exposures. Again, we find clinically that these symptoms tend to remit as levels of the toxicant drop in the patient's body and as time since exposure increases.

C. Assessment of Psychiatric Disorders

Assessment of formal psychiatric disorders may be necessary for purposes of differential diagnosis. The Minnesota Multiphasic Personality Inventory—3 (MMPI–3) can be administered as a screening device (and to evaluate response validity) or the Diagnostic Interview Schedule can be used. Posttraumatic stress disorder (PTSD) is common in patients with certain kinds of exposures, especially if the exposure was for some reason frightening (see the discussion that follows). If the interview suggests that this is a problem, we use detailed questioning or a checklist to explore whether the patient meets diagnostic criteria for PTSD.

D. Diagnosis

Diagnosis of toxicant-induced encephalopathy is based on the finding of dysfunction(s) in the domains known to be affected by the exposure(s) for which the patient is being evaluated. There must be evidence of exposure, and there should be no other reasonable explanation for the findings. Table 15.5 summarizes our experience with the domain-specific effects of exposures to CO, Pb, Hg, pesticides, and solvents (MeHg is not included because our number of adult patients with this exposure is too limited to draw conclusions). Not every patient will show deficits in all domains listed for a particular exposure. Degree and type of dysfunction depend on severity of exposure,

Table 15.5. Commonly Seen Clinical Manifestations of Exposures in Adults

Domain	Carbon monoxide	Lead	Inorganic mercury	Pesticides	Solvents
Motor	×	×	×	×	
Attention	×	×	×	×	×
Executive	×	×	×	×	×
Language					
Visuospatial	×	×	×	×	×
STM: Learning[a]	×	×	×	×	×
STM: Retention	×	×	×		×

Note. STM = short-term memory.
[a]STM learning effects depend on severity of exposure, especially for pesticides and solvents.

degree of recovery from intoxication, the particular form of the toxicant (e.g., type of solvent or pesticide), and interindividual differences. The latter can include vulnerable skill areas or even individual differences in susceptibility to a toxicant or vulnerability of specific brain areas to a toxicant. We have seen patients from the same exposure situation who have had widely varying clinical pictures. In a case of several workers with chronic high-level, mixed-solvent exposure, outcomes ranged from severe cerebellar impairment requiring wheelchair assistance (resolving over time to head bobbing and other residual cerebellar symptoms) to neuropsychological dysfunction suggesting white matter dysfunction. Cases of glue sniffers exposed to toluene show similar variability, with some patients having cerebellar involvement and others presenting with white matter lesions only (Filley, 2012). The presence of deficits in those neuropsychological domains commonly affected—attention, executive function, visuospatial skills—combined with the absence of deficits in those domains typically preserved (e.g., naming) can be informative. Distinctive characteristics of memory and motor function differentiate effects in some types of exposure.

There are other circumstances in which diagnosis of toxicant-induced CNS damage can be especially challenging. These include patients who have had mild, subtle, or subclinical effects from exposure, who may report many of the expected somatic, neurological, and cognitive symptoms but have no conclusive neuropsychological

evidence of exposure. If a patient is seen long after an exposure, recovery can occur, and evidence of any earlier clear-cut encephalopathy may no longer be present. For example, a dry cleaner who was currently working in a plant with a faulty ventilation system was seen by RFW and showed clear evidence of solvent encephalopathy; repeated testing over several years after removal from exposure showed improvement on virtually all tests, with only two tests showing impairment at final assessment. It is doubtful that a retrospective diagnosis could have been made based on the neuropsychological data alone 2 to 3 years after exposure ceased. In some cases that are confusing or mild, follow-up testing after cessation of exposure can be informative when significant improvement occurs. We have examined some patients on an A-B-A type schedule in which we tested them initially while they were being exposed at work, several months after leaving work and experiencing no exposure, and several weeks or months after returning to work and exposure (which may occur with patients who are very unwilling to leave their jobs). When changes in motor and other kinds of functions are associated with exposure in the A condition, conclusions are easier to draw.

E. Differential Diagnosis

Differential diagnosis is especially difficult with patients who have evidence of neurological disorders with overlapping pathology, symptoms, and cognitive deficits. For example, some solvents cause parkinsonian symptoms and a form of toxicant-induced parkinsonism (Feldman, 1999). The neuropsychological picture looks much like it does in idiopathic Parkinson's disease (PD), though there may be evidence on memory testing suggesting true forgetting and solvent-induced hippocampal involvement that will differentiate the two disorders. This is a situation in which repeat testing can be especially helpful—patients with PD generally degenerate, and any improvement seen on cognitive testing is often attributable to medications, whereas patients with solvent-induced damage may improve after removal from exposure. Also, in our experience, medications that benefit patients with PD rarely cause significant improvement in patients with solvent-induced parkinsonism.

Overlapping pathology is also a problem in patients who have exposures and white matter lesions on MRI that resemble those seen in cerebrovascular disease (CVD) and multiple sclerosis (MS). For CVD, the matter is further complicated by the fact that exposure to Pb, MeHg, and solvents can exacerbate known risk factors for CVD such as high blood pressure (Feldman, 1999). Again, historical features related to time of onset and findings on tests of short-term memory can sometimes clarify whether exposures are the main factor

causing the neuropsychological and white matter findings, and repeat testing is sometimes helpful when improvement is seen over time. However, it can be very difficult to determine whether an exposure or exposures contributed to an accelerated or exacerbated presentation of CVD in a patient who was already on course for developing this disorder. MS shows similar diagnostic difficulties, especially because there is a significant literature suggesting that exposure to Pb and other toxicants is associated with diagnosis of this disorder (White et al., 1992); the problem is further complicated by the fact that repeated testing and following a patient over time may be less informative because MS patients often improve from one testing to the next, at least in the short term. A relapsing-remitting course with new development of symptoms suggests that the patient has MS, not simply toxicant-induced white matter disease.

Toxicants such as MeHg and industrial solvents can cause cerebellar damage, and patients with intoxication from these exposures may look much like patients with primary cerebellar degenerative diseases or abuse of alcohol (which is, after all, a solvent). It is critical to consider the typical manifestations of alcoholism, ranging from effects of chronic alcohol ingestion to Wernicke-Korsakoff syndrome, and to determine whether neuropsychological features and historical presentation of symptoms and course point more specifically to industrial chemicals or alcohol-induced damage. It is not yet known whether exposures can trigger primary cerebellar degeneration or disease in patients who are genetically at risk.

We have also been referred patients for differential diagnosis of toxicant-induced encephalopathy versus primary progressive dementias such as Alzheimer's disease or frontal dementias. Although there can be overlapping pathology in frontal and limbic systems, the course is different. Furthermore, loss of semantic memory/naming ability is not typical of exposure to any of these toxicants and is common in the primary progressive dementias, often allowing a clear distinction.

Patients with exposure to the toxicants reviewed here often complain of fatigue, in which case it is important to determine whether they meet criteria for chronic fatigue syndrome (CFS). In our experience, patients with intoxications from industrial chemicals more often have a fatiguing syndrome than CFS, and CFS is not associated with the specific patterns of cognitive dysfunction described here for chemicals. However, CFS can be seen in exposed patients. The situation is similar for multiple chemical sensitivity (MCS). Patients with toxicant-induced encephalopathy may complain of increased sensitivity to some other exposures (e.g., gasoline fumes), but they often do not meet diagnostic criteria for MCS, and the neuropsychological profile for MCS is different from that for the exposures described here.

Psychiatric disorders, including PTSD, are considered in interview (see Section IV), and it is important to raise the issue of PTSD as a premorbid or comorbid diagnosis. As noted above, exposures themselves can trigger PTSD, especially if they are sudden or involve loss of consciousness or near-death experiences. We have seen this especially frequently in patients with CO exposures. In some cases, PTSD is the major health effect associated with an exposure. For example, patients who are awakened in the middle of the night because a CO alarm went off in the home or apartment building may be quite frightened but may not suffer any detectable brain damage from exposure (and may not have significant carboxyhemoglobin or other evidence of CO poisoning at the time). When PTSD occurs as a result of exposure and is found in patients who also develop diagnosable brain damage from exposure, PTSD-related distractibility can make interpretation of neuropsychological test results more challenging.

IV. TREATMENT, INTEGRATION, COMORBIDITY, AND OTHER ISSUES

Some years ago, one of the authors (RFW) reviewed clinical diagnostic outcomes from about 300 patients who had been referred to her for evaluation of possible or known exposure to neurotoxicants. About 18% of these patients were diagnosed with a toxicant-induced encephalopathy. For the whole group, including those diagnosed with CNS effects of intoxication, multiple diagnostic outcomes were common. These included developmental disorders, neurological diseases, and psychiatric diagnoses.

Developmentally based preexposure patterns of cognitive function are important to consider and affect neuropsychological outcomes and their interpretation. At the simplest level, it is easy to underdiagnose toxicant-induced brain damage in patients with high levels of premorbid cognitive function and, similarly, to overdiagnose toxicant-related cognitive impairment in patients whose premorbid function is in the low-average or borderline range. It can also be difficult to determine whether mild deficits in attention noted in patients with current or recent exposures reflect mild effects of exposure or attention-deficit/hyperactivity disorder in patients who have premorbid evidence of this disorder. Retesting following removal from exposure or after longer periods of nonexposure can be informative: Recovery of function suggests that earlier findings were exposure related. Because many toxicants affect visuospatial function, it is important to consider whether a patient may have had nonverbal impairments prior to exposure and whether these deteriorated further following exposure.

Comorbid psychiatric disorders must be considered when evaluating data and are important for treatment planning. It must be emphasized that exposures themselves can cause brain damage that produces symptoms that are commonly categorized as psychiatric, including mood changes, apathy, hallucinations, suicidal or homicidal ideation, and paranoid delusions. These symptoms remit with recovery and generally do not meet criteria for standard *DSM* diagnoses. Reactive depressions and anxiety states are also sometimes seen following occupational and environmental exposures.

Secondary gains in patients with toxicant exposures are typical of those seen following other insults, such as head injury. They range from possible monetary gain from lawsuits or disability claims to the opportunity for extra social support to the excuse to see oneself as ill for people who enjoy that role. All of these motivators can result in exaggeration or "sick role playing." The differential diagnosis of motivational disorders such as factitious disorder, malingering, Ganser's syndrome, or somatoform disorder depends on the acumen of the clinician (see Chapter 26 for a full discussion of somatic symptom disorders). It should be noted that these disorders can be seen comorbidly with brain damage from intoxication. Some patients respond to neuropsychological testing at initial examination with clear-cut evidence of encephalopathy and then exaggerate or show typical patterns of uneven effort at later evaluations.

Treatments for intoxications are quite limited and most efficacious at the time of exposure. Withdrawal from exposure is indicated when there is evidence of intoxication and exposure is ongoing. High levels of exposure to Pb and Hg can be addressed with chelation, though chelating agents have side effects and usually are not administered when biomarkers show relatively low levels of exposure. Hyperbaric chambers are sometimes used for CO exposures, but again only seem to be efficacious immediately after exposure.

The residual effects of brain damage from exposure are difficult to treat: There are no known methods for undoing such damage. Often patients benefit from a careful review of their cognitive strengths and weaknesses, with strategies to overcome the latter. They also often benefit emotionally from being able to attribute certain cognitive and behavioral symptoms to exposure, when that is valid. Other symptomatic approaches include formal cognitive rehabilitation training, alternative and complementary medicine methods, supportive psychotherapy, and empirical application of pharmacological agents to address mood and behavioral symptoms (different patients respond differently to specific medications even following the same exposure or experiencing what appears to be the same symptom). Patients sometimes need to be referred to an attorney for disability compensation, Social Security, or other benefits. They also

sometimes require vocational counseling and rehabilitation to prepare for another career if they will continue to be exposed to toxicants at work in their current occupation.

V. CONCLUSION

The field of behavioral toxicology is still relatively new. There is much left to discover about how the universe of chemicals to which people are exposed affect the brain and the neurological and other health conditions that such exposures might trigger, especially in vulnerable populations. Gene–environment interactions are clearly extremely important mediators of exposure effects but are currently very poorly understood. In addition, single overwhelming exposures are rare—humans live in a chemical environment, and the effects of exposure mixtures or combined exposure effects are not well understood.

Neuropsychological methods are valuable because they can detect far more subtle effects of acute and chronic exposures than current neuroimaging or other techniques, especially in clinical situations. Subtle preclinical manifestations of brain damage remain difficult to document, and the diagnosis of brain damage attributable to relatively high exposures can be challenging in many situations. These include coexposure to multiple chemicals; existence of co-morbid neurological, developmental, and psychiatric disorders; prolonged time intervals between exposure and assessment in which recovery can occur; failure to acquire appropriate biomarkers of exposure; symptom exaggeration in patients with clearcut intoxications, and variability in individual susceptibility to chemical effects.

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Chapter 16

Brigid Waldron-Perrine and Kenneth M. Adams

Alcohol-Related Neuropathology

Alcoholism and alcohol-related syndromes are responsible for a wide variety of neurocognitive deficits, and as a result neuropsychological testing has been used extensively to evaluate individuals with alcohol-related syndromes. This chapter provides basic information needed for neuropsychological assessment of patients presenting with alcohol-related syndromes.

I. DEFINITION/CLASSIFICATION

A. Substance: Biochemistry

Alcohols are organic compounds that include a hydroxyl group (–OH). Ethanol (CH_3CH_2OH), or ethyl alcohol, is a substance that has been consumed in many forms throughout the history of mankind. Ethanol is made by fermentation or distillation and is present in alcoholic beverages in different concentrations. Ingestion of ethanol by volume can be converted on the basis of quantity and frequency

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to an estimate of grams consumed by computing pure ethanol volume in the beverage of choice. Blood alcohol concentration increases within 20 minutes of consumption. Elimination occurs through the kidneys and lungs (about 5% of total volume through each organ), and oxidation occurs primarily in the liver.

B. Epidemiology

In the United States, more than 90% of individuals over the age of 18 report having consumed alcohol at some time in their lives. The lifetime prevalence rate of alcohol use disorders is approximately 19%; approximately 15 million Americans meet the diagnostic criteria for alcohol abuse (Kessler et al., 2005). Men are 2 to 3 times more likely to be diagnosed with an alcohol-related disorder than are women.

C. Intoxication

Common neurological symptoms of alcohol intoxication include slurred speech, incoordination, ataxia, and nystagmus. Increased aggression, fluctuations in mood state, and difficulties in thinking are also often associated with alcohol intoxication. A dose–response relationship has been demonstrated between blood alcohol level and processing speed, accuracy, working memory and executive functioning, with effects evident at a blood alcohol level as low as 0.048% (Dry, Burns, Nettelbeck, Farquharson, & White, 2012; Scholey, Benson, Neale, Owen, & Tiplady, 2012).

D. Physiological Dependence: Tolerance and Withdrawal

Ethanol activates the reinforcement or reward pathways of the brain, resulting in the potential for alcohol dependence. Avoidance of potential alcohol-associated withdrawal symptoms is an additional mechanism for maintenance of drinking behavior. Physiological dependence may develop after prolonged consumption. Chronic use of alcohol creates tolerance to increasing amounts of the substance via neuroadaptive mechanisms.

In persons physiologically dependent on alcohol, withdrawal often occurs within 4 to 12 hours of drinking cessation and almost always within 48 hours. Symptoms of alcohol withdrawal can range in severity from causing discomfort to delirium tremens, which can become a neurological emergency. Mild withdrawal symptoms include

anxiety, irritability, perspiration, increased heart rate, and sleeping difficulty. Severe symptoms may include seizure, hallucinations, and delirium. Most withdrawal symptoms resolve within 1 week after alcohol use has been discontinued; in chronic, heavy users, withdrawal symptoms may be more protracted.

E. Pathophysiology: Neurotransmitters and Neurotoxicity

During alcohol exposure, the *N*-methyl-D-aspartate receptor becomes supersensitive to glutamate stimulation, resulting in excitotoxicity and neuronal cell death. There is also some evidence that alcohol may disrupt GABA-ergic (γ-aminobutyric acid) brain systems, but this does not appear to be an effect specific to use of alcohol (Olsen & DeLorey, 1999). Oxidative stress is another mechanism by which alcohol is presumed to negatively affect neurological functioning (Cederbaum, 2001). Additionally, changes in cholinergic muscarinic and benzodiazepine receptors have been implicated in certain brain areas (Freund & Ballinger, 1988). In general, however, specific mechanisms of alcohol neurotoxicity are not well understood.

Effects of alcohol on the brain are in part indirect. One such indirect mechanism is via dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. It is well-known from a variety of animal and human studies that alcohol stimulates the HPA axis. Following chronic and/or excessive alcohol consumption, the HPA axis becomes dysregulated and the inhibitory control of the axis impaired. The resulting glucocorticoid cascade has downstream effects on information processing and may result in neuropsychological deficits (Rose, Shaw, Prendergast, & Little, 2010).

F. Alcohol-Induced Cognitive Impairment

Of individuals who meet the criteria for alcohol dependence, 31% to 85% have demonstrable neurocognitive deficits evidenced during neuropsychological assessments after a 3- to 4-week period of abstinence (Rourke & Grant, 2009). The emergence of cognitive, perceptual, and motor impairments that persist even after achieving abstinence and sobriety increases as an increasing function of age and drinking history. Brain dysfunction ranges in severity from mild neurocognitive deficit to profound amnestic syndrome and dementias. Cognitive and behavioral dysfunction associated with alcohol use is related to the neurotoxic effects of alcohol as well as to the numerous comorbid factors important to consider in the context of an evaluation.

1. SUBTHRESHOLD IMPAIRMENT

Cognitive deficits related to alcohol misuse can negatively affect everyday functioning and treatment compliance even if they do not result in a diagnosable alcohol-related dementia or persisting amnestic disorder (Davies et al., 2005). Although 90% of individuals with alcohol dependence do not show severe neuropsychological deficits (Goldman, 1983), approximately 50% of these individuals do show mild-to-moderate neuropsychological impairments after a period of sustained abstinence (Davies et al., 2005; Grant, Reed, & Adams, 1987). In 70% to 90% of those who show deficits acutely after cessation of use, neuropsychological functioning improves over a period of months to years; however, in 10% to 30% there is persistence of mild neurocognitive disorder associated with a history of alcohol abuse despite sustained abstinence (Grant et al., 1987).

2. DEMENTIA

Various types of dementia are discussed elsewhere in this volume. Notably, however, it is estimated that severe cognitive disorders occur in approximately 10% of persons diagnosed with alcohol dependence and 25% of elderly patients with a significant history of problematic alcohol use, and 24% of institutionalized elderly people have alcohol-induced dementia (Horvath, 1975; Oslin & Cary, 2003). Onset of alcohol-induced persisting dementia is insidious, and neurocognitive impairment is permanent and persists long after substance use is discontinued. As with other types of dementia, neurocognitive deficits significantly interfere with daily functioning and often involve impairment in intellectual abilities as well as memory, visuospatial abilities, and executive functions (e.g., abstraction, problem solving). Unlike other types of dementia, however, orientation and language abilities remain relatively preserved in alcohol-related dementia. Additionally, individuals with alcohol-related dementia are, on average, 10 years younger than those with other types of dementia and have twice the average length of institutionalization.

G. Alcohol-Induced Persisting Amnestic Disorder: Wernicke-Korsakoff Syndrome

Wernicke-Korsakoff Syndrome (WKS) is associated with alcohol use but is caused by thiamine deficiency, to which alcoholics are vulnerable due to poor nutritional practices and poor absorption of nutrients (see Section V, Nutrition Status). The initial acute encephalopathy characterized by disorientation/confusion, indifference, inattentiveness, ataxic gait, nystagmus, and opthalmoplegia is referred to as Wernicke's encephalopathy. Confabulation is often

seen in these early stages. Some degree of clinical improvement following thiamine replacement is often seen in these patients within 4 weeks, particularly with regard to the delirium, ataxia, and opthalmoplegia, although peripheral neuropathology and amnesia are likely to persist. This persistence of symptoms is referred to as Korsakoff's syndrome, which is characterized by severe anterograde amnesia as well as temporally graded retrograde amnesia. Impairment in executive functioning is also likely in Korsakoff's syndrome, whereas general intellectual abilities and semantic memory are typically preserved. Although Wernicke's encephalopathy and Korsakoff's syndrome are clinically distinct, because they frequently co-occur, they are often referred to as WKS (Caine, Halliday, Kril, & Harper, 1997).

H. Hepatic Encephalopathy

Long-term exposure to alcohol in sufficient amounts can be associated with gradual onset of hepatitis, necrosis, and hardening of the liver (cirrhosis; Lieber, 1998). Hepatic dysfunction (including elevated liver enzymes outside of the context of cirrhosis), subsequently, is known to result in neuropsychological impairment. Hepatic encephalopathy results when the liver is no longer able to remove toxic substances, including ammonia, from the blood. Although potentially related to a variety of causes, hepatic encephalopathy is often the result of alcoholic hepatitis. The initial signs of hepatic encephalopathy are often an inverted sleep–wake pattern and mild neurocognitive deficits followed by marked lethargy and personality changes, worsening confusion and cognitive deficits, and finally, coma and death due to cerebral edema (Cash et al., 2010). Clonus, Babinski sign, and asterixis all signify the presence of the disorder. Other common signs of liver dysfunction may also occur including jaundice, ascites, and peripheral edema. Hepatic encephalopathy can be successfully treated by removing the excess ammonia from the blood with lactulose or nonabsorbed antibiotics. Psychomotor, visuomotor, and executive impairment may improve with treatment, but deficits in memory functioning are likely to persist even after medical intervention, including liver transplant (Arria, Tarter, Starzl, & Van Thiel, 1991).

I. Marchiafava-Bignami Disease

Marchiafava-Bignami Disease (MBD) is a progressive neurological disease characterized by symmetric demyelination of the middle of the corpus callosum and is associated marked impairment in brain

function (Kohler et al., 2000) that appears to have two subtypes, one of which has more prominent mental status features (Heinrich, Runge, & Khaw, 2004). Although a direct alcohol-associated toxic etiology of MBD is possible, and the disease was first characterized in association with red wine consumption, the exact cause is unknown. MBD has been associated with nutritional deficiencies and probable genetic factors (individuals of Italian descent appear to be at higher risk). Clinically, slowed mental processing, changes in personality, dysarthria, incontinence, seizures, changes in motor functioning, and frontal release signs are common (Kohler et al., 2000).

II. FUNCTIONAL NEUROANATOMY/ NEUROPATHOLOGY

A. Areas of Vulnerability/Neuroimaging Findings

1. GENERAL FINDINGS

Chronic excessive use of alcohol has been associated with reductions in brain volume, particularly with advancing age (Harper, 2007). Findings that suggest shrinkage of the neuronal cell body but not actual neuronal loss may explain clinical improvements after a period of abstinence, assuming rearborization is occurring (Harper & Kril, 1990). In general, the pattern of findings of numerous studies of cerebrospinal fluid and brain volume measurement using computed tomography (CT) reveals that alcohol itself appears to affect cortical structures, whereas subcortical structures are more affected by nutritional deficiency and/or age (Rourke & Grant, 2009). Such effects seem to occur in both women and men, although women appear to be affected after a shorter duration of problematic drinking and at lower levels of consumption (Mann, Batra, Gunthner, & Schroth, 1992).

Abnormalities in the superior frontal, temporal, and parietal regions of the cerebral cortex, including white matter damage, are a prominent finding in persons with a history of significant alcohol misuse, with or without cerebellar degeneration. In general, gray and white matter atrophy appears to be most prominent in the frontal lobes (Rourke & Grant, 2009). Findings of frontal atrophy are often associated with executive functioning impairments such as disinhibition, poor cognitive flexibility, and poor working memory (Brokate et al., 2003).

The cerebellar vermis and brainstem are particularly sensitive to the effects of alcohol. Cell death or neuronal dysfunction in these areas commonly contributes to acute confusion, impaired attention, memory problems, impaired eye movements, and gait ataxia.

Impairment in executive functioning due to frontal-cingulate hypometabolism often parallels vermal damage in chronic cases (Adams et al., 1995; Gilman et al., 1990). Injury to the reciprocal connections between the brainstem and the cerebellum are likely responsible for the perceptual motor deficits commonly seen in persons with alcohol use disorders (Sullivan, 2003).

Chronic use of alcohol has been associated with hypertension and associated cardiovascular/cerebrovascular risk. Thus, the same subcortical sequelae associated with vascular risk factors are commonly found in patients with a history of significant alcohol abuse. Magnetic resonance imaging (MRI) studies have demonstrated volume reductions in the caudate and diencephalon and have found significantly more hyperintensities in the subcortical white matter in individuals with a history of alcoholism versus controls (Jensen & Pakkenberg, 1993).

2. SPECIFIC SYNDROMES

a. Wernicke-Korsakoff

Thiamine deficiency causes hemorrhagic lesions in the brainstem and cell loss bilaterally, primarily in the mammillary bodies, dorsomedial nucleus of the thalamus, periaqueductal and periventricular gray matter, and midline diencephalic nuclei (Harper, 2007). There is some evidence of genetic risk for development of WKS.

b. Marchifava-Bignami

Alcohol use (and MBD in particular) has been associated with abnormal signal intensities in the corpus callosum, most pronounced in the genu and body and less so in the splenium, and symmetrical involvement of white matter tracts beyond the corpus callosum (Pfefferbaum, Adalsteinsson, & Sullivan, 2006). Research focused on investigating the integrity of white matter tracts via techniques such as diffusion tensor imaging has found disruption of white matter microstructure (Pfefferbaum & Sullivan, 2005). Numerous studies have implicated white matter vulnerability as a major contributor to alcohol-associated cerebral atrophy, although the mechanism for this is not yet well understood (Harper, 2007).

III. NEUROPSYCHOLOGICAL EVALUATION

A. Cognitive Screening Batteries

In an acute medical setting, clinicians may not have the time to complete a full neuropsychological assessment battery or the expertise to interpret such. Thus, cognitive screening instruments such as

the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), Cognistat (Kiernan, Mueller, Langston, & VanDyke, 1987), and Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, Tierney, Mohr, & Chase, 1998) may be used to briefly assess the likely domains of dysfunction. The advantage of these instruments is that they are brief, but unfortunately they have not been extensively validated in populations with alcohol-related cognitive disorders. Nevertheless, they may provide useful gross information for broadly characterizing possible neuropsychological dysfunction and areas of deficit.

B. Full Neuropsychological Evaluation: Expected Deficits

Appropriate means of conducting full neuropsychological assessments in general with appropriate coverage of individual cognitive domains are discussed in other chapters in this volume. In general, a thorough evaluation of any patient should include assessment of orientation, general intellectual abilities, motor skills, attention, visuospatial and language functioning, memory, and executive functioning using well-validated and standardized assessment measures.

Persons with alcohol use disorders who have recently discontinued drinking and detoxified generally perform comparably with normal controls on verbal and full-scale IQ tests but do worse on performance measures (Parsons & Leber, 1981). The typical pattern of performance of persons with a history of alcohol use disorder who have maintained sobriety for 2 to 4 weeks includes deficits in the areas of executive functions (i.e., cognitive flexibility and problem solving), visual–spatial analysis, learning and memory, complex perceptual motor integration, and speed of processing. This pattern has been found in both women and men, although women have been found to demonstrate deficits after a shorter course and lesser engagement in alcohol use.

Deficits in the domain of attention seem related to processing demand, whereas executive deficits seem related to set shifting and response inhibition (Bartsch et al., 2007; Nöel, Bechara, Dan, Hanak, & Verbanck, 2007). Although the distinction has been a subject of much debate, memory deficits in persons with a significant history of alcohol use disorder appear comparable across the verbal and visual domains and are generally related to a generalized learning impairment but not a deficit in retention of information (Rourke & Grant, 2009).

C. Recovery of Function

There is a great deal of debate regarding the extent to which neurocognitive recovery occurs in individuals with alcohol-related cognitive deficits. In general, most studies have found, on the average, improvements in cognitive functioning with longer periods of abstinence (months to years; Adams, Grant, & Reed, 1980; Grant, Adams, & Reed, 1979). A recent study found that attentional control and spatial working memory were less impaired in alcohol-dependent patients who maintained abstinence for at least 1 year compared with those reporting a shorter period of abstinence (Kopera et al., 2012). Thus, conclusions about persisting alcohol effects should not be made until a significant time has passed after treatment (Rourke & Grant, 1999).

IV. IMAGING FINDINGS: NEUROANATOMICAL AND NEUROPSYCHOLOGICAL CORRELATES

Correlations between CT scans and neuropsychological test performances have been somewhat inconsistent, but associations of brain changes as seen on MRI and neuropsychological functioning have revealed stronger patterns of association. Cerebral blood flow, as assessed via positron emission tomography and single-photon emission computed tomography, has been found to be lower in persons with a history of problematic alcohol use, particularly in the frontal and parietal areas. Blood flow appears to improve, however, after a period of sustained abstinence. Studies utilizing functional MRI (fMRI) spectroscopy have demonstrated that although there may not be performance differences between persons with a history of problematic alcohol use and controls, the pattern of brain activation may be different in the two groups. Attenuation of neural activity in the anterior cingulate cortex has been linked to impaired cognitive control, and impaired deactivation of the posterior cingulate has been implicated in poor automatic implicit learning (Schulte et al., 2012). In general, persons with a significant history of alcohol-related disorders appear to activate more brain regions to accomplish cognitive tasks than do controls, indicating that some neural reorganization may be required to circumvent neural damage due to alcohol consumption (Desmond et al., 2003).

Similar to the pattern of recovery seen on neuropsychological tests, maintenance of abstinence has been associated with stabilization of brain atrophy or increased brain volume (particularly white matter) as measured by structural imaging techniques. Recovery appears to be most rapid in the early stages of abstinence but may

continue for a year or more (Gazdzinski, Durazzo, & Meyerhoff, 2005). Interestingly, whereas women demonstrate neurological changes with less exposure to alcohol than do men, they also demonstrate neurological recovery more quickly (Jacobson, 1986). The mechanisms of this neurological recovery are as yet unclear. These effects do not appear to be explained by hydration but may be related to decreases in inflammation or osmotic stress, reduced suppression of trophic factors, or other molecular changes.

V. COMORBIDITY, INTEGRATION, TREATMENT, AND OTHER ISSUES

A. Comorbidity

1. POLYSUBSTANCE USE

Abuse of one substance is associated with a higher likelihood of abuse of other substances. Thus, it is essential that assessment of alcohol-related disorders include a thorough evaluation of the potential for other substance abuse or dependence in each individual case (Grant et al., 1978). Cognitive dysfunction has been found in up to 50% of polysubstance abusers (Vik, Cellucci, Jarchow, & Hedt, 2004). However, different substances affect cognition differentially, and thus cognitive profiles are likely to vary within this group depending on which substances are abused. Overall cognitive impairment is likely due to combined neurotoxic effects as well as other comorbidities. Nevertheless, the most consistently impaired cognitive abilities are perceptual and sensorimotor skills, problem solving, and memory.

2. OTHER MEDICAL AND PSYCHIATRIC DISORDERS

Individuals who chronically abuse alcohol are likely to have a variety of comorbid psychiatric and medical disorders that may affect their cognitive functioning. Head injuries and seizures are relatively common comorbidities in individuals with a history of alcohol abuse or dependence. Use of alcohol predisposes individuals to situations in which they are likely to experience a traumatic brain injury and may alter their trajectory of recovery. Additionally, resulting cognitive deficits may be related to the interaction of alcohol use and effects of traumatic brain injury. Seizures can be a consequence of alcohol withdrawal and may independently or synergistically affect cognitive functioning (Rogawski, 2005). Medical facilities generally follow a withdrawal protocol typically using benzodiazepines to forestall major withdrawal symptoms, such as seizures.

It is estimated that upward of 80% of persons who misuse alcohol also smoke cigarettes (DiFranza & Guerrera, 1990) and thus are likely to experience cognitive deficits related to hypoxemia as a consequence of chronic obstructive pulmonary disease and other pulmonary conditions. Chronic alcoholism may contribute to nighttime hypoxemic conditions and sleep apnea, which may further exacerbate neuropsychological abnormalities (Roth, Roehrs, & Rosenthal, 1995). Sleep abnormalities are common in persons with a significant alcohol use history and may also negatively affect cognitive functioning. Individuals with a history of alcohol abuse have longer sleep latency, less total sleep time, and rapid eye movement abnormalities, which may be related to cerebral atrophy (Gillin, Smith, Irwin, Kripke, & Schuckit, 1990).

Together, these comorbidities are likely to result in medical conditions such as lung dysfunction and heart disease, also known to have cognitive correlates. It is important to consider, therefore, in the context of assessment of individuals with alcohol use disorders, which findings may be attributable to multiple potential etiologies and may not be specific to consequences of alcohol misuse.

Psychiatric symptoms, particularly depression and anxiety, are common during times of heavy alcohol consumption and detoxification for both biochemical and psychological reasons. Separation of substance-induced anxiety and depression and primary anxiety and depressive disorders is important in the context of differential diagnosis and long-term treatment planning.

In addition to frequently co-occurring with alcohol use disorders, depression, posttraumatic stress disorder, and other anxiety disorders also influence performance on neuropsychological tests, and this needs to be disentangled from neuropsychological deficits directly attributable to alcohol misuse. The combined effects of psychiatric disorders and alcohol misuse on neuropsychological test performance are not yet well understood.

3. AGE

Earlier initial use of alcohol is associated with greater risk for alcohol dependence and sustained abuse (Portnoff, 1982). However, neurological and neuropsychological impairments are not predominant in patients with problematic drinking patterns even in their 30s who have been detoxified after even long-standing abuse (Adams et al., 1980). However, after age 40, continued abuse results in a greater probability of impairment even after detoxification (Adams & Grant, 1986). Mild neurological and neuropsychological impairments may emerge in middle age.

Older adults use alcohol at much lower rates than do young adults, which has been termed *maturing out*. However, between 15%

and 68% of elderly individuals treated for alcohol problems are late-onset drinkers; this is termed *maturing in* and has been associated with late-life challenges. In elderly hospitalized patients, incidence of alcohol abuse has been reported to be as high as 50%. Although research findings are mixed, there is some evidence of an interaction between age and drinking pattern (Kessler et al., 2005). In general, continued excessive use of alcohol may be especially detrimental to older individuals, particularly those in whom there is already evidence of impaired cognitive functioning.

4. GENETICS/FAMILY HISTORY

A great deal of research has demonstrated a genetic propensity for alcohol abuse and dependence. In general, persons who engage in problematic drinking who have a positive family history for alcoholism begin drinking at an earlier age and show evidence of antecedent neuropsychiatric deficits such as a childhood history of learning problems, hyperactivity, and psychiatric and conduct disorders. Thus, there is some suggestion that the neuropsychological correlates of alcohol misuse (i.e., executive deficits) may at least in part be associated with premorbid functioning.

5. DEVELOPMENTAL HISTORY

Extended alcohol use may act in conjunction with other risk factors for impairment in adulthood. These risk factors include birth or early developmental anomalies, learning disorder, or other illnesses that occur throughout development. One hypothesis for the etiology of this increased risk of impairment is the idea of "cognitive reserve" or the idea that a greater disease burden overall and less "reserve" capacity will ultimately result in greater impairment.

Intrauterine exposure to alcohol may result in fetal alcohol spectrum disorders, including fetal alcohol syndrome. Such exposure may predispose an individual to neuropsychiatric abnormalities later in life, including impaired general cognitive abilities, attention, learning, memory, and executive functioning. Number of drinks consumed per occasion and episodes of binge drinking by the mother have been shown to be the strongest predictors of cognitive function in the child (Streissguth et al., 1994). The effect of prenatal alcohol exposure is exacerbated in the context of low parental education and other psychosocial stressors.

6. NUTRITION STATUS

Individuals dependent on alcohol or those engaged in chronic abuse and binge drinking behaviors often have poor nutritional intake that can result in more severe manifestations of alcohol-induced neurological and neuropsychological impairment than might be seen

from excessive use of alcohol alone. Alcohol is known to directly inhibit gastric emptying and absorption of nutrients in the intestine, but lifestyle characteristics (i.e., poor intake) are likely to be the most important contributing factor to general malnutrition (Lieber, 2003). Thiamine deficiency in particular may be responsible to a great extent for the cognitive dysfunction, peripheral sensory loss, nystagmus, and gait difficulty seen in individuals with an excessive alcohol use history. Importantly, however, people differ in their susceptibility to thiamine deficiency.

Other nutritional deficiencies can also co-occur with excessive alcohol consumption and may affect cognitive abilities. For example, pyridoxine deficiency may result in encephalopathy and seizures, folate deficiency may result in peripheral neuropathy and dementia, iodine deficiency may result in thyroid dysfunction and associated cognitive impairment, and B12 deficiency may result in dementia.

B. Treatment

The most important step in the treatment of alcohol-related disorders is discontinuation of exposure to the substance responsible for neurological damage, ethyl alcohol. Acute intoxication and withdrawal must first be addressed from a medical perspective. After successful detoxification, neuropsychologists may play a role in addressing the underlying alcohol dependence, primarily by supporting patient abstinence. Motivational interviewing is an empirically supported approach to treatment of substance dependence that aims to move the patient toward behavior change by resolving ambivalence and increasing motivation for decreasing substance use in a nonconfrontational way (Miller & Rollnick, 2013).

Cognitive impairments such as memory and executive functioning deficits may result in poor treatment outcomes, as individuals may struggle to recall psychoeducational principles that have been presented to them and have difficulty adhering to medically based treatment recommendations. A relationship has been demonstrated between a brief cognitive screening measure (MoCA) and optimal attendance to group treatment sessions for substance abusers (Copersino et al., 2012). Impaired memory and executive functioning have been linked to lower motivation and readiness to change drinking behaviors (Le Berre et al., 2012). Thus, consideration of cognitive deficits is important in treatment planning for individuals with alcohol use disorders. Ecologically relevant cognitive rehabilitation may be an appropriate recommendation to improve treatment compliance and efficacy. Bates et al. (2004) made specific recommendations for remediation of substance-induced deficits.

C. Accurate Diagnosis

1. ALTERNATE ETIOLOGY

Objective evidence is necessary before one concludes that cognitive impairment is a direct result of an alcohol-related disorder. For example, many conditions can affect malabsorption of nutrients or hepatic dysfunction and should be ruled out before concluding on an alcohol-related etiology.

2. ACCURACY OF REPORTED HISTORY

Individuals who have alcohol use disorders often underreport the extent of their consumption of alcohol or deny alcohol use altogether (Del Boca & Darkes, 2003). Additionally, individuals who are actively intoxicated or cognitively impaired because of their alcohol misuse may be unable to give accurate reports of their histories. Thus, accurately quantifying alcohol use as part of assessment and treatment planning is a challenge.

3. METHODS TO INCREASE ACCURACY OF THE DIAGNOSIS

Clinicians who suspect the involvement of alcohol use in a clinical case on the basis of the presentation should thoroughly investigate this possibility via patient report as well as collateral informant, if available, and review of the medical record, including current lab values. Drug and alcohol screening should be recommended to the treating physician if substance use is suspected.

4. ASSESSMENT AND SCREENING OF HISTORY

Structured self-report measures may aid the clinician in their assessment of alcohol use history and current level of abuse and dependence. The Michigan Alcohol Screening Test (Selzer, 1971) and the Rapid Alcohol Problems Screen (Cherpitel, 2000) are brief instruments designed to assess a wide range of alcohol use behaviors and alcohol-related consequences with established cutoffs for indicating risk of alcohol use disorders. These instruments are not intended to be used in isolation, however, and should only augment the clinician's thorough interview and cognitive evaluation.

VI. CONCLUSION

Excessive use of alcohol can be associated with persistent neuropsychological impairment and neurological damage. Reduced learning, perceptual-motor deficits, and impaired executive functioning are the most likely neuropsychological impairments, although acceler-

ated forgetting may be associated with disorders such as Wernicke-Korsakoff's or hepatic encephalopathy that are alcohol related. White matter injury and generalized volume loss appear related to neuropsychological dysfunction, but the cellular mechanisms are not yet well understood. Neuropsychological deficits are not necessarily permanent, however, and with abstinence from alcohol, and without significant complicating factors such as older age and medical comorbidities, some degree of functional improvement can be expected over time. Neuropsychologists are in a prime position to aid in the understanding of deficits related to alcohol use and common comorbid factors and planning for treatment including increasing motivation for behavior change.

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PART III

NEURO-PSYCHOLOGICAL SYNDROMES

Chapter 17

Margaret G. O'Connor and Elizabeth Race

Amnestic Syndromes

Amnesia is defined as circumscribed memory loss resulting from brain injury, illness, or psychological disturbance in the context of preserved general intelligence and other cognitive abilities such as language, attention, executive functions, and perception. The most striking clinical symptom of amnesia is a severe deficit in remembering information from time periods after the onset of amnesia (*anterograde amnesia*). Amnesic patients demonstrate the greatest deficits in *declarative memory*, which refers to memory for information that can be consciously recalled (see Figure 17.1 for diagram of memory subtypes). Declarative memory includes memory for personally experienced events (*episodic memory*) as well as impersonal facts and concepts (*semantic memory*). Amnesic patients demonstrate declarative memory impairments on explicit memory tests requiring conscious retrieval of recent experiences, and they also demonstrate minimal ability to acquire new facts or concepts, particularly when this new information is difficult to incorporate into existing knowledge

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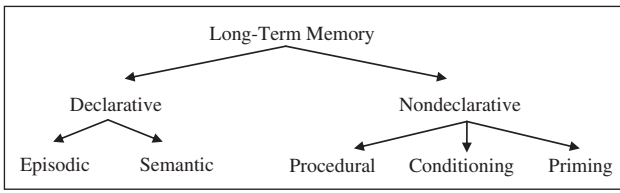
Figure 17.1. Subtypes of memory.



structures (e.g., words that have entered into the vocabulary since the onset of amnesia; Verfaellie, Reiss, & Roth, 1995).

Although amnesia is characterized primarily by impaired memory for facts and events encountered after its onset, memory loss for premorbidly acquired information (*retrograde amnesia*) is also common. Although many premorbid memories can be preserved in amnesia, patients may also demonstrate various profiles of retrograde amnesia. In some instances, retrograde amnesia is limited to days, weeks, or months before the onset of the illness, whereas in other instances it encompasses events and memories that extend back to the distant past. Retrograde amnesia for events immediately preceding the onset of amnesia is particularly pronounced. In addition, temporal gradients of memory loss, in which the magnitude of memory loss is inversely related to the age of the memory, can also be present. Retrograde amnesia that encompasses events from the distant past is associated with extensive neural damage in neocortical brain regions such as the frontal and temporal lobes (Kopelman, Stanhope, & Kingsley, 1999; Rempel-Clower, Zola, Squire, & Amaral, 1996). Cases of retrograde amnesia in the absence of significant anterograde amnesia are rare but have been described (Kapur, 1993a; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992). Retrograde amnesia is not necessarily a permanent condition in amnesia, and memory for various events may return with time. For example, following closed head injury or stroke, more distant memories may return before more recent memories, a phenomenon that has been referred to as *shrinking retrograde amnesia*. However, premorbid memory recovery is not always complete, and events most proximal to the onset of illness are often permanently lost.

In contrast to severely impaired declarative memory in amnesia, *nondeclarative memory*, defined as memory without awareness, is relatively preserved. Nondeclarative memory includes procedural memory (skills and habits), conditioning (learned associations between

two stimuli presented in close succession), and repetition priming (behavioral facilitation when processing repeated compared to novel stimuli). Repetition priming can take the form of perceptual priming (facilitated processing of visual information when visual information is repeated after an initial occurrence) and can also take the form of conceptual priming (facilitated processing of stimulus meaning when analysis of stimulus meaning is repeated).

Amnesic patients typically have intact performance on standard neuropsychological tests of short-term memory (STM) and working memory (WM), in which information is held in mind over short periods of time (Baddeley & Warrington, 1970). For example, amnesic patients are able to retain familiar verbal information, such as words or digits, over short delays of several seconds. However, recent evidence suggests that STM and WM may not be fully intact in amnesia when tests probe relational information (e.g., memory for the contextual features associated with an item). For example, amnesic patients with damage to the medial temporal lobes demonstrate impairments in retaining object-location conjunctions over 8-second delays (Olson, Page, Sledge, Chatterjee, & Verfaellie, 2006).

I. FUNCTIONAL NEUROANATOMY

Amnesia has been associated with damage in three major brain areas: the medial temporal lobe (MTL), diencephalon, and basal forebrain. The landmark case of patient H.M. highlighted the importance of the MTL for new learning (Scoville & Milner, 1957). Following bilateral temporal lobe resection to relieve intractable seizures, H.M. could not acquire new memories despite an above-average IQ and normal performance on tests of perception, short-term memory, and language comprehension. Studies with H.M. set in motion a number of investigations probing the neural substrates of amnesia, both with human and nonhuman primates.

Lesion and neuroimaging studies have shown that MTL subregions, including the hippocampus and adjacent cortical regions such as rhinal (entorhinal and perirhinal), subicular, and parahippocampal cortices, are involved in different aspects of memory. The hippocampus and entorhinal cortex are critical for *associative memory*—the ability to remember relations among items (e.g., a face/name pair)—underscoring their role in the binding of disparate events at the time of encoding and retrieval (Kirwan & Stark, 2004). Dissociable aspects of recognition memory have also been studied. Patients with damage limited to the hippocampus proper have impaired recollection (memory for a prior encounter with its contextual source) but preserved familiarity (subjective feeling of knowing that an item was

previously encountered without any knowledge of the context in which it was encountered; Verfaellie & Keane, 2002). Patients with restricted hippocampal damage perform poorly on free recall tests (an index of recollection), but they demonstrate intact performance on item recognition tests (an index of familiarity). In contrast, patients whose lesions extend into extrahippocampal regions of the MTL, such as perirhinal cortex, demonstrate severe explicit memory impairments that include both recollection and familiarity (Yonelinas et al., 2002) and perform poorly on both recall and recognition tests, although impairments in recall may be more severe than impairments in recognition. Finally, lesions that spare the hippocampus but include the perirhinal cortex produce selective impairments in familiarity. Wolk, Dunfee, Dickerson, Aizenstein, and DeKosky (2011) provided converging neuroimaging support for a double dissociation between recollection and familiarity, emphasizing the role of the hippocampus in recollection and the role of extrahippocampal MTL regions in familiarity.

Amnesia is also associated with damage to midline thalamic structures (including the internal medullary lamina as well as medial and dorsomedial thalamic nuclei) and mammillary nuclei (Cramon, Hebel, & Schuri, 1985; Markowitsch, 1988). Patients with diencephalic amnesia often have deficits in the initial processing stages of memory and lack insight into their memory disturbances. Basal forebrain amnesia occurs as a result of damage in the medial septal nucleus, the diagonal band of Broca, and the nucleus basalis of Meynert (Damasio, Graff-Radford, Eslinger, Damasio, & Kassell, 1985). The basal forebrain is thought to contribute to memory function by providing cholinergic innervation to critical memory structures, including the hippocampus and amygdala. Although basal forebrain damage combined with lesions in striatal and frontal brain areas produces severe amnesia, discrete lesions to the basal forebrain can also result in global anterograde and retrograde amnesia (Morris, Bowers, Chatterjee, & Heilman, 1992).

Other investigations have highlighted the prominent role of the amygdala in emotional learning and memory. The amygdala is extensively connected to other limbic system structures and association cortices. Damage to the amygdala impairs a range of emotional behaviors related to implicit learning (e.g., fear conditioning) as well as explicit memory (Le Doux, 1996). The amygdala acts to enhance the strength of declarative memories for emotional events by modulating the storage of these memories and is important for the explicit learning of emotional properties of stimuli (Phelps et al., 2001).

The extent and location of lesions both within and outside of the MTL greatly impact the nature and severity of memory impairment. The elegant anatomical work of Mishkin and others highlighted

the importance of dual limbic pathways in new learning—a medial circuit (hippocampus, fornix, mammillary bodies, anterior medial nucleus of the thalamus, and cingulate cortex) and a lateral circuit (amygdala, dorsal medial nucleus of the thalamus, orbitofrontal cortex, and uncus). Mishkin opined that disruption in both medial and lateral circuits is necessary for severe anterograde memory loss, but this remains subject to debate, as others have described severe amnesia in the context of isolated hippocampal damage. Additional damage to frontal systems can impact memory by causing dysexecutive syndrome. Specifically, frontal lesions impair executive processes that contribute to memory, such as the ability to mentally manipulate and organize information to be encoded into memory and the ability to initiate and evaluate memory search. Frontal lesions, particularly lesions to the orbital and ventromedial prefrontal cortex, have also been linked to the phenomenon of confabulation. Confabulation is thought to relate to impaired monitoring of information retrieved from memory.

It has been proposed that limbic structures play critical, but temporary, roles in new learning. Observations of intact remote memory in the context of anterograde amnesia suggest that information eventually becomes independent of limbic circuitry. According to the traditional model of consolidation, limbic circuitry is critical for the retrieval of recent memories that have yet to be consolidated (Squire & Alvarez, 1995). However, the presence of extensive temporal gradients of autobiographical memory loss in amnesia is difficult to incorporate into this view, as the loss of such memories extends well beyond the time frame of biological consolidation. An alternative theory of consolidation, multiple trace theory, proposes that limbic regions (and the MTL in particular) are always necessary for the retrieval of episodic memories (including both recent and remote autobiographical memories), but that older memories become more resistant to disruption because each time a memory is retrieved a new memory trace is established and is linked to the older memory traces (Nadel & Moscovitch, 1997). According to this view, older memories are represented by more numerous and stronger traces that are more resistant to partial lesions of the MTL and related memory circuitry, whereas newer memories are represented by fewer and weaker traces that are more vulnerable to neural damage. Thus, the extent of amnesia may be determined by the amount and location of neural damage as well as the number of traces by which a memory is represented. Neuropathological investigations have shown an association between severity of retrograde amnesia and extent of pathology in the hippocampus and adjacent cortices (Rempel-Clower et al., 1996).

II. SUBTYPES OF AMNESIA

Amnesic patients present with a variety of medical conditions and psychosocial issues that influence their patterns of memory loss and residual learning skills. One way of reducing this variability is to group amnesic patients according to sites of neuropathological damage (i.e., medial temporal lobe, diencephalon, or basal forebrain damage; see Table 17.1 for neurological illnesses associated with amnesia). Historically, patients with MTL amnesia have been described as having (a) preserved insight, (b) increased rate of forgetting, (c) limited retrograde amnesia, and (d) lack of confabulation. However, more recent studies demonstrated that accelerated forgetting does not differentiate MTL patients from other amnesic patients (McKee & Squire, 1992), and questions have arisen regarding the notion that patients with MTL amnesia have a limited retrograde amnesia.

Patients with diencephalic amnesia have memory deficits attributed to damage in medial thalamic structures, mammillary bodies, or both regions (Markowitsch, 1982). Patients with diencephalic damage have dense anterograde amnesia but forget information at a normal rate (i.e., their rate of forgetting parallels that of nonamnesic patients). Confabulation and diminished insight often occur in this group as a result of additional disruption of frontal networks.

Patients with basal forebrain amnesia exhibit attention difficulties that adversely affect encoding and retrieval. Under some circumstances delayed recognition is normal, suggesting that consolidation is relatively intact. Patients with frontal amnesia often lack insight into their memory problems, and they tend to confabulate. Deficits are seen on tasks of proactive interference, contextual memory (memory for temporal and spatial aspects of events), and semantic categorization. Some frontal amnesics present with retrograde amnesia due to impaired retrieval of previously stored information.

A number of investigators have argued that anatomically based classification systems are reductionistic because they fail to consider the interplay of processing deficits that affect the memory profiles of amnesic patients (Weiskrantz, 1985). Others have questioned the validity of neuropsychological subtyping because there are inconsistencies in studies on forgetting rates and contextual memory. Bauer (2010) argued that subtype differences may exist but noted that these are largely due to associated pathology in cortical and subcortical structures rather than reflecting differential contributions of core MTL, thalamic, and basal forebrain memory regions. For example, confabulation in the basal forebrain group is likely due to frontal involvement not present in temporal lobe amnesia. Finally, comparisons across subtypes may be influenced by selection biases. For instance, diencephalic amnesia studies are often restricted to patients

Table 17.1. Neurological Illnesses Associated With Amnesia

Illness	Lesion	Disturbance	Reference
Anterior communicating artery aneurysms	Basal forebrain (restricted) Basal forebrain + sriatum	Mild memory problems Severe amnesia	Irle et al. (1992)
Herpes simplex encephalitis	Medial temporal lobe Lateral temporal lobe Lateral temporal cortex	Verbal learning, nonverbal learning, severe anterograde Retrograde amnesia	Kapur et al. (1994) Utley, Ogden, Gibb, McGrath, & Anderson (1997)
Anoxic encephalopathy	Medial temporal lobe	Anterograde amnesia; variable effects on remote memory	Zola-Morgan, Squire, & Amaral (1989)
Posterior cerebral artery infarct	Medial temporal lobe	Material-specific memory loss associated with lesion laterality	Benson et al. (1974); Ott & Saver (1993)
Wernicke-Korsakoff Syndrome	Anteromedial, dorsomedial and intralaminar thalamic nuclei; mammillary bodies and frontal network systems	Anterograde and temporally graded retrograde amnesia	von Cramon et al. (1985); Victor et al. (1989)

with Wernicke-Korsakoff Syndrome (WKS), who have limited education and extensive histories of alcohol abuse. These patients often differ from those with MTL amnesia who have participated in research studies and tend to have higher intelligence and socioeconomic status. It may be that these extraneous differences affect memory differetially, thereby confounding subtype comparisons.

III. MEDICAL CONDITIONS ASSOCIATED WITH AMNESIA

Amnesia can result from a range of medical events as deliberate as surgery or as unpredictable as an infection. In the vast majority of cases, amnesia is a permanent condition. If amnesia is due to a neurodegenerative brain process, such as Alzheimer's disease, the individual's memory will worsen over time. If amnesia is due to a static problem such as a stroke, anoxia, or encephalitis, the memory problem will persist, but it will not worsen beyond normal age-related decline. Some individuals have unusual medical conditions associated with amnestic "spells" from which they seem to recover. They may present with serious memory lapses, but between these spells they seem well able to learn and retain new information.

A. Transient Amnesia Due to Medical Conditions

In most instances, the term *amnesic* is restricted to patients with isolated and stable memory impairment that presents acutely and is permanent. However, some patients suffer from memory disorders that change over time. *Transient global amnesia* (TGA) is a condition involving the acute onset of memory loss for a period of hours to days. TGA may occur as a result of decreased perfusion in hippocampal circuitry (Schott, 2008). Magnetic resonance (MR) spectroscopy studies have shown that TGA is associated with acute but not long-term metabolic changes in the CA1 sector of the hippocampus (Bartsch et al., 2008). Patients with TGA demonstrate profound anterograde amnesia and variable profiles of retrograde amnesia. There is often complete resolution of TGA if testing is conducted weeks or months after the episode; however, some TGA patients have residual deficits on challenging tests of verbal long-term memory. Semantic memory, procedural learning, and implicit memory have been described as intact during the TGA episode.

Transient amnesia has also been described in conjunction with epilepsy. Some patients with temporal lobe epilepsy experience temporary episodes of amnesia referred to as *epileptic amnesic syndrome*

or *transient epileptic amnesia* (Kapur, 1993b). These episodes may occur frequently and may be associated with subtle behavioral disturbances. Performance on formal neuropsychological tests may be normal despite patients' subjective memory complaints. Some patients with temporal lobe epilepsy have extensive remote memory problems in comparison with mild or moderate disturbances of anterograde memory (O'Connor, Sieggrreen, Ahem, Schomer, & Mesulam, 1997). Researchers have identified subtle hippocampal atrophy in the transient epileptic amnesia group correlating with performance on measures of new learning but not with measures of accelerated forgetting or remote memory (Milton et al., 2010).

Electroconvulsive therapy (ECT) has also been associated with amnesia. *ECT-related anterograde amnesia* dissipates within days or weeks following cessation of treatment. A more common and persistent side effect of ECT is retrograde amnesia characterized by deficient memory for events and information learned prior to treatment (Lisanby, Maddox, Prudic, Devanand, & Sackeim, 2000; O'Connor et al., 2008). Investigations of ECT-related retrograde amnesia have relied largely on retrospective analyses of memory for personal and public events from the weeks, months, and years preceding treatment. Early studies by Squire and colleagues demonstrated that bilateral sine-wave ECT disrupted recall of past news events and television programs (Squire, Slater, & Chace, 1975). Studies by Sackheim (2000) have shown that brief pulse ECT has an attenuated effect on new learning. However even brief pulse ECT may interfere with recall of past memories. Of note, events that occur proximal to the initiation of treatment are particularly sensitive to the disruptive effects of ECT (O'Connor et al., 2008).

B. Surgical Ablation

Over the last 40 years, there have been many investigations of H.M., who underwent bilateral temporal lobe resection for treatment of refractory seizures (Milner, 1966; Scoville & Milner, 1957). Findings from these studies greatly influenced theories regarding the neuroanatomical underpinnings and psychological parameters of memory. H.M.'s clinical profile and profound amnesia underscored the critical roles of MTL regions in new learning. More recent work with H.M. supported theories suggesting that distinct brain systems mediate procedural versus declarative memory as well as performance on tasks of implicit versus explicit memory. Surgical intervention remains a treatment option for patients with intractable epilepsy. However, knowledge gained from H.M.'s unfortunate outcome resulted in modifications in epilepsy surgery programs. Surgery is now limited to unilateral temporal lobe removal and is typically performed after

careful neuropsychological evaluation, which includes intracarotid amobarbital studies to minimize the risk of postoperative amnesia. Of note, patients with unilateral temporal lobectomies may have material specific memory problems in the aftermath of surgery. Patients with left cerebral dominance for language may have verbal memory loss following left resection, whereas facial and spatial memory problems may emerge in the wake of a right temporal lobe surgery.

C. Herpes Simplex Encephalitis

Herpes simplex encephalitis (HSE) is the most common cause of nonepidemic, sporadic viral encephalitis in the United States. The diagnosis of HSE depends on identification of herpes simplex virus within the cerebrospinal fluid or within brain tissue by means of brain biopsy. Other methods of diagnosis include electroencephalography and brain imaging studies. Magnetic resonance imaging (MRI), the preferred imaging diagnostic method, often shows edema very early in the onset of the viral infection. The brain involvement is typically diffuse, with petechial hemorrhages and necrosis distributed in an asymmetric fashion throughout the medial temporal and inferior frontal lobes. Kapur, Barker, Burrows, Ellison, and Brice (1994) examined imaging studies of 10 patients with HSE. In their group, lesions always involved brain regions beyond the hippocampus, including the parahippocampal gyrus, the insula, basal forebrain, mammillary bodies, and the fornix. Anterior and inferior temporal cortices were invariably damaged more extensively than superior and posterior temporal gyri. Less common was damage in frontal brain regions and thalamic nuclei.

HSE patients initially present with confusion, impaired memory, aphasia, and agnosia that may gradually resolve to a circumscribed amnesic syndrome. A significantly better outcome occurs in HSE survivors when acyclovir is administered early in the course of illness. There is a great deal of variability in the type and extent of preserved and impaired memory skills in HSE. Specific patterns of memory loss vary in conjunction with the location of the lesion; disproportionate verbal learning difficulties are associated with greater left hemisphere involvement, whereas nonverbal deficits are associated with more extensive lesions in the right hemisphere (Eslinger, Damasio, Damasio, & Butters, 1993). Neuroimaging studies have shown that hypometabolism in retrosplenial and medial temporal regions is associated with amnesia in patients with HSE, whereas frontal hypometabolism may be associated with executive deficits (Reed et al., 2005). Patients with HSE may demonstrate extensive retrograde amnesia. A single case study of an HSE patient with

extensive right lateral and medial damage revealed intact anterograde memory but deficient visual imagery and a profound loss of autobiographical memories dating back to childhood (O'Connor et al., 1992). Other cases of visual memory loss and severe autobiographical amnesia have been described in patients with encephalitis (Greenberg, Eacott, Brechin, & Rubin, 2005). Semantic memory problems, including a loss of knowledge of vocabulary, have also been described in the HSE patient group, and these may extend back for decades. Circumscribed semantic memory deficits can occur that differentially affect memory for concepts pertaining to living versus nonliving things or differentially affect memory for people's names but not for major events related to the same people. In another unusual pattern of memory loss, an HSE patient's inability to generate images for colors of his personal possessions was associated with right temporal and frontal abnormalities on EEG and single photon emission computed tomography (see online resources for a number of relevant papers).

D. Hypoxic Ischemic Brain Damage

Anoxic encephalopathy occurs as a result of cardiac arrest, respiratory distress, strangulation, or carbon monoxide poisoning. When oxygen saturation is depleted for 5 minutes or more, permanent brain damage occurs as a result of the accumulation of pathological excitatory neurotransmitters or lactic acid. A sustained hypoxic episode can result in extensive cerebral and cerebellar brain damage that produces a variety of cognitive, perceptual, and motor abnormalities. However, because the medial temporal lobes are particularly sensitive to oxygen deprivation, hypoxia may result in circumscribed amnesia. Area CA1 of the hippocampus has been identified as particularly sensitive to the effect of hypoxic ischemic damage. An isolated lesion in this area can result in moderate amnesia with minimal effect on remote memory (Zola-Morgan, Squire, & Amaral, 1986). In addition to affecting the hippocampi, hypoxia may affect the integrity of white matter fibers in limbic circuitry (Di Paola, Moscatelli, Bigler, Caltagirone, & Carlesimo, 2011).

The memory impairment following an anoxic event is similar to that of frontal amnesia where the deficit is one of retrieval, rather than encoding, as a result of impaired systematic search initiation processes. Anoxic patients typically benefit from cued and recognition formats. This type of memory disorder can be accounted for by the fact that the sustained oxygen deprivation preferentially damages the watershed zones of the cerebral cortex, including that of the frontal watershed cortex and basal ganglia structures. In addition to amnesia, patients with anoxic encephalopathy may suffer from a

number of other cognitive difficulties, including perceptual and executive deficits as well as motor problems. Alexander, Lafleche, Schnyer, Lim, and Verfaellie (2011) found variable outcomes for survivors of cardiac arrests with slow recovery (i.e., they were comatose for at least 12 hours and confused for at least 7 days). Three months post–cardiac arrest, two thirds of the patient group had moderate deficits in memory and psychomotor functions. The remaining patients had pervasive cognitive impairment in all domains. Residual abilities correlated significantly with coma duration.

E. Cerebral Vascular Accidents

Amnesia secondary to bilateral posterior cerebral artery (PCA) infarction has been well described in the literature. In addition, some investigators have described patients with memory deficits in the wake of unilateral (primary left) PCA infarction (Benson, Marsden, & Meadows, 1974; Ott & Saver, 1993). Unfortunately, many investigators have failed to include measures of nonverbal memory and rate of forgetting in their description of PCA-related amnesia. Consequently, it is difficult to determine whether the memory deficits of patients with unilateral PCA infarction are qualitatively or quantitatively different from those of other amnesic patients. Another vascular event associated with memory loss is infarction of thalamic arteries, particularly the tuberothalamic and paramedian vessels. There is some variability in neuropsychological profiles related to lesion location. A number of cases have been described with memory loss secondary to unilateral damage. Material-specific deficits (i.e., disproportionate impairment for either verbal or nonverbal information) may occur as a result of unilateral thalamic damage (Speedie & Heilman, 1982; see Chapter 8 for a thorough discussion of amnesia in the context of cerebrovascular disease).

F. Anterior Communicating Artery Aneurysms

Approximately 40% of patients who suffer rupture and undergo surgical clipping of anterior communicating artery (ACoA) aneurysms present with impairments in memory and personality changes. Descriptions of patients with ACoA emphasize amnesia, apathy, disorientation, and confabulation, symptoms that may occur secondary to vasospasm, hematoma formation, herniation of the medial temporal lobes, hydrocephalus, and surgical intervention. Heterogeneity in the neuropsychological presentations of these patients is due to variability in the site of neural damage. Brain lesions are seen in basal

forebrain, striatum, and frontal regions. It is widely assumed that basal forebrain damage is the critical underpinning of the memory deficits in this patient group, although some investigators have suggested that combined basal forebrain and striatal lesions may be necessary to account for severe memory problems (Irle, Wowra, Kunert, Hampi, & Kunze, 1992).

Patients with ACoA aneurysms are often described as suffering from attentionally based memory problems. They tend to benefit from recognition cues, perhaps as a consequence of deficient strategic retrieval. Performance on tasks of remote memory varies. ACoA patients may demonstrate retrograde amnesia on tasks of public events knowledge, but this tends to be less severe than that seen in the temporal lobe lesion patients. Patients with ACoA aneurysms are prone to confabulation (Diamond, DeLuca, & Fisher, 2000), which may vary in tandem with poor source monitoring due to frontal systems involvement (D'Esposito, Alexander, Fischer, McGlinchey-Berroth, & O'Connor, 1996).

G. Wernicke-Korsakoff Syndrome

Patients with WKS develop amnesia as a result of chronic alcohol abuse and thiamine deficiency. The onset of WKS is typically marked by an acute phase in which the patient presents with oculomotor palsies, gait ataxia, and encephalopathy, although these symptoms do not necessarily co-occur in the same patient. It has been suggested that at least two of the following criteria should be met for a diagnosis of Wernicke's encephalopathy: (a) altered mental status; (b) dietary deficiency; (c) cerebellar dysfunction; and (d) oculomotor abnormalities (Caine, Halliday, Kril, & Harper, 1997). MRI can inform diagnosis in that, in the early phase, lesions appear within the diencephalon and periaqueductal gray on T2 and diffusion-weighted images. Acute treatment with thiamine results in rapid improvement in neurological signs and MRI signal abnormalities. However, many patients are left with an enduring, dense amnesia and personality changes that are characteristic of the Korsakoff stage of the syndrome.

The chronic phase of WKS is characterized by a dense anterograde amnesia in which patients have difficulty learning new verbal and nonverbal information (e.g., names, faces, facts) and have increased sensitivity to interference (Verfaellie & Cermak, 1992). Patients with WKS are also prone to irritability and apathy, problems that often undermine performance on tasks of new learning. In addition to anterograde amnesia, many WKS patients demonstrate retrograde amnesia characterized by a temporal gradient of memory

loss for autobiographical and semantic information, with relative preservation of more remote compared to more recent information (Kopelman et al., 1999). However, interpretation of retrograde amnesia in WKS is complicated by premorbid lifestyle characteristics related to severe alcohol abuse (e.g., long-standing social isolation and general lack of interest in world events) that can adversely affect performance on tests measuring knowledge of past public events. Confabulation and source memory errors (e.g., "false memories") can also occur in WKS.

The neuropathological profile of the chronic phase of WKS has been well documented by postmortem pathology and in vivo MRI. Structural damage and functional impairment occur most notably in the anteromedial and dorsomedial nuclei of the thalamus and the mammillary bodies and are accompanied by atrophy and neural dysfunction in frontal and parietal neocortical areas (Paller et al., 1997; Victor, Adams, & Collins, 1989). Although the extent to which these areas separately or collectively result in amnesia is controversial, anterograde amnesia has primarily been linked to neuropathology in the limbic system, whereas concomitant neocortical damage (particularly in the frontal lobes) has been emphasized with respect to the neural substrates of extensive, temporally graded remote memory impairment in WKS (Kopelman et al., 1999).

IV. NEUROPSYCHOLOGICAL EVALUATION

The evaluation of amnesia takes place in the context of a comprehensive assessment of intelligence, attention, executive functions, language, perception, and emotional status (see Figure 17.2). Information regarding performance across a broad array of neuropsychological tasks is important for diagnostic and therapeutic purposes (various clinical instruments are reviewed in Table 17.2). A diagnosis of focal amnesia cannot be made unless it is firmly established that the individual is intact in other cognitive domains. Information regarding baseline IQ and other cognitive functions facilitates the determination of the extent of severity of the memory impairment. Individuals with high cognitive reserve may have memory problems that are difficult to detect with standard test measures, and cutoff scores for a diagnosis of memory impairment need to be adjusted with consideration of baseline intelligence. A detailed analysis of attention is conducted to determine the relevance of problems with attention span, vigilance, and selective attention on new learning. Examination of executive functions is very important, because difficulties with them may result in problems in self-monitoring and a propensity for confabulated memories. Examination of language is

Figure 17.2. Evaluation of amnesia.

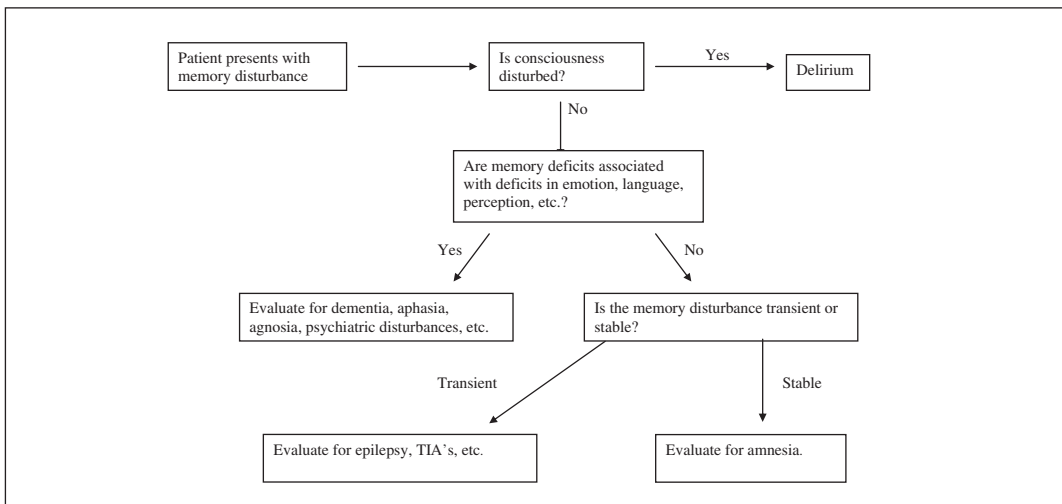


Table 17.2. Clinical Evaluation of Memory

Test	Focus of assessment	Reference
Rey Auditory Verbal Learning Test	Learning curve, recency and primacy effects, proactive and retroactive interference	Rey (1941)
Rey–Osterrieth Complex Figure	Nonverbal (visual) memory	Rey (1941)
California Verbal Learning Test-II	Learning curve, proactive and retroactive interference, semantic memory, forced-choice recognition	Delis, Kramer, Kaplan, & Ober (2000)
Wechsler Memory Scale-IV	Working memory, single-trial learning, learning slope, retention, retrieval	Wechsler (2009)
Biber Figure Learning Test	Non-verbal (visual) memory that parallels verbally based list learning tasks; learning curve recall and recognition, proactive and retroactive interference	Glosser, Goodglass, & Biber (1989)
Warrington Recognition Memory Test	Verbal and non-verbal recognition memory	Warrington (1984)
Doors and People Test	Overall Score; visual-verbal discrepancies; recall-recognition discrepancies, forgetting score.	Baddeley, Emslie, & Nimmo-Simth (1994)
Brief Visuospatial Memory Test-Revised	Visuospatial memory; learning curve; immediate and delayed recall; recognition, alternative forms	Benedict (1997)
Autobiographical Memory Interview	Remote autobiographical memory	Kopelman, Wilson, & Baddeley (1989)
Crovitz Procedure	Remote memory	Crovitz & Schiffman (1974)

Table 17.2. Clinical Evaluation of Memory *(Continued)*

Test	Focus of assessment	Reference
Famous Faces Test	Remote memory for public figures	Albert, Butters, & Levin, (1979)
Transient News Events Test	Remote memory for public events, recognition and recall	O'Connor, Sieggrreen, Ahem, Schomer, & Mesulam (1997)

critical to understand whether difficulties with verbal learning and semantic memory are due to aphasia rather than amnesia.

The clinical assessment of memory has been influenced by historical trends in cognitive psychology research. Early models of amnesia emphasized disruptions in various stages of learning. On the basis of their work with WKS patients, Butters and Cermak (1980) identified encoding deficits as the critical problem in amnesia. Investigations of patient H.M., who underwent resection of bilateral medial temporal brain regions, led Milner (1966) to speculate that amnesia was due to the interruption of information from short- to long-term memory, thereby highlighting the role of consolidation deficits in amnesia. In their studies of patients with various medical conditions, Warrington and Weiskrantz (1970) found that amnesic patients had retrieval deficits. Despite the fact that researchers no longer view amnesia as a unitary deficit in a specific stage of learning, the clinical assessment of amnesia continues to focus on encoding, consolidation, and retrieval deficits. Recognition and recall are compared to determine the extent to which encoding or retrieval is deficient. A failure to respond to retrieval cues and recognition probes suggests that the material was never encoded to begin with. In contrast, a disparity favoring (intact) recognition over (impaired) recall suggests intact encoding and deficient retrieval. Information regarding consolidation is based on a comparison of immediate versus delayed memory. Some individuals, particularly those with medial temporal involvement, are prone to rapid forgetting. Their immediate memory may be intact, despite their markedly deficient performance on delayed memory tasks.

In addition to examining disruptions in memory stages, a comprehensive assessment of memory focuses on the circumstances

that influence the acquisition and retention of new material. Tests vary with regard to processing demands at encoding and retrieval. Manipulations of presented stimuli include duration of presentation, number of items, extent of organization, and nature of to-be-remembered information. Increased stimulus duration facilitates memory. Cognitive studies focused on levels of processing indicated that deeply processed material (i.e., information processed for meaning) is better remembered than information processed according to visual or acoustic attributes. Extent of organization and semantic integration have differential effects on memory. An arbitrary list of words may be challenging for individuals with attention limitations, whereas a story may be problematic for individuals with deficits in discourse analysis due to developmental learning disabilities. List length is another factor that affects memory performance. Individuals with advanced age, intellectual limitations, or attention deficits may be less adept at encoding a lengthy list of items, but they may have reasonable learning curves in that they benefit from repeated exposure to material over successive trials. Serial presentation of a supraspan list (one that exceeds attention-span limitations) provides information regarding the extent to which repetition enhances learning. Encoding processing demands may also vary with regard to whether items are presented as discrete entities or as unrelated items between which the individual is required to form new associations. Research studies have shown that associative memory is more sensitive to hippocampal damage than is item memory (Kirwan & Stark, 2004). Paired associate learning is more challenging when the individual is asked to form associations between dissimilar (e.g., face–name, object–location pairs) versus similar (e.g., word–word pairs) types of information. Other encoding manipulations focus on the nature of the to-be-remembered material (e.g., semantic/episodic; verbal/nonverbal, emotional/neutral). Most amnesic patients have intact semantic memory for information acquired before the onset of amnesia, but they cannot learn *new* semantic information and their episodic memory is impaired. However, individuals with semantic dementia, a form of frontotemporal dementia, demonstrate the opposite pattern in that semantic knowledge is disrupted but episodic memory remains intact. Individuals with lateralized lesions have different learning capacities for verbal versus nonverbal information. Patients with brain damage confined to the left medial temporal lobe have disproportionate problems on tasks of verbal memory (e.g., stories, word lists), whereas individuals with right-sided damage have difficulty learning and retaining facial and spatial stimuli. Emotional salience and personal significance should also be studied, as these factors have significant effects on new learning.

There are many factors that complicate the assessment of retrograde memory. Personal memories from the remote past are difficult

to verify, and it is not possible to determine whether deficient recall is due to inadequate encoding at the time of initial exposure or disruption of the retrieval process. Some individuals, particularly those with frontal systems damage, produce confabulated memories based on actual events that have been erroneously integrated with other information. Other individuals produce well-articulated memories that include spatial and temporal elements (e.g., a memory for sharing a meal with a good friend the prior day). Because these recollections are contextually based, they are considered episodic. The assessment of retrograde amnesia also focuses on recall of information from the public domain (i.e., news events and popular culture). The problem with these queries has to do with the marked variability in individuals' premorbid fund of knowledge. Variations in performance often reflect differences in baseline intelligence and interest in world events.

V. TREATMENT

A detailed review of treatment strategies is beyond the scope of this chapter and may be found in books and manuals about memory remediation. There is no "one size fits all" set of recommendations for individuals with memory problems. Thoughtful recommendations are tailored to each individual's pattern of vulnerabilities as well as his or her residual learning capacities. Treatment interventions encompass medications, technology, mnemonic strategies, and psychosocial support. Medications that enhance attention have been used successfully for individuals with mild encoding problems; however, attention-enhancing medications do not mitigate the deficits of the person with amnesia. Novel technological advances used in the treatment of epilepsy and Parkinson's disease have important implications for memory. Deep brain stimulation of the entorhinal cortex has been shown to have positive effects on memory for spatial information in epilepsy surgical candidates. Electrical stimulation, administered over the course of a year, had lasting effects on neural transmission in entorhinal and hippocampal cortices as well as in the default network in patients with mild Alzheimer's disease (Laxton et al., 2010). These results are preliminary, but they underscore the important role of technology in future memory treatment.

A wide variety of cognitively based mnemonic interventions can be employed. Traditional "internal" memory strategies include imagery, associative strategies, elaborative encoding, and spaced presentation of new information. The use of imagery to augment memory has been known since the time of the ancient Greeks. Although teaching patients to link two words with a mental image,

thereby reducing the informational load and creating a more unique and salient visual cue for subsequent recall, is helpful for individuals with mild memory loss, it has not proven effective for people with amnesia. In fact, there have been only a few studies showing that cognitive interventions benefit people with moderate to severe memory problems. In the 1980s, the "vanishing cues" technique was used by Glisky and colleagues with a densely amnesic patient who was able to learn a computer-based vocabulary (Glisky, Schacter, & Tulving, 1986). The patient was required to produce the desired word in response to its definition. He was initially given as many letters of the word as needed to evoke the correct response. During successive trials, he was asked to recall the correct word in response to fewer and fewer cues. Cues continued to "vanish" until he was able to produce the correct word without any cues. The success of vanishing cues was attributed to intact priming in amnesia; however, learning did not generalize beyond the specific task, and multiple training sessions were needed. More recent studies have used memory interventions with amnesic patients with mild cognitive impairment (Hampstead, Stringer, Stilla, Amaraneni, & Sathian, 2011). Associative imagery training resulted in improved memory outcomes and increased hippocampal activity in this group. Spaced presentation and elaborative strategies have also been used effectively to mitigate mild memory loss, but these techniques are not useful for the patient with amnesia. The most practical treatment for amnesic patients pertains to the identification of pragmatic and accessible supportive resources that are chosen with consideration of each individual's specific family and social circumstances.

VI. CONCLUSION

Over the past five decades, clinical and research investigations of amnesic patients have yielded fascinating insights regarding the psychological parameters and biological substrates of memory. Neuropsychologists have attempted to identify conditions that facilitate learning for memory-impaired patients, including environmental supports, pharmacological intervention, and cognitive remediation. The neuropsychological evaluation provides the framework for remediation. Information derived from clinical assessment highlights residual learning abilities as well as learning deficits. This information may influence whether pharmacological intervention is warranted: Severely amnesic patients do not derive a great deal of benefit from medications, whereas patients with mild attentionally based difficulties may respond to some medications. Pragmatic recommendations should be individually tailored to each patient's cognitive and emotional needs.

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Chapter 18

David S. Sabsevitz and Thomas A. Hammeke

The Aphasias

Language refers to a system of communication that uses a variety of arbitrary symbols to convey meaning. It serves as the foundation for the bidirectional communication of thought. Arguably, the symbolic representation enabled by language underlies most of what we consider uniquely human.

Aphasia is a neurological condition whereby language processing is disturbed as a result of regional brain dysfunction. Aphasia can result in disturbance of language comprehension, production, or both. There is no single behavioral presentation associated with aphasia. Rather, depending on the location and size of the underlying brain lesion, there are constellations of impairments that vary in severity and can cluster into one of the recognized syndromes. Although many of the chapters in this volume include classification schemes along with definitions, the classification of aphasia is complex enough to merit its own section (Section V).

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I. DIFFERENTIAL DIAGNOSIS

Although disorders of speech production and comprehension can co-occur with aphasia, the presence of one is not a reliable indicator of the other. Careful evaluation of the patient's condition is critical to proper diagnosis.

Even though language and speech are closely related functions, many individuals with disorders of speech have normal linguistic capacities. Disorders of language (the aphasias) are associated with impairments in the ability to comprehend, formulate, and produce spoken, written, and gestural symbolic representations, whereas disorders of speech involve impairment in control over the articulatory musculature needed for oral expression. For example, the most common disorder of speech is *dysarthria*—the difficulty in articulation of speech sounds due to weakness, paralysis, or poor coordination of the muscles of the vocal cords, tongue, lips, and/or respiration. If severe enough, dysarthric output may be unintelligible; however, the content and syntax of the intended communication are often normal, as can be shown through inspection of written communication.

Mutism, another form of speech disorder, involves a failure to produce speech sounds that may or may not be accompanied by aphasia. Mutism can result from neurological injury (e.g., akinetic mutism following damage to the cingulate gyrus) or be seen in certain psychiatric conditions (e.g., conversion disorders, selective mutism, catatonia). While mutism can occur during the very early stages of aphasia, most aphasic patients can produce some verbal output. A diagnosis of aphasia should not be given unless there is evidence that language functions are disrupted in addition to the production of speech sounds. *Aphonia* (loss of capacity to produce vocal sounds due to vocal cord dysfunction) and *aphemia* (pure motor aphasia due to apraxia of speech articulation, usually due to a small lesion in the inferior frontal region) are other forms of speech disorders that do not inherently imply that a language disorder is present.

Other conditions can affect input or output mechanisms for linguistic operations and not affect the linguistic processes themselves. For example, isolated sensory-perceptual or motor impairments are not necessarily associated with aphasia. Thus, it can be shown that an individual who has become deaf or blind, either from peripheral or central mechanisms, or hemiplegic in the dominant hand, can demonstrate normal linguistic processes when tested through the preserved modality of sensory input or motor output. Similarly, mispronunciations of words that occur because of cultural development are not disturbances in language.

The disorganized speech that often occurs in schizophrenia is generally not considered a disorder of language but a disorder of

thought content or the executive functions that control linguistic and speech operations (Covington et al., 2005). Still, the clinical presentation of schizophrenia is at times confused with aphasia, typically one of the fluent aphasias (see the classification of fluent aphasias later in this chapter). Table 18.1 summarizes the clinical features that more commonly distinguish the fluent aphasia from the speech abnormalities seen in schizophrenia. The course and context of the clinical presentation often provide helpful distinguishing markers too. For example, a gradual onset in late adolescence or young adult life and having a personal and familial psychiatric history are typical in schizophrenia. Conversely, an abrupt onset in an elderly patient that is associated with other neurological findings (e.g., visual field defect, hemiparesis, hemisensory loss) should prompt a search for a neurological explanation.

Table 18.1. Characteristic Clinical Features That Distinguish Fluent Aphasia From Schizophrenic Speech

Clinical features	Fluent aphasia	Schizophrenia
Spontaneous speech		
Length of utterances	Fluent but shorter	Extended, rambling
Prosody	Intact	Impaired
Content	Empty	Often bizarre and restricted
Paraphasias/ neologisms	Common	Rare
Language test findings		
Repetition speech	Can be impaired	Usually intact
Comprehension	Usually impaired	Usually intact
Naming	Impaired	Intact
Semantic fluency	Impaired	Intact and often bizarre
Reading	Impaired	Intact
Writing	Aphasic	Similar to speech output

Note. See the opening text of this chapter for definitions of terms.

Finally, *aphasia* is typically used to describe acquired rather than developmental or congenital language disorders. A diagnosis of aphasia should be reserved for loss of language functions and not used to characterize cases where language never completely developed. The terms *developmental aphasia*, *developmental dysphasia*, and, more recently, *developmental language disorder* are used to describe the latter.

II. ETIOLOGY

Aphasia can be caused by a wide variety of neurological conditions. The most common cause is stroke; however, traumatic brain injury, brain tumor, abscess or infection, and certain neurodegenerative conditions (e.g., primary progressive aphasia, Alzheimer's disease) can also cause aphasia. Transient aphasia can occur during or following a seizure (e.g., postictal aphasia) in the dominant hemisphere or during a transient ischemic attack or complicated migraine. Although more rare, inflammatory or autoimmune disorders (e.g., multiple sclerosis) can also cause aphasia. The onset and course of aphasia can help inform etiology. An acute or abrupt onset of aphasia is often associated with a cerebrovascular event, whereas a subacute or slower onset with gradual progression is more often associated with tumor, infection, or inflammatory or neurodegenerative process.

Aphasia is usually caused by lesions to the left hemisphere, as the left hemisphere is the language-dominant hemisphere in over 95% of normal right-handers and 60% to 70% of left-handers. In left-handers who develop aphasia following right-hemisphere damage, the aphasia tends to be less severe than aphasia following left-hemisphere damage in right-handers. Aphasia following right hemisphere damage in right-handers is very rare but can occur and is referred to as *crossed aphasia*.

III. FUNCTIONAL NEUROANATOMY OF LANGUAGE

While an understanding that brain damage can cause language impairment dates from ancient Egyptian times, it was not until the 19th century that language was more precisely localized in the brain. The scientific study of aphasia began with Paul Broca's description of a patient (referred to as "Tan" because this syllable was the bulk of his speech output) who lost the ability to articulate but not to comprehend speech following damage to the posterior portion of the inferior frontal lobe. This form of aphasia was later referred to as *Broca's aphasia*. Shortly after Broca's discovery, Carl Wernicke

described a different form of aphasia in which language comprehension was disrupted but not speech articulation. This "sensory" form of aphasia, later referred to as *Wernicke's aphasia*, was associated with damage to the posterior portion of the superior temporal gyrus. On the strength of these clinical-anatomic observations, Wernicke proposed the first brain-language model in which language was localized to two main regions: (a) an area in the left inferior frontal lobe that contained the motor memories responsible for speech production (later referred to as Broca's area), and (b) an area in the left posterior temporal lobe that contained the auditory or phonological images of words responsible for speech perception (Wernicke's area). These two regions communicated with each other through a bundle of fibers later identified as the arcuate fasciculus. This model not only associated specific language deficits with discrete anatomical regions but also offered a theoretical explanation for the deficits seen in Broca's and Wernicke's aphasia and successfully predicted the pattern of deficits seen in conduction aphasia.

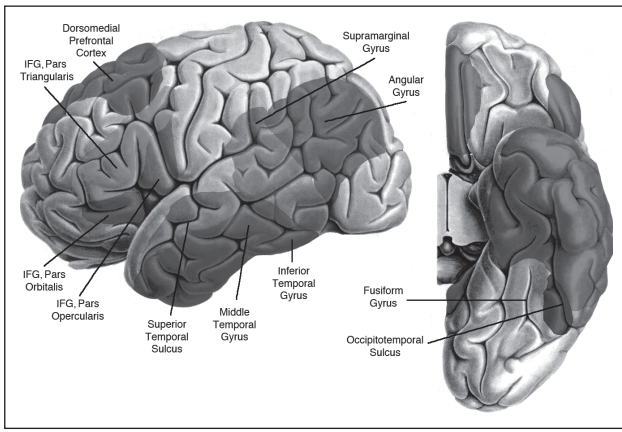
Although the basic tenets of this model still hold true—mainly that the inferior frontal lobe plays an important role in speech production and the posterior middle temporal region is important for speech comprehension—modern structural and functional imaging has led to a better understanding of the neuroanatomical and functional components of language processing (see Binder, 2012, for a review). These studies have provided compelling evidence that the language network is more widely distributed than originally thought and includes several regions outside of the classic language areas.

Language involves a number of conceptually distinct but interacting linguistic subsystems, including systems dedicated to analyzing and processing information concerning written letter combinations (*orthography*), articulatory and perceptual characteristics of speech sounds (*phonology*), information about word meanings and other declarative knowledge of the world (*semantics*), and information about word structure (*morphology*) and sentence-level word ordering that reveal underlying relationships between words (*syntax*). Although a comprehensive review of these subsystems and their anatomical correlates is beyond the scope of this chapter, Figure 18.1 attempts to summarize the major left hemisphere regions involved in language and their respective functions. Please refer to http://pubs.apa.org/books/supp/parsons for a colored version of this figure.

A. Orthographic Processing

The left inferior temporal-occipital region, particularly the fusiform gyrus and occipitotemporal sulcus, has been implicated in orthographic processing (shown in Figure 18.1). While nonletter

Figure 18.1. Left hemisphere regions involved in language.



Note. From *Functional Neuroradiology: Principles and Clinical Applications* (p. 397), by S. Faro and F. B. Mohamed, 2012, New York, NY: Springer. Copyright 2012 by Springer. Reprinted with permission.

visual stimuli activate the primary and association visual cortices, letter strings activate this region to a greater degree. Words activate this region more than consonant strings. Activation in this area has been shown to be modulated by how "wordlike" or common the letter combinations in the stimuli are in the individual's native language. Lesions to this region can cause a form of pure alexia known as *letter-by-letter alexia* or *alexia without agraphia*, in which language functions are normal (including writing, speaking, comprehension) and recognition of individual letters is intact, but reading words is slow and effortful. It has been suggested that this region plays an important role in analyzing orthographic structure.

B. Phonological Processing

Phonological processing involves a network of left hemisphere structures, including the superior temporal gyrus (STG) and sulcus, inferior frontal gyrus, and supramarginal gyrus (shown in Figure 18.1). Evidence from lesion and functional imaging studies supports the existence of separable input and output phonological pathways (see Binder, 2003 for a review). Preferential activation has been reported along the anterolateral portion of the superior temporal sulcus (left greater than right) in response to speech sounds compared with

tones, noise, and spectrally modified speech that maintains the acoustic complexity of the stimuli but renders the phonemes unintelligible. Bilateral and occasionally unilateral lesions to this region can result in pure word deafness, in which the ability to understand oral language is impaired but comprehension of written prose and other aspects of language are unaffected. Patients with this condition have impaired phoneme discrimination but relatively normal auditory acuity. These findings suggest that this region may be involved in processing input phonemes, in particular, mapping acoustic wave forms onto abstract speech sound codes (auditory word-form processing). The selection and processing of output phonemes has been linked to the posterior superior temporal gyrus. Lesions to the posterior superior temporal gyrus can produce selective impairments in selecting and ordering phonemes during production (*phonemic paraphasia*) while leaving phoneme perception and auditory comprehension intact (i.e., features seen in *conduction aphasia*). Electrical stimulation of the posterior STG has been shown to produce phoneme sequencing and selection errors, and functional imaging studies have shown activation in this region in response to tasks requiring phoneme retrieval, such as reading words and pseudowords aloud or silently, overt and covert word generation, and syllable rehearsal. The inferior frontal lobe (in particular, pars opercularis) and the supramarginal gyrus are often activated during tasks requiring maintenance and manipulation of phonological information and consequently have been implicated in phonological buffering and segmentation.

C. Semantic Processing

Storage and retrieval of semantic knowledge is widely distributed throughout the dominant temporal and parietal lobe (shown in Figure 18.1), and to a lesser extent in homologous regions of the nondominant hemisphere. Functional imaging studies have shown that the angular gyrus is consistently activated during semantic relative to nonsemantic tasks, and lesions to this region can cause a wide range of semantic processing deficits, including impairments in spoken word comprehension, semantic categorization, synonym judgment, and object naming (see Binder, Desai, Graves, & Conant, 2009, for a review). Although the precise contribution of the angular gyrus to semantic processing is unclear, its heteromodal nature suggests that it may serve as a convergence zone for bringing together and integrating information across sensory modalities for semantic processing. Brain activation that is specific to semantic content in stimuli has also been reported in the ventral and lateral temporal lobe. Lesions to these areas can cause impairments in semantic processing, and in some cases the impairments can be highly circumscribed (e.g., affecting specific object categories such as tools or fruits and vegetables), suggesting possible category-specific representations in these regions.

The dorsal prefrontal cortex in the superior frontal gyrus has also shown preferential activation in response to semantic tasks, and lesions to this region have been associated with impaired access to semantic knowledge in the absence of constraining cues (fluency tasks) but intact knowledge in the presence of cues, suggesting that this region may be involved in initiating and directing semantic information retrieval. Finally, activation is commonly reported in the anterior portion of the inferior frontal gyrus (pars orbitalis) in response to semantic tasks, and it has been suggested that this region may be involved in semantic selection and retrieval.

IV. NEUROPSYCHOLOGICAL EVALUATION OF LANGUAGE AND APHASIA

Establishing the history surrounding an acquired language disturbance and completing a thorough bedside examination of the patient's language functioning enable the diagnosis and classification of aphasia. A sound understanding of a patient's aphasia and prognosis requires assessment not only of its profile of deficits but also of those factors that provide information about course, etiology, and the patient's premorbid linguistic status and likelihood of having atypical cerebral organization of language functions. Medical records and collateral sources often can provide useful information and should be reviewed if possible to obtain relevant demographic and medical information that enables an understanding of context for current problems and risk for abnormal cerebral organization of language. Thus, in addition to establishing the onset, clinical character, and course of the speech and language difficulties, and identifying any asymmetries in motor or sensory functions, it is useful to know the following: What is the patient's native language? Were there any abnormalities in language or speech prior to the current changes? What is the patient's handedness, and are there any first-degree biological relatives who are left-handed? What is the patient's history of educational achievement? Is there any history of neurological injury, especially in early childhood? Considering a patient's native language and the presence of preexisting language abnormalities is relevant to understanding the patient's premorbid level of functioning and interpreting potential change from this state. Left-handedness and a family history of left-handedness are associated with higher rates of atypical language organization (e.g., bilateral or right-hemisphere dominance), and a history of early injury, especially to the left hemisphere, is associated with potential language reorganization.

When assessing a patient at bedside, the following elements should be covered: (a) spontaneous speech, (b) auditory comprehension, (c) repetition, (d) naming and (e) reading and writing.

A. Spontaneous Speech

The production of spontaneous, meaningful speech involves a dynamic and complex interaction between semantic, syntactical, phonological, and articulatory speech centers. Lexical-semantic regions are needed to conceptualize and form the meaning of the intended communication, whereas syntactical areas are involved in developing the structure and ordering of the communication at the sentence level. The phonological output system is involved during the mapping of semantics onto phonology as the necessary speech sounds are selected to communicate the thought. These codes are then communicated to speech articulation centers for verbal output. Areas in the dorsal prefrontal and inferior frontal lobe likely play an important role in initiating and maintaining semantic search and retrieval during this process. Damage to any of these systems can affect the production of meaningful speech.

The first step in evaluating a patient for aphasia is to assess the person's spontaneous speech abilities. Most important is determining the fluency of the output, as this dimension of speech has localizing value, but close attention to the accuracy of word retrieval and selection and the integrity of grammar and syntax in the production also can be diagnostically useful (see following sections for discussions of these features). Spontaneous speech initially can be assessed by engaging the patient in casual conversation through the use of open-ended prompts (e.g., "Why are you in the hospital?" or "Tell me about your day"). It should be noted that, because casual conversation often includes overlearned phrases or emotional phrases (e.g., profanity) that are typically unaffected in aphasic conditions, an assessment of spontaneous speech that relies only on brief conversation may produce an inflated impression of the integrity of language abilities. Conversation should be supplemented by a more structured assessment of speech. A common strategy is to show the patient a complex picture and ask him or her to describe what is happening in the picture (e.g., Cookie Theft card from the Boston Diagnostic Aphasia Examination).

1. FLUENCY

Fluency is a multidimensional term that refers to the rate, effort, and articulatory precision of word production and the prosody (melodic aspects of speech that include natural rises and falls in inflection denoting questions, imperative statements, and communicative emphases) of speech output. Spontaneous speech can be classified as fluent or nonfluent (audio examples of fluent and nonfluent aphasic speech can be heard at http://pubs.apa.org/books/supp/parsons):

- *Fluent speech* is enunciated well and seemingly requires little effort to produce. It contains at least 100 to 200 words per

minute with a phrase length of five to eight words or more per utterance. It maintains normal prosody.

- *Nonfluent speech* is poorly articulated, often hesitant and halting, and seemingly effortful. It is produced slowly, often having less than 50 words per minute and three words per utterance. It is typically monotonic, lacking in prosody. Nonfluent speech has often been characterized as telegraphic because it contains only content words like nouns and verbs and lacks articles, prepositions, conjunctions, and pronouns. It also lacks syntax, resembling a telegraphic message.

The most severe form of nonfluent speech is typically associated with damage to the posterior portion of the inferior frontal lobe (pars opercularis, pars triangularis) and its underlying subcortical connections (see the later discussion of Broca's aphasia). Less severe forms involve other anterior brain regions of the dominant hemisphere (see the later discussion of transcortical motor aphasia). Fluent speech is more characteristic of posterior brain lesions like those typically associated with Wernicke's, transcortical sensory, and conduction aphasia.

2. WORD RETRIEVAL

Patients with aphasia often complain that they know what they want to say but cannot think of the word (tip of the tongue). The term *anomia* refers to the inability to retrieve content words (*a-*, without + *nomina*, name); *dysnomia* is used to describe a less severe form of naming impairment. Clinically, anomia and dysnomia are often used interchangeably; for the purpose of this chapter, *anomia* will refer to naming problems of any severity. Patients with anomia may exhibit frequent pauses or hesitations in their speech, talk around words they fail to retrieve (circumlocution, e.g., "what you use to cut your food"), and/or substitute a related (usually more common) word for the intended word. Although severe anomia can occur with dominant temporal lobe lesions, anomia in some form occurs in most types of aphasia and has little localizing value. It can be seen following damage to any part of the language network.

3. WORD SELECTION

Patients with aphasia often have problems with inaccurate word selection or production that is referred to as *paraphasic*. While occasional paraphasic errors can occur in normal speech, frequent paraphasic errors are very diagnostic of aphasia. There are several types of paraphasic errors:

- *Literal (phonemic) paraphasia* refers to errors involving substitution of phonemes within words. The phoneme substitution can result in a similar sounding word, such as "log" for dog, or it can result in a nonword, such as "mog" for dog.

The former is referred to as a *formal paraphasia*, whereas the latter is a *neologistic paraphasia*. Literal paraphasias occur at a high frequency with damage to the phonological system needed to generate oral output, including the posterior superior temporal and supramarginal gyrus. Literal paraphasias are a hallmark feature of conduction aphasia.

- *Verbal (semantic) paraphasia* refers to errors involving the whole word. The error usually falls in the same semantic category as the intended word, such as "dog" for cat or "fork" for spoon; however, the word substitution can also produce a word that is similar in both meaning and sound (e.g., "shirt" for skirt or "plane" for train). In the latter case, the error is classified as a mixed error. Verbal paraphasias occur more frequently following damage to the semantic network, including the anterior temporal lobe, middle temporal gyrus, and angular gyrus.
- *Morphemic paraphasia* refers to errors involving word stems, prefixes, and other parts of words. For example, in the case where the word "mommer" is used for mother, the related stem "mom" was inserted into the target word "mother" to produce the error "mommer."

B. Auditory Comprehension

Auditory comprehension requires processing of the phonological elements of speech sounds, retaining phonological information sufficiently long to enable processing its semantic content and, finally, deciphering the semantic content of words and sentences. This includes processing of information contained in the syntax and grammar of linguistic constructions. Lesions to posterior language areas tend to produce more severe auditory comprehension deficits than more anterior, frontal lesions, which produce less severe if any deficits in comprehension (except for problems comprehending complex syntax). When assessing auditory comprehension at bedside, it is useful to be mindful of the factors that influence difficulty level. These factors include word familiarity, predictability, number of elements, semantic category, and syntactic complexity of the communication. It is often useful to start with easy communications and proceed to more difficult ones as performance success dictates.

An initial impression can be formed about a patient's auditory comprehension abilities from the person's responses to questions during conversation. Whether his or her responses are logical and appropriate or illogical and irrelevant to the posed question should be noted. More formal assessment techniques include testing the ability to follow motor commands, responding to yes/no questions,

and performing word–picture matching. Commands that are familiar and have fewer elements to follow are easier to comprehend and execute than commands that are less familiar or novel, have multiple elements, and are more syntactically complex. Examples of commands varying by complexity and familiarity are as follows: (a) simple, familiar commands—"Close your eyes" or "Open your mouth"; (b) complex, familiar commands—"Lift your left hand over your head"; (c) simple, unfamiliar commands—"Grab your shoulder" or "Pull your earlobe"; and (d) complex, unfamiliar commands—"Tap your head with your tongue out" or "Clear your throat as you raise your eyebrows." As examiner, you should be mindful to not provide nonverbal cues that can be interpreted by the nondominant hemisphere, such as closing or squinting your own eyes when asking a patient to close his.

Yes/no questions can also be used to assess auditory comprehension, such as "Can a shark fly?" or "Does a dog bark?" or "Is a hammer good for cutting?" Questions should be asked in both the positive and negative form to control for any response bias (yea-saying). Word–picture matching can also be used. In this method, the patient is presented a picture array and asked to identify various items in response to its name ("Show me the dog"), function ("Show me what you would cut bread with") or defining characteristic ("Show me the animal that barks"). Object pictures, colors, letters, and action scenes can be used to assess comprehension of category specific items.

C. Repetition

Repetition depends on the integrity of the perisylvian phonological system and as such has important localizing value. Extrasylvian lesions can severely affect speech production and comprehension but spare repetition abilities. Key anatomical structures for repetition are the phonological decoding analyzers in the middle and anterior STG and sulcus, phonological selection and output systems in the posterior STG, the phonological buffer located in the supramarginal gyrus, and speech articulation centers in the anterior precentral gyrus and inferior frontal lobe (Broca's area). Historically, the arcuate fasciculus has been included as a core white matter communication pathway between these zones.

Repetition can be assessed by asking the patient to repeat single words and nonwords, phrases, and sentences of varying length. Word frequency, concreteness, and length of words and phrases affect the difficulty of repeating. Repetition tends to be best for common concrete words, while uncommon and abstract words are more challenging, and nonwords are even harder. When assessing repetition, judge the fluency of the output but also listen for paraphasic errors. Some

sample task items broken down by frequency, concreteness, and length are suggested here. Ask the patient to "say what I say":

- Words
  - Common, concrete "dog," "hand," "school," "football"
  - Uncommon, concrete "ink," "wand," "flask," "glacier"
  - Common, abstract "job," "life," "truth," "happiness"
  - Uncommon, abstract "woe," "ruse," "dread," "paradox"
- Nonwords: "wog," "jand," "skoom," "hippadox"
- Phrases and sentences
  - Predictable, short: "down to earth," "electrical outlet"
  - Predictable, long: "They heard him speak on the radio last night," "Near the table in the dining room"
  - Unpredictable, short: "The spy fled to Greece," "Protestant Episcopal"
  - Unpredictable, long: "The barn swallow ate the plump worm," "The cat jumped under the fat log"

The type of repetition impairment has a great deal of localizing value. Fluent but paraphasic repetition (e.g., in the case of conduction aphasia) localizes more to the posterior perisylvian region, whereas nonfluent repetition localizes to the inferior frontal lobe. Repetition characterized by verbal paraphasia and very poor nonword repetition suggests a larger lesion to the posterior perisylvian region (e.g., in the case of Wernicke's aphasia). Repetition characterized by single word omissions or non paraphasic word substitution may reflect fluctuations in attention and not frank aphasia.

D. Naming

Naming is impaired to varying degrees in all types of aphasia and is commonly manifested in the form of word-finding difficulty in conversation. When naming problems are present, they typically are cross modal in that they are apparent regardless of the sensory modality of stimulus presentation. The severity of naming impairment provides a marker of aphasia severity. An exception to this rule is the disproportionate impairment of naming seen with focal lesions of the dominant temporal or parietal lobes. The naming problems may cluster in semantic categories (e.g., living vs. non-living entities, tools, fruits and vegetables, concrete vs. abstract entities) or word class (e.g., nouns vs. verbs), and for that reason assessment should evaluate naming abilities across semantic categories, if possible. In general, proper nouns are more difficult to retrieve than common nouns, as are abstract compared with concrete, low-frequency compared with high-frequency words, and words acquired later in life compared with those acquired earlier.

Naming is typically assessed by having the patient name real objects around the room or through the use of more standardized picture-naming tasks (e.g., Boston Naming Test [BNT]; Kaplan, Goodglass, & Weintraub, 1983; Multilingual Aphasia Examination Naming Test; Benton, Hamsher, & Sivan, 1994). Typically, the patient is asked to first name high-frequency items and then more difficult, lower-frequency items. Other strategies of assessment include naming to definition, or descriptive naming, whereby the patient is given an auditory clue or descriptor and asked to name the object being described: "Tell me what a king wears on his head"; "What is an animal that barks and fetches?"; "Who was the first president of the United States?" Naming can also be assessed through word generative or verbal fluency tasks. There are two broad forms of task, letter fluency and semantic fluency. The patient is asked to name as many words as possible, within a timed interval, that begin with a letter of the alphabet (as, e.g., with the Controlled Oral Word Association Test [COWAT]) or fall into a category (e.g., animal or tool fluency). It is thought that letter fluency places greater demand on frontal word-retrieval systems, whereas category fluency is more sensitive to semantic networks in the dominant temporal lobe.

E. Reading and Writing

The ability to read and write typically parallels spoken speech abilities in aphasia. When disorders of reading (alexia) and writing (agraphia) occur in relative isolation, more circumscribed syndromes (e.g., alexia without agraphia or Gerstmann's syndrome) should be considered. An initial impression can be formed about reading and writing abilities by having the patient try to read material located around the hospital room, such as a get-well card, a food menu, or an excerpt from a magazine or newspaper, and by having the patient write his or her name and address and a spontaneously generated complete sentence. More formal assessment should include oral reading and writing of individual letters and numbers, real words and nonwords, and regularly and irregularly spelled words, phrases, and sentences. Word frequency, concreteness, regularity of pronunciation, and word length all influence task difficulty. Higher frequency, concrete, regularly spelled, shorter length words (e.g., *cat*) are easier to read and write than the converse (e.g., *colonel*). Careful examination of the type of errors produced and dissociations between real and nonword and regular and irregular word reading and writing can provide valuable information about the underlying linguistic processes involved in the impairment.

Information-processing models of reading and writing propose that there are at least two routes through which these processes can unfold. When reading or writing through the direct lexical-semantic

route, words are matched to their corresponding visual word-form entries in the orthographic lexicon, and stored information about their meaning is then accessed. Reading and writing through this route are limited to familiar words because unfamiliar words and nonwords have no stored representations in the orthographic lexicon. When reading and writing through the nonlexical or phonological route, words are decoded using a grapheme-to-phoneme (or print-to-sound) process without access to stored information about the whole word. Regularly spelled words and nonwords can be read through this route; however, irregularly spelled words (e.g., *pint*) cannot, because they violate standard print-to-sound rules. Damage to the lexical-semantic route results in surface alexia/agraphia, in which reading and writing of irregular words is impaired (resulting in regularization errors, such as pronouncing *pint* like *mint*) but regular words and nonwords are relatively preserved. Damage to the phonological route results in phonological alexia/agraphia, in which reading and writing of unfamiliar and nonwords are substantially impaired but reading and writing of familiar words (whether regular or irregularly spelled) are intact. Verbal (semantic) paraphasias are more common when the phonological route is damaged and reading is limited to the lexical-semantic route.

F. Aphasia Assessment Batteries

There are several published collections of stimuli and assessment procedures that aim to provide a relatively comprehensive assessment of aphasia. These include the Boston Diagnostic Aphasia Examination (BDAE; Goodglass, Kaplan, & Barresi, 2001), Multilingual Aphasia Examination (MAE; Benton, Hamsher, & Sivan, 1994); Western Aphasia Battery Revised (WAB–R; Kertesz, 1982); and the Comprehensive Aphasia Test (CAT; Swinbun, Porter, & Howard, 2004). A less comprehensive language screening module is included in the Neuropsychological Assessment Battery (White & Stern, 2003). The BDAE is the oldest and perhaps most widely used battery. Both the BDAE and the WAB–R are designed to facilitate classification of the aphasic syndromes. Other supplementary and standardized tests found useful for assessing aspects of aphasia include the verbal subtests from the Wechsler Adult Intelligence Scale (WAIS–IV; Wechsler, 2008) or Wechsler Intelligence Scale for Children (WISC–IV; Wechsler, 2003).

V. CLASSIFICATION OF APHASIA

Perhaps the best known of the aphasia classification schemes is the so-called Boston neoclassical classification scheme. This classification scheme identifies eight aphasic syndromes that are defined on

Table 18.2. Classic Aphasia Subtypes

Syndrome	Fluency	Comprehension	Repetition	Naming	Paraphasia
Broca's	Nonfluent	Good	Poor	Poor	Rare–literal
Transcortical Motor	Nonfluent	Good	Good	Poor	Rare
Global	Nonfluent	Poor	Poor	Poor	Freq.–mixed
Isolation	Nonfluent	Poor	Good	Poor	Freq.–mixed
Wernicke's	Fluent	Poor	Poor	Poor	Freq.–mixed
Transcortical Sensory	Fluent	Poor	Good	Poor	Freq.–mixed
Conduction	Fluent	Good	Poor	Poor	Literal
Anomic	Fluent	Good	Good	Poor	Rare

Note. Mnemonic: Brilliant Thoughts Mean Great Ideas, When The Sage Classifies Aphasia.

the basis of whether fluency, comprehension, and repetition are impaired or not. Table 18.2 summarizes the main clinical features of these syndromes. Under this scheme, the aphasias can be divided into two broad categories: nonfluent and fluent. The nonfluent aphasias include Broca's, transcortical motor, isolation, and global aphasia; the fluent aphasias include Wernicke's, transcortical sensory, conduction, and anomic aphasia. What follows is a brief description of each syndrome follows.

A. Broca's Aphasia

Broca's aphasia is the best known of the nonfluent aphasias. It is characterized by slow, effortful, and often poorly articulated and aprosodic speech production. Speech output tends to be agrammatic, with the number of content words (nouns and verbs) far outnumbering the number of function words. Speech production tends to improve when the patient is asked to recite overlearned verbal sequences (e.g., Happy Birthday song, days of the week). Paraphasic errors are rare, and when they do occur they tend to be literal in form. Repetition is impaired and often limited to repeating single words or short phrases. Auditory comprehension is superior to speech production; however, it is not normal, especially for more complex syntax (e.g., difficulty comprehending passive or reversible sentences, as in "The girl was kicked by the boy": Who did the kicking?). Naming is impaired. Reading and writing tend to parallel spoken language in that they are slow and effortful and often agrammatic, but comprehension of written text is preserved in the same fashion as auditory comprehension is preserved.

It has generally been thought that Broca's aphasia results from damage to Broca's area, a region corresponding to the posterior portion of the inferior frontal lobe (i.e., pars opercularis and triangularis). However, patients with lesions confined to just Broca's area rarely develop a persistent Broca's aphasia. They may present with an initial period of mutism or nonfluent speech, but this tends to be transient and typically resolves, leaving the patient with only mild fluency and naming problems. Larger lesions to the dominant frontal lobe that also include the insula and underlying subcortical structures are usually required to produce a full and persistent Broca's syndrome. In such cases, patients often present with a total or global aphasia early on that later improves into the more classic Broca's aphasia. The latter has been referred to as a "big" Broca's, the former as "little" or "baby" Broca's.

> Example of verbal output (in response to Cookie Theft card of BDAE): "and . . . uh . . . uh . . . over flowin dishes . . . mother . . . boy . . . um . . . girl . . . backyard,

tree . . . ." An example of effortful, dysfluent speech typical of Broca's aphasia can be heard at http://pubs.apa.org/books/supp/parsons)

B. Transcortical Motor Aphasia

Transcortical motor aphasia (TCMA) is a nonfluent aphasia that resembles Broca's aphasia except that in TCMA repetition is preserved. Speech production is nonfluent, and auditory comprehension is relatively preserved. Articulation is not as affected as it is in Broca's aphasia, and paraphasic errors are rare. The classic lesion location is in the watershed region superior or anterior to Broca's area, with sparing of Broca's area proper. Lesions to the supplementary motor area have also been associated with TCMA.

C. Global Aphasia

Global aphasia is a severe form of aphasia in which all aspects of language functioning are affected. Verbal output is nonfluent and often limited to a few repetitive sounds or words. Auditory comprehension, repetition, naming, and reading and writing are all severely impaired. Global aphasia is analogous to a combined Broca's and Wernicke's aphasia. Global aphasia is usually caused by rather extensive lesions to the perisylvian region. It often evolves into a Broca's aphasia.

Example of verbal output (in response to Cookie Theft card of BDAE): "kaka . . . kaka . . . ka . . . [longer pause] kaka"

D. Isolation Aphasia

Isolation aphasia is a rare but recognized syndrome that comes about when a TCMA occurs along with a transcortical sensory aphasia. This can happen when there are multiple lesions in the watershed territory of the middle cerebral artery, as might occur in the context of a severe hypotensive state. The net effect of the lesions is to "isolate" the core language zones of the perisylvian region from the remainder of the hemisphere, causing a circumstance in which repetition is preserved but comprehension and general speech production are quite limited. Repetition in this case has an echolalic quality and is devoid of semantic comprehension.

E. Wernicke's Aphasia

Wernicke's aphasia is a fluent aphasia defined by a severe disturbance in language comprehension. The patient may be able to fol-

low some simple motor commands (e.g., "Close your eyes," "Stick out your tongue") but is unable to execute more complex, multistep commands or understand and respond appropriately to casual conversation. Verbal output is effortless, normal in rate and prosody, and well articulated, but the content of the output is often nonsensical and incomprehensible because of frequent paraphasic errors (i.e., jargon speech). Both literal and verbal paraphasic errors are produced. Repetition is impaired. Reading and writing are impaired. Patients are often anosognosic, that is, seemingly unaware of their language difficulties, unlike patients with Broca's aphasia, who tend to be more aware of their deficits.

Wernicke's area is classically located in the posterior portion of the STG. Wernicke's aphasia was originally attributed to a lesion in this area; however, lesions confined to this region rarely produce a Wernicke's aphasia. Larger lesions in the posterior perisylvian region, involving not just the posterior STG but also the lateral temporal (middle temporal gyrus) and parietal (angular gyrus, supramarginal gyrus) lobes, are usually required to produce a classic Wernicke's aphasia.

> Example of verbal output (in response to Cookie Theft card of BDAE): "Well this the answers has has aces and has there is oysters. And this here blings blends out to here. . . . And then I see horse and he's gonna make it fence, fencing there fencing that's uh that's old faithful and right there and this one and and this one come out and out ok." An example of fluent but neologistic and paraphasic speech typical of Wernicke's aphasia can be heard at http://pubs.apa.org/books/supp/parsons.

F. Transcortical Sensory Aphasia

Transcortical sensory aphasia (TCSA) is a fluent aphasia that resembles Wernicke's aphasia except that in TCSA repetition is relatively spared. Auditory comprehension, naming, and reading and writing are all impaired. Verbal output is fluent but can be nonsensical because of poor comprehension and paraphasic errors. Comprehension often breaks down at the semantic level rather than at the phonological level as seen in Wernicke's aphasia. Correspondingly, verbal/semantic paraphasias are more common than literal/phonemic paraphasias in TCSA, especially when compared with Wernicke's aphasia. In addition to phonological knowledge, patients with TCSA continue to have access to syntactic knowledge too.

TCSA is associated with lesions in the territories of the posterior branches of the middle cerebral artery and from middle cerebral artery–posterior cerebral artery watershed lesions.

G. Conduction Aphasia

The hallmark features of conduction aphasia are the disproportionately impaired repetition abilities with relatively preserved fluency and auditory comprehension. Literal or phonemic paraphasic errors are prevalent during spontaneous speech, repetition, and naming. Reading comprehension is often unaffected, whereas reading aloud and writing can be abnormal because of paraphasic errors. Patients are often aware of their errors and may attempt to correct them by using successive phonemic approximations (e.g., in response to request for repetition of the phrase "electrical outlet": "lectic let . . . electic let . . . electoric . . . e . . . lectric outtet . . . electet"). Their recurrent effort to successively approximate the desired phonological sequence is known as *conduite d'approche*.

Wernicke proposed that conduction aphasia resulted from a disconnection between the language comprehension and production centers. Lesions to the arcuate fasciculus, a major fiber tract connecting the superior temporal to dorsolateral frontal lobe, can cause conduction aphasia. However, lesions outside this tract in the supramarginal gyrus can also produce this type of aphasia, perhaps by reducing the span memory capacity for phonological information.

H. Anomic Aphasia

Word-finding problems are present to varying degrees in almost all types of aphasia. *Anomic aphasia* is an aphasia in which word finding is the most prominent deficit, other aspects of language functioning being relatively preserved. Verbal output is fluent, well articulated, and grammatically correct, but pauses and hesitations in speech are not uncommon as the patients search for words. They may also "talk around" or use many words (circumlocutions) to describe their intended word. Auditory comprehension and repetition are preserved. Paraphasic errors are rare.

Anomic aphasia has been associated with lesions to a variety of locations, including lesions to the inferior or basal temporal lobe and angular gyrus. Many of the aphasias evolve into an anomic aphasia following a recovery period.

I. Limitations of Classic Taxonomy

The classic aphasia taxonomy allows for general predictions to be made regarding lesion location and can provide a way for clinicians to communicate with each other about the typical constellation of signs and symptoms associated with a given aphasic syndrome. However, the classic taxonomy is limited in several ways. First, it is

rare to find a case of aphasia that conforms to the full pattern of one of the classic syndromes. Indeed, although it is often possible to determine whether speech is fluent or nonfluent, beyond this first level of classification the majority of aphasic patients present with mixed features. The difficulty of classifying aphasia using this taxonomy may stem from its polytypic nature. That is, the classifications of aphasias are based on the presence or absence of impairment across several language domains; however, a given impairment may be part of more than one syndrome. In fact, there is considerable overlap in symptom presentation among the classic syndromes, such as the presence of repetition impairment in Broca's, Wernicke's, and conduction aphasia or the presence of naming impairment in all subtypes. There is also significant variability in symptom presentation and symptom severity, even within a given subtype of aphasia, and categorizing linguistic functions in a dichotomous (impaired or not) fashion is challenging at best and potentially arbitrary at worst. Another major limitation of the classic taxonomy is that it tells us nothing about the underlying functional deficit involved in an aphasic presentation. For example, repetition is impaired in multiple aphasia subtypes, but the underlying component mechanism of the impairment likely differs between the subtypes. Repetition can be impaired as a result of impaired lexical semantic access in Wernicke's aphasia, faulty translation of decoded phonemes to "output" articulemes in the case of conduction aphasia, or impaired motor planning and execution of articulation in Broca's aphasia.

Such limitations highlight the importance of moving beyond this classic scheme in understanding language and aphasia. One alternative to the classic taxonomy is to use a psycholinguistic approach to describe language and aphasia. The psycholinguistic approach attempts to understand aphasia in terms of the specific process or set of processes involved in carrying out a given linguistic operation and identifying at what level the breakdown occurs. A number of "box and arrow" models have been developed to explain the processing pipeline involved in carrying out specific linguistic functions, including models of single word reading, written word production, object recognition, and auditory comprehension of spoken words, to name just a few. These models contain modules (the boxes) that describe a given component process (e.g., phonological input lexicon, orthographic output lexicon) and connections (the arrows) between the modules that describe how they interact and communicate with each other and how information is mapped from one module to the next. Damage can occur to any part or parts of the model, resulting in a very different set of symptoms depending on where the model is disrupted. Unlike the classic taxonomy, which groups patients into a limited number of homogenous syndromes,

this approach allows for individual differences in symptom presentation. Such an approach can also guide rehabilitation efforts in a more specific and individualized manner (more targeted therapy).

J. Other Types of Aphasia and Related Syndromes

1. SUBCORTICAL APHASIA

Aphasia usually results from damage to cortical regions in the dominant hemisphere; however, it can also result from damage to the dominant thalamus and basal ganglia. *Subcortical aphasias* tend to be highly variable in their clinical presentation and are defined more by anatomical location than by a specific set of symptoms. The variability in clinical presentation may relate to the type of injury (infarction vs. hemorrhage), specific subcortical nuclei involved, and time postinjury. Thalamic aphasia tends to be fluent but paraphasic (usually verbal/semantic), with variable auditory comprehension deficits and minimally impaired repetition. Damage to the dominant basal ganglia, in particular, the head of the caudate, anterior putamen, and anterior capsule (striatocapsular region), can result in an anterior subcortical aphasia, in which speech tends to be nonfluent and dysarthric with relative sparing of auditory comprehension and repetition. In general, subcortical aphasias tend to be less severe and to recover better than cortically based aphasias.

2. PRIMARY PROGRESSIVE APHASIA

Aphasias due to underlying neurodegenerative conditions develop insidiously and progress gradually over the course of months to years. *Primary progressive aphasia* (PPA) is a neurodegenerative condition characterized by a gradual and progressive decline in language functioning. It is distinct from other forms of dementia in that language impairment is the sole manifestation during the first 2 years of the illness and remains the most prominent feature throughout the course of the illness. Three PPA subtypes have been identified. The *nonfluent/agrammatic variant* of PPA resembles Broca's aphasia in many ways and is characterized by effortful, halting, and often agrammatical speech, with intact word comprehension and object knowledge but impaired syntactic comprehension. Left anterior perisylvian atrophy involving the inferior frontal and insular region is a common radiological finding. Frontal temporal lobe dementia (FTLD)-tau pathology is the most common histopathological finding on autopsy. The *semantic variant* of PPA is a fluent PPA characterized by loss of semantic knowledge as reflected by poor object naming, single-word comprehension, category fluency, and

knowledge of object features. Surface dyslexia is a common finding on reading tasks. Anterior temporal lobe atrophy is a common radiological correlate. FTLD TDP-43–positive, tau-negative inclusions are the most common histopathological finding. *Logopenic PPA* is characterized by slow speech output with frequent word-finding pauses and phonemic paraphasic errors while grammar remains intact. This is in contrast to the nonfluent variant in which frank agrammatism is more common. Phonological short-term memory is impaired on measures of sentence repetition and span memory tasks, and some consider phonological short-term memory to be the core deficit in the syndrome. Logopenic PPA is often associated with Alzheimer's disease; patients with this variant tend to have poorer episodic memory than those with other forms of PPA. Atrophy of the posterior perisylvian cortex and inferior parietal region is a common radiological finding, and AD pathology is the most common histopathological finding (see Gorno-Tempini et al., 2011, for a more comprehensive review of PPA).

3. ALEXIA WITHOUT AGRAPHIA

Otherwise known as pure alexia, alexia without agraphia is useful for neuropsychologists to appreciate because of its clear implications for localization to the territory of the dominant posterior cerebral artery. Two variations are known. One variation involves damage to the cortical word-form area of the fusiform gyrus and occipitotemporal sulcus that has been implicated in orthographic processing. In this form, letter-by-letter alexia is seen often with preserved visual fields. The other variation is presumed to result from a disconnection of primary visual cortices from orthographic processing zones in the temporal and parietal lobes. This form of alexia is associated with a white-matter lesion that (a) causes a visual field defect (usually right hemianopsia), thereby disrupting the visual processing stream in the dominant hemisphere, and (b) prevents transmission of input to visual cortices in the nondominant hemisphere across the splenium of the corpus callosum to orthographic processing areas in the dominant hemisphere.

4. GERSTMANN'S SYNDROME

Gerstmann's syndrome, a favorite on board examinations, is a collection of four symptoms (agraphia, acalculia, right-left disorientation, and finger agnosia) that are thought to come about from a single lesion to the dominant inferior parietal lobe. In actuality, it is extremely rare to see the full collection of symptoms in isolation from aphasia; however, any two of the symptoms reliably predicts dominant parietal lobe involvement.

VI. RECOVERY FROM APHASIA

Recovery from aphasia depends on the underlying pathophysiological mechanisms and their course. Recovery can be quite rapid, occurring within minutes when the mechanisms are quite transient and reversible (e.g., recovery from aphasia occurring in the context of complex partial seizure or hemispheric sedation used in Wada testing). In contrast, when the mechanism is progressive (e.g., brain tumor, neurodegenerative disease associated with PPA), recovery is generally not likely, and progressive deterioration in linguistic capacities is anticipated. When the mechanism is acute and involves a destructive brain lesion (e.g., ischemic or hemorrhagic stroke), recovery occurs over the course of several months to a year and is often incomplete.

Recovery is also affected by the profile and severity of aphasic features and the size of the underlying brain lesion. In general, global aphasia associated with large brain lesions does not recover well. Large brain lesions and those that include subcortical involvement often have persistent residuals associated with them. An aphasia that is nonfluent from onset and associated with hemiparesis generally persists, albeit with decreasing severity. Many fluent aphasias will eventually recover to what would be characterized as an anomic aphasia, with word-finding and -naming difficulties being prominent but with relatively good recovery of speech fluency and linguistic comprehension. Aphasias associated with an isolated destructive lesion typically show some degree of spontaneous recovery, with most recovery occurring within 3 months of the onset. Formal therapy (speech therapy) often hastens recovery over the short term, but benefits to long-term outcome have been more difficult to demonstrate.

VII. CONCLUSION

Language is critical to most human competencies. Thus, a thorough assessment of language is important to developing a comprehensive understanding of an individual's functional abilities as well as predicting disruption in the anatomical networks that enable linguistic operations. Neuropsychologists, by virtue of their understanding of neurocognitive operations and anatomical correlations and their training in cognitive assessment, are well suited to performing this evaluation for our patients, health care community, and society.

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Chapter 19

Russell M. Bauer

Visuospatial, Visuoperceptual, and Visuoconstructional Disorders

This chapter describes disorders of visuospatial, visuoperceptual, and visuoconstructional ability resulting from acquired brain damage. I first consider key *visuospatial disorders*, including defects in judging orientation and position of objects in space; *topographical disorientation* (inability to find one's way in the environment); and *visual neglect* (pathological inattention to contralateral visual space after a unilateral brain lesion). Then, I describe *visual agnosias*, a rare class of disorders in which a patient with brain damage becomes unable to recognize or appreciate the identity or nature of sensory stimuli. Finally, I review *visuoconstructional disorders*, which result in impairments in graphomotor/drawing performance, block construction, or other visuomotor tasks. Any comprehensive neuropsychological examination should screen for elements of visuospatial, perceptual, and constructional skill, as these disorders may significantly contribute to disability and often have great localizing significance.

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I. DEFINITION AND CLASSIFICATION OF DISORDERS

A. Visuospatial Disorders

1. DEFICITS IN VISUOSPATIAL JUDGMENT

a. Key features

- Failure to judge absolute or relative localization of objects in space on matching or pointing tasks (may be part of egocentric topographical disorientation).

2. HEMISPATIAL NEGLECT

a. Key features

- Pathological inattention to objects or events in visual space contralateral to a brain lesion (note that rare ipsilesional cases have been reported).
- Can exist in visual, auditory, or tactile modality, or may affect mental images.
- Inattention can affect sensory input or motor output (e.g., patient may fail to act in contralateral space even with normal motor function).
- Complex disorder in which varieties of performance have been identified in the near-far and up-down dimensions, and as a function of different axes of orientation (e. g., head, trunk, retinal).

b. Varieties (may overlap)

- *Extrapersonal:* failure to orient to or explore space contralateral to a brain lesion.
- *Personal:* failure to orient, attend to, or recognize body regions or parts contralateral to a brain lesion.
- *Object-centered:* weakness or failure to attend to the contralateral side of specific stimuli *regardless of their spatial location in the environment*.
- *Representational:* failure to attend to or report aspects of mental representations or images that fall in contralateral space.
- *Intentional/Motor:* failure to act in the contralateral space despite normal motor function.

3. TOPOGRAPHICAL DISORIENTATION (TD)

a. Key features

- Failure to find one's way in the environment.

b. Varieties

- *Egocentric disorientation:* deficit representing location of objects with respect to the self (posterior parietal).
- *Heading disorientation:* deficit representing direction of orientation (posterior cingulate).
- *Landmark agnosia:* inability to represent appearance of salient landmarks (lingual gyrus).
- *Anterograde/amnestic disorientation:* inability to create new maps of the environment (parahippocampal gyrus, particularly on right).
- *Developmental TD* has been described in a few cases.

4. BALINT'S SYNDROME

a. Key features

- Impaired visual attention (simultanagnosia, see below).
- Oculomotor apraxia (gaze apraxia).
- Misreaching in space (optic ataxia).
- Defective judgment of distance.

B. Visuoperceptual Disorders and Visual Agnosia

1. VISUAL OBJECT AGNOSIA

a. Key features

- Cannot recognize the meaning of visually presented objects.
- Disorder is not restricted to naming (patient cannot point to the named object or describe/demonstrate its use).
- Recognition may be better for real objects than for pictures or line drawings.
- Can recognize objects when presented in other modalities.

b. Varieties

- *Apperceptive:* cannot demonstrate adequate perception of object through drawing, copying, or matching tasks.
- *Associative:* drawing, copying, or matching tasks bring more success, though performance is sometimes "slavish".
- *Category specific:* recognition disturbance is sometimes worse for certain categories of objects (e.g., living things, tools, etc.); recognition testing should employ various categories of objects.

2. SIMULTANAGNOSIA

a. Key feature

- Patient cannot apprehend the overall meaning of a picture or stimulus but may be able to appreciate and describe isolated elements (e.g., says "leaf" when looking at a "tree").

b. Varieties

- *"Dorsal" simultanagnosia* (bilateral occipitoparietal lesions); cannot see more than one object at a time.
- *"Ventral" simultanagnosia* (left inferior occipital lesions); may be able to "see" more than one object at a time.
- Often considered a variant of apperceptive agnosia.

3. PROSOPAGNOSIA

a. Key features

- Unable to recognize the identity of viewed faces.
- May appreciate aspects of faces such as age, gender, or emotional expression.
- Associative variety can match faces.
- May have defects in configurational processing.

b. Varieties and associated features

- *Apperceptive* and *associative* forms have been identified based on performance on matching tasks.
- *Developmental* prosopagnosia is one that manifests in childhood and cannot be attributed to an acquired brain lesion (familial forms have also been referred to as "congenital" or "hereditary" prosopagnosia).
- Patient may have impaired ability to recognize a unique examplar within a class of semantically or visually similar objects (e.g., recognition of individual chairs, cars, pets).

4. COLOR "AGNOSIA"

a. Key features

- Patient has disproportional impairment in recognizing, naming, or otherwise utilizing color information.
- Since color can be represented only in the visual modality, the concept of a modality-specific recognition defect is controversial.

b. Varieties

- *Central achromatopsia:* acquired deficit in color vision due to CNS disease; cannot match, discriminate, or name colors; suspect bilateral occipital lesions, but more rarely may be unilateral and restricted to one visual field or quadrant.
- *Color anomia:* specific difficulty in naming colors, usually found in the context of right homonymous hemianopia and pure alexia (Geschwind, 1965). Other aphasic signs generally absent; suspect posterior left hemisphere lesion.
- *Specific color aphasia:* seen in the context of aphasia, represents a disproportionate difficulty in naming colors; suspect left (dominant) parietal lobe damage.
- *Color agnosia:* a residual category of patients who have difficulty appreciating the nature or name of color they see, but who do not fall neatly within the categories above.

5. OPTIC APHASIA

a. Key features

- Patient *cannot* name a visually presented object.
- Patient *can* demonstrate its use by gesture, or can point to it when named (this distinguishes it from associative object agnosia).
- May represent a visual–verbal disconnection.

6. NONAGNOSIC DEFECTS IN PATTERN OR FORM RECOGNITION

a. Key features

- Patient has difficulty performing visuoperceptual tasks requiring matching, form discrimination, mental rotation, or visual synthesis.
- Despite these difficulties, no defect in recognizing the identity of viewed object, faces, or colors exists.

b. Varieties

- Defects in form discrimination: Patient has difficulty discriminating forms in overlapping or hidden figures tests or in copying stimuli.
- Defects in matching identical stimuli (faces, line drawings, photographs).
- Defects in matching "transformed" stimuli (stimuli presented from different viewpoints or under different lighting conditions).
- Defects in visual synthesis: inability to mentally combine fragmented pictures or to synthesize incomplete figures.

C. Visuoconstructional Disorders

1. DISORDERS OF GRAPHOMOTOR COPYING OR DRAWING

a. Key features

- Patient is unable to accurately copy or draw designs using a writing implement.
- Disorder may be confounded with defects in fine motor coordination in patients with hemiparesis or arm/hand weakness.
- Qualitative aspects of drawing may have significance for lesion localization:
  - left hemisphere lesions: preserved spatial organization with simplification or omission of internal details
  - right hemisphere lesions: neglect of left side of figure; accurate reproduction of internal details with distortion of spatial relations among design elements; distorted placement of design elements

2. DISORDERS OF TWO-DIMENSIONAL BLOCK CONSTRUCTION

a. Key feature

- Impairment in constructing a two-dimensional design from blocks or other stimuli, such as Wechsler-type block designs.

b. Varieties

- Correct adherence of 2×2 or 3×3 design configuration with errors in assembling internal design details (left hemisphere).
- Breakage of 2×2 or 3×3 design configuration (right hemisphere).
- Concrete or environmentally dependent attempts to represent design elements with whole blocks (e.g., arranging blocks in a "V" fashion to represent ramparts; frontal lobe).

3. DISORDERS OF THREE-DIMENSIONAL BLOCK CONSTRUCTION

a. Key features

- Impairment evident in constructing three-dimensional design from configural elements in the absence of constructional impairment in graphomotor or two-dimensional block design tasks.

- Diagnosis usually requires specialized tests; patients usually do not complain of "constructional impairment" in the same way they report memory or concentration problems.

II. FUNCTIONAL NEUROANATOMY

Functional neuroanatomic correlates of visuospatial, visuoperceptual, and visuoconstructive disorders are summarized in Table 19.1. The appearance of three distinct classes of disorders has its basis in the highly specialized processing of visual information in the human brain. Cortical visual systems derive common input from the photoreceptors but are segregated as early as the ganglion cell level of the retina. Extensive evidence exists for at least two distinct but partially interacting cortical visual systems: one that projects ventrally from the primary and secondary visual areas in the occipital lobe to the temporal lobe, and the other projecting more dorsally from occipital visual areas to superior temporal sulcus and thereafter into parietal lobe (Creem & Proffitt, 2001; Ettlinger, 1990; Haxby et al., 1991). The *ventral stream* is primarily involved in form, color, and shape processing, and the *dorsal stream* is primarily involved in visuospatial processing and visuomotor interaction. These two streams project too many of the same thalamic and cortical regions, but they terminate on different cortical layers and project to different areas of association cortex. Ventral (occipitotemporal) lesions thus tend to produce perceptual defects, whereas more dorsal (parietal or occipitoparietal) lesions produce deficits dominated by spatial impairment.

Visuospatial disorders are typically associated with unilateral or bilateral damage to parietal regions, and often their corticocortical and subcortical connections with temporal and frontal lobe. *Neglect* can result from lesions in the inferior parietal lobe, dorsolateral frontal lobe, cingulate gyrus, thalamus, and mesencephalic reticular formation (Heilman, Watson, & Valenstein, 2012). The most common cause is cerebral infarction (from either thrombosis or embolism) and, in subcortical cases, intracerebral hemorrhage, though neglect can result from rapidly growing tumors such as glioblastoma or metastatic disease. Neglect can be seen, though less commonly, in focal atrophy or in association with Alzheimer's disease (Caine, 2004). Each of the four subtypes of *topographic disorientation* (TD) has its own anatomical localization (Aguirre & D'Esposito, 1999). The most common cause is stroke (infarction), though TD has been associated less commonly with degenerative disorder. *Egocentric TD* is associated with bilateral or unilateral lesions of the right superior parietal lobe. *Heading disorientation* has been associated with damage to the right cingulate cortex, and a case of transient disorientation

Table 19.1. Functional Anatomy of Visuospatial, Visuoperceptual, and Visuoconstructional Disorders

Disorder	Lesion localization	Reference
VISUOSPATIAL DISORDERS		
1) Deficits in Visuospatial Judgment	Posterior right hemisphere disease; more rarely, in patients with right frontal lesions	
2) Hemispatial Neglect		
a) Personal	Right inferior parietal	Committeri et al., 2007
b) Extrapersonal	Right frontotemporal	Committeri et al., 2007
3) Topographical Disorientation		
a) Egocentric	Posterior parietal	Stark, Coslett, & Saffran, 1996
b) Heading disorientation	Posterior cingulate	Greene, Donders, & Thoits, 2006
c) Landmark agnosia	Lingual gyrus	Pallis, 1955
d) Anterograde/amnestic TD	Right parahippocampal gyrus	Habib & Sirigu, 1987
4) Balint's Syndrome	Bilateral superior parietal lobe	Hécaen & De Ajuriaguerra, 1954
AGNOSIA AND VISUOPERCEPTUAL DISORDERS		
1) Visual Object Agnosia		
a) Apperceptive	Diffuse, posterior damage to occipital lobes and surrounding regions	Benson & Greenberg, 1968
b) Associative	Bilateral: Inferior occipitotemporal	Rubens & Benson, 1971
2) Simultanagnosia		
a) Dorsal	Bilateral parietal and superior occipital	Duncan et al., 2003
b) Ventral	Dominant occipitotemporal junction	Kinsbourne & Warrington, 1962

(continued)

Table 19.1. Functional Anatomy of Visuospatial, Visuoperceptual, and Visuoconstructional Disorders *(Continued)*

Disorder	Lesion localization	Reference
3) Prosopagnosia		
a) Apperceptive	Traditionally seen as bilateral in all or nearly all cases; cortex and white matter in occipitotemporal gyrus or projection system	De Renzi, Faglioni, Grossi, & Nichelli, 1991
	More recently a few cases of what appears to be unilateral damage to right visual association cortices within occipital and parietal lobes	Damasio, Damasio, & Tranel, 1990; De Renzi, 1986
b) Associative	Bilateral anterior temporal regions compromising hippocampal and other regions	Damasio et al., 1990
4) Color Processing Disorders		
a) Achromatopsia	Unilateral or bilateral inferior ventromedial region of occipital lobe—involves lingual and fusiform gyri—superior field defects	Damasio, Yamada, Damasio, Corbett, & McKee, 1980
b) Color Anomia	Dominant occipital infarction with corpus callosum involvement	Geschwind & Fusillo, 1966
c) Specific Color Aphasia	Dominant parietal damage coincident with posterior aphasia	Kinsbourne & Warrington, 1964

5) Optic Aphasia	Unilateral: Dominant occipital lobe and splenium of corpus callosum	Geschwind, 1965; Riddoch & Humphreys, 1987
6) Defects in Pattern/Form Recognition	Right occipitotemporal regions, usually involving both visual association cortex and temporal lobe; patient can have specific problem recognizing objects from atypical ("non-canonical") view	Warrington & Taylor, 1978
VISUOCONSTRUCTIVE DISORDERS		
1) Disorders of graphomotor drawing or copying or drawing	Left or right posterior cortical lesions; qualitative differences between groups	Gainotti, D'Erme, & Diodato, 1985; Kirk & Kertesz, 1989
2) Disorders of two-dimensional block construction	Left or right diffuse or focal lesions; qualitative differences between groups; deficits attributable to concreteness or executive failure can be seen after focal frontal lesions	Benton, Sivan, Hamsher, Varney, & Spreen, 1994; Kaplan, 1990
3) Disorders of three-dimensional block construction	Most likely lesion is in right parietal lobe; frontal lobe patients may also fail as a result of perseveration or deficits in planning or self-monitoring	Benton et al., 1994

has been reported following damage to the right dorsomedial and posterolateral thalamus. *Landmark agnosia* has been associated with either bilateral or right-sided lesions of the medial occipital lobe, involving the lingual and fusiform gyri and, less commonly, the parahippocampal gyrus. *Anterograde disorientation* overlaps somewhat with this localization, but causative lesions tend to be clustered within the right parahippocampal gyrus, an area known to be important in declarative memory. *Balint's syndrome* is most commonly associated with ischemic stroke in the superior parietal lobes. Strokes of the posterior circulation are most frequently bilateral.

Regarding *agnosias*, apperceptive agnosias involve more extensive damage to sensory association cortex, whereas associative agnosias result from lesions of corticocortical pathways or from impairment in those areas where semantic representations of objects are stored. In most published cases, lesions are caused by ischemic stroke, though cases of carbon monoxide poisoning, posttraumatic hematoma, and neoplasm have been reported (Bauer, 2012). It is becoming increasingly recognized (most prominently in the visual domain) that apperceptive agnosia can result from degenerative disease, with particular attention being devoted to dementia syndromes presenting with predominant visuoperceptual disturbance and atrophy of the posterior cortex (Andrade et al., 2012; Crutch et al., 2012; Mendez, Ghajarania, & Perryman, 2002; Tsai, Teng, Liu, & Mendez, 2011). *Prosopagnosia* results from bilateral damage to the fusiform gyrus on the underside of the occipitotemporal junction, though occasional right-sided unilateral cases have been reported. Developmental cases of prosopagnosia have been convincingly reported and documented (Behrmann & Avidan, 2005; Susilo & Duchaine, 2013).

III. NEUROPSYCHOLOGICAL EVALUATION

Clinical examination of the patient with a disorder of visual cognition begins with a careful interview with the patient and collateral informant to ascertain the pattern of signs and symptoms and their functional implications. It is important to keep in mind that although patients and collaterals will notice and report some disturbances in this category (e.g., problems recognizing faces and objects), they may not complain of others (e.g., a color-naming disorder or a disorder in three-dimensional constructional praxis) unless such a deficit is revealed in the patient's vocational or avocational activity. Thus, the clinician should be prepared to screen for deficits in all three domains of visual cognition (identification/recognition, spatial ability, and construction) to determine whether unanticipated deficits are present.

A. Clinical Assessment

The clinical assessment of the patient with a disorder of visual cognition has two fundamental goals. First, the possibility that the disorder exists in the context of preperceptual visual disturbance, dementia, aphasia, or gross attention disturbance should be ruled out with standardized neuropsychological testing instruments. Table 19.2 provides a summary of testing instruments that are useful in achieving this goal. Second, the scope and nature of the patient's deficit should be determined. Is the deficit restricted to spatial, perceptual, or constructional function, or does it cross category boundaries? Does it exist only for certain stimuli or classes of stimuli? Under what conditions (if any) can the patient succeed? This phase of the evaluation often requires detailed testing using specially formulated testing materials (e.g., the use of personally familiar faces or environmental scenes) and should be conducted from the point of view of cognitive models of visual cognition. Appropriate referrals for neurologic, neuroradiologic, and basic sensory–perceptual (e.g., ophthalmologic, audiologic) testing, if not already performed, are often important in formulating a clinical diagnosis.

B. Spatial Dysfunction

In evaluating *spatial* dysfunction, it is important to distinguish between person-centered (egocentric) versus environment-centered (allocentric) deficits by testing spatial abilities that do and do not depend on making judgments of stimuli in reference to the patient's location in the environment. When evaluating spatial function in isolation from perceptual or constructional deficits, it is important to include at least some tasks that minimize contributions of constructional impairment by using response modalities that use drawing or reconstruction of the stimulus environment.

C. Perceptual Function

The evaluation of *perceptual function* is guided by models of object recognition (see Figure 19.1) that evaluate levels of ability from elementary sensory-perceptual function to semantic processing. Tasks at each level can be performed to determine whether the patient has the constituent ability. At the *basic perceptual level*, simple perceptual grouping or stimulus matching tasks can be used. To determine whether a patient can achieve an accurate viewer-centered representation of a stimulus, direct matching can be used, but evaluation of the object-centered representation requires the patient to

Table 19.2. Neuropsychological Assessment of Visuospatial, Visuoperceptual, and Visuoconstructional Disorders

Disorder	Neuropsychological examination tool/tests	Reference
VISUOSPATIAL DISORDERS		
1) Deficits in Visuospatial Judgment	Judgment of Line Orientation; tests of mental rotation; map localization	Benton et al., 1994
2) Hemispatial Neglect		
a) Personal	Fluff Test; Comb-and-Razor Test	Beschin & Robertson, 1997; Cocchini, Beschin, & Jehkoven, 2001
b) Extrapersonal	Line bisection, cancellation tasks, drawing tasks (free drawing, Rey Complex Figure), writing tasks	Schenkenberg, Bradford, & Ajax, 1980
3) Topographical Disorientation		
a) Egocentric	Tests of reaching; judging nearness/farness; spatial imagery (how to get from Place A to Place B); mental rotation tasks	Levine, Warach, & Farah, 1985
b) Heading disorientation	Memory for object location (spared); memory for landmarks (spared); map drawing and route knowledge (poor); NAB Map test; drawing of floor plan of home or familiar place (poor)	Takahashi & Kawamura, 2002
c) Landmark agnosia	Map localization (spared); memory for familiar routes (spared); identification of specific pictures of landmarks and buildings (poor)	Pallis, 1955

d) Anterograde/ amnestic TD	Memory for routes first encountered after illness (poor); learning of new route from Point A to Point B in hospital (poor); drawing floor plan or spatial layout of a newly encountered building (poor)	Ross, 1980
4) Balint's Syndrome	Tests for simultanagosia (see 2a-b under Agnosia and Visuoperceptual Disorders); bring objects into view from periphery and have patient change fixation toward them ("psychic paralysis of gaze" will prevent this); have patient reach for, and pick up, objects at various locations in space ("optic ataxia" will make this difficult)	Hécaen & De Ajuriaguerra, 1954
AGNOSIA AND VISUOPERCEPTUAL DISORDERS		
1) Visual Object Agnosia a) Apperceptive b) Associative	Apperceptive-associative distinction is defined by extent to which patient shows early perceptual grouping in vision or can copy or match stimuli. Design copying or simple perceptual tasks (Perceptual Speed, Benton Tests of Facial Recognition and Visual Form Discrimination) are useful. Birmingham Object Recognition Battery (BORB) provides comprehensive assessment.	Benton et al., 1994; Farah, 2004; Riddoch & Humphreys, 1993; Thurstone & Jeffrey, 1987

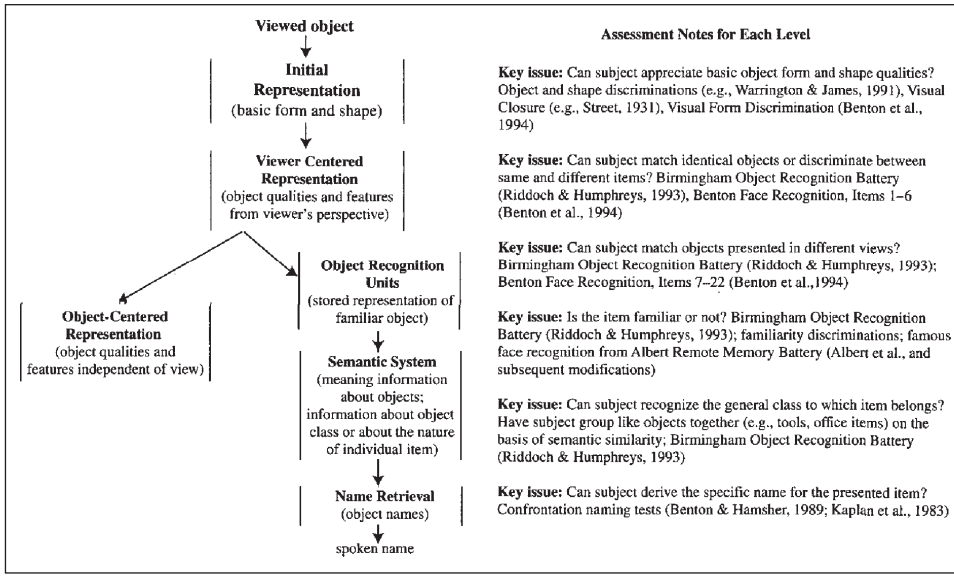
(continued)

Table 19.2. Neuropsychological Assessment of Visuospatial, Visuoperceptual, and Visuoconstructional Disorders *(Continued)*

Disorder	Neuropsychological examination tool/tests	Reference
2) Simultanagnosia		
a) Dorsal	Object naming, picture interpretation tasks (Cookie Theft from BDAE); coin counting; Luria's (1959) tests of space-based vs. object-based attention	Goodglass & Kaplan, 1983; Holmes, 1918; Luria, 1959
b) Ventral	Same as dorsal; add single-word reading tasks to evaluate letter-by-letter reading	Riddoch & Humphreys, 1993; Warrington & Shallice, 1980
3) Prosopagnosia		
a) Apperceptive	Face matching (Benton Test of Facial Recognition) and identification (famous faces); Birmingham Object Recognition Battery; evaluate whether patient can discern gender, emotion, age, etc. from faces (Ekman Faces)	Benton et al., 1994; Ekman & Friesen, 1975; Riddoch & Humphreys, 1993
b) Associative	Same as apperceptive prosopagnosia	
4) Color Processing Disorders		
a) Achromatopsia	Farnsworth D-15 or Ishihara plates; color-to-figure matching (coloring common objects)	Farnsworth, 1943; Ishihara, 1983
b) Color anomia	Ask patient to name colors presented on color swatches. Coloring of Pictures; Wrongly Colored Pictures	Damasio, McKee, & Damasio, 1979

c) Specific color aphasia	Color name sorting, evaluate dissociations between confrontation naming of line drawings, objects, and colors	Beauvois & Saillant, 1985
5) Optic Aphasia	Ask patient to name and demonstrate the use of viewed vs. held objects; optic aphasic will succeed in demonstrating use while visual agnosic will not	Lhermitte & Beauvois, 1973
6) Defects in Pattern/Form Recognition	Design copying; Birmingham Object Recognition Battery; Benton Visual Form Discrimination; Wechsler Symbol Search; Overlapping Figures Test	Benton et al., 1994; Poppelreuter, 1990; Riddoch & Humphreys, 1993
VISUOCONSTRUCTIVE DISORDERS		
1) Disorders of graphomotor drawing or copying	Bender Gestalt; Rey Complex Figure; clock drawing, other free drawing tests	Freedman et al., 1994; Meyers & Meyers, 1995
2) Disorders of two-dimensional block construction	Wechsler Block Designs and Object Assembly	Benton et al., 1994; Kaplan, Fein, Morris, & Delis, 1991
3) Disorders of three-dimensional block construction	Test of Three-Dimensional Block Construction	Benton et al., 1994

Figure 19.1. Clinical application of cognitive neuropsychological model.



match objects presented across different viewpoints or with their major features obscured by rotation. Achievement of the *object recognition unit level* can be evaluated by asking the patient to discriminate real versus unreal objects. The *semantic level* of perceptual processing requires the patient to know whether pairs of stimuli (e.g., trains and railroad tracks, shoes and nails) do or do not belong together. Finally, the ability to extract individual identity of objects and faces sufficient to elicit name recognition can be evaluated by visual confrontation naming tasks.

D. Agnosia

The evaluation of agnosia deserves special consideration. Classically, a distinction between apperceptive and associative forms of agnosia has been made whereby the patient with *apperceptive* agnosia is said to have deficits in early stages of perceptual processing, whereas the patient with *associative* agnosia either does not display such problems or does so to a degree not sufficient to substantially impair the ability to perform perceptual operations. The patient with associative agnosia can typically draw, copy, or match unidentified objects, while the apperceptive agnosia patient cannot. This distinction has been clinically useful, though nearly all patients with agnosia have *some* degree of perceptual (apperceptive) disturbance. It should be remembered that adequate copying or matching *by itself* does not indicate normal perceptual processing (Bauer, 2012).

E. Constructional Disability

Evaluating *constructional disability* utilizes drawing, block design, and block construction tasks specially designed for this purpose (Benton & Fogel, 1962). The neuropsychologist should keep in mind that evaluation of these abilities is made more complicated by significant individual differences in drawing and constructional abilities, and by the fact that fine motor, perceptual, spatial, and attentional factors may, separately or together, affect constructional performance. The examination should strive to separately evaluate stimulus, processing, and output (response) factors that underlie the patient's performance.

F. Differential Diagnosis

The differential diagnosis of these disorders includes consideration of psychiatric and neurologic abnormalities that can produce abnormal performances in spatial, perceptual, or constructional performance.

Attentional disturbances are characteristic of many psychiatric disorders, and these may lead to minor or careless errors. A pattern of deficits on other tasks demanding focused concentration, sustained effort, and cognitive efficiency may help to differentiate psychiatric disorder from neurologic disease. *Dementia* syndromes often produce deficits in visual perceptual and constructional ability, occasionally as the initial presentation. Evaluation of characteristic features of suspected dementia syndromes (e.g., memory in suspected Alzheimer's disease, executive dysfunction in suspected frontotemporal dementia, processing speed in suspected vascular dementia) may help elucidate the picture and distinguish isolated disorders of visual cognition from a more generalized dementia. Confusional states, or *delirium*, are likely to cause deficits on tests of visual perception and constructional ability (Lee & Hamsher, 1988). In this case, laboratory or medical workup for underlying toxic–metabolic disease is critical. In delirium, attentional demands of a broad range of tasks are likely to overwhelm the patient's ability to provide good performances, resulting in generalized deficits across multiple cognitive domains. In studies of constructional impairment, patients with *posterior left hemisphere lesion aphasias (with comprehension deficits)* are the most likely patient group, other than those with posterior right hemisphere lesions, to exhibit impairments on tests of visual perception and construction. Evaluation of language capacity in these patients is critically informative in deciding whether observed impairments in visual cognition are associated with aphasic disturbances.

G. Laboratory, EEG, and Neuroimaging Correlates

Laboratory, neuroimaging, and other neurodiagnostic information should be collected as part of the comprehensive evaluation. As a general neuropsychological classification, spatial, perceptual, or constructional deficits are not associated with any definitive pattern of abnormality in laboratory tests. EEG and neuroimaging findings vary with the type of disturbance, as might be anticipated from lesion localization data presented in Table 19.1. The most common etiologies leading to these disturbances include cerebrovascular accident (CVA), tumor, carbon monoxide poisoning, closed head injury, and CNS infection, although, as indicated earlier, it is becoming increasingly recognized that some cases of degenerative dementia with primary involvement of posterior cortex can present with prominent signs of (primarily apperceptive) agnosia. Medical findings vary with etiology and localization. Because of these considerations, it can be said that laboratory, EEG, and neuroradiological findings per se do not typically play a definitive role in actually diagnosing a disturbance of visual cognition, but they may assist in

understanding whether the disturbance is related to acute (e.g., CVA, traumatic brain injury) or subacute (e.g., tumor) structural damage to the CNS, to metabolic disturbance, or to a dementia syndrome. One exception to this rule is the occasional utility of visual evoked potentials as a way of determining whether a defect exists in the sensory projection areas as opposed to the primary sensory or association cortex. Instead, the clinician should rely on behavioral factors to establish the deficit and should use the physical findings to confirm or rule out etiology.

IV. TREATMENT, COMORBIDITY, AND OTHER ISSUES

A. Treatment

In the majority of deficits described, treatments involve the development of compensatory mechanisms for what, in the majority of cases, are chronic disabilities. Treatment of *hemispatial neglect* assists the patient in using and responding to salient environmental cues designed to bring attention into the neglected hemispatial field. Such treatment is typically gradual, a few degrees at a time, and may be laborious and difficult. A lack of awareness of (anosognosia) or indifference to (anosodiaphoria) the hemi-inattention that lies at the core of the syndrome can pose a significant barrier to positive treatment outcome. Other forms of treatment that have been tested with variable reports of success include prismatic adaptation, in which a prism lens is worn to pull the vision of the patient toward the left, and constrained movement therapy, in which the "good" limb is constrained in a sling to encourage use of the contralesional limb. Eye patching has similarly been used, a patch being placed over the "good" eye. Pharmaceutical treatments have attempted to activate contralateral attention using dopaminergic agents such as bromocriptine, levodopa, and amphetamines, with mixed results. Caloric vestibular stimulation has brought temporary relief in some cases, though it is often associated with unpleasant side effects. Some data suggest that neglect and anosognosia may respond differently to these interventions, with the latter defect being more intractable to therapeutic intervention (Beschin, Cocchini, Allen, & Della Sala, 2012).

There is very little empirical work on effective treatments for perceptual or constructional disturbances, including visual agnosia, and, to our knowledge, no controlled clinical trials have been conducted. Case studies indicate some improvement with intensive rehabilitation, including teaching the patient to use spared function (e.g., verbal encoding) to compensate for impaired ability. For example, in one

study, a patient with congenital prosopagnosia, taught to use *configurational processing*, a type of processing typically impaired in face agnosia, showed improved face recognition, normalization of face-specific evoked responses (N170), and increased functional connectivity in temporal lobe (using fMRI) after training (DeGutis, Bentin, Robertson, & D'Esposito, 2007). Similarly, new treatments are being developed for topographical disorientation. A case study successfully improved topographical orientation in a developmental case involving a school-age child by training in memorization of landmarks and practical steps to route finding within the child's school (Brunsdon, Nickels, Coltheart, & Joy, 2007). Recent advances in assistive navigational technology may also be useful in developing patient-specific routing in cases of navigational disturbances (Torres-Solis & Chau, 2007).

B. Psychological/Psychiatric Comorbidity

The lesions most likely to produce defects in visual cognition often spare limbic, paralimbic, or frontal regions that when damaged, produce primary affective or personality changes. For this reason, specific forms of psychopathology are not obligatory, or even common, accompaniments of these syndromes. However, secondary emotional reactions to the real-life consequences of spatial and perceptual disturbance are common. Factors such as unemployment, changes in social life, dependency on others for help in everyday activities (e.g., dressing, transportation, eating), and boredom are seen. These major lifestyle changes may lead to depression or adjustment disorders in some individuals, whereas others may find adaptive ways to cope. As an excellent example, Humphreys and Riddoch (1987) described in detail how their patient, John, and his wife both coped with John's visual agnosia. Their description contains evidence of both adaptive and maladaptive compensations.

The *neglect syndrome*, as well as its associated impairments in attention and intention, is often associated with elements of *anosognosia*, or *denial of illness* (Adair & Barrett, 2012). The patient may deny that there is anything wrong with his or her visual functioning and may even deny ownership of an affected body part. In patients who do recognize a problem, *anosodiaphoria*, or indifference to disability, may be seen. This is best conceptualized as a basic defect in attention and motivation caused by brain disease, rather than as a psychological attempt to minimize a painful experience.

Patients with visuospatial and visuoperceptual deficits, particularly visual agnosia, often compensate for their visual loss by becoming more reliant on other sensory modalities. This is an interesting and as yet unresearched phenomenon reported in the animal literature (Horel & Keating, 1969), in which the patient comes to rely on

intact sensory modalities (e.g., audition and touch in the case of visual agnosia) in exploratory activity. Whether this represents an attempt to achieve an optimal arousal level through sensory stimulation or an attempt to gain understanding of the world through an intact modality remains to be seen. For example, Bauer's (1984) patient with severe visual agnosia listened to music constantly to lessen the boredom of living with the disorder.

In our experience, *substance abuse* is a risk in the chronic period, possibly in response to the reduced stimulation that results from a reduction in the quality of visual input and possibly a result of premorbid factors. Indeed, it should be emphasized that one problem in understanding psychiatric comorbidity in agnosia is that the relative rarity of these syndromes complicates an analysis of whether such problems are caused or exacerbated by the underlying neurological impairment or whether the appearance of such problems reflects preinjury factors that would have exerted themselves in any event. Such issues await systematic research.

V. SUMMARY

Disorders of visuospatial, visuoperceptual, and visuoconstructive ability are relatively common in the neuropsychology clinic. Clinical presentation can vary from the appearance of full-blown syndromes (e.g., hemispatial neglect, visual agnosia, Balint's syndrome) to the presence of more subtle but measurable weaknesses in all or some of these domains. Such deficits are frequently disabling and can affect patients' ability to navigate through their environment, appreciate the world around them, recognize and utilize everyday objects, or to engage in fine motor manipulation of their surroundings. The complex, parcellated nature of the human visual system sets the stage for "fractionated" defects in spatial, perceptual, or constructive disability, though it is not uncommon for patients with substantial visual symptoms to show impairments in multiple domains. No specific laboratory or neuroradiological markers exist, though orderly anatomic findings have been reported in the literature on these disorders that should allow the clinician to systematically evaluate the scope and limits of the deficit with a combination of standardized tests and customized evaluations. Key symptoms, characteristic lesion locations, and fundamentals of the approach to assessment of these disorders have been summarized in this chapter. Although significant progress has recently been made, much remains to be learned about these complex disorders, and clinicians are encouraged to take a hypothesis-oriented approach in order to enlarge the available knowledge base.

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Chapter 20

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Disorders of Attention

Impairments of attention are among the most common manifestations of brain damage. Many neuropsychological syndromes that result from highly circumscribed focal brain lesions are relatively rare in clinical practice (e.g., visual agnosia). In contrast, disorders of attention are quite common, occurring following damage to a variety of cortical and subcortical brain systems. Attention dysfunction also occurs as a nonspecific effect of neurophysiological factors that affect arousal and metabolic state. Alterations in level of consciousness associated with acute brain dysfunction invariably have a direct impact on attention. It is essential, therefore, that attention be assessed as a standard part of a neuropsychological evaluation.

Patients with attentional dysfunction usually have an inability to allocate cognitive resources effectively to the task at hand. Clinical examination reveals that the patient fails to perform at optimal levels even though primary cognitive resources, such as sensory registration, perception, memory, and associative functions, are intact. Patients with attentional disorders are able to perceive sensory input,

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comprehend language, form and retrieve memories, and perform other cognitive functions, yet they fail to do so consistently. The performance inconsistency that is a hallmark feature of attentional disturbances stems from the fact that attention consists of a set of dynamic processes that influence the interaction between other core cognitive functions, such as perception and memory, and the external environment.

Whereas perception, language, and memory consist of processes that form the substrates of cognition, attention governs the information flow and processing within each of these cognitive domains. Attentional processes facilitate, enhance, or inhibit other cognitive processes. Attention enables people to respond to particular information while either consciously or unconsciously ignoring other potential stimuli. Attention implies cognitive or behavioral withdrawal from some things so that others can be effectively dealt with. Attention results in behavioral orientation toward particular stimuli or response demands associated with the task at hand. Therefore, a primary function of attention is to facilitate selection of salient sensory information for further processing (sensory selective attention). Attentional processes also serve to facilitate responding by influencing the tendency to respond in particular ways to task demands (i.e., response bias). Through the processes of response intention, selection, and control, attentional selectivity relative to available response alternatives is possible.

In addition to being selective, attention governs the intensity of cognitive allocation directed toward a particular stimulus or task. This intensity of attentional allocation is often conceptualized as focus, and subjectively it is experienced as the ability to concentrate. Attentional focus is a direct function of capacity limitations, influenced by both energetic (e.g., arousal) and structural (e.g., processing speed) factors. When attention capacity is reduced, either by structural brain damage or neurophysiological disturbance, people become less able to focus and concentrate. Attention also has a strong temporal dynamic. Whereas the content of associations, language, and percepts can be considered to be independent of the variable of time, what is attended to is usually a direct function of the time period that one examines. Furthermore, the ability of people to attend and focus selectively changes over time. Variation in attention over time is a function of the individual's capacity for sustained attention.

Attention was once conceptualized as a single process, similar to a filter or bottleneck, that restricted the flow of sensory input subject to higher cognitive operations, thereby limiting the amount of information to be processed to manageable levels. Although this model has intuitive appeal, compelling evidence now exists for attention being not a unitary process but a function of the inter-

action of at least four component processes under the influence of multiple brain systems. A variety of attentional disorders can differentially affect the underlying component processes of sensory selective attention, response selection and control, capacity and focus, and sustained attention (Cohen, 1993; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Figure 20.1 depicts the primary factors underlying attention.

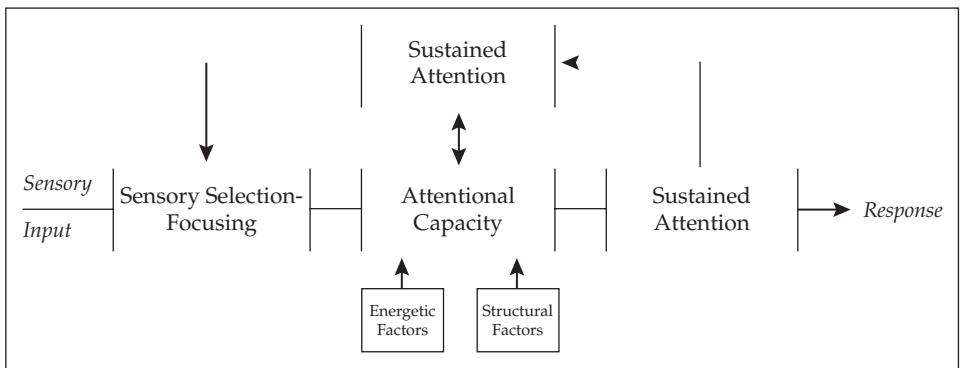
I. DEFINITION/CLASSIFICATION: COMPONENTS OF ATTENTION

A. Sensory Selective Attention

Sensory selective attention refers to the processes by which sensory input is chosen for additional cognitive processing and focus. Perceptual processes are engaged relative to target stimuli and are disengaged from nontargets. It occurs at a very early stage of processing, often before a clear task demand is present. The orienting response (OR), the most elementary behavioral response identified during classical conditioning, is a simple form of automatic sensory selection. Stimuli that are novel, salient, or potentially significant elicit an OR, whereas nonsalient "old" stimuli fail to do so. Salience may reflect perceptual factors, such as figure–ground contrast, or informational value derived from past experience. Sensory selection is contingent on the integration of the following elementary operations:

1. *Filtering.* At early stages of perceptual processing, selection occurs on the basis of sensitivities to or preferences for certain types of sensory features. Input that has these features receives additional processing, whereas input that does not is filtered.
2. *Enhancement.* Prior to the presentation of a stimulus to a particular spatial location, cortical neuronal sensitivity to that location is increased by information that creates an expectancy that an event will occur there. Attentional readiness and expectancy to spatial position form the basis of spatial selective attention. The neuronal substrates of enhancement have been demonstrated in primates (e.g., Goldberg & Bushnell, 1981).
3. *Disengagement.* Once attention has been focused on a particular stimulus, it remains fixed until another stimulus or internal event signals a shift to another spatial location or perceptual feature. This attentional shift requires disengagement from the initial stimulus, before attention can be allocated to new stimuli. Attentional disengagement requires processing resources, and it takes time.

Figure 20.1. Primary factors underlying attention. Flow of information is shown through the four major components of attention: sensory selection and focusing, response selection and control, capacity, and sustained attention. Attentional capacity is influenced by energetic and structural components. Sustanined attention is a product of the information flow through the system and resulting feedback that affects each factor.



B. Response Selection and Control (Intention)

Attentional processes also serve to facilitate action through the selection and control of behavioral responding. *Intention* refers to allocation of attentional resources for response selection and control.

1. Although sensory selective attention is sometimes viewed as an antecedent to responding, in many cases response intention and selection precede sensory selection. For instance, if one loses one's keys, an intent to search and a search strategy may be generated before the perceptual act of selectively attending to a particular spatial location is initiated.
2. Intention depends on the individual being prepared to make a response. The following functional states influence the generation of intention as well as sensory selective attention:
    a. Readiness. The individual must be ready to make a response for optimal performance to occur. Readiness is mediated by arousal and reinforcement associated with a task.
    b. Expectancy. In addition to being ready to respond, one has the expectation that a response will need to be made at a particular time.
    c. Anticipatory response. Preparatory responses in anticipation of the need to respond often serve to facilitate intentional response selection and control.
3. Response selection and control are usually controlled and effortful, in contrast to sensory selective attention, which often is performed more automatically.
4. Conscious awareness usually occurs with response selection and control, whereas sensory selection often occurs without awareness.
5. Sequential processing is usually associated with response selection and control, whereas sensory selection often occurs as a result of parallel processing.
6. Executive functions are strongly linked to response selection and control. Specific executive functions that have direct attentional underpinnings include
    a. Intention. Processes by which response set and preparation are established.
    b. Initiation. Processes by which the response is started.
    c. Generative capacity. Processes that facilitate production of the response.
    d. Persistence. Processes that enable sustained responding.
    e. Inhibition. Processes that prevent or enable cessation of the response.
    f. Switching. Processes that enable a shift from one response to another

C. Attentional Capacity and Focus

Once a stimulus has been selected for further processing, attention is allocated in accordance with the demands of the task at hand. For many cognitive operations, quality of performance is a function of the intensity of directed attention.

1. *Focused attention* controls the intensity and scope of attentional allocation and, consequently, the cognitive resources directed to a particular task or cognitive operation. Conversely, focus is a function of processing capacity limitations (Kahneman, 1973).
2. *Attentional capacity* is governed by both structural and energetic limitations (Cohen, 1993). Energetic capacity limitations tend to be state dependent, composed of factors such as arousal and motivational state. Structural capacity tends to be less state dependent, is determined by factors intrinsic to the individual, and varies greatly across people.
3. *Structural factors* that provide attentional capacity limitations include the following:
   a. neural transmission and processing speed
   b. working memory capacity
   c. temporal processing constraints
   d. spatial processing constraints

D. Automatic Versus Controlled Processing

An important distinction exists between automatic and controlled attention. In many instances, attention is elicited automatically when particular environmental signals occur. Furthermore, some tasks can be performed without the need for much attentional capacity (e.g., typing).

1. *Automaticity* refers to the capacity to attend to and perform particular cognitive operations with minimal effort and without the need for controlled intensive serial processing (Hasher & Zacks, 1979; Schneider & Shiffrin, 1977).
2. Increasing attentional focus relative to the task at hand usually results in a reduction in automaticity.
3. With automaticity, there is usually relatively little demand placed on attentional capacity, and often attention can occur without much awareness or subjective effort (e.g., attending to other cars while driving on a highway with light traffic).
4. Once a task is learned, less working memory is required, and demands for controlled effortful processing are reduced.

5. Automaticity occurs most commonly in the context of sensory selective attention, particularly when involving single-frame parallel processing, in which rapid selection of relevant targets from the larger set of potential stimuli in the environmental field can be accomplished at a very early stage of processing (single frame). Visual selective attention is particularly well suited for single-frame parallel processing. Visual information typically occurs in parallel with a vast array of information reaching the brain almost instantaneously. Automaticity is more difficult to achieve for tasks that require sequential cognitive operations, although greater automaticity is often attainable through practice.
6. Selective response attention (intention) is less likely to occur with automaticity than is sensory selective attention. One reason is that motor responding often requires the sequencing of complex responses. The development of well-learned motor programs (e.g., typing, musical performance) often enables attentional automaticity. Increasing memory demands usually decrease the capacity for attentional automaticity (Schneider & Shiffrin, 1977).
7. Sustained attention often can be performed with automaticity. Yet when long durations of sustained attention or vigilance are required, automaticity decreases and greater demand for controlled attentional processing results. Demands for concurrent attention on more than one task or unit of information often cause a rapid decrease in automaticity.

E. Sustained Attention

The maintenance of optimal performance over time requires sustained attention. When one considers most other cognitive processes, a consistent level of performance is usually assumed. For instance, in a neurologically healthy person, visual perception always occurs when certain psychophysical parameters are met. Similarly, language competence usually implies that once individuals have achieved comprehension, they will always comprehend particular information. In contrast, temporal inconsistency is a defining characteristic of attention because the ability to attend and focus selectively varies over time.

1. The variability of performance over extended time periods illustrates an important feature of attention that distinguishes it from other cognitive processes.

2. *Vigilance* is a special form of sustained attention in which there is a demand for a high level of anticipatory readiness for low-probability targets or stimulus events (Parasuraman & Davies, 1984).
3. Sustained attention is a direct function of the task duration. Any task can be extended to the point that a failure of sustained attention will occur.
4. Sustained attention is dependent on the target:distractor ratio. Generally, sustained performance is most difficult in situations in which target stimuli are rare.
5. Tasks that demand high levels of attentional focus and capacity are usually more difficult to sustain.
6. Energetic capacity, including arousal, is a strong determinant of sustained attention performance.
7. Reinforcement greatly influences sustained attention. Incentive and internal motivational state are important determinants of how attention is maintained over time.

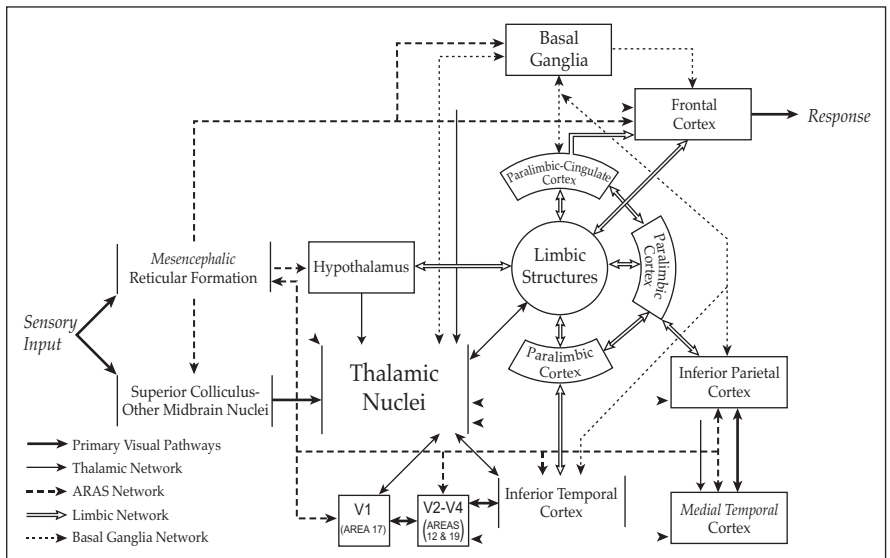
II. FUNCTIONAL NEUROANATOMY OF ATTENTION

Attention cannot be localized to one discrete brain system; rather, multiple brain systems interact in a network to control attention (Cohen, 1993; Heilman, Watson, & Valenstein, 1993; Mesulam, 1981). However, the specific attentional processes are controlled by different brain systems within this network (see Figure 20.2).

The inferior parietal cortex plays a central role in spatial selective attention (Heilman et al., 1993; Heilman, Watson, Valenstein, & Goldberg, 1987; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994; Mesulam, 1981; Posner, Walker, Friedrich, & Rafal, 1987). In primates, area PG of the nondominant hemisphere contains neurons that enhance attentional responses to particular spatial positions. Damage to this area results in impaired spatial attention (e.g., hemineglect). Other posterior cortical areas also appear to be involved in selective attention. For example, the inferior temporal lobes exhibit attentional enhancement, which facilitates higher order sensory analysis, such as object recognition. Attentional enhancement enables selective focus on relevant visual features.

The frontal cortex appears to be important for all four of the attention component processes, and therefore is an essential brain region for attention. The most obvious function of the frontal cortex occurs with respect to executive functions related to response selection and control. However, it also influences most other

Figure 20.2. Functional neuroanatomy of attention. Multiple brain systems interact in a network to control attention.



aspects of attention, including focused and sustained attention and capacity. Even sensory selection seems to be influenced by the frontal cortex, as evidenced by findings of spatial hemi-inattention following unilateral nondominant hemisphere damage. The frontal cortex plays an integral role in switching and search for sensory selective attention.

The orbital frontal region plays a major role in response initiation and inhibition. Damage to this area causes go/no-go impairments, which have direct implications for attention (Fuster, 1989). The medial frontal lobe, including the paralimbic cingulate cortex, plays an important role in the formation of intent to respond, the temporal consistency of responding, and focused attention (Cohen, 1993). The dorsolateral frontal cortex also appears to play a role in attention, although this is less well understood. This region seems to influence response sequencing, persistence, switching, and focus, particularly with respect to integration and responding relative to semantic representations. The frontal eye fields control saccadic eye movements and are important for visual search and looking. Neuronal response of this region is influenced by attention neurons in the parietal cortex. The premotor cortex facilitates planned movements; although it is not in its own right an attentional system, it influences response automaticity.

Limbic system structures, such as the amygdala and septal nuclei, affect attention by influencing motivational and affective processing and establishing salience, which in turn determines the priority given new information as well as existing associations. The limbic system plays an essential role in defining the limits of attentional capacity and focus, and it also is instrumental in determining response biases and propensity (Cohen, 1993; Pribram & McGuinness, 1975). Memory encoding and retrieval functions of the hippocampus constrain attentional capacity. The rate at which short-term memories are encoded into long-term representations influences the ease with which attentional operations can be performed (Schneider & Shiffrin, 1977). Interactions of the amygdaloid, septal, and hypothalamic nuclei are responsible for the creation and experience of motivation and emotions, and ultimately they govern the salience associated with information.

Subcortical systems play a critical role in attention. Thalamic nuclei are involved in both sensory and response selective attention, and they have a gating function as sensory input is relayed through the thalamus to cortical areas. Furthermore, motor control signals sequenced within the basal ganglia are processed through the thalamus and then relayed to supplementary motor and frontal areas prior to motor output, with the thalamus serving as a gatekeeper. The caudate nucleus of the basal ganglia is critically important not

only for the selection of motor responses but also for the selection and coordination of sensory information relative to these responses. There is now considerable evidence that basal ganglia dysfunction plays a significant role in attention-deficit/hyperactivity disorder (ADHD).

Midbrain systems, particularly the mesencephalic reticular system, are essential for production of arousal and activation (Cohen, 1993; Pribram & McGuinness, 1975). Arousal establishes a tonic energetic level, which in turn influences the responsiveness and attentional bias of the system. The reticular system activates the thalamus, limbic system, and cortical areas, and it is therefore critical for maintaining consciousness. Midbrain nuclei are also involved in the control of saccadic movements for visual search.

III. NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS OF ATTENTION

A. Stroke

Focal lesions associated with embolic or hemorrhagic cerebrovascular infarction often produce the most dramatic form of attentional disturbance. Hemineglect, extinction, and hemi-inattention syndromes are among the disorders of attention that are common after stroke. These syndromes are discussed in considerable detail elsewhere in this text and are not extensively reviewed here. However, several key summary points regarding these syndromes are in order.

1. Hemi-inattention and neglect are manifestations of unilateral brain lesions. Striking spatial asymmetry in attentional performance is a central feature of these syndromes.
2. Neglect usually occurs relative to the left side of space, which illustrates the importance of the nondominant cortical hemisphere in spatial attention.
3. Although most patients with neglect have a number of common symptoms, the specific attentional disturbance depends on the exact location of the lesion.
    a. Lesions affecting the reticular system that produce neglect also involve significant arousal and activation impairments.
    b. Unilateral basal ganglia damage often results in both hemiattention and intention impairments, reflecting the importance of this system to sensorimotor integration.
    c. Cingulate lesions are more likely to affect intention than sensory selective attention.

Although hemineglect syndrome is one of the most dramatic forms of attentional disturbance, focal lesions secondary to stroke commonly produce disorders that do not involve hemineglect.

4. Focal frontal lesions may produce impairments of focused attention in addition to the common finding of attentional impairments of response selection and control.
5. Thalamic lesions may result in problems with informational gating and selection regardless of whether unilateral neglect is present.
6. Subcortical lesions often produce impairments of arousal, activation, and information-processing speed, which in turn may limit attentional capacity.
7. Subcortical small vessel disease secondary to cerebral hypoperfusion may result in dementia; this type of dementia seems to affect attention and information-processing efficiency most dramatically.

B. Dementia

Alzheimer's disease and other neurological diseases that result in diffuse global cortical dysfunction often have significant associated attentional impairments. Yet patients with dementia are often able to sit and sustain a general attentional orientation toward the examiner, and automatic attention is usually preserved until relatively late stages of the illness. Therefore, clinicians often conclude erroneously that attention is preserved in these patients.

1. Attentional capacity and focusing ability are almost always impaired early in the disease course, although sensory selective attention tends to be intact.
2. Simple response selection and control are affected to varying degrees in early stages of dementia.
3. Executive functions often fail relatively early.
4. Sustained attention may appear adequate with respect to a patient's ability to sit and respond to the examiner. Yet sustained performance on structured tasks is usually quite impaired, and there may be problems with impersistence.

C. Multiple Sclerosis

Of the cognitive impairments that often accompany multiple sclerosis (MS), the most common disorders involve attention (Cohen, 1993).

1. Fatigue is the most common of all symptoms in MS. Fatigue is associated not only with motor effort but also with attending to and performing cognitive tasks.

2. Subcortical lesions secondary to demyelination may disrupt attentional control.
3. Subcortical white matter lesions also reduce neural transmission speed. Slowed processing time reduces attentional capacity and creates processing bottlenecks.

D. Hydrocephalus

Hydrocephalus often creates pressure on periventricular white matter–subcortical systems, and attention and information-processing problems are quite common. Because ventricular pressure often fluctuates, attentional difficulties frequently exhibit a fluctuating course with this disorder.

E. Head Trauma

Whereas diffuse neuronal injury often results from moderate or severe head trauma, the most common areas of bilateral damage are the frontal lobes, basal temporal lobes, and subcortical brain systems. Brain damage to these areas occurs not only as a by-product of an object hitting the cranium but also as a result of shearing forces, especially when an accident has involved rapid acceleration–deceleration.

1. Attentional impairments of the type described previously for patients with focal frontal lesions are often observed.
2. The shearing effects that damage subcortical white matter often result in arousal and activation deficits.
3. Slowing of information processing is also common.

F. Schizophrenia

Severe attention impairments are common.

1. Problems with informational filtering or gating often exist.
2. Selective attention is often impaired with increased information load.
3. Problems distinguishing relevant from irrelevant input are quite common and seem to belie a problem with the tagging of semantic value of informational input or associations that are attended to.
4. Sustained and focused attention are often poor, and capacity is often limited, particularly for divided attention (concurrent task performance).

G. Affective Disorders

Attentional disturbance is the most common cognitive symptom associated with major affective disorders.

1. Subjective complaints of problems with concentration and focus are among the symptoms that are considered in a diagnosis of depression.
2. Problems with reduced energetic capacity (focused attention) and sustained attention are most common. Response selection and control is often more moderately impaired. Sensory selective attention is usually less affected.
3. Attentional performance is often quite variable over time.
4. The quality of attentional impairments varies as a function of affective state. Manic patients tend to make more errors of commission and failure to inhibit responding, whereas depressed patients make more errors of omission and are likely to show low levels of arousal with psychomotor slowing. Great effort is often required for attention.
5. Given the strong likelihood of attentional disturbance in patients with affective disorders, it is essential that depression be ruled out or factored in when one is assessing attention associated with other brain disorders.
6. Mania or hypomania can cause attentional impairment that looks very much like ADHD on testing; symptoms and disturbance of attention typically start in adolescence or early adulthood, unlike ADHD, highlighting the importance of the clinical history in interpreting test results.

H. Attention-Deficit/Hyperactivity Disorder

The most commonly diagnosed disorder of attention, ADHD, has become one of the most frequently diagnosed disorders within U.S. society. Although a diagnosis of ADHD is now sometimes made on the basis of patient self-reported symptoms, there is considerable evidence that self-reported symptoms do not always correspond well with evidence of attentional impairments observed on assessment. This is particularly true for adults presenting with new concerns about possible ADHD but without a history of childhood ADHD. This disorder is covered in great detail in Chapter 22 of this volume and will not be discussed in great detail here.

IV. ASSESSING DISORDERS OF ATTENTION

Although it is an essential cognitive process, attention is difficult to observe directly or to measure. Unlike other cognitive functions, performance may differ greatly at different points in time; it is this

variability that in fact defines attention. Attention is often situation specific. Attention primarily serves to facilitate other cognitive functions; it enhances or inhibits perception, memory, motor output, and executive functions, including problem solving. Yet attentional performance is measured as a function of performance on tasks that also load on one or more other domains. Therefore, a number of methodological issues need to be considered when attention is assessed.

A. Methodological Issues

1. Pure tests of attention do not exist.
2. Attention usually must be assessed within the context of performance on tasks that load on one or more other domains.
3. Attentional performance is often a function of a derived measure obtained by comparing performance across tasks that load differentially with respect to key attentional parameters (e.g., target:distractor ratio).
4. Absolute performance often proves less informative than measures of performance inconsistencies in the assessment of attention. For example, how performance varies as a function of time, spatial characteristics, or memory load provides more information about attentional dynamics than does the total number of errors on a visual detection task.
5. Because attention is not the by-product of a unitary process, it cannot be adequately assessed on the basis of findings from one specific test. For example, conclusions about attention based solely on digit span performance are misguided.
6. Attentional assessment requires a multifactorial approach.

The specific measures used in an evaluation depend on the overall level of functioning of the patient. For patients with global cognitive dysfunction, it may be difficult to use tasks that require complex responses. For patients with relatively high overall cognitive abilities, tasks should be chosen that require multiple component processes. If the patient is able to perform well on these tasks, severe attentional disturbance involving specific attentional component processes can be ruled out. The Stroop (Golden & Freshwater, 2002) and Trail Making (Army Individual Test Battery [AITB], 1944) tests are examples of tasks that require multiple attentional processes. If impairments are found on such tasks, more extensive testing of specific component processes can be conducted. Whenever possible, efforts should be made to use tasks that incorporate signal detection methods, even when one is not evaluating sensory selective attention per se. These methods provide the best means of accurately summarizing performance relative to all possible types of errors. Also, tasks using a signal detection approach can often be easily integrated with response time measures.

B. Attentional Parameters That Should Be Considered

A thorough assessment of attention should be based on analysis of data from a comprehensive battery of attentional tests (Cohen, 1993) that sample the various component processes of attention (see Table 20.1). These tasks should enable evaluation of performance as a function of different stimulus, response, and task parameters. Tasks should be differentially sensitive to the following attentional parameters:

1. Spatial characteristics
2. Temporal dynamics
3. Memory demands
4. Processing speed requirements
5. Perceptual complexity
6. Demand for different levels of control and sequencing
7. Demand for various types and complexity of cognitive operation
8. Effortful demands
9. Task salience, relevance, and reward value
10. Demand for single-frame parallel and multiframe serial processing

C. Levels of Assessment

Although multifactor neuropsychological assessment provides the best means of evaluating attentional impairments, a comprehensive attentional evaluation may not be feasible in everyday clinical practice because (a) the patient is too ill to participate for long time periods, (b) other functions in addition to attention must be assessed, or (c) there are time constraints in the clinical context. Consequently, clinicians should be aware of the information that can be obtained from different levels of attentional assessment.

1. CLINICAL INTERVIEW

The initial information regarding possible attention disturbance usually comes from available medical records and the reports of patients and their family during the structured interview. In this regard, the assessment of attention is not altogether different from the approach taken when assessing memory or other cognitive functions, though often the clinical context is somewhat different. The nature of the interview will likely vary depending on whether the patient is self-referred, because of concerns about ADHD or recent problems concentrating, versus presenting with a history of stroke

Table 20.1. Component Processes of Attention-Associated Neuropsychological Tests

Component	Tests
Sensory selective attention	Letter and symbol cancellation Line bisection Cued spatial detection (Posner task) Spatial search tasks (span of apprehension) Dichotic listening CPT (D′) Line orientation
Response selection and control	Go/no-go Complex motor programs Rampart figures Trail Making CPT (F+) Porteus Mazes—breaks Sorting tasks—failure to maintain response set Fluency measures (COWAT, design fluency)
Capacity and focus	Digit symbol (Stroop) Paced Serial Addition Test (PASAT) Stroop tests (interference) Reaction time measures Levels of processing (working memory tasks) Timing tasks (motor continuation, duration discrimination) Spatial rotation tasks Dichotic listening (divided attention paradigms)
Sustained attention	CPT vigilance decrement Motor persistence tasks (sustained finger tapping) Variation across session on repeated administration of task

or other neurological disorder. In the latter case, the symptoms of attention impairment to be questioned in the initial clinical workup are likely to occur relative to other cognitive and behavioral problems, which will establish a different emphasis with respect to how attention is assessed. Furthermore, the clinical assessment and interview related to attention will likely vary depending on the age of the patient (child, young adult, geriatric), whether the problems are occurring in the context of an educational or occupational problem, or other clinical factors, such as psychiatric comorbidity. Accordingly, the path of clinical interview and initial screening needs to be approached with some clinical flexibility.

The interview should, nonetheless, invariably cover certain topics. Almost always a detailed description of the symptoms of attention disturbance, medical and psychiatric history, and assessment of psychosocial, educational, and occupational issues should be obtained. It is important that the clinician observe the behavior of the patient to determine whether there are obvious abnormalities of consciousness, orientation, arousal, alertness, activity level, mood, and thought process and content (see Chapter 2, this volume, for useful techniques). Furthermore, specific observations should be made regarding the patient's behavioral orientation toward the examiner, including posture, eye contact, and interactiveness. Although the clinical interview often provides useful information, the following key problems arise if one relies only on this source of information:

a. Subjective complaints of attentional problems often do not correlate well with actual impairments on attentional tests. Patients may describe, in some cases quite eloquently, the nature and severity of their deficits in attention, yet the complaints may not be corroborated by external sources.
b. Patients with the most severe attentional problems often have little awareness of their impairments.
c. Family members frame their experience of symptoms on the basis of their own tolerance for certain types of behavior, so their data are of questionable validity.

2. BEHAVIORAL OBSERVATION

The clinician assessing attention should be sensitive to particular qualitative aspects of the patient's behavior. Is an individual very distractible? Does the patient seem disinhibited behaviorally or in discourse? Do speech and thinking appear tangential or goal directed? Does the patient seem obsessed with particular thoughts, stimuli, actions, beliefs, or emotional content? Does he or she appear dulled or apathetic? Does this person seem weakly responsive to stimuli or events? The clinician ultimately should obtain data

regarding these questions from the clinical assessment and also from a description of objective observers of patient's behavior in the natural world. This kind of information is often obtained from family members, but it should be corroborated by reports of clinicians, educators, coworkers, or others who may be more objective in their impressions. Many occupations require sustained attention to tasks, in spite of their repetitive nature. It is frequently a coworker or supervisor who first notices a problem with sustained attention. Psychiatric or neurological disorders that affect a person's ability to maintain a thread of thought may be first noticed by family members because of increased difficulty in carrying out a discussion with the patient.

a. Behavioral observation methods enable systematic recording during the examination of behavioral events that reflect attentional problems. These methods include event recording of behavioral frequency, interval recording of the presence of an event at certain times, and scan sampling of duration of events per unit of time. The importance of the behavioral observation might be most applicable during the bedside evaluation. A bedside assessment of attention requires some mental flexibility from the clinician, as the testing environment and process are dynamic and the clinician will likely need to overcome a variety of obstacles (e.g., interruptions by house staff, frequent external noises, presence of individuals in the room). As much as these factors place some limits on the testing process, they can also serve as useful sources of information.
b. Behavioral observation methods often provide the most ecologically valid measures of attention. However, the following limitations apply to their use:
   - Behavioral observation methods can be quite labor intensive.
   - The methods require long recording periods to detect low-frequency events.
   - Behavioral observation does not directly measure or provide much information regarding the cognitive processes underlying inattention symptoms.

3. SYMPTOM RATING SCALES

Inventories designed to assess the behaviors of children and adults with suspected attention problems provide a means of obtaining indirect information about these behaviors. Inventories enable parents, teachers, and clinicians to rate various behaviors and symptoms for a particular patient and to compare the resulting behavioral profile to normative data. Although most of these rating scales were

explicitly designed for assessing ADHD (e.g., the Conners rating scales; Conners, 2004), they sample symptoms of attention disturbance broadly and may have clinical value for deriving behavioral rating of attention symptoms along with neuropsychological test findings.

The Neuropsychiatric Inventory (NPI; Cummings et al., 1994) is particularly useful for rating apathy, impulsivity, aggressiveness, and other related symptoms in elderly patients and in patients with established neurological disease. Paul Malloy and Janet Grace at Brown University developed the Frontal Systems Behavioral Scale (FrSBe; Grace & Malloy, 2001), which provides a valid assessment of three behavioral problems related to executive attention: apathy, impulsivity, and executive disturbance. Inventories are used in the assessment of apathy (see Chapter 26 for a more detailed discussion). The assessment of impulsivity can be facilitated through the use of inventories such as the Barratt Impulsivity Scale (Patton, Stanford, & Barratt, 1995). The value of these types of inventories is that they enable quantification of symptoms of attention impairment, executive dysfunction, and related behavioral problems that can be compared with established normative data. Yet they also present potential pitfalls for clinicians. In particular, a dilemma arises in cases where there is a discrepancy between neurocognitive findings and symptom report. For many ADHD specialists, the symptom report is to be believed because it most directly reflects how the patient's functioning is perceived by significant others. But what does it mean if a patient exhibits severe elevations on the inattention or impulsivity indices of an ADHD inventory, yet shows no objective findings of problems with inattention, inhibitory control, or other neurocognitive problems? Conversely, what if major disturbances are evident on neurocognitive assessment without corroborating evidence from rating scales?

4. NEUROPSYCHOLOGICAL ASSESSMENT OF ATTENTION

a. Traditional psychometric approaches

Many psychological tests that were not designed specifically to assess attention have been used for this purpose. Most notably, the Wechsler Adult Intelligence Scale—IV (WAIS–IV; Wechsler, 2008), originally developed as an intelligence test, is widely used to provide information about specific cognitive functions, including attention. Attentional functions correlate most closely with the Working Memory and Processing Speed indices of the WAIS–IV. In addition, attentional problems may also be identified on the basis of the patients' response characteristics, such as inter-time variability and

inter-subtest variability. However, caution should be used when interpreting attentional impairments on the basis of performance variability, because variability may also reflect the standard error of measurement and subtle psychometric factors associated with test construction.

Ideally, however, the assessment of attention should include neuropsychological tests that have been developed to be sensitive to the different component processes of attention. With the use of these tests, impairments of attention can be more easily dissociated from other cognitive problems. Norms exist for many of these tests.

b. Sensory selective attention

Tests used in the assessment of neglect syndromes provide a foundation for the assessment of sensory selective attention.

Letter and symbol cancellation tasks are useful for detecting abnormalities in both the spatial distribution of visual attention and general signal detection capacity. Cancellation tasks require visual search and selective attention and can be sensitive to interference. The inclusion of a cancellation task on the WAIS–IV (Wechsler, 2008) illustrates the perceived importance of this cognitive function, and widespread use of this instrument is likely to yield considerable data in coming years. Other tests of cancellation include the Ruff 2 & 7 Selective Attention Test (Ruff, Niemann, Allen, Farrow, & Wylie, 1992), the Visual Search and Attention Test (Trenerry, Crosson, DeBoe, & Leber, 1990), the d2 Test of Attention (Brickenkamp & Zillner, 1998), and the Digit Vigilance Test (Lewis & Rennick, 1979). These cancellation tasks combine measures of selective attention with other attentional capacities, such as sustained attention, or of lateralized attention impairments such as those seen in neglect. The tasks are sensitive to attentional disorders that are due to a number of conditions, including right hemisphere damage, consistent with expectations regarding the role of the nondominant hemisphere in spatial selective attention.

Other measures of visual/spatial attention include tests of line bisection and extinction to double simultaneous stimulation, which are critical in the assessment of the neglect syndrome. (See the discussion of these techniques in Chapter 2, this volume.)

The analysis of the spontaneous drawings of objects and copying of figures may point to lateral differences in attention to detail or spatial quality.

In addition to the tests above, which primarily assess attention through visual or tactile modalities, there are numerous measures of sensory selective attention that use the auditory/verbal method of administration, including the Brief Test of Attention (Schretlen, 1997). This test, which involves auditory presentation of letters and

numbers, samples several attention domains, including selective attention, focused attention, and divided attention.

Although paper-and-pencil tests, simple behavioral paradigms, and auditory attention tasks provide a useful method for initial assessment, computerized tests based on experimental paradigms provide for a more thorough evaluation of sensory selective attention. Other approaches include dichotic listening, span of apprehension, covert orienting of attention, and backward masking, to name a few. Unfortunately, they have not yet been developed and standardized for widespread clinical use.

- *Dichotic listening paradigms*, which involve the presentation of different information to the two ears, provide a way of assessing auditory attentional selection under different conditions of discriminability and response bias. However, this paradigm also involves divided attention and reflects capacity limitations as well. Dichotic listening has been employed in shadowing paradigms, which require the participant to repeat material being presented auditorily in one ear while processing a competing message in the other ear. Participants have great difficulty extracting information from the nonshadowed ear during dichotic listening, but they can detect physical changes in the stimuli to that ear. Participants also show little memory of material presented to the nonshadowed ear, although they attend better to the nonshadowed channel when different modalities were used and after they have learned to attend to the nonshadowed channel.
- *Spatial search tasks* provide an excellent means of assessing the spatial distribution for visual attention. Tachistoscopic or computerized presentation of an array of visual stimuli enables attentional search to be evaluated as a function of the time taken to scan the visual array for a particular target (visual spatial search tasks). By mapping this spatial distribution as a function of attentional parameters, it is possible to determine what factors influence search. Search accuracy tends to be best above the fixation point, whereas extreme points in the vertical dimension are the least likely to be accurately searched. Selection has also been shown to vary greatly along the horizontal axis, and search times are greatest when there is high similarity between targets and distractors. The accuracy of visual search depends on the attentional demands of the task. Accurate detection should occur at an almost perfect rate when the location of the target is obvious and not difficult to discriminate. Reduced speed and accuracy occur when targets are shifted in the visual field and the location is uncertain.

- *Spatial cue paradigms*, which measure the influence of attentional bias in anticipation of spatial position, provide another important method for assessing visual selective attention (Posner et al., 1987). Although a variety of spatial cue paradigms exist, the principles underlying these tasks are generally the same. A neutral cue is presented at some spatial location prior to the onset of a target. On some trials, the cue correctly signals the future position of a target stimulus, whereas on other trials the information provided by the cue is incorrect. The accuracy of detection and reaction times can then be measured as a function of the anticipatory cue to either correct or incorrect spatial position.

c. Intention/response selection and control

A large number of tasks are available for use in assessing response selection and control. Many of these tasks fall within the rubric of tests of executive functions. These tests are differentially sensitive to the executive functions of intention, initiation, generation, persistence, inhibition, and switching that were described previously. Simple motoric response control may be assessed by tasks such as double alternating movements, alternating graphic sequences (e.g., Rampart Figures), motor impersistence, and the go/no-go paradigm. Tests such as Trail Making (AITB, 1944), the Stroop tasks (Golden & Freshwater, 2002), the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss 1993), and the Porteus Mazes (Porteus, 1965) provide a means for assessing higher order executive functions such as goal-directed behavior, response planning, and active switching of response set.

1. Response selection and control are predicated on the formation of intent to act. Although intent is often inferred rather than measured directly, there are ways of assessing intentional impairments.
   a. A failure to initiate a search or goal-directed behaviors despite motivational feedback that provides incentive for such action suggests an intention impairment.
   b. Failure to persist in a search strategy (impersistence) may also reflect impaired intention.
   c. The quantity and quality of spontaneously initiated behaviors, including the ability to generate alternative creative solutions to problems, may provide the best intention index.
2. Capacity for initiation, generation, and persistence can be measured in a number of different ways.
   a. Verbal and design fluency not only indicate the total quantity of response output for a circumscribed time

period but also can point to problems with initiation and persistence.
   b. Simple and choice reaction time may help to characterize response initiation problems.
   c. Tests of motor functioning such as the Grooved Pegboard Test (Matthews & Kløve, 1964) measure generation of and persistence in fine motor response production.
   d. Motor system deficits need to be considered when one is assessing whether a response-generation deficit relates to attentional-executive impairments; occasionally, problems in the motor domain may present a confounding variable in the interpretation of neuropsychological results. Deficits in the ability to persist on motor tasks may also reflect problems with attention and executive functioning. For instance, patients with multiple sclerosis show fatigue that extends beyond their motor deficits. This fatigue has been shown to be related to attentional deficits in these patients.
3. Response inhibition can be measured through a number of different tasks. Interference tasks such as the Stroop test (Golden & Freshwater, 2002) determine the ability to inhibit attentional response to one stimulus characteristic while responding to another characteristic. The go/no-go paradigm and continuous performance tests (CPTs) also provide information regarding the patient's ability to inhibit false positive responses. Intrusion errors on these tests point to failed response inhibition.
4. Response alternation and switching can be measured. Several of the tasks described previously (alternating graphic sequences, go/no-go) require the alternation of response pattern and therefore provide information about this capacity. The Trail Making Test (AITB, 1944) is one of the most commonly used tests of response-switching ability and mental control. Errors occur when the patient fails to alternate between letters and numbers or when there is a break in the sequence and a particular item is omitted.

d. Attentional capacity and focus

Many paradigms are available for assessing attentional capacity and focus. Although these tasks are similar in that they require attentional focus, the cognitive operation that is necessary to perform the task may vary. Therefore, patients may exhibit performance inconsistencies across tasks according to their ability to perform certain cognitive operations. Tests of attention span provide a means of assessing capacity limitations associated with short-term or working memory.

Digit Span Forwards (Wechsler, 2008) is an example of such a test that also illustrates a problem associated with the traditional interpretation of attentional deficits. Digit Span Forwards has often been used as a general index of attention, yet strong performance is usually possible with minimal demand for attentional focus. Performance on this test is most strongly associated with short-term memory, working memory, and the language requirement of repetition. Performance is dependent on the ability to hold a string of items for a brief interval until a response is required.

Weak performance on Digit Span Forwards is not very informative in its own right, although, when analyzed in relation to other findings, it may provide clinical information about working memory as well as the motivation of the patient. Considerable inter-item variability, such as missing some short sequences but correctly repeating longer sequences, is significant, because it suggests a lapse of attention. Other tests, such as the Corsi Blocks (Milner, 1971) and the Knox Cube Test (Knox, 1914), provide an opportunity to measure brief span in the visual-spatial modality. However, poor performance on spatial span tests may reflect spatial selective attentional deficits as well.

Assessing attentional capacity depends on tasks that demand effortful processing. This occurs when the tasks require working memory and/or rapid processing speed. Furthermore, tasks that demand inhibition of interference or place the subject at the mercy of concurrent tasks demands or executive control and sequential processing demands will provide measures of capacity. The ability of people to focus their attention effectively varies as a function of structural and energetic capacity limitations in relationship to the inherent complexity and cognitive demands of the task at hand. Capacity limitations in the short-term memory buffer, efficiency of encoding, neural transmission rate and cognitive processing speed tend to be associated with intrinsic individual differences.

Transient energetic capacity limitations also affect focused attention. For example, sleep deprivation will often result in some reduction in performance. Similar energetic effects can be caused by medications that affect arousal. Factors that affect the reward tied to the assessment may also affect energetic capacity. Unfortunately, it is often difficult to assess for these effects in the context of a standard clinical assessment, unless the patient is seen over multiple sessions during which these states have been controlled for. However, it is possible to examine some of these effects by repeating tasks at several points in the assessment. For example, comparing performance on mental control tasks, such as Digit Span Backwards (Wechsler, 2008), early during the assessment and again toward the end of the assessment may provide useful information about the fatigue effects.

Similarly, examining performance after a neurophysiological state has been altered via a pharmacological intervention can provide useful information regarding the degree to which attentional focus can be enhanced. This is commonly done when a child with ADHD is assessed before and after treatment with a stimulant medication.

The general principle guiding the assessment of focused attention is that performance must be compared across tasks that challenge different constraints on attentional capacity. This is typically done by comparing performance on alternate forms of particular task. An illustration of this is the use of both Trail Making A and B (AITB, 1944) for the assessment of switching. Similar contrasts can be conducted by comparing performance between tasks with and without demands for rapid processing and responding, tasks varying with respect to the extent of interference, and so forth.

Many tasks that are part of current and widely used neuropsychological batteries provide data that can be used to assess focused attention, particularly if efforts are made to employ alternative versions of the tasks that increase demands for controlled processing. For example, we have conducted a study in which the Digit Symbol task was modified to include a symbol–symbol coding task with increased demand because of the absence of numbers that are already well learned for most people. All participants exhibited some slowing on the high-effort versions of these tasks. However, these effects were amplified among patients with unipolar and bipolar affective disorders, as both slowing and reduced performance occurred when tasks had greater attentional demand.

Since the publication of the earlier editions of this handbook, a number of attentional tests have been developed that employ this assessment strategy. For example, within the attention module of the Neuropsychological Assessment Battery (NAB; Stern & White, 2003), Stern provided a standard letter cancellation task designed to assess visual search and selective attention, followed by a conditional cancellation task with greater cognitive demand. Contrasting performance on these two tasks provides an index of focused attention. Similarly, in addition to measuring sustained attention, the Test of Variables of Attention (TOVA; Leark, Greenberg, Kindschi, Dupuy, & Hughes, 2008) has two different ratios of targets to distractors embedded in the task. When fewer targets to distractors are present, greater demand for attentional focus exists, as the subject must sustain an anticipatory state waiting for a less frequent event.

The Digit Symbol subtest of the WAIS–IV (Wechsler, 2008) and the Symbol Digit Modality Test (SDMT; Smith, 1991) are the best-known examples of coding tests, useful in the assessment of focused attention. They require rapid information processing and the integration of multiple cognitive operations, placing significant

demands on processing speed and working memory. While the underlying cognitive operations are not conceptually challenging, the cognitive task itself is rather complicated, requiring visual tracking, selective attention to featural characteristics of symbols, visual-motor integration, and motor control (copying). For this reason, when interpreting performance on these measures, it is necessary to rule out other sources of impairment, such as fine motor disturbance. Assuming that the problem is not attributable to these other factors, then it is likely that poor performance is indicative of reduced capacity and difficulties with attentional focus. For people with motor impairments, it is possible to use an oral version of the SDMT in which digits associated with symbols are reported orally rather than by writing on the answer form (but see Chapter 13, this volume, for limitations of this technique).

The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) is an example of a highly controlled test of attention that requires both focused and sustained attention. The PASAT is quite sensitive to subtle attentional impairments. Because considerable effort is required for adequate performance, however, the PASAT cannot be used with patients with severe brain dysfunction. Also, poor motivation or reduced arousal greatly affects performance on the PASAT.

e. Divided attention

Some tasks place demands on attentional capacity and focus because of the requirement for divided attention. Tests of the ability to inhibit interfering stimulus characteristics while responding to a target feature demonstrate how divided attention taxes capacity limitations. The Stroop test (Golden & Freshwater, 2002) fits this category. Interference is created by the fact that the color of the printed word conflicts with the color denoted by the word itself. Concurrent production tasks (e.g., finger tapping while demonstrating verbal fluency) also provide a vehicle for assessing capacity limitations associated with divided attention. The task of finger tapping with fluency is useful for assessing response to the demands associated with two forms of response production. Alternatively, dichotic listening paradigms provide a way of assessing focused attention in the context of sensory selective attention.

f. Sustained attention and vigilance

Tests that measure performance over time provide a means of assessing sustained attention and vigilance. The assessment of sustained attention ultimately requires that the temporal characteristics of performance be measured. As noted, this can be accomplished

through modification of the standard recording procedures on many neurocognitive tests. For example, recording the number of words generated per 15-second interval on verbal fluency measures provides a means of determining whether patients are able to persist in their word generation. Similarly, breaking down performance over time periods for tests like the Digit Symbol subtest of the WAIS–IV (Wechsler, 2008) and Grooved Pegboard (Matthews & Kløve, 1964) provide similar information with respect to sustained performance. Modifications of this type represent qualitative methods that may be useful clinically, with the caveat that little normative data are generally available to support firm conclusions. Some attention tests designed to assess selective attention (e.g., Ruff 2 & 7 Selective Attention Test; Ruff et al., 1992) also provide measures of sustained attention, with some supporting evidence.

The most well-established method for assessing sustained attention and vigilance is through use of continuous performance tests (CPT). The CPT paradigm measures signal detection performance over blocks of trials. Many versions of the CPT exist, all consisting of the same basic paradigm. Either visual or auditory stimuli (usually letters) are presented sequentially. Intermixed among distractor stimuli are particular target stimuli. The task is to respond to the target and inhibit response to the distractors. The attentional demands of the task can be modified on many CPT tests by changing the ratio of targets to distractors, total number of stimuli, total time of the test, perceptual complexity of the stimuli and background, interstimulus interval (ISI), and use of anticipatory stimuli. A variety of signal detection measures, such as misses, false positives, inconsistency, and vigilance decrement, can be determined that help to quantify impairments of sustained attention. The Conners CPT—II (Conners, 2004), which takes 14 minutes to administer, has strong normative data and multiple ISIs, and performance can be examined as a function of ISI. The Test of Variables of Attention (TOVA and TOVA-A; Leark et al., 2008) contains both visual and auditory tasks, varies target:distractor ratio, and measures attention, impulsivity, habituation, and response inhibition. Finally, the Adaptive Rate Continuous Performance Test (ARCPT; Cohen, 1993) differs from the others mentioned in several important ways: (a) the task demand is conditional; (b) the ISI is adaptive; and (c) the stimulus presentation rate is rapid. It measures processing speed vigilance and the temporal consistency of performance.

Information about sustained attention can also be derived from other neuropsychological measures. For instance, symbol cancellation tests require sustained attention in addition to the sensory selective attention demands detailed earlier. Similarly, symbol coding tasks may also be used to assess sustained attention by comparing

performance during the early and late stages of the task. Similar modifications can also be made on tasks that involve more complex cognitive operations to make them more sensitive to impairments of sustained attention. In a complementary fashion, tests of sustained attention, such as CPTs and symbol cancellation tests, can be modified to increase the demand for focused attention. On the CPT this can be done by increasing the complexity of rules governing target selection, by adjusting parameters such as memory load, interstimulus times, or the presence of more than one stimulus in a target field on a trial. This is particularly useful in experimental studies, although it is somewhat problematic for clinical use because modifying task demands invalidates comparison to standardized, normative performance.

D. Assessment Strategy

The primary disadvantage of most traditional neuropsychological tests of attention is their reliance on a paper-and-pencil format. Although such methods typically provide useful data about error characteristics, they are not well suited for response time measurement, and they do not provide adequate information about inter-item variability or change in performance across the task duration. For these reasons, it is recommended that efforts be made to use some computerized tests of attention that enable greater control over stimulus and response parameters, such as the rate of stimulus presentation, the spatial characteristics of visual stimuli, and response times.

The demands of the clinical environment and important patient considerations will largely determine the breadth and nature of assessment aimed at attentional function. For example, use of a computer to administer a sustained vigilance task may not be feasible; alternatively, the patient's stamina may limit the total scope of a comprehensive neuropsychological assessment, and changes in the reimbursement structure for neuropsychology may impose even more stringent limitations. Whenever the testing conditions allow, however, it is important to administer measures that will provide some information about each attentional component process.

An example of a core mini battery would include the WAIS–IV Digit Symbol subtest (Wechsler, 2008), Trail Making (AITB, 1944), a letter cancellation task, and a CPT. The Digit Symbol subtest provides information about focused attention, working memory, and processing speed. Trail Making provides information about spatial search and response-switching ability. Letter cancellation provides information about visual search and sensory selective attention. The CPT is the best available means of assessing sustained attention.

Expansion of this battery for a more comprehensive clinical assessment could include: the PASAT (Gronwall, 1977), Letter Number Sequencing from the WAIS–IV (Wechsler, 2008), Stroop (Golden & Freshwater, 2002), and WCST (Response Selection; Heaton et al., 1993), Line Bisection, Clock Drawing (Sensory Selective Attention), and one of the continuous performance tasks.

Several test batteries have been developed that provide a standardized approach to assessment of attention. These include the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), d2 Test of Attention (Brickenkamp & Zillner, 1998), Behavioral Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), and the Integrated Visual and Auditory Continuous Performance Test (IVA; Sandford & Turner, 2004) among others. The d2 Test of Attention and the IVA provide measures of several aspects of attention, including vigilance and impulsivity, and are similar to the CPT in format. These measures can be completed in fewer than 20 minutes. The TEA and BIT require more time to administer, but both provide information regarding attention function using tests with high face validity and ecological relevance. For example, subtests of the TEA include visual search of a geographic map, vigilance on a simulated lottery game, and focused attention tests using a simulated elevator. The BIT was initially developed to identify neglect following stroke, and as such the battery is heavily weighted toward assessment of attention allocation across visual space. Additional clinical information can be obtained from subtests that provide information regarding the real-world impact of visual neglect on tasks such as map navigation, coin sorting, and use of clocks.

E. Steps in Decision Making When Assessing Attention

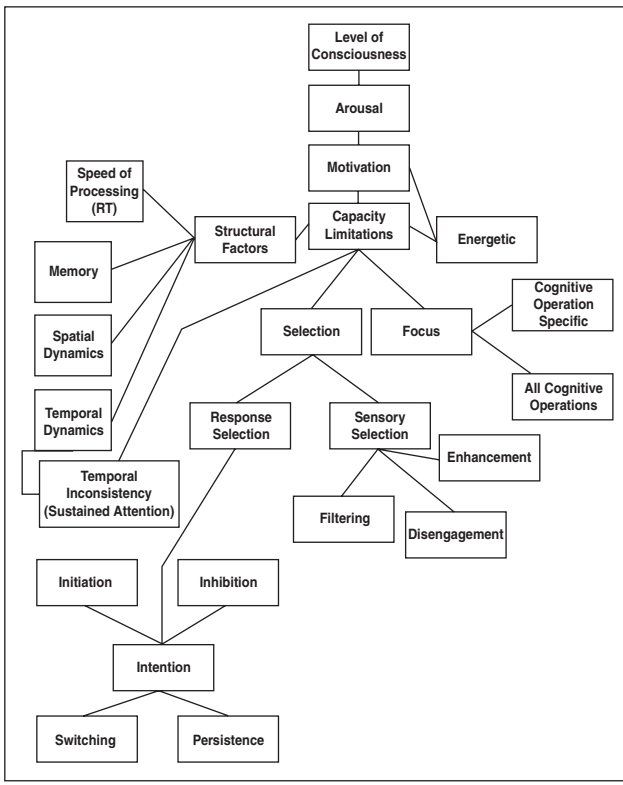
Regardless of the battery that is chosen, the assessment of attention depends on a logical, stepwise decision process. A decision tree for evaluation of attention disorders is provided in Figure 20.3.

Step 1: Level of consciousness. Is the patient fully alert? Is lethargy or fatigue evident? Can this person respond to basic questions and perform simple tasks, such as mental arithmetic?

Step 2: Arousal. Is activity level within normal limits, or is the patient slowed or agitated? Does the patient maintain eye contact, or look away frequently? Does he or she fidget?

Step 3: Motivation. Does the patient seem to exert adequate effort? Are consistent scores obtained on tests that measure similar functions? Are embedded and/or stand-alone symptom validity measures passed?

Figure 20.3. Interrelated functions to be evaluated systematically according to the recommended steps and decision making during an examination of attention.



Step 4: Are sensory, perceptual, and motor functions intact? Are glasses and hearing aids worn, if needed? If not, it is essential to factor in the contribution of impairments.

Step 5: Is attentional capacity reduced? Do impairments consistently appear on tasks requiring high levels of focus, working memory, or effort?

Step 6: Is reduced capacity general or limited to specific operations or modalities? If it is operation specific, attentional effects may be secondary to the greater effort required for tasks that are more cognitively demanding for the patient.

Step 7: If a general capacity problem is present, limiting factors should be examined in detail. This involves assessing factors such as processing speed and memory influence. It is important to ascertain that attention is not simply reduced as a general covariant of global cognitive efficiency or intelligence.

Step 8: Is attentional performance temporally inconsistent? Is there a performance decrement? If so, a more thorough assessment of sustained attention is in order.

Step 9: Is the attention problem limited to sensory selection or to response selection and control? Is it limited to the visual domain, or is it also impaired for nonspatial visual and/or auditory tasks?

Step 10: Are response selection problems related to specific problems with intention, initiation, inhibition, persistence, switching, or other executive functions? If executive functions are broadly impaired, a frontal lobe syndrome may be implicated rather than an isolated impairment of attention.

V. CONCLUSION

Disorders of attention are common sequelae of a wide variety of brain injuries or diseases. The components of attentional control are complex and are mediated by an elaborate and highly integrated series of neural systems. The proper evaluation of attentional dysfunction is an integral, routine, and necessary portion of a complete bedside or outpatient examination.

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Chapter 21

Darlene Floden

Frontal Lobe Function

The frontal lobes are, in many ways, the most enigmatic of brain regions. This large mass of tissue was long thought to be largely "silent" because no obvious deficits may appear despite large lesions. However, a series of landmark cases and increasingly sophisticated physiological investigations have changed that view. The role of the precentral gyrus in motor control was firmly established by Penfield (Penfield & Boldrey, 1937). However, the functions of the prefrontal cortex, the area anterior to the premotor area and precentral gyrus, have been harder to nail down. Careful observation and study of larger groups of patients with prefrontal damage, often courtesy of large-scale wars and popular psychosurgical procedures, led to the concept of a *frontal lobe syndrome*. Technological advances in neuroimaging and continued development of behavioral and physiological measurements have allowed refinements of this framework in terms of both regional and functional specificity within the prefrontal cortex. Today, the prefrontal cortex is thought to mediate a broad range of cognitive and metacognitive abilities.

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This chapter begins with a classification scheme for the behavioral syndromes that spurred interest in the nonmotor functions of this brain region. Short descriptions of real patients are presented to illustrate each syndrome. A brief overview of the structural organization and connectivity of the frontal lobes provides a framework for functional specificity within the frontal lobes. The focus then shifts to the current state of knowledge about the functions of the prefrontal cortex. The major categories of dysfunction associated with prefrontal damage are reviewed, as well as the methods to evaluate them. Finally, brief consideration is given to current and promising future approaches to the treatment or rehabilitation of frontal lobe dysfunction.

Four preemptive qualifiers are necessary. First, this chapter is an introductory review of an incredibly complex topic. Readers are encouraged to delve into the more detailed sources in the suggested readings available at http://pubs.apa.org/books/supp/parsons. Second, many of the functions here are discussed in terms of modular frontal cortical areas. However, frontal abilities are more accurately conceived of as the result of processing within networks or circuits and, therefore, the regions discussed here should always be considered in the context of their connectivity with other brain regions. Third, there are many diseases, disorders, and injuries that reliably produce frontal lobe damage or dysfunction. This chapter does not review common etiologies, as many are dealt with in detail in other chapters (see Part II: Neurological Disorders, in this handbook, for in-depth discussions). Finally, the information in this chapter pertains largely to adults rather than children. The ongoing development of the frontal lobe throughout childhood and adolescence makes measurement of frontal lobe function a moving target at those times. See the suggested readings online for other sources that deal specifically with the pediatric population.

I. CLASSIFICATION: THE FRONTAL LOBE SYNDROMES

The three classic frontal lobe syndromes—the dysexecutive syndrome, the disinhibition syndrome, and the apathetic syndrome—are relatively distinct in presentation, although any individual patient may show elements of more than one. These syndromes are typically observed in patients with relatively large frontal lesions or with more widespread dysfunction as may occur in traumatic brain injury or neurodegenerative diseases that affect the frontal lobes. They are less common in patients with small focal lesions and therefore, as a result of improvements in detection and early treatment of neurological

conditions such as tumor and stroke, fulminant versions of these syndromes may be less common than they once were.

A. Dysexecutive Syndrome

The *dysexecutive syndrome* (see Exhibit 21.1) is characterized by difficulties in executing complex goal-directed behavior due to problems with organization, planning, sequencing, and strategy selection or implementation. Patients may exhibit poor working memory or mental inflexibility leading to "stuck in set" or perseverative responses. These patients may have difficulty with temporal or spatial context memory and show poor free recall in contexts where encoding strategies would normally bolster learning and later retrieval. In severe presentations, patients may require guidance and structure to accomplish daily activities. In more subtle cases, patients may be seen by others as forgetful or unreliable. Dysexecutive syndrome is often associated with dorsolateral prefrontal damage.

B. Disinhibition Syndrome

The *disinhibition syndrome* (see Exhibit 21.2) is a dramatic condition in which the patient often seems to lack impulse control or a social filter. Depending on the severity of the syndrome, comments or conversation may be slightly insensitive, socially inappropriate, or blatantly sexual or offensive. The patient's interpersonal manner may

Exhibit 21.1. The Dysexecutive Syndrome: Mrs. C

Mrs. C is a 44-year-old woman who underwent a large resection involving bilateral dorsolateral and superior frontal regions to treat a large frontal meningioma. She had previously worked as an administrative assistant managing a busy office environment. One year after her surgery, she had been unable, because of significant disorganization, to return to work. She typically required around four hours to accomplish her morning routine of showering, dressing, and preparing and eating breakfast because she could not complete each activity in a systematic way. She would jump back and forth between steps of each task, assembling needed items haphazardly, only to misplace some item or become distracted by an element of another task. She was aware that it took her entirely too long to get anything done, but she could not account for how or why this happened.

Exhibit 21.2. The Disinhibition Syndrome: Mr. M

Mr. M. was a 56-year-old farmer who sustained bilateral polar and orbitofrontal damage in a motor vehicle accident. His wife reported that prior to the accident, he was a kind and soft-spoken person who was heavily involved in his church and his short-wave radio hobby. When he was referred for neuropsychological assessment 9 months later, he made loud, inappropriate comments and told sexually explicit jokes throughout the evaluation. His wife provided a file that contained, among other things, a copy of the restraining order from a woman at their church and a letter banning him from his short-wave radio club for inappropriate behavior despite multiple official warnings. When these materials were reviewed with Mr. M, he was aware of the contents and could recount the behaviors that he had engaged in, but did not appear to appreciate why this was unsettling to others.

be overly familiar or aggressive. Behavior appears driven by automatic stimulus-reward associations, and there is little oversight to suppress habitual responses or to delay gratification. Importantly, these behaviors can vary in frequency (does it happen once in a while or every hour?) or in magnitude (does the patient reach for a candy bar at every store, or does she reach for food on strangers' plates?). Insight is often impaired to some extent. In most cases of disinhibition syndrome, the patient fails to recognize his or her own behavior as inappropriate and is often unable to restrain that behavior despite feedback. If presented with a vignette describing someone else engaging in a similar disinhibited behavior, the patient may recognize the behavior as inappropriate. The disinhibition syndrome is often associated with damage to the ventral or orbital aspects of the frontal lobes.

Utilization Behavior, described in an interesting paper by Lhermitte (1983), is a dramatic form of disinhibition that some consider to be related to this syndrome. Also called *Environmental Dependency Syndrome*, Utilization Behavior refers to the tendency for a patient to reflexively use stimuli that are available in the environment but are not appropriate to the context. Lhermitte noted a number of demonstrations, from a series of five frontal lobe patients, that ranged from the inane, such as pouring water from an available pitcher and drinking, to the bizarre. In one example from neuropsychology lore, a patient who had previously worked as a nurse proceeded to give Dr. Lhermitte an injection when a needle was placed nearby. (Incidentally, Dr. Lhermitte had lowered his trousers, which

Exhibit 21.3. The Apathetic Syndrome: Mrs. Y

> Mrs. Y was a 48-year-old nurse who suffered multiple ruptures of an arteriovenous malformation in the right superior medial frontal lobe despite several embolization procedures. When she had a ventriculoperitoneal stent introduced via the left dorsal frontal lobe to treat obstructive hydrocephalus, the procedure caused additional bleeding that resulted in left superior medial damage as well. At this point, she developed a profound akinetic mutism. Two years after this procedure, she still required full-time care. She rarely spoke, even in response to her husband or two preteen children. Her muscles had wasted and she was very thin. She could be led to eat or attend to some stimulus but would do so only briefly before resuming her general inertia.

may also make you question the doctor's frontal lobe function; author's note—this examination technique is not recommended.) However, this highlights one of the main objections that some investigators have raised about this syndrome—namely, the role of demand characteristics in producing these behaviors in the clinic. It is important to be mindful that humans may behave in the way that they believe an authority expects them to behave, and this should not be taken as evidence of brain damage.

C. Apathetic Syndrome

The *apathetic syndrome* (see Exhibit 21.3) is marked by a relative dearth of behaviors. Apathy is a complex phenomenon and can occur in motor, cognitive, and emotional domains. There is also a continuum of apathy severity. At the milder end of the spectrum, a patient may initiate behavior but exhibit motor impersistence or failure to maintain behavior. There is a dampening of curiosity or interest in enjoyable activities. Patients may also feel less emotionally connected or lack concern about themselves or others. Indeed, mild apathy can easily be mistaken for depression. *Abulia* represents a more significant lack of motivation or drive. At the extreme other end of the spectrum lies the syndrome of *akinetic mutism.* This involves a veritable absence of activity such that the patient is mute, may not eat when hungry, and can even develop pressure sores from failure to shift positions. This syndrome, somewhat unlike the dysexecutive and disinhibition frontal lobe syndromes, has a fairly consistent localization to the medial surface of the frontal lobes. Some degree of supplementary motor area or anterior cingulate

damage is typically present, and the greater the lesion, the more dramatic the syndrome, with akinetic mutism typically occurring only with bilateral lesions.

D. Caveats

Depending on their severity, these syndromes can be more or less difficult to identify. In many patients, they are often evident during interaction with the patient during interview and testing. In more subtle presentations, the patient may appear completely normal in casual interaction. Unfortunately, neuropsychological testing is not always illuminating. It is not unusual for these patients to perform very well on neuropsychological measures, including executive function measures. Indeed, Mr. M's (Exhibit 21.2) cognitive performance was fully intact on every frontal lobe test he was given. This is due to the degree of structure that the assessment context provides: In attempting to constrain behavior in order to measure it systematically, we limit our ability to observe that behavior. In other words, the examiner may "become the patient's frontal lobes!" Such cases require careful observation of qualitative aspects of the patient's behavior, adept probing during family and patient interviews for inconsistencies and clues, and creativity in conducting bedside and nonstandardized procedures that "pull" for frontal behaviors (see Chapter 2, this volume, for a thorough description of such techniques).

Current thinking favors the view that these syndromes should not be viewed as singular clinical entities but rather as compilations of impairments that arise from damage to multiple areas. The study of patients with smaller lesions, together with nonhuman animal and neuroimaging data, has supported the view that the frontal lobes are involved in a broad range of more discrete functions. However, there is no agreement on the precise nature of particular functions or the optimal conceptual framework to characterize fractionated frontal functions. A basic knowledge of the frontal lobe's cellular structure and organization helps to understand the basis for functional differentiation and how discrete areas of damage may result in separable impairments.

II. FUNCTIONAL NEUROANATOMY OF THE FRONTAL LOBES

Current structural neuroimaging techniques in clinical use employ a fairly coarse resolution relative to the scale of functional neuronal ensembles in the frontal lobes. Thus, the functional neuroanatomy of the frontal lobes is typically discussed in terms of

gross anatomical divisions rather than cytoarchitectonic regions. This chapter discusses six anatomical subdivisions: primary motor, premotor, lateral, orbital/ventromedial, superior medial, and polar. These general regions were selected on the basis of several factors. First, neuropsychological studies show good evidence for functionally distinct roles for each of these subdivisions (for review, see Stuss et al., 2002). Second, they broadly respect gross anatomical divisions based on gyral/sulcal landmarks and cytoarchitectonic trends. Third, several common etiologies produce fairly consistent patterns of frontal lobe damage that are more or less constrained to a limited subset of these regions—which may make these divisions more relevant to clinical practice. However, note that the subdivisions used here may vary in important ways from classification systems employed elsewhere because the number, character, and boundaries of theoretical frontal divisions are subjects of intense debate.

A. Cytoarchitectonic Structure of the Frontal Lobes

The relative complexity of prefrontal functions is suggested by the fact that they are, from an evolutionary point of view, relatively recent; they are more developed in humans than in other primates. Briefly, the frontal lobes are composed almost entirely of neocortex (*neo*-reflecting its relatively recent development) with a highly developed six-layer structure (Petrides & Pandya, 1994). It evolved out of two streams of phylogenetically older cortex: the archicortical and paleocortical trends. The *archicortical* trend extends radially along *lateral* and *medial* cortex (dorsolateral, ventrolateral, and superior medial regions) and has its origins in the hippocampal formation. The *paleocortical* trend extends along the *orbital* surface onto the frontal pole (orbital/ventromedial and polar regions) and has its origins in olfactory cortex. The distinct sources of neocortical development imply different functional roles for each trend. Moreover, as one traces each trend away from its source (i.e., in the anterior direction away from hippocampal/olfactory areas), the layers of cortex have greater differentiation, suggesting changing processing roles for areas within each trend.

There are several exceptions to the six-layered cortex within the frontal lobes. First, primary motor cortex loses the fourth layer during development and becomes agranular (premotor cortex is transitional, as the fourth layer is very faint). In addition, there are two areas of transitional limbic cortex: the cingulate gyrus that surrounds the corpus callosum on the medial surface and an area of proisocortex at the caudal portion of the orbital surface. These transitional limbic areas are included in the functional subdivisions

outlined here, although it could be argued that these regions should not be considered part of the frontal lobe at all.

B. Frontal Lobe Connectivity

Frontal lobe connectivity can be confusing, and it is tempting to assume that every region of frontal lobe is connected to just about every other brain region. However, there is a basic organization to frontal connectivity. Namely, the origin and layered structure of a frontal region determines its connectivity (Barbas & Pandya, 1989; Yeterian, Pandya, & Tomaiuolo, 2012). The majority of connections within the frontal lobe occur between areas in the same architectonic trend. When connections between the two trends exist, they tend to occur between regions at the same level of architectonic differentiation. This is also true of connections between frontal and nonfrontal neocortical areas.

Input to the frontal lobes from other neocortical regions can be roughly divided into functional streams that travel in association pathways that have both a dorsal-ventral and rostral-caudal organization (see Table 21.1; for a full review, see suggested readings online at http://pubs.apa.org/books/supp/parsons). Broadly speaking, the dorsal and medial prefrontal regions receive projections from dorsal sections of post-Rolandic areas. The orbital and inferior prefrontal regions, on the other hand, receive projections from ventral sections of post-Rolandic areas. At the same time, caudal areas of prefrontal cortex receive input from modality-specific regions of visual, auditory, and somatosensory association areas. Input to rostral regions, however, originates largely in multimodal areas, including the limbic system. These connections imply a spatial- versus object-based processing in the dorsal-ventral axis and an abstract versus sensory-based processing in the rostral-caudal axis.

Unlike the neocortical connections, limbic projections to the frontal lobes do not show a vertical (dorsal-ventral) preference for termination sites. Rather, limbic input from the parahippocampal region (which includes entorhinal, perirhinal, and parahippocampal cortex) has direct connections to the frontal lobes via two major reciprocal pathways that terminate largely in rostral prefrontal areas. The ventral pathway links the parahippocampal region with orbital, polar, and rostral lateral regions via the uncinate fasciculus and claustrum. The dorsal pathway links the parahippocampal region with rostral aspects of medial, dorsal, and orbital areas via the cingulate bundle. Thus, anterior regions of both cortical trends are situated to combine regional processing with more primitive emotional information processed in limbic areas.

Table 21.1 Frontal–Nonfrontal Connectivity

Frontal region	WM tract	Nonfrontal region	Purported function
Primary motor	Local horizontal connections	Primary somatosensory	Proprioception function
	IC/CR	Ventrolateral thalamus	Motor control
Premotor	SLF-I	Superior and medial parietal	Body part location for higher-order motor regulation
	IC/CR	Ventrolateral thalamus	Occulo/motor preparation
Lateral	SLF-II	Posterior inferior parietal, occipitoparietal	Visuospatial attentional control
	SLF-III	Supramarginal gyrus	Higher-order somatosensory info (gestural/linguistic), abstract action (oral/manual) coding
	IC/CR	Ventrolateral thalamus (pc), dorsomedial (mc/pc)	Working memory processing
	Arcuate	Caudal superior temporal lobe	Auditory spatial (nondom) or linguistic (dom) processing
	Extreme capsule	Middle superior temporal lobe	Auditory object info, linguistic processing
	Ventral limbic via extreme capsule	Parahippocampal, entorhinal	Memory monitoring
	Cingulate bundle	Thalamus, retrosplenial, cingulate cortex	Working memory processing

Table 21.1 Frontal–Nonfrontal Connectivity *(Continued)*

Frontal region	WM tract	Nonfrontal region	Purported function
Orbital/ ventro-medial	Uncinate	Rostral superior temporal, inferotemporal, parahippo-campal	Affective response to auditory info
	Ventral limbic via uncinate	Parahippocampal, entorhinal	Value-regulated influence on encoding, self-regulation
	IC/CR	Medial ventro-anterior (mc), dorsomedial (mc) thalamus	Emotional processing/ reward learning
	Cingulate bundle	Thalamus, retro-splenial, cingu-late cortex	Novelty processing
Superior medial	Cingulate bundle	Thalamus, retro-splenial, cingu-late cortex	Working memory processing
	IC/CR	Dorsal dorsome-dial (mc) thalamus	Motivational processing
	Ventral limbic via cingulate bundle	Parahippocampal, entorhinal	Memory modulation/ motivational value, self-regulation
Polar	Extreme capsule	Middle superior temporal lobe	Auditory object info, linguistic processing
	Ventral limbic via uncinate	Parahippocampal, entorhinal	Value-related influence on encoding, self-regulation

Note. WM = white matter; IC/CR = internal capsule/corona radiata; SLF = superior longitudinal fasciculus (divisions I, II, and III); pc = parvocellular division; mc = magnocellular division. Data from Alexander, DeLong, and Strick (1986) and Petrides and Pandya (1994).

Finally, the functional specificity of the frontal lobes is also reflected in connections with subcortical regions. Distinct fronto-striato-thalamo-cortical networks have also been described with two motor circuits (primary motor and oculomotor) and three prefrontal circuits (dorsolateral, orbitofrontal, and anterior cingulate) that maintain their topographical organization throughout the circuit (Alexander, DeLong, & Strick, 1986). The cerebellum also sends information to vast areas of prefrontal cortex via the thalamus (Middleton & Strick, 2000).

C. Functional Subdivisions of the Frontal Lobes

1. PRIMARY MOTOR CORTEX

The primary motor cortex is the origin of the corticospinal tract. The primary motor area lies within the precentral gyrus and is somatotopically organized in a manner that corresponds to the motor homunculus. As a rule, body parts capable of fine motor control (i.e., hands, mouth) occupy more "real estate" along the motor strip. Damage to the primary motor cortex produces initial paralysis in the contralateral area corresponding to the part of the homunculus that is involved. This can resolve into a spastic paresis, depending on the severity/chronicity of damage.

2. PREMOTOR AREA

The premotor area along the lateral and medial surfaces lies just anterior to primary motor cortex. These regions aid in preparation or programming of complex sequences of movements. Damage can result in apraxia, which is more common with lesions of the left hemisphere. Damage to premotor regions involved in programming oral/lingual movements results in articulation deficits. The frontal eye fields (FEFs) are a subregion of the premotor area that deserve special mention. The FEFs are important for volitional conjugate gaze in the contralateral direction. Damage to the FEFs results in impaired eye movements to the contralesional side on command while sparing passive gaze in the same direction.

3. LATERAL

The superior and middle frontal gyri comprise the *dorsolateral prefrontal cortex*. The *ventrolateral* portion consists of the inferior frontal gyrus. Some argue that dorsal and ventral regions differ in terms of cognitive processes, whereas others suggest that they perform the same functions using different types of information. Fairly compelling data support the functional subdivision of these regions, which are thought to be involved in multiple domains of cognitive

processing. Generally speaking, the lateral cortex is necessary for a range of cognitive functions that fall under the umbrella of executive function, including working memory, task setting/switching, decision-making, complex attention, and strategic cognitive control. Damage to this region results in reduced span of attention, problems with mental manipulation of information, poor planning, and perseverative tendencies. Lateral prefrontal cortex dysfunction also impacts memory because it generates problems in imposing organization or context on incoming information, resulting in inefficient encoding and poor strategic search for stored information.

There is also good evidence for hemispheric specialization for the lateral areas, although the exact nature of left/right differences is debated. For example, Tulving and colleagues (Habib, Nyberg, & Tulving, 2003) have argued, based on meta-analyses of functional imaging studies, that there are lateralized roles of this region in encoding (left) and retrieval (right) of episodic memories. The model has mixed support from studies of patients with focal lesions as well as transcranial magnetic stimulation studies in normal subjects (see suggested readings). Potential modality asymmetries may also exist in both memory and executive processing, such that left lateral regions preferentially process semantic/linguistic information from more posterior areas and right lateral regions predominantly process spatial sensory/motor information.

4. ORBITAL/VENTROMEDIAL

The orbital/ventromedial areas are thought to play a role in incentive value and reward processing, consistent with their origins and connections with limbic structures and input from multiple sensory modalities. Evidence suggests that the motivational value of a stimulus is coded within orbital cortex and that this is important for rapid learning and reversal of stimulus-reward associations (Rolls, 2000). Some theorists have proposed that this area plays a role in behavioral inhibition, given observations of increased susceptibility to interference after damage (Fuster, 1997). The medial aspect of orbital cortex and the ventromedial region have been hypothesized to record past links between context and the somatic states associated with them (Damasio, 1996). Patients with damage to ventromedial cortex and the underlying structures can also demonstrate memory impairments, including encoding deficits and confabulation. Such deficits may be related to damage that extends to the septal area and the fornix, which travels in this region.

Etiologies that lead to damage in orbitofrontal regions may also impair sense of smell. Anosmia, or loss of smell, can occur when coup-contrecoup forces shear the olfactory receptor neurons that transit the perforations in the cribriform plate, or are due to direct

damage to the olfactory bulb and tract, which lie within the olfactory sulcus toward the medial aspect of the orbital surface. There is also evidence to suggest that impaired smell discrimination can occur with damage to the orbitofrontal olfactory area at the caudal boundary of the orbital surface (Jones-Gotman & Zatorre, 1988; Tanabe, Iino, & Takagi, 1975).

5. SUPERIOR MEDIAL

On the medial surface, the cingulate gyrus sits above the corpus callosum. The paracingulate gyrus rings the cingulate cortex, but its presence, in whole or in part, is highly variable across individuals. The mesial aspect of the superior frontal gyrus sits above this. The cingulate and paracingulate gyri have several proposed roles, including error correction, conflict monitoring, and initiation and maintenance of behavioral or cognitive activation. There is an additional secondary motor region within the anterior cingulate gyrus, and connections with limbic regions suggest that cingulate motor areas may play a role in biasing motor function based on reward value. Anterior cingulate cortex also contains von Economo cells, which are hypothesized to participate in social behavior (Nimchinsky et al., 1999). The supplementary motor area lies within the posterior regions of the superior frontal gyrus and damage can result in alien hand syndrome or supplementary motor area syndrome (see suggested readings).

6. POLAR

The polar area has received more attention in recent years. Several theories of polar function suggest that this area plays a role in humor appreciation and theory of mind, where the perspective of another is adopted (Stuss et al., 2002). Others hypothesize that this area is a mental gateway, important for the ability to switch between external sensory focus and internal mental focus (Burgess, Gilbert, & Dumontheil, 2007). Focal lesions of this area can produce prospective memory deficits in the absence of episodic memory impairment (Uretzky & Gilboa, 2010).

III. NEUROPSYCHOLOGICAL EVALUATION OF FRONTAL LOBE FUNCTIONS

The following is a brief survey of selected tools available for measuring frontal lobe function, including a few well-known techniques from the cognitive science literature that have not yet been formally adapted to standardized testing. The reader is encouraged to consult helpful compendiums (e.g., Strauss, Sherman, & Spreen, 2006) for a broader sampling of neuropsychological measures.

A. Evaluation of Primary Motor and Premotor Cortex

Primary motor function should be evaluated bilaterally in face, arms, and legs to test for lateralized weakness. Observations of the patient are often sufficient to identify unilateral weakness. In particular, gait impairments (e.g., subtle limp), using only one hand/arm (e.g., while gathering belongings or shaking hands), or facial asymmetries (e.g., lopsided spontaneous smile) are often evident in the initial contact with the patient. These can be further evaluated with components of the neurological examination. A range of techniques can be used at bedside to evaluate motor strength and speed (see Chapter 2, this volume, for a review). However, more structured examination procedures could include use of a hand dynamometer (Reitan & Wolfson, 1985) to evaluate grip strength. Upper extremity motor speed can also be evaluated with a finger tapping board (Reitan, 1969).

Premotor function can be tested by asking the patient to perform a series of pantomimed movements. Praxis screening should be performed bilaterally to test for unilateral impairments. In addition, screening should include transitive (tool based), intransitive (gestural/communicative), buccofacial, and whole body commands. Problems with sequencing oral/lingual movements may result in poor articulation and/or other speech impairments. Careful comparison of the speed and clarity of mouth and tongue movements during linguistic versus nonlinguistic tasks can help to differentiate speech impairments from language impairments (see Chapter 18, this volume). Most comprehensive language batteries (e.g., Boston Diagnostic Aphasia Examination [Goodglass, Kaplan, & Barresi, 2001]; Multilingual Aphasia Examination [Benton, Hamsher, & Sivan, 1994]) include relevant screening tests. More structured tasks of premotor manual functions include Grooved Pegboard (Matthews & Kløve, 1964) or Purdue Pegboard (Tiffin & Asher, 1948).

Eye movement impairments are also evaluated as part of the neurological examination. Patients with frontal eye-field damage will be able to follow the examiner's finger with their eyes when it is moved into the contralateral field. However, the patient will be unable to independently shift gaze from the examiner's face to the examiner's finger held in the contralateral visual field. This differs from eye movement deficits arising from hemispatial neglect, in which passive gaze is also impaired, or from damage to cranial nerves III, IV, or VI, where active and passive movements are usually impaired in only one eye.

B. Evaluation of Prefrontal Cortex

As noted earlier, the challenge of assessing the integrity of the prefrontal cortex lies in the fact that deficits are often most salient in unstructured contexts (i.e., situations in which behavior or choices are not constrained). Neuropsychological testing materials and procedures typically impose structure on task performance. Environmental distractions are kept to a minimum and task duration is quite short. To facilitate standardization, task stimuli are salient and limited response options are available. Nonetheless, there are a range of available measures that have demonstrated *sensitivity* to frontal lobe damage. The multifaceted nature of the tasks—in other words, the lack of process purity in tests of executive function—reduces their regional specificity, and one should always be mindful of this.

Observation of errors and response patterns offers opportunities to discern disordered frontal lobe function on almost any neuropsychological test. Evidence of perseveration, passivity or lack of initiative, concrete thinking, stimulus-bound behavior, impulsivity, or impersistence can appear throughout the assessment. Here, I review some standard executive function tests with demonstrated clinical utility, as well as some of the newer procedures available through standardized batteries and experimental cognitive neuroscience as tools to spur creativity in clinical hypothesis testing. One should not be afraid to stray from standardization when appropriate in order to understand a patient's deficits. It is also typically advisable to use more than one test to assess prefrontal function, given the complexity of prefrontal abilities and the low specificity of individual measures.

1. ATTENTION

Abilities subsumed under the general heading of attention are sustained attention, divided attention, switching attention, selective attention, and working memory. Chapter 20 of this handbook contains a more in-depth discussion of these abilities, they are discussed briefly here in the context of frontal lobe function.

To evaluate *sustained attention*, the patient must be engaged in a task that involves maintaining performance levels over time. One should always consider the influence of sustained attention problems when performance is poor on tests that require extended performance over time. For example, patients may "space out" while being presented with stories to recall, leading to poor single-trial learning. Likewise, a tendency to lose set (i.e., change category) during the performance of any test can be an indication of poor sustained attention. Continuous performance tasks are designed to tax

sustained attention; they tend to be long and require repetitive responses that lull patients into autopilot mode. Most measure reaction time consistency (increased variability may indicate waxing and waning of attention), the ability to inhibit a prepotent response, and sensitivity to varying inter-stimulus delays (attention is more difficult to maintain over longer intervals between stimuli). Studies of patients with focal lesions suggest that lesions of the superior medial region are particularly related to deficits in sustained attention.

Divided attention is also a very important function of the lateral prefrontal regions, and impairments in simultaneous tasks have been well documented in the cognitive neuroscience literature using dichotomous listening or dual task paradigms. Among the very few standardized tests of divided attention are the Test of Everyday Attention (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) and the Auditory Consonant Trigrams (Brown, 1958; Peterson & Peterson, 1959) test.

Switching attention is a component of several available measures, although deficits can sometimes be observed in the (in)ability of patients to move on to the next measure during testing or the next topic during conversation. Among formal measures, the Trail Making Test (Army Individual Test Battery, 1944) is one of the very earliest—it was used to evaluate troops in WWII. There are multiple versions available, including a Color Trails task (D'Elia, Satz, Uchiyama, & White, 1996) that is helpful in evaluating patients with limited facility with the English alphabet. Most normative data available examines time to completion, and the naive approach to this task is to look at performance on attentional switching (Trails B) in isolation, without consideration of performance on the control condition which helps factor out the influence of general slowing of visuomotor tracking (Trails A). However, this is clearly inappropriate and can lead to erroneous conclusions about frontal lobe function. One of the strengths of this task is its general sensitivity to brain dysfunction, which also means that slow performance on Trails B is not specific to frontal lobe dysfunction. Presence of more than two sequencing errors on Trails B, however, does appear to be indicative of frontal lobe dysfunction (Struss et al., 2001). The Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001) battery incorporates switching requirements into a number of measures, including Verbal Fluency and the Color–Word Interference subtest (Stroop, 1935).

The Stroop Test (Stroop, 1935) is a classic measure of *selective attention*, the ability to suppress a prepotent response in favor of a more controlled one. Again, several commercially available versions exist. This task is widely used in the cognitive and neuroscience fields, and comprehensive reviews are available. Mounting neuroimaging, neurophysiological, and neuropsychological evidence

suggest that the anterior cingulate and left lateral prefrontal regions are involved in Stroop performance. Of note, Ruff's 2&7 task (Ruff & Allen, 1996), a digit monitoring task, also requires selective attention to discriminate targets from non-targets. Note, however, that many selective attention tasks tend to be fairly long or involve a large number of stimuli and therefore also have substantial sustained attention requirements.

Working memory is perhaps the most researched prefrontal function in the human and nonhuman cognitive neuroscience literature. There is fairly uniform agreement that the lateral prefrontal cortex is crucial for this function. Within clinical neuropsychology, many measures require working memory. The most straightforward of these are probably the subtests of the Wechsler Scales including Digit Span, Spatial Span, and Letter Number Sequencing (Wechsler,1997a, 1997b, 2008), although the Paced Auditory Serial Addition Task (Gronwall & Wrightson, 1974) is another good example. Indeed, any task that requires the patient to manipulate information held in mind, either through reordering, updating, categorizing, arithmetic, or other processes, can be considered to tap working memory.

2. PLANNING, STRATEGY USE, INITIATION, AND PROBLEM-SOLVING

Tower tests are helpful for examining planning abilities, and many variations are available, each with slightly different parameters (e.g., Delis et al., 2001 [DJEFS Tower]; Saint-Cyr & Taylor, 1992 [Tower of Toronto]; Shallice, 1982 [Tower of London]). The efficiency of planning, loss of set, rule breaks, and timing can be important observations of executive function as well. Qualitative analysis of Complex Figure tests, such as the Rey–Osterrieth (Osterrieth, 1944), can provide a wealth of planning and strategy information in patients with prefrontal dysfunction. Did the patient use an optimal strategy in the order and organization of the drawing? Are there indications of perseverations in the figure details or repetitive marking of the outline? Is the contour too small to fit details or too large for the page? These considerations are important for differentiating low scores due to planning versus visuospatial impairments.

In the verbal domain, phonemic word generation (e.g., Controlled Oral Word Association Test; Benton, Hamsher, & Sivan, 1994) provides useful insight into initiation, strategy use, set maintenance, and flexibility. Semantic word generation also requires these processes but may be more sensitive to degraded semantic knowledge/access following damage in more posterior regions, particularly anterior temporal damage (see Chapter 18, this handbook, for a more in-depth discussion). Moreover, generalized slowing of verbal responses/processing speed should be considered when interpreting

total scores. The qualitative aspects of performance are important: Was the patient slow to begin? Did they get stuck or seem to run out of ideas long before the end? Was a strategy evident in the patient's production (e.g., initial letter pairs, barn animals)? Did the patient perseverate (same word or last category) or lose set (switch to a different letter/category)? Analogous tasks in the nonverbal domain, such as the Ruff Figural Fluency test (Ruff, 1988), are also useful, and similar scrutiny of qualitative performance is telling. The lateralizing value of verbal versus nonverbal generative tasks has yet to be definitively demonstrated.

The Wisconsin Card Sorting Test (Heaton, 1981) is a standard measure in the neuropsychological arsenal. It requires the examinee to use nondirective feedback to discern an abstract conceptual rule for categorizing stimuli as well as the ability to maintain and abandon an established response set, and switch between stimulus dimensions. It was demonstrated to be sensitive to damage in multiple frontal lobe regions, but numerous studies have shown that patients with nonfrontal lesions may also perform poorly on this task. The Category Test (Halstead, 1947) has similar demands and is also sensitive to frontal lobe damage.

To enhance the ecological validity of executive function assessments, investigators have begun to design standardized tasks that mirror everyday situations that pose problems for patients with frontal lobe damage. On the Multiple Errands test (Shallice & Burgess, 1991), patients are given a to-do list (e.g., mail a letter, purchase particular items) and a set of rules to abide by and are then accompanied into the real world to complete their tasks. Obviously, this is a resource-heavy procedure that does not fit well into the time constraints of a standard neuropsychological evaluation. Paper-and-pencil versions also exist, such as the Modified Six-Elements subtests of the Behavioural Assessment of the Dysexecutive Syndrome (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). The basis for these measures is that the patient is provided with tasks to do and minimal constraints to consider, and then allowed to accomplish the task in whatever way he or she prefers. The efficiency, strategy, and rule breaks provide indications of goal-directed behavior problems.

3. MEMORY

As noted previously, memory performance can also be an important complaint and indicator of prefrontal cortex dysfunction. The Hemispheric Encoding and Retrieval Asymmetry Hypothesis (Habib et al., 2003) discussed earlier is one theoretical model of how prefrontal cortex is engaged in memory processing (i.e., left lateral cortex aids encoding whereas right lateral cortex aids retrieval). In the clinic, most cases of memory impairment arising from prefrontal

dysfunction are associated with impaired control processes that normally facilitate encoding and retrieval. Often memory complaints will take the form of attentional problems (e.g., losing train of thought, poor memory for conversations or details, although events are remembered well). As noted above, problems with attention can affect encoding. However, patients may also demonstrate poor strategy use for encoding, failing to make use of semantic groupings or "chunking" information to bolster learning, resulting in shallow learning curves. Frontal patients may show similar problems with strategic search at retrieval that can be overcome with increased retrieval support such as cues or recognition testing. This leads to a pattern of impaired free recall with intact recognition or cued recall. Problems with context or source memory can lead to intrusions from distracter lists or prior tests. Recall may be marked by perseverative responding or intrusion errors.

As noted in Chapter 17 of this handbook, certain patterns of frontal lobe damage are capable of producing anterograde amnesia. Typically, these lesions occur in the ventromedial or posterior orbital regions where damage extends to the Basal Nucleus of Meynert and anterior nodes within the limbic circuit including the septal nuclei and fornix. In these patients, hippocampal-like deficits can be observed with primary encoding deficits and loss of information over a delay.

4. REWARD PROCESSING, DECISION-MAKING, AND EMOTION

There are newer tasks developed to examine reward processing and decision-making functions of the orbital and ventromedial prefrontal regions. The Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994) examines the ability to adapt responses to changing reward contingencies. It should also be noted that this task, like most others, are not process-pure and patients with damage to more lateral regions of the frontal lobe can also show impairments unrelated to reward-based deficits. Many other tasks are available in the literature, and the reader is referred to the suggested readings. In the cognitive neuroscience literature, several paradigms are sensitive to orbital and ventromedial damage, including reversal learning tasks.

Some test development has focused on emotional or social cognition processing relevant to prefrontal cortex. For example, the Assessment of Social Inference Test—Revised (McDonald, Flanagan, & Rollins, 2011) uses video vignettes to probe facial emotion recognition and explicit use of other social cues. The Emotional Stroop paradigm, on the other hand, is an implicit measure of emotional processing. Many research-based facial and auditory emotion recognition stimuli are available online (e.g., Ekman & Friesen, 1976).

Many experimental procedures have been developed to probe more abstract abilities and functions of the prefrontal cortex. In particular, theory of mind (TOM) tasks have garnered significant attention. These TOM tasks are well-known in the pediatric and animal literatures where development of an "other" perspective signals increasing cognitive development. The false-belief paradigm (Wimmer & Perner, 1983) is a common paradigm wherein the child hears a short vignette and has to "put themselves in someone else's shoes" in order to answer questions correctly. Similar procedures can be adapted, with some creativity, to gauge these higher-level deficits in adult patients.

5. SMELL

The Smell Identification Test (Doty, 1995) can be helpful in detecting frontal dysfunction given that etiologies that damage orbitofrontal regions will also often impair smell. Moreover, reduced sense of smell is an early sign in many neurodegenerative disorders including Parkinson's disease and Alzheimer's disease. Keep in mind, however, that there are many other causes of anosmia (i.e., smoking, congestion, medications) that should be considered.

IV. REHABILITATION AND TREATMENT OF FRONTAL LOBE IMPAIRMENT

Efforts to rehabilitate frontal lobe functions are relatively early in development. Perhaps not surprisingly, the majority of efforts to rehabilitate frontal damage have focused on motor impairments. For example, there is very good evidence for the benefit of constraint-induced movement therapy. Here, however, I focus on rehabilitation of the cognitive functions of the prefrontal cortex.

Cognitive rehabilitation approaches can be roughly divided into those that seek to restore impaired function and those that seek to compensate for impaired function. The techniques focused on restoring function attempt to capitalize on brain plasticity either through experience-dependent changes or through exogenous physiological encouragement in the form of pharmacological or electrophysiological methods applied to facilitate neuronal or synaptic adaptations. Several important factors such as age at injury, injury severity, the timing or schedule of intervention, and the patient's psychological/physiological attributes (e.g., mood disturbance, activity level, stress, hormones) likely influence neural restoration, although exactly how these factors interact remains unclear.

A. Restorative Approaches

It is well accepted that experience can change the structure of cortex (Kolb & Wishaw, 2008). Rehabilitation methods that involve practicing the impaired skills are efforts to use experience to "rewire" the brain for that activity. These are typically hierarchical techniques where patients are provided with simple versions of tasks (e.g., the steps to make toast) and the tasks get more complex as performance improves (e.g., the steps to prepare a full meal). These types of practice-based interventions can be helpful for specific activities, but they often have poor generalizability outside of the trained context.

A recent trend in restorative experience-based techniques has been to supplement them with electrical stimulation; the goal being to externally stimulate neuronal plasticity during performance in order to facilitate recovery of function. These efforts have largely employed repetitive transcranial magnetic stimulation (Miniussi & Vallar, 2011). Current questions concern the timing of intervention (early vs. late), schedule of treatments for optimal plasticity (spaced vs. massed), and the location of stimulation. For example, should stimulation be directed towards neighboring cortex likely to "annex" the functions of damaged tissue? Or should one stimulate plasticity in the same (damaged) region of the opposite hemisphere?

Other exogenous interventions are more invasive and remain at the experimental stage, although they hold immense promise for promoting neural regenesis. For example, work in animals with brain injury has shown that psychomotor stimulants, neurotrophic factors, and gonadal hormones promote neural changes and dendritic branching. Stem-cell and gene-therapy research are further from application for cognitive rehabilitation but have tremendous potential for promoting restoration of function.

B. Compensatory Approaches

Alexander Luria, one of the godfathers of neuropsychology, felt that all action is accomplished through language. In this view, the formulation, execution, and monitoring of intentions, plans, and actions can be directed by internal or external speech. Work in rehabilitation of frontal lobe deficits in initiating and sustaining a plan of activity has capitalized on these ideas and some success has been demonstrated using self-talk procedures. For example, one case study used cues to trigger an apathetic patient to ask himself whether he had spoken aloud recently (Sohlberg, Sprunk, & Metzelaar, 1988). The patient's verbal output increased substantially in the presence of cues and persisted even after the explicit cues were removed. Goal

management training (e.g., Sohlberg, Mateer, & Stuss, 1993) is another self-talk technique to improve patient's ability to formulate a task goal, maintain attention to the task, monitor progress towards task completion, and adapt performance when activities are not resulting in progress. This technique is employed to improve everyday tasks such as following a recipe or cleaning up the yard. For patients with dysexecutive syndrome, goal management training is most appropriate when there is no amnesic component to their presentation. In addition, difficulty with time-sense can derail monitoring. Some techniques introduce an intermittent signaling to cue patients to stop and evaluate their attention to task and progress towards the goal. External cueing to "attend" can be very helpful in these patients.

C. Environmental Support

Environmental supports are among the simplest and most effective interventions. They may include modifying the demands placed on the patient by changing or avoiding certain tasks. It is often helpful to organize the patient's environment to minimize distractibility, establish routines, and streamline procedures (e.g., establish a whiteboard task/reminder station, reduce clutter, place checklists for tasks). Memory books can also be a useful compensatory strategy in frontal lobe damage. They may take the form of a physical book or journal, but the smartphone and tablet computer have expanded the possibilities of memory books as a resource. In essence, an external prop to plan, organize, cue, remind, direct, or guide complex behaviors is a powerful tool in compensating for prefrontal dysfunction in daily life.

Finally, environmental interventions can target the caregiver rather than the patient. Education for the patient's caregiver in behavior modification techniques can be very useful in reducing unwanted behaviors or promoting adaptive behaviors. This can range from basic knowledge of reward contingencies to structured token economy techniques.

D. Other Observations Regarding Treatment

Lack of awareness of deficit can throw a wrench in rehabilitation efforts because it is difficult to treat an impairment that the patient is not aware of. This can pose particular problems for patients whose deficits include poor social comportment or impaired higher level behavior control. Thus lack of awareness should be a target of rehabilitation early in the treatment process. It is important to institute

feedback systems in these patients to draw attention to impairments and to train them to monitor their own behavior in order to facilitate rehabilitation efforts.

When making recommendations for specific rehabilitation procedures, be mindful that rehabilitation goals and needs will change over time. Change can be due to recovery of neurological or physical capabilities, particularly in the first year following a neurological event. It is often beneficial to move from external supports to more training-based interventions, depending on the capacity of the patient and his or her level of insight/motivation. Changing rehabilitation needs can also arise from changes in the patient's social, residential, or financial context. Demands for independent function may increase or decrease depending on family support—parent caregivers may take in a patient or may pass away, or a spouse caregiver may file for divorce. Reduced income may force a patient to move from an assisted living facility to a more independent setting, while patients with sufficient financial support may move in the other direction. For all patients, it is important to carefully assess their cognitive difficulties and match their current needs to the nature of the intervention in order to strike a balance between support and functional independence.

There are often major knowledge, financial, and access barriers to obtaining rehabilitation services. Patients and families, and many physicians, are unaware of potential rehabilitation methods and the qualities or characteristics that are positive and negative indicators for rehabilitation success. Another major challenge for many patients is cost—rehabilitation is expensive. This is true for the patient and the health care provider. As a result, few centers provide extensive cognitive rehabilitation, and waiting lists for existing programs are often long. Access may be restricted on the basis of health insurance coverage, referral source, or etiology. It is incumbent on neuropsychologists to do some research about the cognitive rehabilitation resources available in their area to best provide useful and appropriate referrals for their patients.

V. CONCLUSION

Perhaps more than with any other type of brain dysfunction, the evaluation of frontal lobe function requires vigilance and creativity on the part of the examiner. The nature of the neuropsychological assessment context can mask frontal deficits, and many of the currently available tools are complex and may lack sensitivity or specificity for regional frontal lobe impairment. For these reasons, it is necessary to conduct a careful interview, use keen observation skills, and think outside the box to capture the cognitive deficits

that influence the daily function of these patients. Ongoing research seeks to improve our knowledge of frontal lobe functions, our methods for assessing them, and our ability to treat them.

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PART IV

PSYCHIATRIC DISORDERS AND BEHAVIORAL SYNDROMES

Chapter 22

Lisa L. Conant

Neuropsychological Assessment of Developmental Disorders: Learning Disabilities, Attention-Deficit/ Hyperactivity Disorder, Autism Spectrum Disorders

This chapter is a brief treatment of an extremely complex topic. Developmental disorders are highly heterogeneous both across and within diagnostic categories, and they show a substantial level of comorbidity. In addition, there are a number of controversies surrounding the developmental disorders, and the diagnostic criteria for all categories are currently in a state of flux, having undergone significant revisions in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5;* American Psychiatric Association, 2013). The developmental disorders discussed in this chapter are specific learning disorder (SLD), attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD, previously referred to as pervasive developmental disorders [PDDs]). This chapter is

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structured like others in this section of the book, with the issues of definition/classification, functional neuroanatomy, and neuropsychological assessment considered for each disorder, although the sequence of the last two sections is reversed in order to introduce the neuropsychological constructs prior to discussing their neural substrates. To fit the format of this handbook, only the most central references are provided at the end of this chapter, and an extended suggested readings list accompanies the material on the online resource (http://pubs.apa.org/books/supp/parsons).

Importantly, diagnosis in the latter two categories of disorders is based purely on behavioral symptoms and is not contingent on cognitive testing. Because of this, the clinical interview, behavioral questionnaires, and observation play a greater role than cognitive testing in determining whether individuals meet the diagnostic criteria for the disorders; however, such testing can still play an integral role in diagnosis and management. Specifically, it can aid in excluding other diagnoses that may be accounting for the behavioral symptoms as well as determining the presence of potential comorbidities. In addition, developmental disorders are strongly associated with cognitive dysfunction, and therefore cognitive assessment can make a substantial contribution by elucidating specific areas of strength and weakness on an individual level, thereby allowing for more targeted intervention strategies. Because test selection for each of these disorders will vary substantially according to the age, degree of overall impairment, and specific referral question, a prototypical battery is not given for each disorder. Instead, the neuropsychological domains frequently affected in each of the disorders is discussed in the text and commonly used measures of these domains as well as the normative age range and approximate administration times are provided in tables on the online resource.

I. SPECIFIC LEARNING DISORDER

SLDs have undergone substantial changes in the *DSM–5* (American Psychiatric Association, 2013). In the previous version of the *DSM*, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM–IV–TR;* American Psychiatric Association, 2000), there were four distinct diagnostic subcategories of Learning Disorders: Reading Disorder, Mathematics Disorder, Disorder of Written Expression, and Learning Disorder–Not Otherwise Specified. In *DSM–5*, the subcategories have been eliminated and replaced by specifiers, which are added to the overall diagnosis of SLD to indicate the particular areas of impairment observed at the time of the assessment. These specifiers include the three academic domains

previously represented as subcategories as well as key subskills within each domain (e.g., word reading accuracy, reading fluency, and reading comprehension in the domain of reading). This new system is intended to capture more detail regarding both the nature and either the specificity or co-occurrence of deficit(s) while accommodating potential changes in presentation over development (Tannock, 2013).

Another change in *DSM–5* is the inclusion of the requirement that impairments persist at least 6 months despite intervention efforts directed at these deficits, which may help minimize the possibility that learning problems are secondary to inadequate educational experience. With regard to the psychometric criterion for SLDs, in the *DSM–IV–TR* a significant discrepancy was between general ability, or IQ, and achievement level. In the *DSM–5*, there has been a move away from the requirement of a specific IQ–achievement discrepancy. Instead, performance on a standardized measure of the academic skill in question must be substantially below the level expected on the basis of the individual's age. Although a performance threshold of at least 1.5 standard deviations below the mean is suggested, it is recognized that selection of a threshold is somewhat arbitrary and may vary depending on the measure(s) used or on the basis of clinical judgment, taking into account information from other sources such as academic history. With regard to the latter, the *DSM–5* allows standardized assessment to be replaced by a documented history of learning impairment in individuals ages 17 and above.

This move away from the IQ–achievement discrepancy follows multiple studies comparing IQ-discrepant and IQ-consistent poor readers, which have failed to show any meaningful group differences in prognosis, underlying cognitive abilities, or instructional response, after accounting for definitional variability. The discrepancy model is also problematic, because by the time many children fall far enough behind in an achievement area that they start to show a significant discrepancy, they are beyond the age at which remediation has its greatest chance of success. Furthermore, children with learning disabilities tend to show a decline in IQ over time and may have deficits in working memory and processing speed associated with the learning disability itself that also contribute to a lower overall IQ score. In this regard, at least 70% of children with learning disorders have been found to show a lower score when the Working Memory and Processing Speed Indices are included in the ability calculation; therefore, the General Ability Index of the Wechsler Intelligence Scale for Children—Fourth Edition (WISC–IV; Wechsler, 2003), which does not include these indices, has been proposed as a possible substitute ability score when an ability–achievement discrepancy is used.

These changes in the defining features of SLDs follow similar ones in the 2004 reauthorization of the Individuals With Disabilities in Education Improvement Act (IDEA, 2004), which is the federal law governing the provision of special education services to children with disabilities by states and public agencies. Previous iterations of IDEA had also required an IQ–achievement discrepancy. However, as of IDEA 2004, states may no longer *require* that local educational agencies use a discrepancy criterion to define an SLD (although continued use of the discrepancy model as an option is still permitted), and they must allow the use of a process based on a child's response to evidence-based intervention. Because there is room for regional variability in the specifics of the special education eligibility criteria and many school districts may be transitioning between identification models, it is important for neuropsychologists to determine what the inclusion criteria are for SLDs used by their local school districts.

Because of the space limitations, all types of SLDs cannot be covered here. The most common (i.e., dyslexia) and the most controversial (i.e., nonverbal learning disability [NLD]), were selected for further discussion.

A. Dyslexia

1. DEFINITION/CLASSIFICATION

Dyslexia is, by far, the most common of the learning disabilities, affecting approximately 80% of individuals identified as having learning disabilities (Lerner, 1989). It is not only widespread but also persistent and costly because of its association with elevated risks for multiple long-term adverse psychosocial and economic outcomes. The definition of dyslexia adopted by the National Institute of Child Health and Human Development and the International Dyslexia Association states that dyslexia is characterized by problems with accurate and/or fluent word recognition and by difficulties with spelling and decoding (pronouncing nonwords). Although some individuals with dyslexia will develop age-appropriate decoding and word recognition skills over time, they frequently continue to show significant problems with regard to reading rate and spelling. The importance of reading fluency previously went unrecognized in diagnostic or inclusion criteria, but this has now changed in IDEA 2004 and *DSM–5*. In *DSM–IV–TR*, a reading disorder must involve either impaired reading accuracy or reading comprehension. Although the term *dyslexia* is not used as a diagnostic category in *DSM–5*, it is recognized in the text.

Deficits in phonological processing are generally considered to constitute the core cognitive difficulty in most cases of developmen-

tal dyslexia. Phonological processing is a complex multidimensional construct that is composed of multiple component processes involved in making use of phonological information in spoken and written language. *Phonological awareness* (PA) refers to an understanding of the segmental nature of spoken language and the ability to identify and manipulate the constituent phonological segments. It has been found to have the strongest relationship with level of reading acquisition, and there is evidence that this relationship is a causal one. In this regard, early performance on PA measures is strongly predictive of later reading skills, and early explicit instruction in PA enhances the acquisition of reading skills.

In clinical settings, PA can be measured using a number of different oral language tasks, including rhyme detection or generation, word-to-word matching, sound-to-word matching, phoneme blending, phoneme counting, phoneme segmentation, and phoneme deletion. Most of these tasks have been used in efforts to predict and remediate reading difficulties; however, they are not all equally effective across all age ranges. Phoneme deletion and blending tasks tend to be the most commonly used currently.

Research has suggested that deficits in another processing area, *naming speed*, may also be a source of reading difficulties, giving rise to the double-deficit hypothesis that proposes the existence of three dyslexia subtypes: one characterized by a deficit in PA; one characterized by deficits on tasks requiring the rapid retrieval of names of stimuli such as letters, numbers, objects or colors; and one characterized by impairments in both PA and rapid serial naming, termed a *double deficit* (Wolf & Bowers, 1999). These deficits may have an additive effect such that more severe reading problems are seen in those who have a double deficit than in those with a deficit only in one of the two areas. The question of whether rapid naming (RN) should be subsumed under the rubric of phonological processing remains controversial. In this regard, although some emphasize the involvement of multiple processes in naming speed including perceptual, attentional, conceptual, memory, semantic, and articulatory functions, others have conceptualized the naming deficit as being primarily phonological in nature, involving difficulties in phonological recoding in lexical access or the rapid retrieval of the phonological codes associated with specific visual stimuli. The inability to rapidly retrieve these codes or to activate them in sufficiently close temporal proximity then precludes the development of strong associations between graphemes/phonemes that often cluster together, thereby interfering with the detection of orthographic regularities and the development of automaticity in word recognition.

The independent contribution of naming speed to reading difficulties has been supported by the finding that RN accounts for

unique variance in reading performance beyond that accounted for by PA and that PA and RN appear to be differentially related to different reading skills. Whereas PA has a stronger relationship with decoding accuracy, RN shows a stronger relationship to orthographic skill. However, not all studies have found RN to have a significant unique contribution, with some studies finding that only PA continues to show a relationship with reading when the variables are simultaneously examined. Also, children with a double deficit have been found to exhibit more severe impairment in each of the deficit areas, suggesting that their poorer outcome could reflect the greater severity of the PA deficit rather than the additional impairment in RN.

A third phonological processing ability that has been found to be associated with reading is *verbal* or *phonological memory*. However, the nature and extent of the relationship between this ability and both reading and PA are unclear, with different studies yielding divergent results. One source of variability is the variety of memory measures and constructs that have been included within this category. Many studies have focused on measures of verbal or phonological short-term or immediate memory, with individuals with dyslexia exhibiting difficulties on tasks requiring the recall of lists of letters, digits, or words (Hulme & Roodenrys, 1995); however, the predictive power of these tasks with respect to reading abilities has not always been found to be significant after accounting for general verbal and other phonological processing abilities. Studies have also suggested a relationship between reading ability and phonological working memory (Leather & Henry, 1994), the latter referring to the maintenance of information online while actively processing or manipulating information. These more complex memory tasks may show a stronger relationship with reading abilities than simple memory span tasks. Another type of test used to assess this construct is nonword repetition, but, importantly, there are a number of functions that affect performance, including perceptual and articulatory processes, making interpretation of impairment somewhat more difficult. Phonological memory and PA have been found to be strongly correlated with each other, much more so than either domain is with RN (Wagner, Torgesen, & Rashotte, 1999). This relationship may in part be due to the demands that PA tasks place on phonological memory. Also, performance of both types of tasks is likely contingent on the quality of the underlying phonological representations, and deficits at earlier levels of processing such as impairments in specific auditory processing skills or categorical speech perception could affect the development of phonological abilities. The results of research looking into these earlier aspects of processing are mixed, but suggest that at least some children may have deficits in these areas (Hämäläinen, Salminen, &

Leppänen, 2013; Manis et al., 1997; Mody, Studdert-Kennedy, & Brady, 1997; Serniclaes, 2001).

2. NEUROPSYCHOLOGICAL ASSESSMENT OF DYSLEXIA

When assessing for dyslexia, it is important to include measures not only of single-word and nonword reading accuracy but also fluency, spelling, and PA and RN. Although a deficit in reading comprehension is not necessary in terms of diagnosing dyslexia, it may be a secondary effect, and being able to understand what one reads is the ultimate goal of reading. Reading comprehension is obviously influenced by not only reading accuracy and fluency but also a number of other language and cognitive abilities, such as executive functions, and therefore impaired reading comprehension can occur in the context of adequate reading accuracy and fluency. Unfortunately, the development of good reading comprehension measures has proven challenging. The Passage Comprehension subtest of the Woodcock measures, Woodcock-Johnson Tests of Achievement—Third Edition (Woodcock, McGrew, & Mather, 2001) and Woodcock Reading Mastery Test—Third Edition (Woodcock, 2011), use very brief passages and a cloze procedure, which may be lacking in ecological validity. Text-based reading comprehension measures better replicate the naturalistic demands confronted when reading, but studies have found that it is possible to perform above chance without reading the passages on two of the most commonly used of these measures, the Gray Oral Reading Test (Keenan & Betjemann, 2006) and the Nelson-Denny Reading Test (Coleman, Lindstrom, Nelson, Lindstrom, & Gregg, 2010). Thus, caution must be used in interpreting the results of these instruments.

Given the high rates of comorbidity with ADHD and communication disorders, evaluation with attentional measures and broader oral language measures are also important. Furthermore, social and emotional functioning is important to assess as problems in these areas can be associated with learning disabilities of all types.

3. NEUROANATOMY OF DYSLEXIA

The very few postmortem studies that have been done in dyslexia have found subtle cortical abnormalities suggestive of disrupted neuronal migration preferentially affecting the perisylvian regions in the left hemisphere (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Further support for anomalous migration in dyslexia comes from the findings that several of the candidate dyslexia susceptibility genes, such as *KIAA0319* and *DCDC2*, have been implicated in neuronal migration (Scerri & Schulte-Körne, 2010).

Overall, structural and functional neuroimaging studies have most consistently implicated left temporoparietal and ventral occipitotemporal regions, whereas significant variability has been found with regard to patterns of left inferior frontal cortex involvement. Specifically, recent quantitative meta-analyses of functional neuroimaging studies comparing activation associated with print stimuli in individuals with dyslexia with that in nonimpaired readers found maxima of hypoactivation in superior, middle, and inferior temporal regions as well as the supramarginal gyrus and fusiform regions in close proximity to the visual word form area. Other recent studies have shown regions of hypoactivation and hyperactivation when comparing these groups. Diffusion tensor imaging has been used to investigate the relationship between white matter integrity and reading ability, with results suggesting relationships between reading abilities and connectivity, particularly in left temporoparietal pathways but also in connections with or within frontal regions (see the suggested readings list at http://pubs.apa.org/books/supp/parsons for a listing of recent imaging studies of dyslexia).

B. Nonverbal Learning Disability

1. DEFINITION/CLASSIFICATION

NLD is a controversial category, and it is not recognized as a learning disorder subtype in the *DSM–IV–TR*, *DSM–5*, or IDEA 2004, although some of the areas of academic impairment that may be seen as part of this syndrome, such as mathematics and written expression, are. NLD is thought to be delineated not only by a set of deficits but also by a specific set of assets; however, there is a lack of consensus regarding what the essential components are. In general, the hypothesized deficits include the following domains: visual and tactile perception; visuospatial organization and construction; complex fine motor skills, with potentially greater difficulty on the left; executive functions, including conceptual reasoning and problem solving; academic achievement in mathematics calculation and reasoning, reading comprehension, and written expression; speech prosody and pragmatics; and social perception and interaction. Possible assets may include simple motor skills, auditory perception, rote verbal learning and memory, phonological skills, word decoding, and spelling (Pelletier, Ahmad, & Rourke, 2001).

2. NEUROPSYCHOLOGICAL ASSESSMENT OF NLD

Overall, a significant difficulty with NLD as a potential diagnostic entity is that, after more than three decades since its proposal, there remain significant questions regarding the necessary defining features,

the prevalence of the disorder, and the neurobiological underpinnings. Some neuropsychologists have suggested that the problem is that it is not a single unitary disorder but there are subgroups within NLD, but these also await more in-depth examination and validation (Grodzinsky, Forbes, & Bernstein, 2010). In general, the literature in this area is plagued by small sample sizes, lack of exclusionary criteria, poor attention to comorbidities, and vague sample descriptions; however, it is clearly an area that needs further investigation, particularly given that this "diagnosis" is getting made with significant frequency.

3. NEUROANATOMY OF NLD

Because of the greater impairment in processing of visuospatial and more novel information relative to verbal, more routinized information, this cluster of symptoms was originally considered to be indicative of dysfunction or reduced access to right hemisphere systems. However, the theoretical neuroanatomical basis for the syndrome was later revised and expanded to include more of an emphasis on white matter dysfunction. Rourke (1987) proposed that the integrity of white matter in the right hemisphere was necessary for the development and maintenance of its specific functions, particularly intermodal integration when novel information was being processed, whereas white matter in the left hemisphere was considered to be necessary for the development but not the maintenance of its functions. Overall, the white matter hypothesis is vague and somewhat confusing, and even though this syndrome and its hypothetical neuroanatomical basis have been proposed for many years, there have been no functional neuroimaging or diffusion tensor imaging studies published. Instead, the majority of the support for the possible existence of NLD and its proposed pathophysiology has come from studies of clinical populations with white matter abnormalities, such as those with agenesis of the corpus callosum or hydrocephalus. The only published neuroimaging study of NLD showed a finding that was unexpected even to the researchers (Semrud-Clikeman & Fine, 2011). The intent of the study was to use advanced analysis techniques to investigate and compare structural differences on magnetic resonance imaging (MRI) in and among children with NLD, children with Asperger's disorder, and typically developing children, but the researchers unexpectedly found that 25% (seven of 28) of the group with nonverbal learning disability actually showed a gross brain abnormality, whereas a rate of 4% was seen in the Asperger syndrome and the control group (one each of 26 or 24, respectively). The abnormalities fell predominantly in occipital or temporal regions (3 and 2, respectively, either right or left) with one bilateral cerebellar and one left frontal abnormality.

II. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. DEFINITION/CLASSIFICATION

The previous diagnostic criteria for ADHD in the *DSM–IV–TR* required the individual to show six or more symptoms of inattention and/or six or more symptoms of hyperactivity/impulsivity that had been present at least 6 months, were inconsistent with developmental level, and caused impairment in social or academic/occupational functioning. Examples of inattentive symptoms include making frequent careless errors or failing to attend to details, problems sustaining attention, failing to finish activities, organizational difficulties, avoidance of or reluctance to engage in activities requiring sustained mental effort, distractibility, and forgetfulness. Among the symptoms of hyperactivity or impulsivity are fidgeting, leaving one's seat inappropriately, behaving as if "driven by a motor," talking excessively, problems waiting for one's turn, and intruding on or interrupting others. At least some of these symptoms must have been present prior to the age of 7. In addition, clinically significant impairment must be seen across at least two settings, for example, at home and at school or work. Three subtypes are delineated in the *DSM–IV–TR:* (1) Combined Type; (2) Predominantly Hyperactive–Impulsive Type; and (3) Predominantly Inattentive Type.

There are a number of changes in the *DSM–5*, particularly with regard to the diagnosis in individuals over the age of 17. It has long been recognized that the symptom profile of ADHD changes over the life span, with a reduction in number of symptoms, particularly of hyperactivity. For this reason, there is now a reduction from six to five in the number of symptoms required to make the diagnosis in adults. Although the same symptoms are being retained, another change has been the addition of examples that are more relevant to adolescents and adults. In addition, the age by which an individual must be showing symptoms has been changed from 7 to 12 years, and the three original subtypes have been reconceptualized as "current presentations" as opposed to subtypes. Finally, previous criteria excluded an ADHD diagnosis if the individual met criteria for a PDD, which was a concern for a number of reasons, including the fact that a significant proportion of individuals with PDD who also meet ADHD criteria respond to pharmacological treatment of the latter condition (Murray, 2010). This exclusion has been eliminated.

B. NEUROPSYCHOLOGICAL ASSESSMENT OF ADHD

The role of neuropsychological testing in the assessment of ADHD is a hotly debated topic (for a more complete review of this

issue, see Pritchard, Nigro, Jacobson, & Mahone, 2012). Because the criteria are purely behavioral, neuropsychological assessment is not necessary to determine if an individual meets diagnostic criteria for ADHD, and there are a number of studies that call into question the utility of neuropsychological test measures for making the diagnostic classification. Although group analyses frequently find deficits in executive functions, no one test or even one set of tests has been found to reliably differentiate an individual with ADHD from one without. However, there are two ways in which a neuropsychological assessment can be very useful. First, there are a number of other conditions that can result in a behavioral symptom profile consistent with ADHD or be comorbid with ADHD, such as other neurodevelopmental or psychiatric disorders, which psychometric testing can help appropriately diagnose. Thus, neuropsychological testing can be useful in teasing apart the diagnostic possibilities. In addition, although there is significant heterogeneity in the neuropsychological functioning of individuals with ADHD, ADHD is frequently associated with cognitive impairment, particularly on measures of executive functioning. Establishing what a given individual's strength and weaknesses are can play an important role in determining how best to help them.

With regard to ruling out other possible explanations for attentional complaints, it is important to consider the fact that there can be strong external incentives for receiving such a diagnosis, particularly for adolescents and adults. Such incentives include academic or workplace accommodations and access to stimulant medications for either academic performance enhancement or recreation. Sullivan, May, and Galbally (2007) found that nearly half (47.6%) of college students being evaluated only for ADHD failed a symptom validity test, the Word Memory Test. Self-report, behavior-rating checklists have high face validity, and several studies have shown that individuals asked to simulate ADHD are able to convincingly do so on multiple behavioral questionnaires. There are no clear differences on behavioral rating scales between individuals with ADHD and those deemed noncredible. Suhr, Buelow, and Riddle (2011) developed an Infrequency Index (CII) for the Conners' Adult Attention Deficit/Hyperactivity Rating Scale (CAARS; Conners, Erhardt, & Sparrow, 1999), and they reported acceptable sensitivity and strong specificity of the CII for failure of the Word Memory Test, suggesting that this measure holds promise as a means of detecting malingered ADHD on this rating scale.

With regard to neuropsychological performance measures, studies of malingering have yielded mixed results, and some studies have suggested that, although ADHD simulators or probable malingerers as a group tend to perform lower on some measures of attention, processing speed, or working memory, they often do not score so low that their performances are not believable. The neuropsychological measures that appear to show the most promise for detecting feigning

tend to be the continuous performance tests (CPTs) and the Stroop test. The most recent update (8.0) of the Test of Variables of Attention actually contains a Symptom Exaggeration Index that was developed based on work with individuals in litigation for mild head injury who were judged to be probable malingerers as well as college students asked to feign ADHD, and it was refined through a reanalysis of these data incorporating intraindividual response time differences (Hughes, Leark, Henry, Robertson, & Greenberg, 2008). However, there do not appear to be independent assessments of its sensitivity and specificity at this time. Measures originally developed to detect malingering of cognitive symptoms, principally memory complaints, have also been examined in ADHD. In both simulator studies and studies with clinical populations, effort measures have generally shown strong specificity but generally low sensitivity.

With regard to the neuropsychology of true ADHD, there is substantial evidence of executive or self-regulatory dysfunction associated with this disorder, and deficits in this domain have been found as early as 3 to 5 years of age, persisting through adulthood (for a review, see Seidman, 2006). Importantly, executive functioning is clearly not a unitary process, and the specific executive functions most implicated in ADHD are still being investigated. Behavioral inhibition has been postulated by some researchers to be the core deficit in ADHD (Barkley, 1997), potentially underlying deficits in other aspects of executive functions such as working memory as well as planning and organization. However, although deficits in this area are frequently reported, they are not present in all individuals with ADHD, and some of the differences found on tests of inhibition may not, in fact, specifically reflect an inhibitory deficit. For example, the Stop-Signal task has frequently been found to distinguish children with ADHD from controls, with Stop-Signal reaction time being one of the most consistent differentiating measures in this population (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), but findings of slowed and more variable reaction time to the Go stimuli complicates interpretation of the difference as specific to inhibitory control. In their meta-analysis, Willcutt et al. (2005) reported that, in addition to the Stop-Signal reaction time, the tests that most consistently differentiated between individuals with ADHD and typically developing controls include the CPT omission errors, measures of planning, and measures of spatial working memory. Another review added the Trail Making Test and the Controlled Oral Word Association Test as measures that distinguish ADHD samples from typically developing controls (Seidman, 2006), with the two reviews discrepant with regard to the Stroop Color–Word Test. Although differences on the Wisconsin Card Sorting Test frequently have been found in child studies, this is not the case in studies with adults, which

have generally found this measure to be ineffective in differentiating groups, possibly due to a ceiling effect.

Although there is substantial evidence supporting a relationship between ADHD and the cognitive aspects of executive functions, it is also clear that deficits in this domain are not universal. Some researchers have started focusing on a second potential area of deficit, specifically, dysfunction of motivational or affective processing, particularly surrounding reward processing and response to delays. Some theorists have conceptualized both the cognitive and motivational sets of processes under the rubric of executive functions, referring to them as *cool* or *hot* executive functions, respectively. The primary hot executive function that has been postulated to play a significant role in ADHD is delay aversion. It has been hypothesized that some children with ADHD may show impulsivity not due to an impaired ability to inhibit a response but to a difficulty waiting for a valued outcome (Sonuga-Barke, 2005). Studies that have looked at both measures of response inhibition and delay aversion have found difficulties on both types of tasks and have suggested that they may be independent predictors of ADHD status.

C. NEUROANATOMY OF ADHD

The two aspects of executive functions have been associated with distinct fronto-striatal circuits, and functional MRI (fMRI) studies have implicated these different circuits in ADHD. Across studies examining inhibition and attentional control, fMRI studies have shown functional abnormalities in dorsal anterior cingulate and dorsolateral prefrontal, ventrolateral prefrontal, caudate, and parietal regions in individuals with ADHD (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Fewer studies have used tasks assessing hot executive functions. Those that exist have shown dysfunction in orbitofrontal cortex, ventral striatum, and temporal regions, including the amygdala, during reward processing tasks, although Cubillo et al. (2012) cautioned that most studies have not considered the presence or absence of comorbid conduct disorder, and there is some evidence suggesting that abnormalities in these regions only occur in ADHD with comorbid conduct disorder.

III. AUTISM SPECTRUM DISORDER

A. DEFINITION/CLASSIFICATION

In the *DSM–IV–TR*, these disorders are termed *Pervasive Developmental Disorders;* however, this term has been replaced by the label *Autism Spectrum Disorder* in general usage and in the *DSM–5*. These

disorders have undergone dramatic changes in the *DSM–5*. In the *DSM–IV–TR*, there are four specified diagnostic entities: Autistic Disorder, Asperger's Disorder, Rett's Disorder, and Childhood Disintegrative Disorder, as well as the ill-defined category Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS). The *DSM–IV–TR* criteria involve a symptom triad, including impairments in social interaction, impairments in communication, and the presence of repetitive or restricted patterns of behavior or interest. Examples of social impairments include a failure to form developmental-level-appropriate peer relationships, diminished social–emotional reciprocity, and impaired use of nonverbal behaviors to regulate social interaction. In the communication domain, possible symptoms include impaired or absent language, difficulties sustaining conversations, and stereotyped or idiosyncratic language. Exemplar repetitive or restricted behavior patterns include an encompassing interest in one or more circumscribed topic areas, repetitive or stereotyped body movements, and rigid adherence to nonfunctional routines. In Autistic Disorder, it is necessary to have at least six symptoms across all three categories, with at least two from the social domain, and one each from the other two domains. In Asperger's Disorder, there is no requirement for a deficit in the communication domain, and there is a requirement that early language development as well as general cognitive ability, adaptive behavior, and curiosity about the environment not be significantly delayed. Importantly, if a child meets criteria for Autistic Disorder, Asperger's Disorder cannot be diagnosed.

In the new *DSM–5* criteria, the classification is dimensional rather than categorical. There are no specific diagnostic entities within the overarching diagnosis of ASD. In addition, the social interaction and communication symptom clusters have been combined. To meet criteria, children must show all three of the symptoms listed in the resulting social communication domain, which include impairments in social–emotional reciprocity, the formation of developmental-level-appropriate relationships, and nonverbal communication. Two of four possible repetitive or restricted behavior symptoms are also required, with the options including intense, restricted interests; repetitive or stereotyped movements or speech; rigid adherence to routines or resistance to change; and unusual reactivity to sensory stimuli. The ASD diagnosis is then individualized using clinical specifiers, such as the level of symptom severity, and the presence of any associated features, such as an identified genetic or medical disorder, intellectual disability, or current structural language impairment.

The most contentious of the changes is the elimination of Asperger's Disorder as a diagnostic entity distinct from Autistic

Disorder. This change follows the accumulation of substantial evidence that the *DSM–IV–TR* criteria for Asperger's Disorder do not work in clinical practice, with several studies indicating that it is very hard to meet criteria for the disorder, in large part due to the criterion stating that the diagnosis of Asperger's Disorder should not be used if the child meets criteria for Autistic Disorder (Mayes, Calhoun, & Crites, 2001). In this regard, most children who would otherwise be considered to have Asperger's do have social communication deficits, such as impaired nonverbal communication and difficulties sustaining conversations, and early structural language delay is not required for a diagnosis of Autistic Disorder. In fact, even the original four cases described by Asperger would not meet *DSM–IV–TR* criteria for Asperger's Disorder because they meet criteria for Autistic Disorder.

With regard to other efforts to differentiate these diagnostic subtypes, a highly influential study by Klin, Volkmar, Sparrow, Cicchetti, and Rourke (1995) suggested that the majority of cases of Asperger's disorder could be distinguished from high-functioning autism (HFA) by the presence of an NLD profile in the former. Although partial overlap was suggested by a few studies, it has proven difficult to replicate findings of NLD as a differentiating cognitive profile. In general, research investigating potential subtype differences has failed to provide clear, consistent evidence for qualitatively distinct diagnostic categories of Asperger's and HFA on the basis of etiology, clinical features, neuropsychological profiles, or prognosis (Macintosh & Dissanayake, 2004). Importantly, in the context of these diagnostic issues along with the poorly specified criteria for PDD-NOS, a striking lack of reliability has been found across different centers with regard to the subtype classifications made and how these diagnoses were determined, raising further concerns regarding the validity and utility of these subtypes (Lord et al., 2012).

B. NEUROPSYCHOLOGICAL ASSESSMENT OF ASD

Like ADHD, this diagnosis is based on behavioral, not cognitive, criteria. Thus, for diagnostic purposes, the clinical interview and direct observation of the patient are the most essential tools. These can be unstructured or structured. Many consider the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule–Second Edition to be the gold standards for diagnosis. However, their use may not always be practical in a clinical setting due to issues of length, cost, and training requirements. There are some much less extensive (and less expensive) parent-report questionnaires, such as the Social Responsiveness Scale–Second Edition, as well as observational rating scales, such as the Childhood Autism

Rating Scale–Second Edition. None of these should be used exclusively for diagnosis.

In terms of qualitative behavioral observations and history, there are important social communication features that may aid in differential diagnosis. First, approximately 15% to 37% of children ultimately diagnosed with an ASD have been reported to show language regression, most typically between 17 and 21 months of age, and usually after only acquiring a few words used in a meaningful way. It may be preceded by a plateau in word acquisition and is typically accompanied by a regression in social skills such as eye gaze, participation in social games, and use of gestures. Such regression tends to be specific to ASD, rarely being seen outside of this diagnostic category. Also unlike other developmental disorders, gestural communication, including pointing, is often significantly impaired in ASD. The impairment tends to be more severe with regard to protodeclarative pointing, or pointing to show something of interest to another, relative to protoimperative pointing, or pointing to indicate a want. The former is a joint attention behavior, involving the shared experience between two people, which is an area of impairment highly associated with ASD.

Echolalia may also occur in ASD, but it is not specific to ASD and, in fact, is seen in typical language development starting at 18 months and tapering off by 3 years of age; however, it tends to be more frequent and longer lasting when it occurs in ASD. Echolalia may be immediate or delayed, and it may involve only the words, or the prosody may be echoed as well. Although delayed echolalia may serve no purpose, there are times in which it actually carries an idiosyncratic meaning for the child with autism. For example, if a child became anxious in an elevator, and someone said, "It's just an elevator," a child may associate the phrase with his feeling at the time and repeat this phrase in other contexts in which he feels anxious. Errors in personal pronouns such as reversal of first- and second-person pronouns may also be seen in association with echolalia, and it is thought that these errors occur because first- and second-person pronouns do not have fixed, concrete meanings but rather change based on perspective. Thus, children will refer to themselves and others as they hear others refer to them (Siegel, 1996).

Another atypical communication pattern that may be seen in higher functioning children with ASD has been termed *pedantic*, or "little professor," speech. Specifically, children with ASD may not do well with turn-taking or gauging another person's level of interest in or background knowledge of a topic, engaging in monologues rather than dialogues. They may talk extensively about a particular topic of interest to them and resist or not follow changes in subject initiated by another, using vocabulary and structure more often encountered in formal writing than conversation.

The nature of the social dysfunction in ASDs is also heterogeneous. It is a common misconception that individuals with ASD avoid or are disinterested in social interaction. Although some individuals are not interested in engaging in social interaction, some would like to interact with and may approach others, but they do not do so appropriately. They may actually appear overly intrusive, which can lead to rejection by peers, potentially resulting in depression and anxiety.

The appropriate assessment instruments necessarily differ not only with the age of the child but also the severity of dysfunction in multiple domains, such as general cognitive function and language ability. At times, older children may need to be assessed with instruments normed for much younger age groups, with the intent to get more of a qualitative sense of their abilities in different domains. In addition to a standard measure of general cognitive function, children with significant language impairment may also be given a more specific measure of nonverbal intellectual ability, which is also essential to assess adaptive functioning.

With respect to more specific neuropsychological domains, the three most influential theories regarding core cognitive deficits in ASD have focused on theory of mind impairments (Baron-Cohen, 1995), executive dysfunction (Ozonoff, Pennington, & Rogers, 1991), and weak central coherence (Happé & Frith, 2006). Theory of mind (TOM) refers to the ability to infer or predict the mental states of others. First-order TOM is demonstrated by most typically developing children by the age of 4, whereas second-order TOM (i.e., inferring what an individual believes is the mental state of another) is typically mastered between the ages of 6 and 7. False belief tasks have often been used to assess this construct, but most of these tend to have a low ceiling. A few tests of advanced TOM have been developed, such as the Reading the Mind in the Eyes Test and the Faux-pas Test, which are available for free at the Autism Research Centre website (http://www.autismresearchcentre.com) but are for research purposes only. For children between 5 and 12, the Strange Stories Test (O'Hare, Bremner, Nash, Happé, & Pettigrew, 2009) and the NEPSY–II Theory of Mind Subtest are available for clinical use. Correlations among measures of TOM have been reported to be low, suggesting that they may not be measuring a unitary construct. Although there are numerous studies that find deficits in TOM in individuals with ASDs, a deficit in TOM is not universally seen, and individuals with autism show social deficits prior to the age at which TOM typically emerges, suggesting a problem at an earlier level of processing.

Executive dysfunction is frequently found in older children and adults with ASDs, and it has been linked to the repetitive and restricted patterns of behavior seen in the ASDs. As in ADHD, the specific aspects of executive functions that are most affected in this

population are a matter of debate, with substantial variability across studies. One recent study found significant impairments on measures involving inhibition of a prepotent response and planning, with intact performance on measures of cognitive flexibility and verbal fluency (Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009). Another study examining relationships between specific functions and the severity of restricted or repetitive symptoms found significant relationships with response inhibition, cognitive flexibility, and working memory but not with planning or fluency (Lopez, Lincoln, Ozonoff, & Lai, 2005). In relation to executive function in individuals with ADHD, studies have suggested more pervasive executive function deficits in those with ASDs, particularly showing greater difficulties in planning and cognitive flexibility. However, unlike ADHD, studies conducted in preschoolers have found no deficits on executive function tasks at early ages, arguing against it as a core or primary deficit (Yerys, Hepburn, Pennington, & Rogers, 2007).

The weak central coherence theory is unique in that it provides an explanation for heightened abilities that some individuals with ASD show with regard to the processing of details. Central coherence involves integrating local, featural level information into a context, allowing for the derivation of global meaning. Overall, although some studies have suggested a tendency toward enhanced processing of local-level information in ASD, the evidence for a failure to integrate at the global level may be more variable.

Certainly, dysfunction in each of these three areas has been seen in individuals with autism, but, importantly, none are universal or specific to ASDs, and there are abnormalities in functioning that predate the emergence of these deficits, suggesting they are not at the core of ASDs. As with ADHD, the role of motivational processing is now being considered. In trying to delineate core deficits, it is important to consider the first observed symptoms in ASD. A recent study using eye tracking during viewing of videotaped social scenes did report decreased attention to the scenes, the person within the scenes, and specifically the face of that person in 6-month-olds at familial risk who were later diagnosed with ASDs, relative to those showing typical development and those with atypical development but not ASD; however, multiple studies of infants as young as 6 months old have not found differences when examining live, face-to-face interactions with parents or an examiner (Chawarska, Macari, & Shic, 2013). Werner, Dawson, Osterling, and Dinno (2000) examined home videos made of 8- to 10-month-old children who were later diagnosed with autism and a group of typically developing children and found that the behavior of orienting to one's own name led to a 78% classification accuracy. In first birthday party videos (Osterling & Dawson, 1994), the following four predictors led to a

91% classification accuracy: looking at the faces of others, showing objects, pointing, and orienting to name. Thus, the initial deficits were seen in the areas of orientation to social stimuli and joint attention. Similarly, another prospective study following children at familial risk of autism and controls (Zwaigenbaum et al., 2005) found several problems in social functioning present at 12 months to be predictive of a diagnosis of autism at 24 months, including impairment in the following areas: eye contact, orienting to name, imitation, social smiling, and social interest. This study also found augmented responsiveness to nonsocial stimuli, such as the presence of self-stimulatory use of play materials, intense responses to sensory input, and increased fixation on nonsocial aspects of the visual environment, as well as some difficulties in visual attention generally and in affective regulation. These observations have led to the idea that there may be an initial deficit in social motivation. This diminished social motivation may ultimately lead to reduction in social inputs, social learning, and ultimately expertise in social cognition. This theory fits with the developmental time course of deficits, with secondary impairments emerging in other areas such as executive functions and TOM later in the course of the disorder.

C. NEUROANATOMY OF ASD

There has been substantial research into the neural substrates of ASD using a variety of different methodologies. One of the most consistent findings has been increased whole brain volume. Studies have suggested that there is a specific temporal pattern to the increased volume (Courchesne et al., 2007), with normal volumes in neonates but greater cerebral and cerebellar volumes seen in children ages 2 to 4 years by a margin of approximately 10% over their typically developing peers and with peak overgrowth seen in frontal and temporal regions. Although whole brain volume in general may stay slightly above average by about 1% to 3% at older ages, by adolescence, greater white matter volumes have been seen in typically developing individuals relative to those with ASD. Courchesne et al. (2007) proposed that an early overgrowth of neurons in frontal and temporal regions could reduce available synaptic space, and the greater numbers and reduced transmission time could allow them to overcompete, diluting signals from distal afferents and permitting excessive local connections while impeding the development of the distal connections necessary for higher social and communicative functions. This idea of local overconnection and distal underconnection has also provided a potential neural mechanism for the strength in local or more detailed processing in some children with ASD. Functional imaging studies have supported the hypothesis of a

disrupted pattern of connectivity in individuals with ASD (Courchesne et al., 2007). Some additional evidence for abnormalities in connectivity arise from postmortem studies that found alterations of radial columnar morphometry (Casanova & Trippe, 2009) and higher spine density in the late maturing cortical layer II in the frontal, temporal, and parietal regions, with the majority of connections in this layer being within hemisphere.

Much of the recent functional imaging work has focused on areas associated with aspects of social cognition (for recent functional imaging studies, see the suggested readings list at http://pubs.apa.org/books/supp/parsons), including areas associated with face processing (e.g., the fusiform face area) and its association with emotional processing regions (e.g., amygdala), TOM (e.g., medial prefrontal cortex, posterior cingulate/precuneus, posterior superior temporal sulcus, and the angular gyri, particularly on the right), and mirror-neuron-like activity (e.g., inferior frontal gyrus/ventral premotor, posterior parietal). Of note, many of these areas are involved in multiple higher order cognitive processes, with many of them also comprising what has been called the default-mode network and the semantic network. Overall, it does seem clear that ASDs are characterized by extensive, distributed abnormalities.

IV. CONCLUSION

The developmental disorders are highly complex and variable in their manifestations, and many of their aspects are still not well understood. Because of their complexity, changes in the diagnostic criteria will likely continue, particularly as more is learned about the genetics and neurobiology of these disorders. Overall, neuropsychologists are in a prime position to characterize the specific cognitive and behavioral features of the disorders that are present in a particular individual, which should assist in guiding interventions and accommodations.

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Chapter 23

Robert M. Bilder

Schizophrenia

Schizophrenia is a highly prevalent disorder, affecting about 1% of the population worldwide. This syndrome is one of the leading causes of disability among young adults. It is now recognized that substantial proportions of this disability and limitations in the potential for rehabilitation are mediated by pervasive and severe neuropsychological deficits. For several decades, pharmacological treatment with first-generation antipsychotics (FGAs; e.g., chlorpromazine, haloperidol, fluphenazine) has done a good job of ameliorating the "positive" symptoms of schizophrenia (e.g., delusions, hallucinations), but these treatments provide at best partial normalization of neuropsychological deficits. Second-generation antipsychotic agents (SGAs; e.g., clozapine, risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole) may have comparable efficacy on positive symptoms and minimize some of the adverse effects associated with conventional treatments. However, the initial spirit of therapeutic optimism that SGAs yield greater cognitive benefits has faded in the face of large-scale studies showing little benefit of the newer agents relative to low

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doses of the older agents. Major efforts continue to find new treatments for the cognitive deficits of schizophrenia, particularly adjunctive treatments. Some efforts are exploring novel pharmacological mechanisms of action. There is also great current interest in pursuing nonpharmacological treatments, including psychotherapeutic, cognitive remediation, and other neuroplasticity-oriented strategies. The clinical assessment of schizophrenia therefore benefits more now than ever from an understanding of the cognitive features of the syndrome, given that these may prove to be most informative with respect to rehabilitative, educational, and vocational planning.

I. DEFINITION/CLASSIFICATION

The diagnosis of schizophrenia (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [*DSM–5;* American Psychiatric Association, 2013]) is based on clinical observation of characteristic symptoms (two or more from the following list):

- delusions,
- hallucinations,
- disorganized speech,
- grossly disorganized or catatonic behavior, and
- negative symptoms (e.g., affective flattening, alogia, or avolition).

There must also be a significant deterioration in work, interpersonal relations, or self-care compared with premorbid levels, and symptoms must have persisted for at least 6 months. The diagnosis also requires a series of rule-outs (see Section II. D. Competing Diagnoses). The idea of including cognitive impairment in *DSM–5* was considered and rejected because of its lack of diagnostic specificity and limited information about the impact of such a change (Barch & Keefe, 2010). It was considered a key aspect of schizophrenic psychopathology, however, and is recommended as one key dimension to be measured across patients with a psychotic disorder (American Psychiatric Association, 2013). Therefore, for the foreseeable future, diagnosis will likely continue to be based exclusively on clinical observation of the patient and observations gleaned from collateral sources without reference to neuropsychological assessment. The proposed new criteria are almost identical to the previous criteria (American Psychiatric Association, 2000), but the disorganization criterion focuses more on motor behavior and avoids ambiguity of characterizing other forms of disorganized behavior. From the neuropsychological perspective, it may be noted that there is usually little correlation between delusions and hallucinations and the level or

pattern of deficit observed on neuropsychological testing. In contrast, prominent disorganization and negative symptoms have shown moderate correlations with neuropsychological impairment. It is also particularly useful for neuropsychological assessment to consider carefully the nature of deterioration and the degree to which this deterioration includes cognitive dysfunction as a mediator of the impairments in work, educational achievement, and social functioning.

II. FUNCTIONAL NEUROANATOMY

The etiology and pathophysiology of schizophrenia remain unknown. It is generally presumed that schizophrenia has a neurodevelopmental origin. There is a known genetic risk, and overall heritability of schizophrenia is approximately 80%. For the monozygotic twin of an individual with schizophrenia, the risk is about 50%, and for first-degree family members of an individual with schizophrenia, there is approximately a 10% likelihood of developing the syndrome. There are also subtle deficits in neurocognitive functioning even among the unaffected family members of people with schizophrenia. The nature of the genetic contribution remains unclear. Recent studies have implicated some specific common genetic variants with very small effects, as well as some rare genetic variants associated with larger effects on risk for schizophrenia, but overall the emerging consensus is that a very large number of variants (perhaps thousands) will be necessary to help explain the overall high heritability of the syndrome (Bilder, Howe, Novak, Sabb, & Parker, 2011; International Schizophrenia Consortium et al., 2009).

The age of onset for schizophrenia is modally in late adolescence or early adulthood, but there is a broad spectrum of onset ages from early childhood throughout the senium, with some debate about whether early-onset and late-onset cases may comprise etiologically distinct syndromes. Some clinical signs of illness may be apparent from birth. One series of studies showed that infants who would later develop schizophrenia can be distinguished from their siblings who do not develop schizophrenia by examining behavior on home movies of first-birthday parties. Other data suggest there may be increasing social or cognitive deficit in early adolescence, before any other signs of the syndrome appear (Bilder et al., 2006). The findings are sometimes difficult to interpret, however, because the onset of psychotic symptoms varies markedly, with some patients showing a gradual onset of social isolation and dysfunction without any overt psychotic symptoms and others showing an abrupt break from apparently normal behavior to florid psychosis. In a study of

first-episode patients, for example, it was found that the average duration from the first appearance of overt psychotic symptoms to the time at which patients were hospitalized for treatment was more than 1 year, and more subtle signs of behavioral change often had been detected years previously (Bilder et al., 2000, 2006). There does appear to be an association of earlier onset with greater severity of neuropsychological deficits, and the pattern of deficits in early-onset cases is more likely to include deficits in verbal abilities (Bilder et al., 1991).

A. Schizophrenia Subtypes Disappear in *DSM–5*

Schizophrenia has long been characterized by subtypes, including the paranoid type, disorganized type, catatonic type, undifferentiated type, and residual type. The *DSM–5* has abolished these subtypes because they lack longitudinal stability and clinical utility. There are also multiple course descriptors that note whether the course is continuous, episodic (recurrent episodes with or without residual symptoms), or single-episode. For reasons that remain unclear, the catatonic type of schizophrenia is less frequently observed today than it was in the era before the widespread use of antipsychotic drugs. Although *DSM–5* has eliminated a catatonic subtype, it retains a specifier to indicate if the syndrome is accompanied by catatonic features. Older literature generally suggested that cognitive deficits are less severe in the paranoid type compared with other subtypes. There are relations of illness course characteristics with cognitive deficit. Typically, early-onset, continuous, or recurrent illnesses with residual symptoms have more severe cognitive deficit than do later onset, single-episode, or recurrent episodic illnesses without residual symptoms.

In the 1980s, a distinction was made between Type I and Type II schizophrenia. The Type I syndrome was putatively characterized by more positive and fewer negative symptoms, good response to treatment, and relatively normal-appearing brain structure and cognitive function. The Type II syndrome was thought to be marked by more negative symptoms, poor treatment response, abnormal brain morphology, and more severe neurocognitive deficits. Although these broad distinctions are not without merit, it has become clear that there is enormous variability and that clear distinctions do not mark these two syndromes. A stronger case has been made for the distinction between deficit and nondeficit schizophrenia (Carpenter, Arango, Buchanan, & Kirkpatrick, 1999), and although it is clear that individuals with the deficit syndrome have more severe neurocognitive deficits, the pattern of deficits may not be distinctive.

The *DSM–5* workgroups developed a series of nine dimensions on which people with schizophrenia may be rated on a severity spectrum from not present to severe (Hallucinations, Delusions, Disorganization, Abnormal Psychomotor Behavior, Restricted Emotional Expression, Avolition, Impaired Cognition, Depression, and Mania). Although this is not a mandatory component of diagnosis, it is hoped that such dimensional assessments will become commonplace and help advance research, particularly as electronic medical record systems are being implemented nationally as a component of health care reform. It should also be noted that the National Institute of Mental Health (NIMH) has inaugurated an initiative known as the Research Domains Criteria Initiative (RDoC) to examine psychopathological syndromes, including schizophrenia, using dimensional approaches that include efforts to understand the underlying neural and cognitive systems (Bilder, Howe, & Sabb, 2013; Cuthbert & Insel, 2013; Insel et al., 2010).

B. Neuropathological–Neurochemical Correlates

Although there is persuasive evidence that schizophrenia is marked by pathological changes in brain structure and a diversity of neurochemical abnormalities, none have yet proved to be either diagnostic or clearly related to neurocognitive profile or prognosis. In general, modest correlations have been observed between neurocognitive deficits and generalized markers of cerebral pathology, as observed in enlargement of the ventricular system, reduction in overall brain volume—or more specifically, the reduction in cortical gray matter, reduction in markers of white matter integrity (e.g., fractional anisotropy observed on diffusion weighted images), or the size of specific subcortical and limbic regions. These correlations are not sufficiently robust to be useful in the assessment of individual cases. There continues to be hope that unique pathologies or response to treatments will be associated with distinctive genetic variants, but so far we possess neither useful genetic subtyping of pathology nor any unique pharmacological response within a genetically defined subgroup.

C. Functional Neuroanatomic Correlates

Considerable interest in schizophrenia research has centered on attempts to identify the pathological substrate(s) of the syndrome, and both functional neuroimaging and neuropsychological assessment have been prominent in these efforts. Multiple studies have focused on dysfunction of frontal lobe systems and their prominent projections to basal ganglia and temporolimbic targets (Bilder et al., 1995; Bora et al., 2011; Szeszko et al., 2003). It has been difficult to

determine unequivocally whether these dysfunctions are more likely attributable to specific regional deficiencies in key frontal, limbic, diencephalic, or striatal function or whether a widespread neurochemical dysfunction (e.g., in the broad populations of brain cells that rely on *N*-methyl-D-aspartate receptor function) may best account for these observations. It is also possible if not likely that a wide variety of different causes account for the observed cases. Regardless of the causes, it is clear that people with schizophrenia tend to show marked deficits on functional measures usually associated with the integrity of these regions (e.g., deficits of executive and learning–memory functions are prominent), and functional neuroimaging experiments have repeatedly shown that patients either fail to appropriately activate relevant frontal and limbic regions or show excessive activation in these regions (which has been interpreted as inefficiency of the relevant neural networks).

Neuropsychologists should be cautious in drawing any conclusions about possible neuroanatomical substrates of functional deficits in schizophrenia, and similarly, avoid drawing functional conclusions if neuropathology has been documented in a particular case of schizophrenia, because the pathology is likely to be neurodevelopmental in origin and thus inferences based on evidence from "classic" lesion studies may be misleading (Bilder, 1992). For example, although hippocampal volume deficits may be prominent in schizophrenia, there is little evidence that these volume reductions are linked to memory deficits, as might be suspected from the study of patients who have a history of normal development and then have focal lesions to the hippocampal region. Instead, it is suspected that the volume reductions in the mesiotemporal lobe may reflect altered connectivity between frontal and limbic regions, and thus the overall integrity of this integrated system may be compromised, affecting attentional or executive functions. In general, however, evidence of frank neuroanatomical compromise will not be apparent on routine clinical examination, because the deficits are usually subtle (e.g., volume reductions of 5% or even smaller), so neuroradiological reports will most often be negative or comment only on the appearance of the ventricular system or subarachnoid cerebrospinal fluid (CSF) spaces being slightly enlarged with respect to expectations for age. If focal lesions are noted in frontotemporal or limbic regions, this may suggest that schizophrenia is not the most appropriate diagnosis, and every effort should be made to rule out other possibly treatable diseases.

D. Competing Diagnoses

Because the diagnosis of schizophrenia is still based on clinical observation of characteristic psychopathological symptoms and

their course, as well as on overall impairments in social and occupational function, the neuropsychological exam is usually not critical to differential diagnosis. It is crucial, however, to rule out other possible causes of psychosis, and particularly in the initial diagnosis, neuropsychological assessment may play an important role. Key rule-outs include psychotic disorder due to a general medical condition, delirium, and dementia. History is usually the key to making these determinations, and thus the neuropsychological examination of a patient for whom the diagnosis of schizophrenia is suspected must incorporate appropriate consideration of other medical disorders, including results of laboratory tests and physical examination. Drug and alcohol abuse and withdrawal syndromes are sometimes confused with schizophrenia, with particularly problematic cases sometimes arising in cases of stimulant, phencyclidine, or ketamine abuse (indeed, valuable experimental models of schizophrenia are based on exposure to these agents). Neuropsychologists should consider the typical presentation and increase suspicion of psychosis explained by other medical conditions if the presentation deviates substantially from these expectations.

Although there is great variability, the typical presentation (a) involves generalized cognitive deficit with most striking deficits in memory, executive, and attentional functions but does not include focal or strongly lateralizing signs on the neuropsychological or neurological exam; (b) is more likely to involve a period of decline prior to onset of psychosis, and less frequently includes history of acute onset, without any deterioration in social, occupational, or vocational functioning; (c) may include auditory hallucinations along with hallucinations in other modalities, but the observation of hallucinations limited to visual, olfactory, gustatory, or somatic modalities is rare; and (d) involves age of onset in late adolescence or early adulthood, with onset in early childhood and late life being relatively uncommon.

E. Diagnostic Clues From Medical History

Medical history is usually of primary value in the negative, that is, by ruling out other medical causes of psychosis and schizophrenialike symptoms. At the same time, the history of individuals who will go on to develop schizophrenia is often marked by subtle delays in neurodevelopmental milestones, including motor, language, and social skills development. Subtle generalized cognitive deficits may be noted, and academic problems are common. Some research has suggested that there are associations of schizophrenia with obstetric complications or maternal influenza infection (particularly during the second trimester of gestation), but these findings are seldom of use in individual case diagnosis or prognosis, and it is likely that only a small

proportion of all cases may have neurodevelopmental disturbances caused by viral pathology (Torrey, Bartko, Lun, & Yolken, 2007). Great care should be exercised in the initial diagnosis of schizophrenia, however, to rule out possible associations with a broad range of systemic illnesses, because diseases affecting a diversity of organ systems can yield psychotic symptoms that may masquerade as schizophrenia. Diagnostic errors occur frequently in cases in which psychosis is caused by toxic–metabolic encephalopathies (including psychoses associated with drug or alcohol abuse) and delirium.

F. Sensory, Motor, and Other Physical Symptoms

Schizophrenia may involve a broad range of subtle deficits in sensory and motor functioning. Formal testing typically reveals "soft" sensory abnormalities; for example, on tests of double-simultaneous stimulation in auditory, visual, or tactile modalities, extinctions are often found, although these tend not to aggregate strongly to indicate lateralized deficits. Olfactory sensitivity, and particularly olfactory discrimination ability, may be compromised. Tests of motor speed and dexterity uniformly reveal slowing and discoordination, although these deficits are usually comparable in magnitude to the degree of generalized cognitive deficit observed on other formal tests of memory and executive function.

G. Electroencephalography and Neuroimaging Correlates

There are no pathognomonic signs of schizophrenia on electroencephalography (EEG) or neuroimaging, but there are clear abnormalities. Decreased magnitude of the P300 event-related potential is among the most consistent findings in schizophrenia research, and the frontal P300 may be particularly robust as a marker of genetic vulnerability to schizophrenia (Turetsky, Cannon, & Gur, 2000). Structural neuroimaging consistently has revealed increased ventricular size and increased sulcal CSF volumes, widespread decreases in the volumes of cortical gray matter, and decreases in the volume of the hippocampal formation, particularly in its anterior and middle lateral aspects (Narr et al., 2004). Several studies using diffusion tensor imaging suggest that there may be decreases in fractional anisotropy consistent with abnormalities in white matter structure. Functional magnetic resonance imaging (fMRI) has revealed both decreased activations in response to cognitive challenges, suggesting failure of patients to marshal appropriate neural systems, and increased activation thought, reflecting inefficiency of neural systems and thus

a need for excess recruitment (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Positron emission tomography (PET) imaging examining overall patterns of regional cerebral blood flow or cerebral metabolic rates during rest or cognitive activations has paralleled the findings from fMRI. PET imaging using specific ligands has suggested that there may be increased release of dopamine from presynaptic terminals in response to stimulant medications (Howes & Kapur, 2009). Unfortunately, none of these methods has yet led to enhanced diagnosis or treatment of schizophrenia.

III. NEUROPSYCHOLOGICAL EVALUATION

The neuropsychological examination of an individual with schizophrenia is usually most important for characterization rather than differential diagnostic purposes. The characterization of cognitive strengths and weaknesses may be particularly important for treatment and vocational planning. Because the average age of onset for schizophrenia is in late adolescence or early adulthood, assessment of an individual with schizophrenia of relatively recent onset often must consider educational planning as well. Given these goals, a broad assessment is typically warranted that takes into consideration general intellectual abilities and academic skills, along with more specific neuropsychological abilities that are frequently found to be impaired (e.g., learning–memory, executive, attentional, visuospatial, and psychomotor abilities; see Table 23.1).

The first aim of neuropsychological assessment in schizophrenia, as in assessment of other disorders, is to gain the fullest appreciation of the goals and current understanding of the patient, the family if involved, and the referral source. It is critical to determine the extent to which patient and caregivers are familiar with the disorder, its typical course, and its typical consequences. One of the greatest challenges in working with patients suffering an initial episode of schizophrenia is that they, and their families, often have enormous difficulty accepting the validity of the diagnosis and prognosis. History taking may most fruitfully adopt the perspective of schizophrenia as a neurodevelopmental disorder, and frequently findings include early signs of developmental delay in motor, cognitive, social, or academic skills. It is not uncommon, however, for subtle deficits to go unnoticed by family members, and a period of 1 to 2 years frequently elapses between the initial overt signs of psychosis and the time at which patients first come to clinical attention. It is also important to recognize that schizophrenia is a highly heritable disorder, with risk for first-degree family members that is

Table 23.1. MATRICS Battery for the Assessment of Cognitive Deficits in Schizophrenia

Domain	Test	Time estimate (min)
Speed of processing	Category fluency	2
	Brief Assessment of Cognition in Schizophrenia (BACS)—Symbol Coding	3
	Trail Making A	2.1
Attention/ vigilance	Continuous Performance Test—Identical Pairs (CPT–IP)	13.4
Working memory	University of Maryland—Letter–Number Span	5.9
	Wechsler Memory Scale (WMS)—III Spatial Span	5.1
Verbal learning	Hopkins Verbal Learning Test (HVLT)—Revised	4.1
Visual learning	Brief Visuospatial Memory Test (BVMT)—Revised	4.7
Reasoning and problem solving	Neuropsychological Assessment Battery (NAB)—Mazes	11.2
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)—Managing Emotions	12
Total time		63.5

approximately 10-fold that for unrelated individuals. Thus, a comprehensive family history is often useful both in modulating clinical confidence in the diagnosis itself and in gaining understanding of the family network within which the patient may continue to live and draw support (i.e., if the patient has a family member with schizophrenia, the likelihood that schizophrenia is the correct diagnosis is greater, and clinicians should be alert to possible psychopathology and cognitive weaknesses among family members). Even when overt signs of schizophrenia or other mental illness are not apparent in family members, they may nevertheless manifest cognitive impairment, and as noted below, studies of cognition in the undiagnosed first-degree family members of people with schizophrenia have revealed cognitive deficits that are intermediate between affected (diagnosed) and unrelated individuals.

The neuropsychological examination results themselves are most likely to show a pattern of generalized impairment across multiple cognitive domains, with most prominent deficits in verbal learning and memory, executive functions, and attentional functions, and relative sparing of basic reading–writing skills, vocabulary, and general information. On average, deficits range from one to two standard deviations below the appropriate norms for healthy individuals from similar sociocultural backgrounds. We have found that virtually all patients, including those with the least severe general cognitive deficits, tend to have relative weaknesses on tests of learning and memory, whereas patients with more severe global deficits tend to have additional relative impairments of executive functions (Bilder et al., 2000). It also should be recognized that more severe deficits in learning–memory, vigilance, and executive function have been linked to poorer performance on a variety of social, vocational, and rehabilitative outcome measures (Green, 1996; Green, Kern, Braff, & Mintz, 2000).

Even if an individual patient is not functioning in the impaired range on neuropsychological testing, that individual is very likely to have deficits relative to the levels that they likely would have achieved were it not for developing schizophrenia. For example, in studies of identical twins discordant for schizophrenia, the twin with schizophrenia almost always has lower cognitive functioning compared with their well co-twin, even though both twins may be functioning at above average levels (Goldberg et al., 1995). This discrepancy between expected performance and actual performance is often more disturbing to patients and their family members than the actual level of dysfunction.

A significant challenge for assessment and effective use of neuropsychological results is posed by difficulties that patients and their families may have in accepting the gravity of the prognosis. It is typical for individuals and their loved ones to be overwhelmed by a recent

diagnosis of this lifelong and disabling disorder, and particularly given the efficacy of current treatments against the most florid symptoms of the syndrome, they may feel, after initial treatment and resolution of these symptoms, that there is no need for continued treatment and no need to proceed conservatively with respect to reengaging in stressful activities. A strong psychoeducational approach should therefore be advocated to increase patient and family understanding of the risks of relapse following medication discontinuation (which are severe and well documented, with more than 50% of patients likely to relapse within the first year of discontinuation, a rate approximately threefold higher than those who remain in treatment), and the likely effects of stress on relapse (which are probably moderate, although documentation of this is less robust; Robinson et al., 1999, 2002). Other research has shown that patients who have lower estimated premorbid cognitive ability and poorer executive function are more likely to discontinue medication during maintenance treatment phases (Robinson et al., 2002), so these factors may alert the neuropsychologist to implement additional recommendations to assure adequate compliance with treatment.

A. Key Neuropsychological Measures Important to Differential Diagnosis

As noted earlier, the neuropsychological examination is often less critical to differential diagnosis of schizophrenia than it is for characterization of deficits and formulating treatment plans. In general, a broad neuropsychological battery that includes measures of general ability and provides adequate measurement of memory, attention, and executive functions will be most informative with respect to clinical decision making. Measures of basic academic achievement are often important to help make decisions about appropriate educational plans and to determine which basic skills for independent living are available and which may require support. It is usually critical to go beyond the psychometric assessment of cognition and achievement to evaluate other features important to the capacity for independent living, and some scales have been developed recently to determine what impact deficits in cognitive functioning may have on activities of daily living and social–vocational adjustment (e.g., Cognitive Assessment Interview; Ventura et al., 2013).

To the extent that differential diagnosis is important, the neuropsychological exam should include measures that can help rule out other focal disturbances of brain function. To the extent that this is important, more detailed assessment of lateralized sensory and motor functions is appropriate, and more detailed

language examination may help rule out variants of aphasia that may masquerade as "formal thought disorder" (e.g., jargon aphasia or the "word salad" seen in Wernicke's aphasia).

The NIMH awarded a contract to the University of California, Los Angeles (Steven Marder, principal investigator; Michael F. Green, coprincipal investigator) to generate a consensus neurocognitive test battery that could be useful for clinical trials of drugs that may benefit cognition in schizophrenia. This project, titled "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS), has generated a consensus about the cognitive domains that would be important to measure and determined which tests would be best to assess those domains. The final battery is listed in Table 23.1, and further details are available online at http://matricsinc.org/MCCB.htm.

This battery or similar alternatives would not be adequate to provide the kind of assessment that would be helpful in either differential diagnosis of schizophrenia or treatment planning, but it does provide a good summary of current cognitive functioning in an individual with an established diagnosis of schizophrenia and should serve well its intended goal—namely, to help clinicians document the effects of treatments (both psychopharmacological and rehabilitative or psychotherapeutic). One brief battery has been assembled specifically for the assessment of cognition in schizophrenia (Battery for the Assessment of Cognition in Schizophrenia [BACS]; Keefe et al., 2004), and other very brief selections of selected tests may explain most of the variance in much longer batteries (e.g., Brief Cognitive Assessment Tool for Schizophrenia; Hurford, Marder, Keefe, Reise, & Bilder, 2011).

Neuropsychologists should also be aware of more novel experimental and cognitive methods being developed for the assessment of schizophrenia. For example, following the MATRICS initiative, the NIMH sponsored the CNTRICS initiative (Cognitive Neuroscience Treatment Research to Enhance Cognition in Schizophrenia; see UC Regents, 2011b), which was then followed by the CNTRACS (Cognitive Neuroscience Test Reliability and Clinical applications for Schizophrenia Consortium; see UC Regents, 2011a). Although the tests developed in this work may not be immediately applicable to clinical practice, by following this work, the practitioner will learn more about current concepts regarding the most important and treatable cognitive deficits.

B. Psychological–Psychiatric Comorbidity

It is interesting that many comorbid psychological conditions considered by some scientists to be prevalent in schizophrenia are

typically ruled out by the current psychiatric nosology as manifest in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association, 2000). For example, depression, anxiety including prominent obsessive–compulsive or phobic components, and multiple personality disorders are unlikely to be diagnosed if the symptoms are "better accounted for" by the diagnosis of schizophrenia. Some specific personality disorders (schizoid, schizotypal, or paranoid) may presage the initial diagnosis of schizophrenia, but it remains unclear whether these are predisposing factors. It also remains unclear whether individuals who have the diagnosis of schizophrenia and who have comorbid mental disorder syndromes differ substantially from individuals who do not have these comorbid syndromes. Some have suggested that depression and obsessive–compulsive and panic disorders in schizophrenia are not only common but also important and independently treatable syndromes (Bermazohn et al., 2000).

A major problem in schizophrenia is posed by comorbid substance use disorders. Smoking is extremely prevalent in schizophrenia, is associated with smoking-related health disorders, and thus may be an important component of the overall reduced life expectancy associated with this disorder (acknowledging that the rate of suicide is also elevated in schizophrenia and contributes to decreased life expectancy). Alcohol and drug use disorders also frequently complicate the diagnosis and management of people with schizophrenia.

IV. TREATMENT, RECOMMENDATIONS, AND OTHER ISSUES

The medical management of schizophrenia almost always involves the use of antipsychotic drugs. The majority of patients today receive what are widely referred to as SGA drugs (including clozapine, risperidone, olanzapine, ziprasidone, quetiapine, and aripiprazole), whereas a substantial minority receive FGAs (including haloperidol, fluphenzaine, and perphenazine). All effective drugs tend to have activity as antagonists at the D2 dopamine receptor (Kapur & Seeman, 2001), and some theories explain both FGA and SGA potency via the qualities of binding at these receptors, whereas other theories differentiate the SGA by other properties (e.g., the degree to which they also affect serotonin or other receptor systems). The SGAs were earlier called atypical antipsychotics because they appeared to have lower liability for extrapyramidal side effects (primarily parkinsonian symptoms) compared with FGAs.

However, now the SGAs are not atypical and are receiving wide use. A large federally funded study, Clinical Antipsychotic Trials of Antipsychotic Effectiveness (CATIE), examined the effectiveness of multiple SGAs versus an FGA (perphenazine) and found very little difference between FGAs and SGAs. Olanzapine had slightly greater effectiveness but also caused major weight gain and other metabolic effects. However, publication of the CATIE results has not led to major shifts in prescribing practices, and current prescribing practices may be more closely related to minimizing possible adverse effects (e.g., weight gain) rather than perceived differences in efficacy (Berkowitz, Patel, Ni, Parks, & Docherty, 2012; Lewis & Lieberman, 2008).

The early research reports suggested that there may be cognitive benefits of treatment with atypical compared with conventional antipsychotic drugs. Recent evidence, including results from the CATIE study and another large-scale study in Europe known as the European First Episode Schizophrenia Trial (EUFEST), suggests that this benefit may be relatively modest, particularly when the atypical antipsychotic drugs are compared with lower doses of conventional agents (Davidson et al., 2009; Keefe et al., 2007).

Multiple new avenues for adjunctive treatment specifically to enhance cognitive functioning in schizophrenia are under development, although some already have been shown ineffective in clinical trials. There is continued interest in glycinergic modulation (although addition of glycine, D-cycloserine, and D-serine have so far not yielded replicable benefit, there have been some promising results from an agent that inhibits the glycine transporter), and there also has been continued interest in cholinergic modulation (although cholinesterase inhibition has shown minimal or no effect, there is other work involving more specific agents that modulate nicotinic cholinergic transmission). Other procognitive strategies are also being examined, including notably agents targeting various other serotonergic, cholinergic, glutamatergic, and GABA-ergic mechanisms.

Nonpharmacological treatments are also being actively pursued, with some researchers using cognitive–behavioral psychotherapy and others applying more specific cognitive remediation strategies similar to those used for patients following known neurological insults. Particularly exciting are recent results that follow from basic research on neuroplasticity and that suggest that intensive computerized training may yield normalizing effects on brain function, reality-monitoring disturbances, and social functioning that are sustained over at least 6 months following the end of treatment (Subramaniam et al., 2012).

So far, however, there is no widely accepted treatment path for enhancing cognitive function in people diagnosed with schizo-

phrenia, and individual design of treatment programs remains extremely difficult and largely limited by lack of adequate resources. The neuropsychological exam may benefit, however, from routinely checking several features of the current treatment algorithm for a given patient. First, it is well demonstrated that high levels of anticholinergic activity may have prominent adverse effects on learning–memory functions, and patients with schizophrenia, particularly those treated with conventional antipsychotic drugs, may receive anticholinergic treatments for control of parkinsonian signs (McGurk et al., 2004; Perlick, Stastny, Katz, Mayer, & Mattis, 1986; Strauss, Reynolds, Jayaram, & Tune, 1990; Tune, Strauss, Lew, Breitlinger, & Coyle, 1982).

Improvements in cognitive function can sometimes be affected by reducing the antiparkinsonian treatments (usually requiring a parallel dose reduction in the antipsychotic agent) or by reducing adjunctive benzodiazepine treatments. Some patients may also be receiving higher doses of conventional antipsychotic drugs than are warranted on clinical grounds (the tendency in some practice is to increase the dose if symptoms do not respond well, and this is sometimes done despite lack of significant improvement in symptom control). Many patients, particularly those with treatment-refractory symptoms, also receive multiple different antipsychotic agents or multiple antipsychotic agents in conjunction with mood stabilizers. Although some of these treatment regimens may be beneficial, their efficacy remains largely untested, and our clinical experience is that some patients show some improvement in cognitive function solely through simplification (elimination or reduction) of current pharmacological treatments. Of course, such treatment recommendations must be suggested and implemented only with the greatest caution and attention to the possible adverse impact of psychotic symptom relapse, along with consideration of the possibility for suicide or other adverse consequences.

V. CONCLUSION

This chapter presented an overview of the diagnosis, possible etiologies, and epidemiology of schizophrenia. Approaches to the classification of the range of clinical presentations for this disease were described, as were the neuroimaging and other neurological correlates. The chapter also discussed recent attempts to improve on the neuropsychological assessment of patients with schizophrenia (e.g., the MATRICS, CNTRICS, and CNTRACS initiatives), as well as the NIMH RDoC Initiative, and the range of currently available treatment options.

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Chapter 24

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Late-Life Depression

Following a brief description of the clinical features of late-life depression (LLD), this chapter (a) provides an overview of the neuropsychological features associated with LLD, (b) discusses the neurobiologic and physiologic correlates proposed to underlie these deficits, (c) considers the impact of various types of antidepressant treatments on neuropsychological performance, and (d) outlines the role of neuropsychological assessment in the diagnosis and treatment of LLD.

I. DEFINING LATE-LIFE DEPRESSION

A. Clinical Presentation

In general, *late-life depression* refers to the presence of a significant clinical depression, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM–5;* American Psychiatric

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Clinical Neuropsychology: A Pocket Handbook for Assessment, Third Edition, Michael W. Parsons and Thomas A. Hammeke (Editors)

Association, 2013) criteria, in individuals more than 60 years of age. Lifetime prevalence rates for major depression in this age cohort are estimated at approximately 10.6% in the United States (Kessler et al., 2005). The rates are higher among specific subpopulations, such as older adults who are hospitalized (10%–12%) or living in long-term-care facilities (12%–20%). Point prevalence rates in community dwelling adults are 1% to 4%, and similar rates have been consistently documented in several different countries (Beattie, Pachana, & Franklin, 2010). These rates rise even more substantially if subsyndromal or minor forms of depression are taken into account (17%–35%) and are also associated with functional impairment, chronic medical burden or aggravation of existing medical conditions, and lower quality of life. Indeed, estimates suggest that approximately one quarter of individuals who have experienced a myocardial infarction suffer from major depression, and an additional 25% suffer from minor depression (Alexopoulos, 2005; Lebowitz et al., 1997; Mulsant & Ganguli, 1999). Unlike midlife, during which women experience a much higher incidence of major depression compared with men, this gender difference is greatly reduced in later life (Steffens, Fisher, Langa, Potter, & Plassman, 2009).

From a diagnostic perspective, LLD is often underreported, underrecognized, misdiagnosed, and undertreated. Older adults with depression are more likely to endorse physical symptoms, such as lack of energy, anhedonia, appetite loss, and sleep disturbance, as well as psychomotor retardation and apathy (Alexopoulos, 2005; Jeste, Blazer, & First, 2005). These somatic complaints are less useful indicators of depression in older adults than in young adults, because they are often manifestations of the normal aging process and/or the comorbid illnesses so common in this population. Several measures of depressive symptoms for older patients, such as the Geriatric Depression Scale (GDS; Yesavage et al., 1982), have been developed to exclude questions pertaining to somatic complaints, focusing instead on the worries of the older adult and how they interpret their quality of life (O'Hara & Yesavage, 2002).

LLD is more chronic and can be more difficult to successfully treat (i.e., achieving and maintaining remission) than midlife depression, which is partly attributable to medical comorbidities, the presence of cognitive impairment or dementia, lack of social support, and poor self-rated health (Blazer, 2003). Major depression increases the mortality of associated medical comorbities and also is a major predictor of suicide in older adults, particularly among older men, who experience the highest suicide completion rate among all demographic groups. Because of its association with significant morbidity and mortality, the accurate diagnosis and treatment of LLD is extremely important.

Although researchers hypothesize that individuals with a later age-of-onset of the first lifetime depressive episode (referred to as *late-onset depression*) may have a different etiology or presentation from those with an earlier age-of-onset, LLD is typically defined as major depression during late life independent of age-of-onset, and this is the definition we use here. Nonetheless, where appropriate, we highlight recent research findings or etiological hypotheses regarding early-onset versus late-onset depression.

A key feature of LLD is the presence of cognitive complaints. Several studies have documented the presence of significant cognitive impairment in many of these patients, ranging from mild to more disabling levels of impairment. Between 20% and 50% of patients with LLD are estimated to have cognitive impairment greater than that observed in age- and education-equated controls (Butters et al., 2004; Sheline et al., 2006). Cognitive deficits in depressed older adults appear to have significant clinical consequences and have been associated with increased rates of relapse, disability, and poorer response to antidepressant treatment. Recent studies suggest that therapeutic approaches to LLD may partially ameliorate the cognitive deficits associated with this disorder—but much of the impairment persists after treatment (Bhalla et al., 2006, 2009; Butters et al., 2000)—and that LLD could be a risk factor for dementia (Butters et al., 2008; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). The persistent cognitive deficits in older depressed patients have led some researchers to suggest that LLD is a syndrome that is distinct from depression in younger patients, especially in those with late-onset depression (i.e., age > 60). Others argue that the cognitive impairments observed in many depressed patients are simply exacerbated with increasing age. These issues remain to be more fully elucidated, but overall the data suggest that appropriate neuropsychological characterization of patients with LLD may have significant implications for diagnosis, prognosis, and treatment.

B. Neuropsychological Features

Early studies on cognitive function in LLD were characterized by inconsistent and variable results, at least some of which were related to methodological differences across studies. Recent more methodologically robust studies have consistently documented cognitive deficits associated with LLD. For the purpose of this review, data are drawn largely from studies that focused on individuals with a clinical diagnosis of major depression, a comprehensive assessment of cognition, and a psychiatrically healthy comparison group. Several such studies have documented deficits in episodic memory, speed of

information processing, executive functioning, and visuospatial ability (see Herrmann, Goodwin, & Ebmeier, 2007, for a review). Deficits in speed of information processing and executive functioning appear to be particularly pertinent (Sexton et al., 2012). Three studies reported that slowed speed of information processing or working memory deficits appear to predominantly mediate the cognitive impairment associated with LLD (Butters et al., 2004; Nebes et al., 2000; Sheline et al., 2006).

A range of patient characteristics are associated with worse neuropsychological performance in LLD, including older age, later age of onset of depression, greater severity of depression, more medical comorbidity and presence of preexisting cognitive impairment (Reynolds, Alexopoulos, Katz, & Lebowitz, 2001).

The differentiation between cognitive functioning in those individuals with early-onset recurrent depression (EOD) versus late-onset depression (LOD) has been particularly salient in the literature, due in part to different proposed neurobiological etiologies (see below). In terms of an operational definition, there has been some variability, but LOD can generally be defined as depression developing for the first time after the age of 60. From a cognitive perspective, there has been some inconsistency with regard to whether EOD and LOD are associated with worse or different cognitive profiles. Some have characterized individuals with LOD as exhibiting disproportionate difficulties in aspects of executive functioning and speed of information processing (Herrmann et al., 2007). Some studies have found that EOD is associated with disproportionate episodic memory impairment relative to LOD (Rapp et al., 2005), but others have reported the opposite (Salloway et al., 1996). A recent meta-analysis found equivalent levels of memory impairment across the groups (Herrmann et al., 2007).

In terms of other demographic and clinical risk factors, Butters et al. (2004) reported that older age and worse baseline depression severity were associated with slower speed of information processing, but that education was protective. Overall medical burden was not associated with poorer cognitive functioning.

Several studies suggest that certain cognitive impairments are associated with negative clinical outcomes. Deficits in executive functioning have been associated with poor or delayed antidepressant treatment response and increased relapse and recurrence rates in some studies (Alexopoulos et al., 2000, 2005; Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004) but not others (Butters et al., 2004). Worse memory performance has been associated with increased risk of dementia and poorer antidepressant response. Overall, these studies suggest that patients with LLD who also exhibit executive dysfunction may be at particular risk for poor clinical outcomes.

C. Neuropsychological Functioning Following Treatment Response

There is also a growing literature showing that when cognitive impairment accompanied an episode of LLD, it tends to persist even after efficacious treatment of mood and that depression can increases the risk of cognitive decline and dementia in some individuals (Bhalla et al., 2000, 2006, 2009; Lee, Ogle, & Sapolsky, 2002; Murphy & Alexopoulos, 2004; Nebes et al., 2003). Last, although some cognitive improvement has been noted immediately following depression treatment, certain risk factors, including lower baseline cognitive levels, older age, later age-of-onset, and greater vascular burden, are associated with less cognitive improvement (Barch et al., 2012).

D. Neurobiologic Basis of LLD

Several recent studies have highlighted structural and functional brain abnormalities that are associated with LLD. Findings from structural magnetic resonance imaging (MRI) studies, diffusion tensor imaging studies, and magnetic resonance spectroscopy studies suggest that LLD is associated with both gray and white matter structural brain changes. Some of this evidence is reviewed below. For more extensive reviews on the subject, readers are referred to recently published reviews (Andreescu & Aizenstein, 2012; Disabato & Sheline, 2012; Sexton et al., 2012).

1. REDUCED FRONTAL AND HIPPOCAMPAL VOLUME

Several structural MRI studies have documented the presence of greater gray matter structural changes in individuals with LLD relative to comparison subjects. Structures within the frontal-limbic pathway, including the orbitofrontal cortex, gyrus rectus, and anterior cingluate cortex (Ballmaier et al., 2004; Kumar, Bilker, Lavretsky, & Gottlieb, 2000; Lai, Payne, Byrum, Steffens, & Krishnan, 2000; Lee et al., 2002); parts of the basal ganglia, including the putamen (Tupler et al., 2002) and caudate (Butters et al., 2009); the amygdala (e.g., Burke et al., 2011); and the hippocampus (e.g., O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004), are frequently affected in LLD, both in those with EOD and LOD. Studies have also suggested that hippocampal volume is reduced in LLD (Andreescu et al., 2008; Steffens et al., 2000) and is inversely related to the duration during which depressive episodes went untreated with antidepressant medication (Sheline, Gado, & Kraemer, 2003) and the lifetime duration of depression (e.g., Bell-McGinty et al., 2002). One potential explanation for this association is that the reductions in hippocampal

volume accrue over time from depression-associated hypothalamic–pituitary–adrenal (HPA) axis dysfunction. Reduced hippocampal volume in LLD also seems to be associated with LOD (Steffens et al., 2000) and also to future dementia diagnosis (Steffens, Bosworth, Provenzale, & MacFall, 2002).

Gray matter brain changes might also be associated with poor treatment in LLD, although this relationship needs further elucidation. Both reduced anterior cingulate (Gunning et al., 2009) and reduced hippocampal volume (Hsieh et al., 2002) have been associated with poor short-term treatment response in some studies but not others (Janssen et al., 2007).

2. WHITE MATTER HYPERINTENSITIES

White matter hyperintensities are a proxy for ischemic small vessel disease. Periventricular and deep subcortical white matter changes have been documented in LLD, as well as decreased fractional anisotropy in prefrontal white matter, and may be especially common in LOD (Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Salloway et al., 1996; Sheline et al., 2008; Taylor et al., 2004). Increased presence of deep white matter lesions in LLD have been associated with increased mortality (Levy et al., 2003), poorer treatment response (e.g., Alexopoulos et al., 2008; Sheline et al., 2010), inability to sustain remission (Taylor et al., 2003), and impairments in motivation, concentration, and other cognitive abilities (Nebes et al., 2001, 2002). Others have found that white matter hyperintensity burden is not associated with treatment response (e.g., Salloway et al., 2002). The colocalization of atrophy and white matter lesions, the fact that both relate to advanced age and to factors predisposing to vascular disease, and the similarity of the location of lesions in poststroke depression has led to the hypothesis that in some older adults LLD constitutes a distinct syndrome, with a vascular component underlying both the depressed mood and the cognitive impairments (Drevets, 1994). A recent meta-analysis found that LLD and, to a greater extent, LOD, were characterized by more frequent and intense white matter abnormalities (Herrmann, Le Masurier, & Ebmeier, 2008).

3. VASCULAR DEPRESSION HYPOTHESIS

As highlighted above, the role of vascular risk factors in the etiology and persistence of LLD, and LOD depression in particular, has been well documented (e.g., Sheline et al., 2010). In 1997, Alexopoulos and colleagues postulated the vascular depression hypothesis, which proposed that cerebrovascular disease was implicated in the predisposition, development, and maintenance of depressive symptoms in older adults.

The depression–executive dysfunction (DED) syndrome of late life (Alexopoulos, 2001) argues that frontostriatal dysfunction contributes both to the development of LLD and to the executive dysfunction that frequently accompanies LLD and that it might be associated with poor treatment response. Some (e.g., Alexopoulos et al., 2005; Potter et al., 2004) but not all studies (Butters et al., 2004) have found that executive dysfunction is associated with poorer antidepressant treatment response. Nonetheless, vascular depression is purported to be directly related to cerebrovascular disease and is considered different from other causes of depression. By contrast, the DED syndrome is only partially etiologically related to vascular disease, with additional contribution from age-related cognitive changes, degenerative brain changes, or a combination of these factors (Alexopoulos, 2006).

The vascular depression model attempts to explain the development and persistence of not only mood but also cognitive symptoms in LLD. Several other proposed mechanisms and pathways for persistent cognitive impairment in LLD have been postulated, particularly in the context of mechanisms that may underlie the elevated risk for dementia borne by individuals who experience LLD (e.g., Butters et al., 2008; Byers & Yaffe, 2011).

4. FUNCTIONAL IMAGING STUDIES

Similar to structural imaging studies, many functional imaging studies, including blood oxygen level-dependent functional MRI, single-photon emission computerized tomography, and positron emission tomography studies have documented functional differences in activity between individuals with LLD and comparison subjects. These include reduced regional and global cerebral blood flow and decreased activation in the prefrontal cortex, the anterior cingulate cortex, and hippocampus (see Andreescu & Aizenstein, 2012, for a review). One study suggested that there might be both state-related (which improved following 12 weeks of treatment with paroxetine) and more stable, persistent changes in the executive-control circuit of individuals with LLD, which could have an effect on vulnerability for recurrence of depressive episodes (Aizenstein et al., 2005). One more recent study reported that there is altered default mode connectivity in LLD and highlighted the role of vascular changes in the etiology of LLD (Wu et al., 2011).

5. THE ROLE OF NEUROTRANSMITTER DEFICITS

Deficits in serotonin, dopamine, norepinephrine, and the cholinergic system have not only been implicated in depression but also are associated with age-related changes in cognitive function. A further review of this data is beyond the scope of this chapter, but the

reader is referred to the following studies for additional information (Meltzer et al., 1999; Nobler, Pelton, & Sackeim, 1999).

E. LLD as a Risk Factor for Dementia

LLD is associated with cognitive impairment and neuropathologic brain changes in some individuals. There is growing literature suggesting that LLD is associated with an increased risk of dementia.

1. STUDIES AND REVIEWS

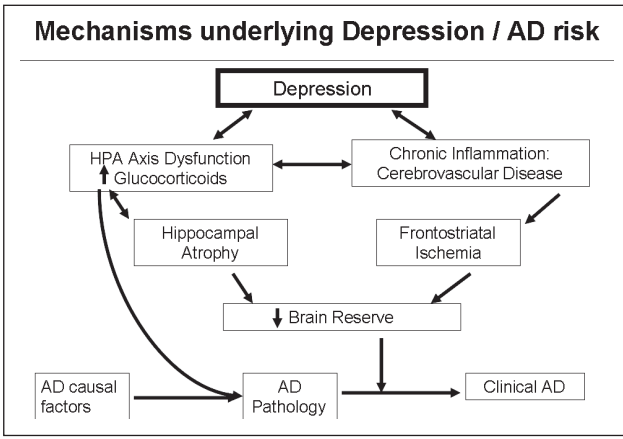
Data from recent epidemiologic studies suggest that LLD is associated with an approximately 50% increased likelihood of developing dementia in general (Diniz et al., 2013; Ownby et al., 2006), including both Alzheimer's disease (AD; Green et al., 2003; Ownby et al., 2006) and vascular dementia (Diniz et al., 2013). Another epidemiologic study highlighted that baseline depressive symptoms independently predicted a subsequent diagnosis of mild cognitive impairment (MCI) 6 years later (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006). Longitudinal data from the Women's Health and Aging Study similarly showed that baseline depressive symptoms predicted subsequent cognitive decline (Rosenberg, Mielke, Xue, & Carlson, 2010). Other studies have reported that either a remote history or number of past depressive episodes appears to increase the likelihood of later developing dementia (Green et al., 2003). By contrast, some epidemiologic studies have not found an association between depression in late life and subsequent development of dementia (Becker et al., 2009; Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Lindsay et al., 2002).

A recent review examining the 16 studies published since 2000 examining the association between dementia and depression concluded that EOD appears to be associated with a greater than twofold increase in dementia risk (Byers & Yaffe, 2011). Further, LOD also appears to be associated with an increased risk of developing dementia, although the data are less clear in this regard. This lack of clarity is related in part to the challenges in clearly elucidating whether LOD is truly a risk factor for dementia, a symptom of a prodromal dementia, or the consequence of an already present dementia. Level of depression severity, gender, educational level, and apolipoprotein E e4 status are potentially important factors that could be related to dementia risk.

2. PROPOSED MECHANISMS

A proposed mechanism (see Butters et al., 2008) for how depression might increase the risk for AD is presented below (see Figure 24.1). This model is based on findings that LLD is associated

Figure 24.1. A proposed mechanism for how depression might increase the risk for Alzheimer's disease (AD).



Note. From "Pathways Linking Late-Life Depression to Persistent Cognitive Impairment and Dementia," by M. A. Butters et al., 2008, *Dialogues in Clinical Neuroscience*, 10, pp. 347. Copyright 2008 by Les Laboratoires Servier. Reprinted with permission.

with both chronic elevation of adrenal glucocorticoid production and cerebrovascular disease. Together, these factors may lead to hippocampal atrophy and generalized ischemia; generalized ischemia often has a predilection for frontostriatal regions, leading to abnormalities that could also serve to maintain or cause subsequent depressive episodes. These factors likely also lower brain reserve, which, in addition to other preexisting AD casual risk factors, can hasten the progression of underlying AD pathology to clinical manifestation of AD. Brain/cognitive reserve is a key mechanism in this model (Stern, 2002). In addition to other processes, depression further injures neurons, which further lowers reserve, resulting in earlier and/or more frequent expression of progressive loss and dementia. In this model, it is the differing individual thresholds of reserve that can account for variability in the rate of expression of cognitive impairment or dementia. For additional supporting literature on the biological relationships between depression and AD,

including the role of glucocorticoids, the HPA axis, and cerebrovascular disease, see Butters et al. (2008).

II. NEUROPSYCHOLOGICAL ASSESSMENT AND ANTIDEPRESSANT TREATMENT

A. Antidepressant Medications

Recent studies investigating the relationship of treatment to cognitive performance in LLD have yielded promising but varied results. Complexities of depression as a syndrome, the variability among the methodologies and measures used, and the different antidepressant treatments studied have all contributed to the inconsistent findings across studies. Overall, findings suggest that impaired cognitive function improves with treatment in a subset of LLD subjects (e.g., Doraiswamy et al., 2003), but a significant a proportion of individuals with LLD have cognitive deficits that are unaffected by improved mood (see above).

Some antidepressant medications may impair cognition, particularly in older adults. Tricyclic antidepressants (TCAs), for example, have anticholinergic properties that may cause cognitive dysfunction (especially memory impairment), delirium, constipation, dry mouth, blurred vision, and increased intraocular pressure. Several reviews suggest that in spite of their efficacy in the treatment of LLD, TCAs—especially amitriptyline, desipramine, imipramine, and fortryptiline—have so many undesirable effects that their value in the treatment of older adults is limited (e.g., Amado-Boccara, Gougoulis, Poirier Littré, Galinowski, & Lôo, 1995; Ellsworth, Witt, Dugdale, & Oliver, 2003; Fotuhi, 2006). However, even among the selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, certain antidepressant treatments, such as Paxil (paroxetine) and Lexapro (escitalopram), have been observed to result in impairments in memory and visuospatial ability (Ellsworth et al., 2003). Other recent studies have reported that antidepressant use is not associated with poorer cognitive performance (assessed by the Mini Mental State Examination; Folstein, Folstein, & McHugh, 1975) in LLD and may be related to slightly improved cognitive scores in those with minor depression (Han, McCusker, Cole, Capek, & Abrahamowicz, 2011). In general, antidepressants with anticholinergic, sedative, or orthostatic side effects should not be a first choice for older depressed patients, in part because of their negative impact on cognitive functioning. Those with possible anticholinergic side effects include amitriptyline, bupropion, desipramine, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, and

venlafaxine. Some researchers suggest that the presence of white matter hyperintensities may put a patient with LLD at increased risk for developing delirium or cognitive disorders after treatment with TCAs or electroconvulsive therapy (Drevets, 1994).

In conclusion, studies to date indicate a modest effect of antidepressant treatments on cognitive deficits associated with LLD. Even modest improvements in cognitive function may have functional benefits.

B. Psychotherapy

Psychotherapy aimed at depressive ideation and rehabilitation efforts focused on instrumental activities of daily living (IADLs) might improve the outcome of geriatric depression (Alexopoulos et al., 1996). Impairment in IADLs is associated with advanced age, severity of depression, and medical burden. Anxiety and depressive ideation, as well as psychomotor retardation and weight loss, are also associated with impairment in IADLs. However, application of these techniques may be very difficult. Patients with severe neurocognitive disorder, psychomotor retardation, or sensory impairment (making communication difficult) are not capable of entering into demanding psychotherapeutic procedures. Severe symptoms due to general medical condition, such as physiological instability, may also restrict the therapeutic maneuvers or significantly delay the process. Problem-solving therapy is an efficacious psychotherapeutic intervention that teaches individuals to mobilize their coping resources by systematically approaching self-identified problems and exerting control over them (Arean et al., 1993). Because problem-solving therapy teaches problem-solving skills, it is particularly appropriate for individuals with cognitive impairment. Alexopoulos (2003) and Alexopoulos et al. (2008) reported that modified problem-solving therapy improved problem-solving skills, depression, and disability in individuals with LLD–executive dysfunction syndrome. There also is evidence that intensive integrated pharmacotherapy with psychotherapy may be more effective than usual standard treatment (Unützer et al., 2002).

C. Electroconvulsive Therapy

In cases where pharmacotherapies have not provided relief, electroconvulsive therapy (ECT) is generally considered safe and is preferable to withholding treatment. ECT is recommended for geriatric depression, according to the directives of the American Psychiatric Association (Sackeim, 1994). It might be particularly useful in managing suicidal ideation in older depressed adults as well as psychotic

depression (Dombrovski & Mulsant, 2007). The greatest risk is for patients who have had a stroke, and ECT is not recommended for such patients until 6 months after the stroke. There is a body of literature documenting cognitive impairment, particularly in retrograde memory, both during the course of and following ECT treatment, but others have suggested that there is no long-term impairment in anterograde amnesia or reasoning; more objective data are needed. The reader is referred to an article by Dombrovski and Mulsant (2007) for a review on ECT treatment for severe LLD and associated cognitive consequences. There are additional, cutting edge neuromodulatory interventions for treatment-resistant depression in various stages of development and study; see the recent review by Moreines, McClintock, and Holtzheimer (2011) for preliminary data on their neuropsychological effects.

D. Cognitive Augmentation

As a result of the persistent cognitive impairments in LLD and their association with poorer clinical outcomes, some investigators have suggested that both pharmacological and nonpharmacological augmentation strategies may prove useful for ameliorating the cognitive deficits in LLD (Fava, Ruini, & Sonino, 2003). In this regard, pharmacologic augmentation with agents such as the cholinesterase inhibitors might be more helpful in LLD, particularly in those with cognitive impairment, but it does not appear to have a benefit for cognitively normal LLD patients (Reynolds et al., 2011).

Augmentation strategies might also include memory or cognitive training aimed at enhancing cognitive performance. Some investigators have argued that the effortful processing necessary to implement cognitive training strategies may be particularly impaired in depressed older adults (e.g., Taconnat et al., 2010), but others have suggested that "external" memory strategies are less effortful than "internal" strategies and are among the easiest memory techniques to use, can help with organization and self-confidence fairly quickly (decreasing minor memory lapses), and are therefore important for care providers, patients, and families to learn about (Scogin & Prohaska, 1993).

External strategies involve the use of physical reminders in one's environment that are prearranged to serve as automatic reminders of what need to be recalled. Three types of physical reminders in particular are recommended (Scogin & Prohaska, 1993):

1. Immediately writing things down on a pad, in a "memory" notebook, in a calendar, on a checklist, in an electronic organizer, or on Post-its. Additional external reminders for help with immediate recall also include watches that

state the time at the push of a button and/or buzz at preset times, digital voice recorders, and sounding devices.
2. Placing reminders in prominent places that are in one's line of sight (e.g., the bathroom mirror, the refrigerator, the back door, next to one's wallet).
3. Associating objects (that are used and lost frequently) with preestablished locations. This helps with objects such as keys, wallets, glasses, and even gifts for family members. The idea here is to first make a list of objects that are frequently misplaced; second, choose a familiar location for each object; and third, practice putting the objects *only* in their designated location.

Specific descriptions of how to teach both external and/or internal strategies to older adults are included in many books and articles in the literature. A few (but certainly not all) are included here for the reader's use: Nelson (2005), *The Harvard Medical School Guide to Achieving Optimal Memory;* Crook and Allison (1992), *How To Remember Names;* Hill, Beckman, and Neely (2000), *Cognitive Rehabilitation in Old Age;* and Scogin & Prohaska (1993), *Aiding Older Adults With Memory Complaints*.

In conclusion, it is important to note that a comprehensive treatment approach to LLD, combining pharmacologic and psychologic interventions and social support, can achieve a response rate of up to 90% (Gottfries, 2001).

III. NEUROPSYCHOLOGICAL ASSESSMENT OF PATIENTS WITH LLD

A. Clinical Assessment of Depression in Older Adults

Depression commonly accompanies both AD (the most common dementia) and MCI. According to the recent literature, between 20% and 50% of both AD patients (Holtzer et al., 2005; Starkstein, Mizrahi, & Power, 2008) and MCI patients report depressive features (Feldman et al., 2004; Lyketsos & Olin, 2002).

For geriatric neuropsychologists, memory problems represent the most common presenting complaint. However, memory problems are not restricted to purely cognitive disorders but are also commonly seen in LLD. As a result, clarifying whether cognitive deficits are attributable to (a) dementia or MCI, to (b) "pure" depression, or to (c) both, is one of the most frequent referral questions in geriatric neuropsychology (Twamley & Bondi, 2004).

Moreover, there is a growing literature suggesting that cognitive impairment that accompanies depression tends to persist in a subset of individuals following depression remission (Basso, Miller, Estevis, & Combs, 2013). Patients with significant cognitive impairment *and* affective disturbance might therefore have two co-occurring (and potentially etiologically related) disorders: depression and a neurodegenerative disorder. Given these points, the traditional "depression versus dementia" conundrum has become something of a false dichotomy. Nevertheless, when conducting a neuropsychological evaluation of an older adult, both depression and cognitive function should be assessed.

Differentiating depression and dementia is complicated by symptom overlap—for example, changes in attention/concentration, memory, behavior, sleep patterns, and energy level (Twamley & Bondi, 2004). For this reason, it is important to use measures with established validity and reliability in assessing depression in older adults and in assessing those who have cognitive impairment in particular.

1. SELF-REPORT CHECKLIST MEASURES

Multiple measures are available for the detection of depression in older adults. The focus of research over the past two decades has centered on the utility of brief self-report checklist measures. There is broad consensus in the literature (Kaszniak & Scogin, 1995; Lichtenberg, 1994; Scogin, 1994) that two measures are particularly useful clinically: the Beck Depression Inventory (BDI/BDI–II; Beck, 1987) and the Geriatric Depression Scale (GDS; Yesavage et al., 1982). Both are brief (5–10 minutes) and easily scored.

2. THE GDS

The GDS was developed using a sample of older adults and is the easiest measure to administer, especially with patients who have cognitive impairments (Yesavage et al., 1982). The long form (30 items) has the best combined sensitivity and specificity for outpatients older than age 55 (e.g., 96% using a cutoff of 10; Olin, Schneider, Eaton, Zemansky, & Pollack, 1992), although a short form (15 items) is also available. One shortcoming is that high-functioning patients often find the yes/no format too limiting. Notably, somatic symptoms are not included on the GDS as they were found to be not diagnostic of LLD.

3. THE BDI (NOW THE BDI–II)

The BDI was developed on a younger sample but has been used widely with older adults by both researchers and clinicians. However,

the rating system is often too complex for use with patients who are cognitively compromised. Importantly, Items 15 through 21 involve somatic symptoms that have been found typical of normal aging rather than indicative of geriatric depression per se (Bolla-Wilson & Blecker, 1989). These researchers have suggested using only Items 1 through 14 with older adults, with a cutoff score of 5. An excellent review of the strengths and weaknesses of the GDS, BDI, and other checklist measures may be found in Scogin (1994).

One caveat with regard to the use of these checklist measures is that they only reflect as much as a patient is willing to divulge. Another limitation is that they are reportedly not effective in identifying either dysthymia or a lifetime history of depression (Scogin, 1994). They are best used as guides for further assessment that ideally includes an in-depth clinical interview, use of an interview-based assessment measure, collateral information (including use of an observational rating scale such as the Cornell Scale For Depression In Dementia; Alexopoulos, Abrams, Young, & Shamoian, 1988, described below), and/or additional testing with actuarial measures such as the restandardized Minnesota Multiphasic Personality Inventory (MMPI–2; Butcher, Dahlstrom, Graham, Tellegan, & Kasmmer, 1989) and Millon Clinical Multiaxial Inventory—III (MCMI–III; Millon, 1993) that have validity and/or specific scales reflecting depressive tendencies.

4. INTERVIEW-BASED MEASURES

Many interview-based measures are available. Two well-known structured measures are based on criteria of the *Diagnostic and Statistical Manual, Fourth Edition* (*DSM–IV;* American Psychiatric Association, 1994): the Structured Clinical Interview for *DSM–IV* (SCID; Spitzer, Williams, Gibbon, & First, 1990) and the Diagnostic Interview Schedule (Robins & Helzer, 1985). Their primary drawback is administration time.

One interview-based measure that has been noted in the literature as both economical and useful in (a) estimating severity of depression over time and (b) assessing cognitively impaired or hospitalized patients is the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). It also emphasizes somatic symptoms (that have been found more typical of normal aging than diagnostic of LLD). However, it takes a lot of practice and effort to administer the HRSD reliably (although the 17-item version is easier to administer). Some clinicians screen initially with one of the checklist measures. If a patient scores above the cutoff, the HRSD can then be used to confirm/provide a quantitative severity rating.

5. COLLATERAL INFORMATION

Collateral information should be included in the assessment process whenever possible. This ideally includes information from

family and/or health care providers relevant to (a) the course and history of symptoms; (b) daily functioning; (c) the medical, psychiatric, and neurologic history; and (d) recent imaging studies. In the case of patients for whom self-report is not feasible because of cognitive impairment or hospitalization, there are observational measures for care providers that target depressive symptoms in particular. One such measure is the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos et al., 1988). The CSDD asks caregivers to rate symptoms in the following areas: mood, behavioral disturbance, somatic signs, cyclic functions, and ideation (suicidality, self-esteem, pessimism, and delusions). A proviso noted in the literature (La Rue, Watson, & Plotkin, 1992) is that lay caregivers such as relatives (and especially relatives who themselves are depressed or anxious) tend to overrate patients in estimating mood and/or affective symptoms compared with professional caregivers, such as nursing staff.

6. ACTUARIAL MEASURES

The MMPI–2 (Butcher et al., 1989) has been widely used with older adults and has specific scales and subscales reflecting depressive tendencies: for example, the D Scale, Subtle and Obvious measures, Harris-Lingoes Scales, and the Content Scales. These scales facilitate differential diagnostic considerations that the briefer screens do not provide. However, for cognitively impaired and/or hospitalized older adults, administration of the MMPI–2 is not feasible. One alternative is to administer only the first 370 items, which contain Scales 1–10, the Obvious/Subtle Items, and the Harris-Lingoes Subscales. In this regard it should be noted that even if the D Scale is normal, the Obvious/Subtle items are important because the "subtle" items reflect the vegetative signs of depression that tend to be endorsed by more mildly depressed individuals, whereas severely depressed patients tend to endorse the "obvious" items.

7. THE PERSONALITY ASSESSMENT INVENTORY

The Personality Assessment Inventory (PAI) is a 344-item inventory that is composed of 22 nonoverlapping full scales and 11 clinical scales, as well as a number of validity scales (Morey, 2007). Specific subscales assess cognitive, affective, and physiological symptoms of depression, and several anxiety symptoms, as well as somatic complaints.

8. THE MCMI–III

The MCMI–III contains both depression and dysthymia subscales, can be answered in about 30 minutes, and is more easily administered to older patients (Millon, 1993). However, its strength is with Axis II rather than with Axis I diagnoses. Depending on the

older adult in question, administration of the MCMI–III may not be realistic.

B. Clinical Assessment of Cognitive Domains in LLD

Neuropsychological test findings in LLD suggest that speed of information processing and executive functioning are especially important to assess. Findings also suggest that patients with LOD can perform more poorly in these specific areas than those with EOD (Herrmann et al., 2007). Nonetheless, a thorough assessment of multiple cognitive domains is recommended. Table 24.1 contains cognitive domains and suggested measures for use in the assessment

Table 24.1. Neuropsychological Assessment of Late-Life Depression by Cognitive Domain

Cognitive domain	Tests suggested for clinical use
Attention/working memory	CVLT–II, Trial I D-KEFS Color-Word Interference Test Trail Making Test: Part A or Conditions 2 and 3, D-KEFS WAIS–IV: Digit Span, Coding, Letter-Number Sequencing WMS–IV: Digit Span, Spatial Addition, Symbol Span RBANS Attention Scale Stroop Color–Word Test
Visuospatial skills	BVRT, BVMT–R, or LMII Copy Clock Drawing or CLOX 1 and 2 Judgment of Line Orientation Rey Complex Figure Test-copy WAIS–IV or WASI–II: Block Design, Visual Puzzles, Matrix Reasoning RBANS Visuospatial/Construction Scale
Language (verbal fluency in particular)	D-KEFS Verbal Fluency Test: letter vs. category fluency Boston Naming Test NAB Naming Test Form I or II Token Test RBANS Language Scale

Table 24.1. Neuropsychological Assessment of Late-Life Depression by Cognitive Domain *(Continued)*

Cognitive domain	Tests suggested for clinical use
Memory (recall and recognition)	CVLT–II Regular or Short Form Hopkins Verbal Learning Test WMS–IV: Visual Reproduction I and II, Logical Memory I and II BVRT (Memory and Copy) BVMT–R (Memory and Copy) RBANS Immediate and Delayed Memory Scales
Executive functions (verbal fluency measures are especially sensitive)	DKEFS: Verbal Fluency Test, Color–Word Interference Test, Tower Test, Trail Making Test Stroop Color–Word Test Trail Making Parts A and B Wisconsin Card Sorting Test
Psychomotor speed	D-KEFS: Trail Making Test (Condition 5) Symbol Digit Modalities or WAIS–IV Coding Grooved Pegboard
Mood and anxiety	Beck Depression Inventory–II Cornell Scale for Depression in Dementia Geriatric Depression Scale Beck Anxiety Inventory Geriatric Anxiety Inventory State Trait Anxiety Inventory

of individuals with LLD. The list is by no means exhaustive, but the measures presented are normed, standardized, reliable, and valid for use with older adults.

C. Differential Diagnosis

As noted earlier, the overlap in symptoms as well as the comorbidity of dementia and depression can make differential diagnosis challenging. Nevertheless, the neuropsychological literature (Basso et al., 2013; Kaszniak & Christenson, 1994; Kaszniak & Scogin, 1995; Nussbaum, 1998) has delineated differences in (a) clinical course

and history, (b) clinical behavior, and/or (c) test findings, which can help in differential diagnosis of relatively pure cases of depression or dementia. Table 24.2 is taken directly from the literature, with updated modifications, because of its utility in differentiating between dementia (AD in particular) and depression.

1. ALZHEIMER'S DISEASE

In terms of differential diagnosis, LLD patients often show mild-to-moderate impairment in free recall on list-learning tasks, but a disproportionate improvement on recognition recall, with normal or slightly elevated false positives. They also benefit from cueing and

Table 24.2. Differential Diagnosis of Dementia and Depression

	Depression	Dementia
Clinical course and history	Onset well demarcated	Onset indistinct, insidious
	History short	History long
	Rapidly progressive course	Slow course; early deficits often missed
	Prior psychiatric history or recent crisis	Prior psychiatric history uncommon
Clinical behavior	Detailed complaints of cognitive dysfunction, especially memory	Complaints of cognitive loss uncommon
	Put out little effort	Struggle with tasks but tries
	Persistent depression	Apathy with shallow emotions
	Hyperawareness of deficit	Diminshed awareness of deficit
	Self-appraisal diminished	Self-appraisal variable
	Mood congruent delusions	Mood independent delusions
	Dressing apraxia rare	Dressing apraxia common

Table 24.2. Differential Diagnosis of Dementia and Depression *(Continued)*

	Depression	Dementia
Test findings		
—Free recall	Often impaired	Impaired
—Learning curve	Reduced; U-shaped	Flat
—Don't know errors	Usual	Unusual
—Perseveration errors	Uncommon	Common
—Recognition memory	Relatively intact	Impaired
—False-positive errors	Uncommon	Common
—Performance on tasks of similar difficulty	Variable	Constant
—Rate of forgetting	Relatively normal	Rapid
—Executive functions: verbal fluency measures	Semantic fluency more impaired than phonemic fluency	Semantic fluency more impaired than phonemic fluency
—Speed of processing	Often impaired	Impaired
—Intellect, language, and visuospatial skills	Infrequently impaired	Impaired

Note. Sources for this table include Storandt and VandenBos (1994), Snyder and Nussbaum (1998), and Arnett (2013).

show a low intrusion rate (in the normal range). In contrast, AD patients show a rapid forgetting rate, highly elevated false-positive errors on recognition testing, and a high rate of intrusions, with particular elevations on cued trials.

2. SUBCORTICAL DEMENTIA

A leading source of misdiagnosis in distinguishing between patients with LLD and subcortical dementia is their similar pattern of

performance on some cognitive tests: For example, both show a relative sparing on tasks of recognition memory, naming, and visual perception (Welsh-Bohmer, 2001). Also, in cases of subcortical dementia, psychomotor retardation often leads to the misdiagnosis of depression, and these realities point to the importance of including measures of mood in any neuropsychological battery of older adults. It should also be noted that individuals with subcortical disorders manifest (and/or report) depression more often than individuals with cortical disorders. This may be partly due to the increased insight that subcortical patients have about their condition compared with that of AD patients (Huber & Paulson, 1985). It may also be due to what Steffens, Taylor, and Krishnan (2003, p. 1754) described as the "intertwining course" of LLD and cognitive deficits in subcortical ischemic disease.

3. ANXIETY AND OTHER PSYCHIATRIC ILLNESSES

About 38% to 58% (Alexopoulos, 1991) of older adults with major depression also fulfill *DSM–IV* criteria for an anxiety disorder. Anxiety in late life can also be associated with cognitive impairment (see Beaudreau & O'Hara, 2008; Butters et al., 2011). It is helpful to screen for anxiety as well as for depression in order to provide complete information to patients, families, and referring care providers. In this regard, three checklist measures—the BAI, the Geriatric Anxiety Inventory (GAI; Pachana et al., 2007), and the State Trait Anxiety Inventory (STAI: Spielberger, Gorush, & Lushene, 1970)—are brief and easy to administer to older adults and provide a measure of self-perceived anxiety. The GAI was validated with older populations and is specifically targeted at older adults.

4. COMORBID ILLNESSES

There are several diseases that may have depressive or depressive-like symptoms as their only early manifestations, including (a) endocrine disorders such as diabetes, hypothyroidism, and hypo/hyperparathyroidism; (b) cancers (especially pancreatic cancer); (c) metabolic disorders such as problems with calcium metabolism; (d) subcortical neurologic disorders such as multiple sclerosis (which can exacerbate depression) and early HIV encephalopathy; and (e) menopause. In most cases it is not depressed affect, but feelings of indifference, apathy, or fatigue that are experienced. The presence of medical conditions that mimic depression must also be ruled out before any psychiatric or cognitive diagnosis can be conferred.

It is also important to be aware of the high comorbid prevalence rates of major depression in medical disorders, including diabetes,

cerebrovascular disease, chronic pulmonary disease, rheumatoid arthritis, and myocardial infarction in older adults (Watkins et al., 2003). Depression screening is especially important as depression is often underrecognized, and therefore undertreated, in these patients.

5. OTHER CONSIDERATIONS

Alcohol or drug dependence can trigger or exacerbate depression and possibly increase the risk that it will become refractory. Therefore, it is also important to question patients and/or caregivers regarding substance use history. There are also two brief screens for alcoholism available for use with older adults: the CAGE questionnaire (with CAGE being a mnemonic for four questions about alcohol use; Fleming, Evans, Weber, & Chulka, 1995) and the Michigan Alcohol Screening Test (Selzer, 1971).

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Chapter 25

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Neuropsychology of Illicit Drug Use and Impulse Control Disorders

A rapidly growing literature shows unexpected and important similarities between substance use and impulse control disorders. The sections in this chapter summarize the cognitive impairment and neuroimaging findings in persons with these disorders. Specifically, this chapter first discusses the prevalence and diagnostic systems for illicit drug use and abuse and then reviews the neurocognitive effects of the most commonly abused illicit drugs, including cannabis, cocaine, amphetamines and methylendioxymethamphetamine (MDMA), opioids, benzodiazepines, and polysubstance abuse. The effects of alcohol are not discussed, as this topic is addressed in Chapter 16. Finally, a review of the cognitive and brain consequences of impulse control disorders—obsessive compulsive disorder (OCD), Tourette's and tic disorders, gambling, kleptomania, trichotillomania, intermittent explosive disorder, pyromania, and paraphilias—concludes the chapter.

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Clinical Neuropsychology: A Pocket Handbook for Assessment, Third Edition, Michael W. Parsons and Thomas A. Hammeke (Editors)

I. NEUROPSYCHOLOGY OF ILLICIT DRUG USE AND ABUSE

An estimated 22.6 million Americans used illicit drugs in the past month, with 4.2 million meeting criteria for drug dependence or abuse (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011). Marijuana is the most commonly used illicit drug (17.4 million past-month users) followed by psychotherapeutics (e.g., stimulants, sedatives, pain relievers), cocaine (1.5 million), and hallucinogens (1.2 million; SAMHSA, 2011). The rates for substance abuse or dependence are twice as high for males, and illicit drug use is greatest among African Americans (10.7%), followed by Whites (9.1%), Hispanics or Latinos (8.1%), and Asian Americans (3.5%; SAMSHA, 2011).

Recent data estimate the total economic cost of illicit drug use to be $193 billion, attributable to crime, health, and lost productivity (i.e., treatment costs, incarceration costs; see U.S. Department of Justice, National Drug Intelligence Center, 2011). Illicit drug use disorders are associated with many adverse outcomes, including unemployment, violence, incarceration, psychiatric disorders, and elevated risk of suicide, HIV/AIDS, and death. Most relevant to the current review is the fact that illicit drug use is also associated with significant deficits in neurocognitive functioning (see Fernández-Serrano, Perez-Gracia, & Verdejo-Garcia, 2011).

A. Diagnosis/Classification

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM–5; 2013*) defines substance use disorders as a cluster of cognitive, behavioral, and physiological symptoms, with continued substance use by the individual despite substance-related problems. Specifically, diagnosis of a substance use disorder is based on the pathological behaviors related to substance use that are categorized by the *DSM–5* into four criteria: impaired control, social impairment, risky use, and pharmacological criteria. *Impaired control* involves ingestion of the substance in larger amounts or for a longer period than intended, persistent desire to cut down and unsuccessful attempts to do so, excessive time trying to obtain the substance or recovering from the effects, and intense cravings. *Social impairment* includes failure to meet obligations at work, school, or home and continued use despite persistent social or interpersonal problems caused by the substance. *Risky use* is characterized by recurrent substance use in physically hazardous situations and continued use despite knowledge of physical or psychological

problems caused by the substance. Last, *pharmacological criteria* refer to increased tolerance to the substance and evidence of withdrawal symptoms when blood or tissue concentrations of a substance decline in an individual. The *DSM–5* further classifies substance use disorders according to severity, with mild severity as two to three symptoms, moderate as four to five symptoms, and severe as six or more symptoms.

Substance intoxication and withdrawal are also delineated. *Substance intoxication* is defined as a reversible substance-specific syndrome due to recent consumption of a substance, with accompanying adverse behaviors directly related to the physiological effects of the substance on the central nervous system. Most common changes involved with intoxication include disturbances in perception, wakefulness, thinking, judgment, psychomotor behavior, and interpersonal behavior. Signs and symptoms vary with acute versus chronic intoxications. Substance withdrawal is not always associated with substance use disorders. Nonetheless, the *DSM–5* emphasizes the main characteristic of substance use disorders to be an underlying change in brain circuits extending beyond detoxification. As outlined in the literature, such effects are likely to result in adverse brain changes and deficits in cognitive function.

B. Common Illicit Drugs and Their Effects

The effects of illicit drug use on cognitive function and the brain are well documented. However, the deficits observed on neuropsychological testing are often mild, and inconsistencies are also found throughout the literature. This is likely representative of the many challenges presented in conducting neuropsychological research within substance use populations. The following subsections present a review of the established effects of illicit drug use on cognition and any inconsistencies observed in the literature.

1. CANNABIS

An estimated 17.4 million Americans used cannabis in the past month, and approximately 4.5 million met criteria for abuse or dependence (SAMHSA, 2011). Rates of cannabis use were higher among men than women in 2010 (9.1% vs. 4.7%; SAMHSA, 2011). Cannabis is obtained from the plant *Cannabis sativa*, and the principal psychoactive ingredient is delta-9-tetrahydrocannabinol (THC). Consumption of THC results in activation of CB1 and CB2 cannabinoid receptors. The highest concentrations of CB1 may be found in the basal ganglia, prefrontal cortex, anterior cingulate cortex (ACC), and hippocampus, whereas CB2 are mainly located within immune cells and peripheral tissues (Pertwee & Ross, 2002).

a. Intoxication, abuse, and dependence

Cannabis intoxication develops within minutes, and the effect lasts about 3 to 4 hours. Intoxication includes fluctuations in mood (i.e., euphoria, anxiety) and cognitive function (i.e., short-term memory, impaired judgment, altered sensory perceptions). Increased appetite, bloodshot eyes, dry mouth, and tachycardia may also occur during cannabis intoxication. Regular cannabis use is also associated with weight gain, sinusitis, and multiple respiratory conditions. Cannabis at high doses results in withdrawal symptoms similar to those of tobacco and includes increased irritability, anxiety, aggressive behavior, anger, decreased appetite, sleep problems, and stomach pains (Budney, Moore, Vandrey, & Hughes, 2003).

b. Neuropsychological findings

Cannabis produces neurocognitive impairments through its interaction with CB1 receptors in the brain (Fernández-Serrano et al., 2011).

i. Acute deficits

Acutely intoxicated individuals exhibit worse performance on cognitive tests of memory, including immediate and delayed recall of word lists, prose, and nonverbal stimuli. Other acute effects of cannabis consist of decreased performance on measures of inhibition (i.e., stop reaction times, stop-signal task) and risky decision making (for a review, see Gonzalez, 2007). Cannabis use also has negative acute effects on attention and concentration. Interestingly, the acute effects of cannabis use have been suggested to be stronger in less experienced cannabis users relative to those with higher drug tolerance, which may partially explain some findings in the literature that demonstrate minimal acute cognitive effects of cannabis use.

ii. Long-term deficits

Cannabis use has most consistently been shown to produce long-term neuropsychological deficits on tests of memory (i.e., verbal memory, learning, forgetting). However, evidence for lasting adverse effects on measures of executive function, inhibitory control, psychomotor and information processing speed, and decision making has also been found (see Gonzalez, 2007). Despite such findings, the literature examining the long-term cognitive effects of cannabis use is not entirely consistent, and such effects are likely dependent on factors such as quantity and duration of use. In addition, the neurocognitive impact of cannabis use may also be moderated by comorbid psychiatric and/or medical conditions. Supporting this notion is recent work that shows that patients with Bipolar I Disorder with a history of cannabis use exhibit better neurocognitive test performance relative to bipolar

patients without such history (Braga, Burdick, Derosse, & Malhotra, 2012). Differential neurocognitive effects of cannabis use have also been demonstrated in patients with schizophrenia.

c. Neuroimaging findings

Meta-analysis (Martin-Santos et al., 2010) suggests that cannabis effects are evident on multiple imaging modalities.

i. Acute effects

Single-photon emission computed tomography (SPECT)/positron emission tomography (PET) studies reveal increased global cerebral blood flow and increased activity in the ACC, insula, prefrontal and orbitofrontal cortices, and the cerebellum following THC ingestion. Such findings are consistent with the high concentration of CB1 receptors expressed in many of these areas. THC-attenuated activity of the right inferior frontal cortex and anterior cingulate gyrus on tests of motor inhibition and amygdala activation during tasks of emotional processing, such as the presentation of threatening faces (see Martin-Santos et al., 2010).

ii. Long-term effects

Neuroimaging studies in cannabis users are inconsistent. Structural magnetic resonance imaging (MRI) studies show that frequent cannabis users have smaller gray matter volume in the right parahippocampal gyrus and greater white matter volume in the left parahippocampal and fusiform regions. Bilateral volume reductions in the hippocampus and the amygdala have also been observed. However, other studies find no differences, and prospective studies are needed to clarify possible effects. Functional imaging studies indicate lasting effects during task completion, including decreased activation in frontal brain regions and increased in cerebellar (see Martin-Santos et al., 2010).

2. COCAINE

Approximately 1.0 million Americans were dependent or abusive of cocaine in 2010 (SAMHSA, 2011). The 12-month estimates of cocaine use disorders in the United States are 0.2% among 12- to 17-year-olds and 0.3% among individuals more than 18 years old (American Psychiatric Association, 2013). Women have a greater vulnerability to cocaine abuse than men (Cotto et al., 2010) and are at greater risk for relapse (Fattore, Altea, & Fratta, 2008). Cocaine originates from the coca plant and is the active ingredient in coca leaves, coca paste, cocaine hydrochloride, freebase, and crack. Although the effects of crack have an extremely rapid onset, at comparable doses, crack and cocaine produce similar effects.

a. Intoxication, abuse, and dependence

Cocaine intoxication can produce a series of changes, including euphoria, gregariousness, hypervigilance, interpersonal sensitivity, anxiety, grandiosity, nausea, muscular weakness, cardiac symptoms, seizures, and coma. Cocaine abuse is characterized by sporadic episodes of consumption of high doses followed by a prolonged period of occasional use or abstinence. The extreme euphoria produced by cocaine increases the risk for rapid development of dependency. Tolerance is quickly developed with repeated use. Regular use of cocaine commonly results in paranoid ideation, aggressive behavior, anxiety, depression, and weight loss. Heavy and regular use of cocaine may result in withdrawal symptoms that develop within a few hours to several days after cessation. Withdrawal symptoms include dysphoric mood, fatigue, sleep disturbances, increased appetite, and psychomotor agitation or retardation. Depressive and unpleasant feelings often develop following episodes of repetitive consumption of high-dose cocaine use, though they typically resolve.

b. Neuropsychological findings

Chronic cocaine users frequently exhibit impairments on neuropsychological tests assessing attention and executive function, including problem solving, working memory, mental flexibility, moral judgment, and information-processing speed. Less commonly, impairments in verbal and visual memories are also found. Deficits may resolve following sustained abstinence, though findings vary (see Jovanovski, Erb, & Zakzanis, 2005). Findings for reversibility of deficits are at least partly dependent on the extent of structural brain damage.

c. Neuroimaging findings

Cocaine harms the brain through a combination of vascular damage, ischemia, and adverse effects on monoamine transports and multiple neurotransmitters (Fernández-Serrano et al., 2011; Rojas, Riascos, Vargas, Cuella, & Borne, 2005). Cocaine abusers exhibit significant atrophy of frontal and temporal regions, with greater use associated with greater atrophy (Rojas et al., 2005). Diffusion tensor imaging studies reveal reduced white matter integrity of the frontal lobes, particularly among those with the longest history of use (Lim et al., 2008). Functional MRI (fMRI) studies indicate hyperactivation of the prefrontal cortex and basal ganglia and hypoactivation in dopaminergic nuclei (Tomasi et al., 2007). PET/SPECT reveals decreased metabolism and hypoperfusion in the orbitofrontal cortex (OFC) among abstinent cocaine abusers (see Fowler, Volkow, Kassed, & Chang, 2007).

3. AMPHETAMINES AND MDMA

Amphetamine-type stimulant use disorder has an estimated 12-month prevalence of 0.2% in the United States among 12- to 17-year-olds and 0.2% among individuals more than 18 years old (American Psychiatric Association, 2013). Amphetamine-type stimulants can be classified into two groups: amphetamine group substances (amphetamine, methamphetamine, methcathinone) and ecstasy group substances (MDMA). Amphetamines are mainly synthetic, psychoactive drugs with properties similar to cocaine, though the psychostimulant effects of amphetamines last longer and can be more potent. Although nonmedical use can be common (SAMHSA, 2006), amphetamine group substances are often obtained through medical prescriptions to treat conditions such as obesity, attention-deficit/hyperactivity disorder (ADHD), and narcolepsy. MDMA use has become an emergent public health concern due to rising prevalence and its association with polysubstance use (Wu et al., 2009). MDMA also contains hallucinogenic properties and disrupts neuronal communication within seroronergic connections. As a result, MDMA influences mood regulation, aggression, sexual activity, and pain (National Institute on Drug Abuse, 2010).

a. Intoxication, abuse, and dependence

Amphetamine intoxication occurs within 1 hour of ingestion and includes euphoria, gregariousness, hyperactivity, interpersonal sensitivity, anxiety, alertness, grandiosity, and impaired judgment. Common physiological changes consist of tachycardia or bradycardia, papillary dilation, altered blood pressure, nausea or vomiting, and cardiac changes. The behavioral patterns associated with amphetamine use and dependence are similar to those with cocaine and often involve episodic binges. Chronic use of amphetamines may cause aggressive and violent behavior in addition to intense anxiety, paranoid ideation, and schizophrenia-type traits. Although tolerance to amphetamines may develop, sensitization to amphetamines has also been documented. Withdrawal symptoms may develop within 1 hour to several days following cessation of use and consist of dysphoric mood, sleep disturbances, increased appetite, and psychomotor agitation or retardation.

b. Neuropsychological findings

i. Amphetamines

Studies examining the neuropsychological effects of illicit amphetamine use are limited, though multiple deficits in executive function have been observed (e.g. cognitive flexibility and control, sustained attention, strategic planning, and decision making).

Impairments in learning and memory have also been observed among acute and chronic amphetamine users, though such deficits have been suggested to be a product of executive dysfunction (i.e., encoding, organizing, and retrieval). Many of the neuropsychological impairments demonstrated by amphetamine users appear to diminish following abstinence (see Ersche & Sahakian, 2007).

ii. MDMA

MDMA users have been found to exhibit impairments in verbal memory, which appear to be dose related and exacerbated by prolonged MDMA use (see Hanson & Luciana, 2010). Less commonly, MDMA users also exhibit impairments in working memory and verbal fluency (see Hanson & Luciana, 2010).

c. Neuroimaging findings

i. Methamphetamine

Methamphetamine use is linked to decreased gray matter density, decreased white matter integrity, and greater white matter hyperintensities in frontal brain regions. Atrophy of cortical gray matter in the occipital, temporal, and insular lobes have also been documented (Nakama et al., 2011). Interestingly, methamphetamine users have been shown to exhibit enlarged basal ganglia structures due to compensatory mechanisms to maintain function, including inflammatory and glial responses (Chang et al., 2005).

ii. MDMA

Findings from neuroimaging studies among MDMA users are limited due to the many methodological difficulties in working with this population, including polysubstance abuse. However, disruptions in the 5-HT (serotonin) system are evident, including reduced 5-HT transporters, decreased density of 5-HTT, reduced postsynaptic serotonin receptors (5-HT2A; Cowan, 2007). MDMA use has also been linked with decreases in white matter integrity and reductions in cerebral blood flow among the visual cortex, caudate, superior parietal, and dorsolateral frontal regions (Chang et al., 2000; de Win et al., 2007). Functional MRI studies show altered patterns of activations during MDMA intoxication, including multiple frontal and occipital regions (Jager et al., 2008).

4. OPIOIDS

Opioids are classified as naturally occurring substances (e.g., morphine), semi-synthetics (e.g., heroin), and synthetics with morphine-like action (e.g., codeine). The 12-month prevalence of opioid use disorder is estimated to be 0.37% among adults more than 18 years old, though this may be an underestimate (American Psychiatric

Association, 2013). Heroin is the most commonly abused drug within this class, and because most users inject the drug intravenously, HIV is found in up to 60% of heroin-dependent individuals. There are an estimated 1.2 million heroin users within the United States, and this estimate has remained relatively stable since 2000 (United Nations Office on Drugs and Crime, 2008).

a. Intoxication, abuse, and dependence

Opioid intoxication produces pupillary constriction, drowsiness or coma, slurred speech, initial euphoria followed by apathy, dysphoria, psychomotor agitation/retardation, and impairments in judgment and attention. Symptoms of intoxication typically last several hours, though the magnitude of the effects depends on the dose and individual characteristics (e.g., tolerance, frequency of use). Following an overdose, severe intoxication can lead to respiratory depression and death. Individuals who abuse opioids generally use less frequently and do not typically show withdrawal symptoms. Dependent individuals demonstrate high levels of tolerance and experience significant withdrawal symptoms upon abrupt discontinuation, with dysphoria, nausea, anxiety, restlessness, and an "achy feeling" in the back and legs. Withdrawal symptoms of short-acting opioids (e.g., heroin) may begin within 6 to 12 hours, whereas symptoms may take 2 to 4 days to emerge following the last dose of a long-acting opioid (e.g., methadone). Withdrawal symptoms typically subside within a few days, though some (e.g., anxiety, anhedonia, dysphoria) can last for weeks to months.

b. Neuropsychological findings

Research on the cognitive effects of long-term chronic opiate abuse is fairly limited and is often confounded by polysubstance use. Impairment of at least two standard deviations below normative data on two or more neuropsychological tests has been found in 60% of current opiate users. The majority of the research has focused on heroin users, with deficits being found in aspects of executive function, learning and memory, attention, and psychomotor speed. However, it is noted that the severity of the deficits and the consistency with which heroin users differ from controls varies across studies (for a review, see Yücel, Lubman, Solowij, & Brewer, 2007). In addition, the limited research on "pure" heroin users has shown impaired decision-making abilities, though better performance on visual episodic memory and problem-solving when compared with individuals who use alcohol alone or in conjunction with heroin has been found (for a review, see Fernández-Serrano et al., 2011). The confounding effect of HIV-associated cognitive impairment should also be considered by clinicians and in future research.

c. Neuroimaging findings

Heroin has significant adverse effects on the brain, including development of neurovascular disorders, atrophy, and leukoencephalopathy. Ischemia is common and is associated with intravenous injection. Ischemic injury in the globus pallidus is observed in 5% to 10% of chronic abusers. Diffuse, symmetric, and bilateral subcortical or periventricular white matter hyperintensities may also be observed. Acute heroin-induced leukoencephalopathy is only observed after heroin inhalation and can occur with brain edema. However, chronic subacute encephalopathy is more common and produces spongiform degeneration of the white matter, particularly in the corticospinal and solitary tracts. On histopathology, multivascular degeneration of oligodendrocytes is also observed in persons with significant history of heroin use. Infections following endocarditis are also common secondary complications of heroin abuse, as 45% to 58% develop neurological complications including septic emboli from brain abscesses and mycotic aneurysms resulting from inflammatory damage (for a review, see Geibprasert, Gallucci, & Krings, 2010). Additional adverse effects of opioid use include reduced activity in the ACC, greater inferior parietal activation, reductions in frontal and temporal volumes, and reductions in the availability of striatal dopamine transporter and midbrain serotonin transporter (Gruber, Silveri, & Yurgelun-Todd, 2007).

5. BENZODIAZEPINES

Benzodiazepines are widely prescribed drugs, and depending on the dose, can act as hypnotics, anxiolytics, or sedatives. The use of benzodiazepines to treat anxiety and insomnia is common among elderly persons, but can produce delirium.

a. Intoxication, abuse, and dependence

Benzodiazepine intoxication produces slurred speech, gait instability, nystagmus, mood lability, impaired judgment, and stupor/coma. The disinhibitory effect of benzodiazepines can also produce paradoxical effects including increased anxiety, acute excitement and hyperactivity, and aggressive impulses associated with hostility and rage. Significant levels of physiological dependence, marked by tolerance and withdrawal, can develop with use. Withdrawal can include symptoms of autonomic hyperactivity (e.g., increased heart rate), insomnia, anxiety, nausea, psychomotor agitation, and seizures. Hallucinations can occur during severe withdrawal but are more commonly present in the context of delirium. Depending on the half-life of the substance ingested, symptoms can emerge within hours or a few weeks following the last use. However,

more chronic symptoms (e.g., anxiety, difficulty sleeping) can persist for several months.

b. Neuropsychological findings

i. Acute effects

Short-term administration of benzodiazepines produces dose-related deficits in learning and memory, attention, and psychomotor speed. Although memory for events prior to administration remains intact, acquisition of memory following administration is impaired. Differences are also noted between benzodiazepine compounds. For example, implicit memory and priming generally remain intact, except following use of lorazepam.

ii. Long-term effects

The cognitive effects of chronic benzodiazepine use are similar to those of acute use, although of increased severity. Additional deficits have also been observed in aspects of visuospatial abilities and executive function.

iii. Discontinuation

In general, discontinuation of benzodiazepines leads to the steady resolution of cognitive effects. Observed cognitive improvements likely depend on the dose the individual is withdrawing from and the complexity of the task (for a review, see Lader, 2011).

c. Neuroimaging findings

PET findings from sleep studies have shown reduced cerebral blood flow in numerous frontal, temporal, and striatal regions. Reduced glucose metabolism is found in similar regions (for a review, see Nofzinger, 2005). The literature on structural neuroimaging is limited, and current findings suggest no meaningful differences between users and controls (for a review, see Lader, 2011).

6. POLYSUBSTANCE USE

Polysubstance use is common, reported by 56% of the individuals admitted to publicly funded treatment facilities in 2002. Polysubstance abuse was more common among younger individuals, and alcohol was the most commonly reported substance used in conjunction with other drugs (SAMHSA, 2005).

a. Intoxication and dependence

Symptoms of intoxication vary considerably depending on the substances involved. Multiple substances are often taken together, and because the interaction can increase or attenuate the effects of

the drugs, clinicians should be mindful of such interactive effects during evaluation. An individual must have used three substances (excluding nicotine and caffeine) within the same 12-month period, during which time no substance predominated, to meet diagnostic criteria for Polysubstance Dependence. The combined effects of the multiple substances must meet criteria for Dependence, and meeting Dependence criteria for a single substance precludes this diagnosis. It is noted that research on polysubstance use often includes those who meet Dependence Criteria for multiple substances.

b. Neuropsychological findings

A recent review summarized the aspects of cognition impacted in polysubstance users with different principal drugs of choice (Fernández-Serrano et al., 2011):

- Cannabis: memory, attention, executive dysfunction, psychomotor speed, and visuospatial abilities. Following abstinence, cognitive effects are attenuated, with the exception of adolescent use.
- Cocaine: memory, executive function, attention, psychomotor speed, and emotional decoding.
- Methamphetamine: memory, executive function, psychomotor speed, and emotion processing.
- MDMA: memory and executive function.
- Opioids: memory, executive function, psychomotor speed, attention, and altered emotional reactivity.
- Alcohol: memory, executive function, and psychomotor speed.

c. Neuroimaging findings

Neuroimaging findings among polysubstance users are dependent on the substances they use, and the literature examining the broad pathophysiological effects of polysubstance use is scarce. However, some work has found decreased ventromedial cortex and right dorsolateral prefrontal cortex activation (Tanabe et al., 2007) and reduced bilateral dorsolateral frontal lobe cerebral oxygenation (Hammers & Suhr, 2010).

II. NEUROPSYCHOLOGY OF IMPULSE CONTROL DISORDERS

Impulse control disorders and substance abuse are highly comorbid, and these disorders demonstrate important clinical and neurocognitive similarities. In turn, the chapter concludes with a review of the cognitive and brain consequences associated with impulse control

disorders. It is noted that neuroimaging and neuropsychological studies of these disorders are limited in number, and thus, results of imaging and cognitive functioning should be interpreted with caution. In addition, findings suggestive of dysfunction in frontal and limbic systems is common, though it is unclear how impairments in these areas manifest as impulse disorders and why they manifest in such dissimilar ways.

A. Diagnosis/Classification

1. OCD

OCD is comorbid in more than 25% of substance abusers and precedes the onset of substance abuse disorders in 70% of individuals (Mancebo, Grant, Pinto, Eisen, & Rasmussen, 2009). OCD is characterized by an inability to control impulses and is often compared with impulse control disorders such as trichotillomania and Tourette's disorder. Individuals with OCD experience excessive obsessions, which are recurrent and persistent thoughts or impulses that cause anxiety or distress and are unable to be ignored or suppressed. They may also experience compulsions such as repetitive behaviors (i.e., hand washing or checking) or mental acts (i.e., praying or counting). The 12-month prevalence of OCD in the United States is 1.2% and internationally is 1.1% to 1.8%.

a. Neuropsychological findings

On neuropsychological testing, OCD patients exhibit significant impairments on tasks of executive function, attention, set shifting, and inhibition (Lawrence et al., 2006). Persons with OCD also display impaired verbal and nonverbal memory function (Segalàs et al., 2008), although this may be due to an inability to originally organize information as it is being processed. Patterns of neuropsychological performance may differ based on severity (Van der Linden, Ceschi, Zermatten, Dunker, & Perroud, 2005), types of symptoms (Lawrence et al., 2006), and age of onset, with late-onset patients displaying poorer verbal and visual memories, executive function, and attention (Segalàs et al., 2008).

b. Neuroimaging findings

Dysfunction of the orbitofrontal-striatal circuit is often considered the source of OCD pathology. Increased metabolism has been found in both the orbitofrontal and medial frontal cortex (Sawle, Hymas, Lees, & Frackowiak, 1991), and decreased volume in frontal brain regions is common. Associated areas such as the thalamus, cingulate gyrus, and cerebellum are affected in OCD patients (van

den Heuvel et al., 2009), though findings for the basal ganglia are mixed (Radua & Mataix-Cols, 2009).

2. TOURETTE'S AND TIC DISORDERS

Tics are sudden, stereotyped motor movements or vocal sounds that are reoccurring. They can be distinguished as simple (e.g., eye blinking, grunting) or complex (e.g., jumping, single words, phrases). Tics can be suppressed for periods of time, but they are precipitated by an urge or tension before the tic and a sense of relief or tension relief after. The *DSM–5* defines tic disorders as a Stereotypic Movement Disorder, and there are three tic-related disorders: Tourette's Disorder, Persistent Motor or Vocal Tic Disorder, and Provisional Tic Disorder (American Psychiatric Association, 2013). All of these disorders have an onset before the age of 18, are not due to a substance or medical condition, and produce tics multiple times a day nearly every day with no tic-free period of more than 3 consecutive months.

a. Neuropsychological findings

Persons with Tourette's disorder display impaired functioning on tasks of motor functioning, visuospatial processing, attention, and executive functioning (Bloch, Sukhodolsky, Leckman, & Schultz, 2006). Areas of executive functioning affected include working memory, verbal fluency, and inhibition (Mahone, Kohn, Cutting, Singer, & Denckla, 2001). Memory deficits have also been found in this population, affecting procedural and strategic memory (Stebbins et al., 1995), as well as tasks requiring inhibitory processes (Mahone et al., 2001). The presence of comorbid ADHD or OCD can exacerbate these cognitive difficulties.

b. Neuroimaging findings

Neuroimaging studies of Tourette's disorder illustrate decreased volume of the basal ganglia bilaterally, specifically the striatum (Singer et al., 1993). Likewise, functional imaging studies show striatal hypoactivity, whereas the motor cortex displays hyperactivity (Rickards, 2009). Increases in volume have been found in the hippocampus, amygdala, thalamus, and prefrontal cortex (Peterson et al., 2001).

3. GAMBLING

Pathological gambling is defined by a persistent and recurrent gambling behavior. Individuals are preoccupied with gambling, need to gamble, and need increasing funds to achieve excitement, are unable to withdraw and become irritable or restless when attempting to do so, often return after losing money to regain losses, lie to others about gambling habits, commit illegal acts to continue, have prob-

lems with relationships or opportunities because of these habits, and rely on others to finance the habits, and behaviors are not better explained by manic episodes. General population lifetime prevalence rates range between 0.4% and 1.0% (American Psychiatric Association, 2013).

a. Neuropsychological findings

Individuals with pathological gambling often display specific deficits on tasks mediated by frontal brain regions. Executive dysfunction is evident (specifically planning, flexibility, set shifting, impulsivity); however, attention processes appear unaffected (Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002).

b. Neuroimaging findings

During functional imaging, pathological gamblers have been shown to demonstrate decreased activation in the orbitofrontal and ventral medial prefrontal cortex on tasks of inhibition and risk taking (Dannon et al., 2011). This pattern is similar to the decreased activation in similar regions when pathological gamblers experience a gambling urge (Potenza et al., 2003).

4. KLEPTOMANIA

Kleptomania is defined as the inability to resist impulses to steal objects that are not needed for personal use or monetary value. This stealing is not to express anger, to sabotage, or to respond to delusions or hallucinations. Individuals experience an increase in tension before stealing and a sense of relief or pleasure after stealing. The prevalence of kleptomania in the general population is 0.3% to 0.6% and occurs in 4% to 24% of individuals arrested for shoplifting (American Psychiatric Association, 2013).

Few studies have looked at neurocognitive aspects of kleptomania. Kleptomania has been suggested to be associated with reduced white matter volume in inferior frontal brain regions (Grant, Correia, & Brennan-Krohn, 2006). A case study also illustrates an association between kleptomania and a right frontolimbic lesion (Nyffeler & Regard, 2001). Those with more severe symptoms perform worse on executive functioning and mental flexibility tasks (e.g., Wisconsin Card Sorting Test; Grant, Odlaug, & Wozniak, 2007), which suggests inhibition difficulties.

5. TRICHOTILLOMANIA (HAIR-PULLING DISORDER)

The hallmark feature of trichotillomania (TTM) is the repeated urge to pull out one's hair, resulting in significant hair loss. This can include any area of the body where hair grows and can occur intermittently throughout the day or during sustained periods. Those

with TTM must experience an increase in tension before pulling their hair and a feeling of pleasure or relief after the event, and this action should cause significant distress or functional impairment (American Psychiatric Association, 2013). The 12-month prevalence for TTM in adults and adolescents is estimated to be 1% to 2% (American Psychiatric Association, 2013).

a. Neuropsychological findings

Patients with TTM have been shown to exhibit impaired impulse control on neuropsychological testing (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2006) and exhibit restricted divided attention, but perform normally on other forms of attention tasks (Stanley, Hannay, & Breckenridge, 1997). They do not show the same cognitive inflexibility and executive function deficits as those with other impulse disorders. On memory tasks, TTM patients perform worse on spatial working memory tasks compared with healthy controls, but not on visual recognition memory (Chamberlain et al., 2007). The severity of the neuropsychological impairment often correlates with the severity of the disorder (Chamberlain, Blackwell, et al., 2006; Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006).

b. Neuroimaging findings

Neuroimaging indicates increased gray matter volume in the left striatum, left amygdala and hippocampus, and various cortical regions (Chamberlain et al., 2008). Cerebellar abnormalities are found in TTM, including smaller cerebellar volumes (Keuthen et al., 2007) and differences in glucose metabolism (Swedo et al., 1991). Findings for basal ganglia regions are mixed. Although left putamen volumes have been shown to be reduced in TTM (O'Sullivan et al., 1997), these results were replicated but only after treatment with citalopram (Stein, Coetzer, Lee, Davids, & Bouwer, 1997). Finally, although TTM is frequently compared with OCD, fMRI studies suggest that TTM does not share the same cortico-striatal deficits (Rauch et al., 2007) and does not show caudate reductions (Stein et al., 2002).

6. INTERMITTENT EXPLOSIVE DISORDER

Characterized by anger that is disproportionate to the situation, intermittent explosive disorder (IED) often leads to aggressive or destructive behaviors. IED is a relatively uncommon diagnosis, with lifetime prevalence between 5.4% and 7.3% (Kessler et al., 2006). Diagnosis for IED requires multiple episodes during which the individual is unable to resist aggressive behavior, which is grossly out of proportion to the stressor and is not better accounted for by another diagnosis (American Psychiatric Association, 2013). One-year prevalence for IED in the United States is 2.7% (American Psychiatric Association, 2013).

Serotonin is believed to play a role in the impulsive aggression characteristic of IED, with reduced serotonin levels and reduced binding in limbic and orbitofrontal areas found in IED as well as violent offenders and arsonists (Coccaro, Lee, & Kavoussi, 2010). Neuroimaging findings illustrate an exaggerated amygdala response and reduced orbitofrontal activity when comparing IED patients with healthy matched controls (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Likewise, IED patients performed similar to those with amygdala or orbital-frontal lesions on tests of frontal lobe functioning, including gambling tasks and facial emotion recognition (Best, Williams, & Coccaro, 2002).

7. PYROMANIA

Pyromania is an impulse disorder characterized by a pattern of setting fire for satisfaction or to relieve stress. Individuals must also feel tension or arousal before setting fire and have a fascination, interest, or curiosity about fire. These actions also must not be to benefit the individual in any way except to relieve tension, such as monetary gain, sabotage or revenge, criminal activity, or as a result of impaired judgment (American Psychiatric Association, 2013). Prevalence of pyromania is unknown, but the lifetime prevalence for fire setting only is 1.13% (American Psychiatric Association, 2013).

Neuropsychological research on pyromania is severely limited. One case study utilizing SPECT imaging suggests a correlation between pyromania and reduced left inferior frontal perfusion (Grant, 2006). In a case study, an individual with pyromania had impairments in attention, executive function, and verbal and visual memory that were displayed before treatment (Parks et al., 2005). Some of this knowledge base comes from case studies or work on arsonists. These results should be taken with caution, however, as they do not necessarily evaluate people who experience tension prior to setting fires and relief after the event and thus do not fulfill the diagnostic criteria. Case studies of individuals who began firesetting after brain injury identify areas such as the left internal capsule (Bosshart & Capek, 2011) and cerebellar vermis (Heidrich, Schmidtke, Lesch, Hofmann, & Becker, 1996), with associated deficits in memory, executive function, and attention. With regard to neuropsychological performance, adolescents who had a history of fire setting but were not formally diagnosed with pyromania were found to have an attentional bias when given a modified Fire Stroop task (Gallagher-Duffy, MacKay, Duffy, Sullivan-Thomas, & Peterson-Badali, 2009).

8. PARAPHILIC DISORDER

Paraphilic disorder consists of a number of subtypes, including exhibitionism, fetishism, frotteurism, pedophilia, sexual masochism,

sexual sadism, transvestic fetishism, and voyeurism. These paraphilias typically involve intense and persistent sexual interest that extends beyond sexual interest in genital stimulation or preparatory fondling with normal, mature, and consenting human partners (American Psychiatric Association, 2013).

Research on paraphilias in regard to neuroimaging or neuropsychological testing is sparse. Much of the research thus far has investigated pedophilia specifically. Volume reductions in bilateral orbito-frontal regions, temporal-parietal lobes, limbic gyri, and the ventral striatum have been found in pedophiles (Hucker et al., 1986). However, performance on neuropsychological measures in this population is mixed. When compared with healthy controls, sexual offenders showed no differences on tests of memory, intelligence, or overall cognitive functioning (Langevin, Wortzman, Frenzel, & Wright, 1989). In contrast, deficits on executive function and verbal abilities in sexual offenders have been found in few studies. It is important to note that, unless specifically defined with a disorder, the above findings were completed with sexual offenders who may or may not have met diagnostic criteria for a paraphilia.

B. Neuropsychological Assessment of Impulse Control Disorders

Overall, persons with impulse control disorders exhibit prominent impairments in inhibitory control and a pattern of frontal systems deficits, including in attention, executive function, and motor abilities. Memory impairments are also evident, likely secondary to impaired attention and organizational abilities. Thus, a comprehensive neuropsychological battery (with emphasis on assessment of higher ordered frontal-mediated abilities, inhibitory processes, and interference control) is recommended in order to capture deficits likely to interfere with daily functioning and lead to risky behaviors. Table 25.1 was adapted from the literature and lists suggested neuropsychological measures in the assessment of impulse control disorder.

III. INNOVATIONS AND FUTURE DIRECTIONS

A. Obesity as a Model for Addiction or Impulse Control Disorder

Obesity has been shown to be an independent risk factor for many adverse neurocognitive outcomes, including accelerated cognitive decline, Alzheimer's disease, stroke, and vascular dementia. More

Table 25.1. Suggested Neuropsychological Measures for the Assessment of Persons With Substance and/or Impulse Control Disorders

Global cognitive function	Modified Mini-Mental State Exam, Wechsler Abbreviated Scale of Intelligence, Repeatable Battery for the Assessment of Neuropsychological Status
Attention	Digit Span, Continuous Performance Test; Paced Auditory Serial Addition Test; Trail Making Test A
Executive function/ response inhibition	Trail Making Test B; Frontal Assessment Battery; Wisconsin Card Sorting Test, Stroop task; Iowa Gambling Task; Porteus Maze Test; The Matching Familiar Figures Test, Go/No-Go tasks
Memory	California Verbal Learning Test–Second Edition; Brief Visuospatial Memory Test–Revised
Language	Boston Naming Test; Controlled Oral Word Association, Animal Naming
Motor function	Grooved Pegboard
Visuospatial abilities	Block Design; Complex Figure Test Copy
Effort	Test of Memory Malingering, Word Memory Test
Psychopathology	Minnesota Multiphasic Personality Inventory–Restructured Form

recent research demonstrates that obesity is associated with cognitive dysfunction even in young and otherwise healthy persons, including deficits in memory, complex attention, and executive function (as reviewed by Stanek-Sellbom & Gunstad, 2012). For example, up to 24% of bariatric surgery candidates exhibit clinically meaningful impairment on testing (Gunstad et al., 2011). Neuroimaging studies reveal that obesity is linked to greater atrophy, reduced functional connectivity, and altered frontal metabolism. Although comorbid conditions such as hypertension and Type 2 diabetes partly account for obesity-related cognitive

dysfunction, other factors such as adipokines, inflammatory markers, glycemic control, and many others have been suggested as important contributors (Stanek-Sellbom & Gunstad, 2012). Interestingly, weight loss following bariatric surgery is associated with improvements in multiple cognitive domains (Alosco et al., 2013; Gunstad et al., 2011).

Obesity research may provide important insight into the neural aspects of both addiction and impulse control disorders. In terms of obesity as addiction, a series of studies found surprising similarities in both neurobiological and behavioral responses to food and substance use. However, there are important limitations in applying the addiction model to obesity, and continued research is needed. Similarly, although obese persons with binge eating disorder report elevated levels of disinhibition, they do not always exhibit greater impairment on neuropsychological testing (Galioto et al., 2012).

Given these findings, neuropsychological research in obese persons may eventually serve as a model to promote understanding of mechanisms for the development and reversal of cognitive dysfunction. Fluctuations in weight status over time provide the opportunity to examine its effects on neuroimaging and neuropsychological measures.

B. Summary

The high personal and societal costs of substance use and impulse control disorders encourage continued research. For example, cognitive impairment among substance-dependent individuals predicts poor treatment outcomes and higher dropout rates (Vocci, 2008). Similarly, preoperative memory and executive function predict weight loss outcomes in bariatric surgery patients. Over time, neuropsychologists will likely play an expanding role in the identification of persons at risk for developing these disorders—helping to individualize treatment plans, monitoring progress over time, and reducing risk of relapse.

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Chapter 26

Dawn Bowers, Jenna Dietz, and Jacob Jones

Assessment of Emotion, Mood, and Affect Associated With Neurologic Disorders

This chapter is divided into four parts. We begin by examining some underlying assumptions and organizing principles of emotion. This is important because the way one views emotion can partially dictate and guide the assessment approach. We then briefly review neurobiological substrates of emotion. This is followed by a description of assessment strategies and tools within the context of a componential model. Finally, we describe emotional sequelae associated with common neurocognitive disorders and diseases.

Before turning to basic definitions, it is important to emphasize that the evaluation of emotion, mood, and affect should be an integral part of any neuropsychological examination. Not only can mood and emotional states (i.e., anxiety) detrimentally influence test performance, they can also modulate the quality of the information that is provided during a diagnostic interview. Particularly relevant for the neuropsychologist, neurologic disorders can induce emotional changes (Heilman, Blonder, Bowers, & Valenstein, 2012) in several ways. First, receiving a diagnosis of a neurologic illness, such as a

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brain tumor, can prompt psychological distress. This is akin to a normal reaction one develops in response to any life-threatening or life-altering disease. Second, neurologic symptoms themselves can induce pain (e.g., headaches), stress, or alter the quality of one's life. Thus, patients with essential tremor whose quality of life is affected by severe hand tremors (e.g., can no longer bring a cup to their mouth, apply makeup) may experience irritability, despondency, and depression. Third, and particularly germane for this chapter, some neurologic disorders disrupt neural systems within the brain that are linked to emotional behavior and emotional experience. These neural systems include key limbic regions along with overlying cortical regions (i.e., frontal) that modulate these systems.

I. DEFINITIONS

A. Emotion, Mood, and Affect

Psychologists and psychiatrists draw distinctions between three commonly used terms: emotion, mood, and affect.

1. EMOTION

Emotions are relatively transient, affectively "intoned" subjective experiences that are often triggered by specific events, either environmental or internal. They range in intensity, from "heat-of-the-moment passion" to minimal perturbations and can be fleeting or longer lasting. Certain emotions are considered primary, such as anger, fear, happiness, disgust, and sadness, whereas other emotions, such as guilt and pride, are viewed as blends of primary emotions.

2. MOOD

Mood refers to an enduring emotional state that can persist for extended periods (hours, days, weeks, months). Mood states typically lack the acute intensity of transient emotional reactions. Common mood abnormalities include depression/sadness, euphoria, anxiety, and perhaps apathy, though it remains unclear whether apathy is a true mood or is a motivational disorder.

3. AFFECT

Many clinicians, especially psychiatrists and physicians, define *affect* as the manner by which emotions are displayed on the face, via tone of voice (prosody) or gesture. In this context, affect refers to the external display of emotion via nonverbal signals. In contrast, many emotion theorists use affect interchangeably with emotion (i.e., both refer to subjective experience). For the purpose of this

chapter, we will follow the medical tradition with respect to the definition of affect as an observable display of facial expression, prosody, and behavior.

B. Organizing Principles: Specific Emotions Versus Dimensions of Emotion

Two historical precedents have set the stage for current approaches for understanding emotion, its neural instantiation, and measurement. As described below, they are not mutually exclusive, and most clinical neuropsychologists implicitly incorporate both frameworks.

1. DISCRETE EMOTIONS APPROACH

In this view, there are a group of fundamental emotions (e.g., fear, anger, joy) that are associated with specific neural circuitries within the brain. This view follows the tradition of Darwin (1872) and Ekman (1972), who argued that basic or core emotions developed during evolution as adaptive survival strategies. Darwin was not concerned with subjective feelings and instead advocated that emotions (or their expressions) acted as signals that communicated important information about behavioral intent. Each core emotion has specific eliciting conditions and specific physiologic, expressive, and behavioral reactions. This framework maps onto contemporary neural evidence that discrete limbic regions are associated with specific emotions (e.g., amygdala: fear; nucleus accumbens: intense pleasure; insula: disgust). More complex emotions, such as guilt or pride, are viewed as blends of these primary emotions.

2. DIMENSIONAL APPROACH TO EMOTION

A second conceptual approach is that emotions are organized along three independent dimensions: valence (pleasant to unpleasant), arousal (low to high), and movement/action (i.e., movement toward vs. movement away). This dimensional approach began with Wundt (1905) and gained momentum with Lang (1988, 2010). Using this approach, one can map specific emotions into a three-dimensional space by plotting valence, arousal, and movement. Some emotions like fear and anger are similar on two dimensions (i.e., valence and arousal) as both are negatively valenced and both are arousing. What distinguishes them, however, is their position on the movement dimension: anger is associated with movement towards (e.g., fighting), whereas fear is associated with movement away (e.g., running) or perhaps a lack of movement as in freezing. This type of approach is not antithetical to the discrete emotions perspective and offers a means for quantification.

3. MULTIPLE RESPONSE SYSTEMS APPROACH: THE COMPONENTS OF EMOTION

Emotion can also be viewed from the perspective of multiple response systems (Lang, 1988). These response systems represent ways that emotion is manifested and is thus measurable (see Table 26.1). Emotion response systems include (1) physiological arousal/activation, which can be measured autonomically (e.g., skin conductance, pupillary responses), by temporal and spatial patterns of brain electrical activity (e.g., EEG, event-related potential [ERP]), or by functional imaging (positron emission tomography, task-specific or resting-state functional MRI); (2) overt behaviors, ranging from social

Table 26.1. Response Systems of Emotion

Response system	Measures
1. Verbal report	Mood measures (depression, apathy, anxiety)
	Other emotion measures
	Perception/interpretation of affect and emotion
	Facial expression, prosody
	Emotional pictures, words, sentences
2. Behavior	Facial behavior: behavior ratings
	Face digitizing
	Electromyogram
	Vocal/prosody: amplitude, pitch
	Gestures: observation
	Whole body behavior: observation
3. Physiologic activation/ arousal	
Peripheral/autonomic	Skin conductance, pupil responses
Central	Startle response magnitude
	Electroencephalogram (EEG, ERP)
	Functional brain imaging (fMRI, PET)

Note. ERP = event-related potential; fMRI = functional magnetic resonance imaging; PET = positron emission tomography.

displays (e.g., facial expression, tone of voice) to broad-based behavioral repertoires such as avoidance, withdrawal, attack, and appetitive approach; and (3) verbal reports and cognitions about one's emotional experience. This can be broken down into (a) appraisal or interpretation of one's internal state and (b) perception and interpretation of external stimuli such as facial expressions/tone of voice, emotional pictures, and situational context.

There are several critical points regarding this componential framework. From a practical perspective, some components can be formally assessed during the neuropsychological exam (i.e., verbal reports about mood, perception of affective stimuli, observations about arousal level), whereas others are typically beyond the scope of a clinical exam (i.e., formal measurement of physiologic reactivity). From a more theoretical perspective, these various components of emotion (arousal, behavior, cognitions) are typically experienced as a uniform subjective experience, not as fragmented components. Even so, these components can be widely divergent, and we frequently see dissociations among normal, psychiatric, and neurologically impaired patients. Thus, patients with Parkinson's disease (PD) exhibit blunted facial expressions (called "masked facies"), yet nevertheless insist their experience of the world is as intense as those of others (e.g., Mikos et al., 2009). This represents a dissociation between expression of emotion (or affective display, overt behavior) and verbal report of subjective experience. Conversely, the patient with pseudobulbar affect can have abrupt outbursts of crying (or laughter), yet deny experiencing true sadness or pleasure. This situation represents a dissociation between one's verbal report of subjective experience and vocal/facial displays of emotion. What these and other dissociations suggest is that various components of emotion are mediated by distinct neural systems in the brain and that examining these components can set the stage for a meaningful assessment strategy.

II. NEURAL SYSTEMS THAT MEDIATE EMOTIONAL BEHAVIOR

Emotional behavior is mediated by a complex interplay between cortical and underlying limbic subcortical systems that are richly interconnected and involve multiple neurotransmitter systems. It is beyond the scope of this chapter to provide a detailed overview of the neurobiology of emotion; however, in broad conceptual strokes, one can view cortical systems as involved in the regulation of emotional behavior via modulation of subcortical and limbic circuitry.

A. Limbic/Subcortical Contributions

Evidence from clinical, animal, and experimental studies suggest a role for specific limbic regions in certain discrete core emotions that are likely important for survival of the species and survival of the individual. Some limbic regions and their associated "emotions" include the following: (a) amygdala: fear, anxiety, apprehension, defensive motivation; (b) ventral striatum (nucleus accumbens): pleasure, euphoria, reward circuitry; (c) insula: disgust; and (d) septal region: aggression, rage.

Thus, discrete intense feelings of fear and panic can occur as an aura at the onset of temporal lobe seizures, presumably due to activation of the amygdala and aversive circuitry networks. Stimulation of the nucleus accumbens during deep brain stimulation surgery (for treatment of intractable obsessive compulsive disorder) has been associated with laughter, smiling and intense feelings of pleasure/euphoria (Okun et al., 2004). These pleasurable feelings relate to stimulation of dopaminergic-rich circuitry associated with the brain's reward systems (e.g., mesolimbic). Of note, opposite emotional effects often occur depending on whether there is activation of a particular limbic region (i.e., an "irritative lesion") versus an ablative lesion. For example, stimulation of the amygdala by seizure activity (or as part of a normal reaction to a threatening situation) can induce feelings of fear. Yet, removal of the amygdala has been associated with passivity and docility, as initially described by more than 80 years ago by Klüver and Bucy (1937). Similarly, lesions of the septal region in rodents have been associated with aggressive behavior (i.e., septal rage), whereas stimulation in this same region is associated with reward-seeking behavior.

B. Cortical Contributions to Emotion

Cortical systems play a unique role in at least three aspects of emotion processing: emotion regulation and sensitivity to behavioral consequences, emotion semantics, and interpretation/expression of emotional signals (e.g., expressions, gestures). *Emotion regulation* refers to the ability to modulate reactivity and behavior. From a neural systems perspective, it occurs via direct modulation of limbic/subcortical systems by the prefrontal cortex, especially orbitofrontal cortex. Although the orbitofrontal cortex plays a prominent modulatory role, more "cognitive" dorsolateral control systems are also important. The following are common behavioral signs and symptoms related to disruption of orbitofrontal, dorsolateral, and mesial frontal circuitries:

- orbitofrontal: impulsivity, irritability, disinhibition, overly familiar demeanor, hypersexuality, risk taking, excessive

jocularity; emotional lability; mood changes include mania, depression and lability;
- mesial prefrontal/anterior cingulate: impaired motivation, abulia/apathy, emotional flattening, decreased initiative, indifference, poverty of behavior, slowness of behavior and thought (akinesia, bradykinesias); and
- dorsolateral prefrontal: cognitive/executive deficits that can influence judgment and emotion regulation.

In addition to emotion regulation, cortical systems also play an important role in the *cold cognitions* of emotion. This term refers to affect judgments and knowledge that can be detached from the more personal experience of an emotional state. One type of cold cognition is conceptual knowledge about the meaning of situational determinants of emotion and behavior. Thus, most people know that being robbed elicits fear and anger, whereas death is usually associated with grief, and a smiling face is associated with happiness. This type of knowledge is known as *emotional semantics*. Like general semantic knowledge, this type of knowledge is acquired early in developmentally normal children and is relatively impervious to neurologic disease (i.e., a type of "hold" function). Even patients with large orbitofrontal lesions maintain knowledge about appropriate rules of conduct and emotional semantics (see suggested readings online at http://pubs.apa.org/books/supp/parsons); however, they fail to utilize this knowledge in their day-to-day life. Emotional semantics is thought to be a broadly distributed system in the brain (Blonder, Bowers, & Heilman, 1991).

Another type of cold cognition involves the processing of nonverbal affective signals. This includes the ability to perceive and interpret the emotional meaning of facial expressions, emotional prosody (how something is said), and emotional gestures (e.g., upraised fist). Again, the core ability to perceive/discriminate and understand these nonverbal affect signals is normally acquired early in life and remains relatively stable throughout the adult life span. A large body of literature over the past 50 years has indicated that focal lesions of the right hemisphere induce greater deficits in affect perception and production than left hemisphere lesions (for reviews, see suggested readings). Although nonspecific perceptual difficulties associated with right hemisphere lesions contribute to this asymmetry, some have argued that the right hemisphere may contain an affect lexicon (Bowers, Bauer, & Heilman, 1993), similar to the verbal lexicon of the left hemisphere. Regions within the occipitotemporal cortex (inferior occipital gyrus, fusiform gyrus), amygdala, and ventral prefrontal cortex have been implicated in processing of facial affect in humans.

C. Hemispheric Laterality Models of Emotion

Hemispheric models of emotion initially emerged from observations of differing emotional reactions after left compared with right hemisphere strokes (Gainotti,1972; Goldstein, 1948). Left hemisphere lesions have been linked to excessive emotionalism (catastrophic reaction) and depression. Right hemisphere lesions have been associated with emotional blunting and flatness, which has been attributed in part to defects in arousal. The three predominant hemispheric laterality models of emotion include variants on (a) a right hemisphere model, (b) a bivalent hemisphere mode, and (c) a hybrid model. According to the right hemisphere model, the right hemisphere has a special role in perceiving, interpreting, and producing facial expressions and emotional prosody. Support for this view is drawn from a large body of literature showing that affect processing defects are more strongly linked to focal right hemisphere lesions. Moreover, these deficits exist above and beyond simple perceptual difficulties that are also associated with right hemisphere lesions. According to a second "bivalent" model (see Davidson, Ekman, Saron, Sunulis, & Friesen 1990), each hemisphere is specialized for distinct emotions: the left hemisphere is more involved in approach, affiliative emotions and the right more involved in more aversive, negative emotions. Support for this view derives from studies of mood-related EEG asymmetries and different poststroke mood reactions. A third hybrid model incorporates the distinction between the perception and experience of emotion, with anterior regions (i.e., frontal) being differentially involved in the experience of emotion (i.e., left more negative, right more positive), and the right hemisphere being more involved in perception/interpretation of emotional stimuli. Laterality views with respect to approach and avoidance were further articulated by Heller (1990).

III. GUIDELINES FOR ASSESSING AFFECT, EMOTION, AND MOOD

Assessment of mood, affect, and emotion is easily incorporated into any neuropsychological exam. Depending on the initial impression and hypotheses formed by the clinician during the clinical interview, the evaluation can proceed in different ways with use of general and specialized emotion measures.

A. Detailed Clinical Interview

From the perspective of mood/emotion, the purpose of the interview is threefold. The first is to obtain a history of current and past

emotional/mood changes, along with a timeline for their emergence. An interview with collateral sources (i.e., spouse, family member, friend, or others) who can provide a corroborating report of current and previous emotional functioning is important. This becomes more critical if there are any concerns regarding the patient's ability to provide an accurate self-assessment.

Second, the clinical interview is an opportunity to observe interpersonal behaviors that may provide clues regarding atypical or aberrant modes of interacting. The clinician should be particularly attentive to facial expression, prosody (tone of voice), gestures, eye contact, and conversational turn-taking. The following questions should be considered. Is the patient's affect flat or muted? If so, it is important to rule out a primary mood disturbance (i.e., depression or even anxiety). One must consider whether the affective blunting is a normal variant or whether it represents a symptom of a psychiatric (e.g., schizophrenia, autism) or a neurologic disease/disorder. If the latter, then one might entertain possibilities of basal ganglia disease (i.e., masked face of parkinsonism) or lesions affecting the right hemisphere or the mesial frontal or thalamic region. Does the patient have awareness of their affective inexpressivity? Alternatively (or perhaps concomitantly), does the patient seem to have difficulty interpreting nonverbal social cues? If so, one might consider ruling out basic perceptual difficulties that might be contributory, or, are these difficulties due to aberration in right hemisphere systems that are important for processing these signals? Finally, does the patient exhibit heightened emotional lability and/or difficulty modulating emotional behavior? Is this present during the interview as well as in the home environment, based on patient and/or family report? Depending on the nature and severity of these difficulties, one might entertain possibilities of frontal lobe or limbic dysfunction.

Third, as alluded to above, the clinical interview enables one to discern (or attempt to discern) whether the history, current symptoms, and behaviors are more in line with a primary neuropsychiatric disturbance (i.e., major depressive disorder) or whether changes/symptoms are related to a primary neurologic disease or disorder. Although beyond the scope of this chapter, it is imperative that the neuropsychologist be acutely skilled in differential diagnosis of primary psychiatric disturbances including mood disturbances (depression, anxiety), personality disorders, schizophrenia, and other disorders. The following are several behavioral presentations that are sometimes pathognomonic of underlying neurologic disease:

- *Witelsucht*. Witelsucht refers to inappropriate jocularity, laughter, and joke telling that is typically associated with lesions (vascular, tumor) of the orbitofrontal regions Witelsucht was originally described more than 100 years ago

by Oppenheim (see suggested readings). Despite their heighted jocularity, patients with Witelsucht have little appreciation of the humor of others. Witelsucht is also a prominent feature of the behavioral variant of frontotemporal dementia, which involves progressive declines in social conduct, insight, and emotional reactivity secondary to frontal and/or anterior temporal lobe degeneration (see Chapter 11, this volume). It is important to distinguish Witelsucht-like behavior from euphoric effects of acute substance abuse.

- *Moria.* Moria refers to excessive euphoria and childlike silliness that can occur in conjunction with Witelsucht. Like Witelsucht, it is associated with orbitofrontal lesions and can be observed in individuals with the behavioral variant of frontotemporal dementia.
- *Pathological crying or laughter (i.e., pseudobulbar affect).* Pseudobulbar affect refers to transient episodes of crying or laughter that abruptly occur out of context and seem largely unprovoked. These episodes are short-lived, and the patient will deny experiencing a true emotion (e.g., sadness). There is a disconnect between subjective experience and affective display. Sometime pathological crying seems to be triggered when talking about a sad topic, though the reaction is well beyond what is normal. Many patients have white matter lesions that disrupt inputs to limbic and descending bulbar motor pathways, causing a lack of control/inhibition by higher cortical centers over lower subcortical centers that contain routinized motor programs for these displays. Pathological crying is more common than pathological laughter.
- *Apathy/Abulia.* Apathy is a disorder of motivation that manifests in behavioral, cognitive, and affective domains (see suggested readings for reviews). Affectively, it presents with blunted affect and reduced responsiveness to positive or negative stimuli. Behaviorally, it presents with reduced productivity, lack of effort, and reliance on others to structure daily activities. Cognitively, it presents with a lack of concern and reduced interest. Many apathetic patients are aware of their lack motivation and can clearly articulate that they have "lost their get up and go." Apathy can be a core symptom of depression; however, it is also manifests as an independent syndrome in neurologic conditions such as dementia, PD, and lesions of the frontal lobe and/or basal ganglia (Assal & Cummings, 2002; Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006). A key distinction between apathy and depression is the lack of dysphoria that is symptomatic of depression. Although *Diagnostic and Statistical*

Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013) does not provide diagnostic criteria for apathy as an independent syndrome, provisional criteria have been proposed, originally by Marin in 1991 and more recently by others (see Mulin et al., 2011; Starkstein, Petracca, Chemerinski, & Kremer, 2001). The neuropathophysiology of apathy includes hypoactivity within the mesial frontal-anterior cingulate cortex and the nucleus accumbens due to reduced dopaminergic input to the ventral striatum. The circuit involving the ventral striatum is the primary circuit involved in human motivation (Berridge & Robinson, 1998). It also underlies reward-based learning, in which an organism acquires knowledge about future rewards and punishments based on informational cues in the environment.

B. Common Tools for Assessing Emotion Components

In addition to a clinical interview, the use of assessment tools and measures may aide in screening and providing a description of symptoms. Table 26.1 provides a brief schematic for conceptualizing the emotion assessment from a componential perspective: physiological arousal/activation, overt behavior, and verbal report.

1. PHYSIOLOGICAL AROUSAL/ACTIVATION

Rarely are direct measures of physiological arousal/activation (e.g., skin conductance response and ERP) included in the typical neuropsychological evaluation. Incorporation of such measures is expensive, timely, and beyond the scope of most clinical evaluations. However, one can obtain subjective ratings of arousal and energy level, using simple Likert scales.

2. OVERT BEHAVIOR

Observations of behavior are an integral part of the interview and, in fact, of the entire neuropsychological exam, as described in the interview above. Most clinicians are adept at forming impressions about behavior and affect. Though rarely used in a clinical setting, more formalized methods for quantifying facial expressivity and prosody are available and include rating scales for facial and vocal expressivity, techniques for digitizing facial expressions, and methods for measuring facial muscle activity (i.e., EMG; see suggested readings).

3. VERBAL REPORT MEASURES OF MOOD, EMOTION, AND AFFECT PERCEPTION

In this category are verbal report measures assessing mood and emotion, along with special batteries designed to assess perception/interpretation of affective signals and situational contextual information. Table 26.2 provides an overview of commonly used questionnaires for indexing severity of depression, apathy, and anxiety symptoms.

Note that these questionnaires are not diagnostic of a syndrome, but are a gauge for symptom severity. Measures of anhedonia (loss of pleasure) and other emotion questionnaires are described in Table 26.3. Recently, there has been growing interest in the distinction between anticipatory and consummatory anhedonia, in part due to different underlying neural circuitries. Finally, Table 26.4 describes several formal batteries for evaluating the perception of nonverbal affect stimuli, as well as large-scale standardized sets of emotion stimuli (scenes, words, faces). Although Section III is not a comprehensive review of all measures, it provides an overview of commonly used questionnaires and/or batteries that can be used as relevant in the course of the neuropsychological exam.

IV. EMOTIONAL CHANGES IN COMMON NEUROLOGIC DISORDERS

A. Parkinson's Disease

PD is characterized by high rates of apathy, depression, and anxiety. Emerging evidence indicates that apathy may be the core neuropsychiatric signature of PD. Rather than a mood disorder, apathy is a motivational disorder involving goal-directed behavior across affective, cognitive, and behavioral domains. It is distinct from depression, affects between 30% and 70% of patients with PD in cross-sectional studies (see suggested readings), and progressively worsens with disease severity. Current estimates of depression in PD range from 19% to 35%, depending on whether strict diagnostic criteria or scores on mood scales are used for classification (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). It can be difficult to diagnose depression in PD because of overlap between depression symptoms and symptoms of the disease itself (e.g., facial masking, cognitive slowing, sleep disturbance). In fact, an aggressive approach for diagnosing depression has been recommended because of concerns that depression might be missed and patients might not be treated. However, such an approach likely results in overmedication with antidepressants. In fact, certain pharmacologic therapies for depression

Table 26.2. Self-Report Measures of Mood and Motivation

Domain	Measure; Source	Description
Depression	Beck Depression Inventory—II (BDI–II) Beck et al. (1996)	Widely used 21-item self-report questionnaire, each rated on 4-point scale. Contains "somatic" items and "emotion" items. Some items (e.g., sleep, appetite, fatigue, concentration problems) can be due to neurologic disorder rather than depression. Good psychometric properties.
	Geriatric Depression Scale (GDS) Yesavage et al. (1983)	30 yes–no questions, minimal emphasis on physical symptoms. Yes–no format minimizes cognitive demands. Ideal for elderly or those with cognitive deficits. 15-item short form available.
	Hamilton Depression Inventory (HDI) Reynolds & Kobak (1995)	Self-report questionnaire modeled after the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960); HDI has two versions: a 23-item and 17-item version. A short 9-item version is also available. Adequate psychometric properties.
	Inventory of Depressive Symptomatology (IDS) Rush, Gullion, Basco, Jarrett, & Trivedi (1996)	Self-report of clinician rated questionnaire. Original version consists of 30 items, whereas the Quick Inventory of Depressive Symptomatology (QIDS; Rush et al., 2003) contains 16 items. Modeled after *DSM–IV* criteria for major depression disorder. Adequate psychometric properties.
	Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999)	Depression Subscale (Zigmond & Snaith, 1983) is a 9-item self-report questionnaire, each item rated on 4-point scale. Each item assesses *DSM–IV* symptoms for major depression disorder. First two items make up the abbreviated 2-item PHQ-2 (Kroenke, Spitzer, & Williams, 2003). Adequate psychometric properties.

(continued)

Table 26.2. Self-Report Measures of Mood and Motivation *(Continued)*

Domain	Measure; Source	Description
Apathy	Apathy Evaluation Scale (AES) Marin, Biedrzycki, & Firinciogullari (1991)	Consists of 18 items rated on 5-point Likert scale. AES measures 3 components of apathy (emotion, behavioral, cognitive). Adequate psychometrics. Informant questionnaire also available.
	Apathy Scale (AS) Starkstein et al. (1992)	Most widely used self-report measure of apathy. 14-item scale measures cognitive, behavioral, and emotional components of apathy. Items are rated on a 0–3 Likert scale. The AS was abridged from the original 18-item AES by removing 4 items and simplifying wording. Adequate psychometric properties. Informant and clinician versions available.
	Lille Apathy Rating Scale (LARS) Sockeel et al. (2006) Zahodne et al. (2009)	Semi-structured interview consisting of 33 items that cover 9 domains. Items are scored yes–no except first three items, which involve Likert scale rating. Takes 20 minutes to complete. Four composite subscales: Intellectual Curiosity, Emotion, Action Initiation, and Self-Awareness. Validated in European and U.S. samples. Adequate psychometrics. Patient and informant versions available.
Anxiety	State Trait Anxiety Inventory (STAI) Speilberger (1999)	Consists of 40 statements rated on a 4-point Likert scale. Contains 2 subscales of 20 items each: One measures current or "State" anxiety and the other measures general or "Trait" anxiety. Good psychometrics.
	Beck Anxiety Inventory (BAI) Beck & Steer (1990)	Consists of 21 items rated on a 4-point Likert scale. Contains 2 subscales: Cognitive (fearful thoughts) and Somatic (physical symptoms of anxiety). Does not distinguish between current and enduring anxiety. A new measure was recently developed to measure trait anxiety (BAIT).
	Beck Anxiety Inventory Trait (BAIT) Kohn, Kantor, DeCicco, & Beck (2008)	

Note. DSM–IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994).

Table 26.3. Other Self-Report Measures

Domain	Measure; source	Description
Anhedonia	Snaith Hamilton Pleasure Scale (SHPS) Snaith et al. (1995)	Self-report questionnaire of 14 items rated on a 4-point Likert-type scale. Brief statements describing pleasurable activities are presented. Provides overall index of anhedonia. Adequate psychometrics.
	Temporal Experience of Pleasure (TEPS) Gard, Gard, Kring, & John (2006) Jordan, Zahodne, Okun, & Bowers (2013)	Self-report questionnaire of 18 items rated on 4-point scale. Contains 2 subscales: one measuring "anticipatory" anhedonia and another measuring "consummatory" anhedonia. Anticipatory subscale beneficial for assessing reward pathways. Anticipatory anhedonia corresponds to apathy in Parkinson's disease and corresponds to depression in major depressive disorder.
Emotion	Profile of Mood States (POMS) McNair, Lorr, & Droppleman (1971)	Self-report 65-item scale that involves endorsement of various mood/emotion states. Results in 6 subscales: tension, anger, fatigue, depression, vigor, and confusion. Useful for tracking acute fluctuations in mood/emotion states. Updated version (POMS-2; McNair, Lorr, & Droppleman, 1992) consists of 60 items. Shortened versions are also available.
	Positive and Negative Affect Schedule (PANAS) Tellegen et al. (1988)	Self-report questionnaire consisting of 20 affect adjectives rated on a 5-point Likert scale. Contains 2 subscales: one Negative and one Positive.
Other	Frontal Systems of Behavior Scale (FrSBe) Grace & Malloy (2001)	Self-report questionnaire consisting of 46 items and 3 subscales that theoretically maps onto 3 major frontal circuitries: Apathy (mesial), Disinhibition (orbitofrontal), and Executive (dorsolateral). Patients rate current status on 46 items and also status before "injury" or event, enabling a pre–post comparison from perspective of patient. Informant version is also available. Good psychometrics.

Table 26.4. Affect Batteries and Emotion Stimulus Sets

Domain	Task-Stimuli	Description
Facial and prosody perception	Florida Affect Battery (FAB) Bowers, Blonder, & Heilman (1991)	10 subtests for measuring affect perception and processing including 5 facial, 3 prosodic, and 2 crossmodal tasks. Based on cognitive information processing model. Norms for ages 18–85 years. Separate norms for patients with unilateral strokes, temporal parietal strokes, and epilepsy. Designed to detect "pathological" functioning and should be used to detect emotional processing deficits as opposed to subtle differences among normally functioning individuals.
	Comprehensive Affect Testing (CAT) Froming, Levy, Schaffer, & Ekman (2006)	13 subtests that measure perception, recognition, naming, and matching of affective faces and prosody. Accuracy and reaction time data obtained. Norms available for children, adults, and patients.
Affect perception and expression battery	New York Emotion Battery (NYEB) Borod et al. (2000)	Examines 3 "channels" of emotion: facial, prosodic, and lexical, and nonemotional control tasks. Expression of emotion (facial, prosodic) measured by trained raters; Normative data available from adults and neurologic patients.

Standardized emotion-affective stimuli	International Affective Picture System (IAPS)–emotional pictures Lang, Bradley, & Cuthbert (1999)	Standardized set of more than 800 emotional images. Pictures normed for valence (negative to positive) and arousal (high to low). Categories of children, sports, sex, animals, mutilations, food, attack, and more. Validated against psychophysiologic measures of arousal (Skin Conductance Response) and valence (startle eyeblink). Widely used in experimental studies. Available for free.
	Pictures of Facial Affect Ekman & Friesen (1975)	Photographs of facial expression. Includes Caucasian male and female faces displaying six core emotions: fear, anger, disgust, surprise, fear, happiness, as well as neutral.
	Affective Norms for English Words (ANEW) Bradley & Lang (1999)	Standardized set of emotion words that are normed for valence (negative to positive) and arousal (high to low).

(e.g., selective serotonin reuptake inhibitors) may worsen apathy because of downregulation of dopamine.

Emotional dysfunction in PD may be related to multiple etiologies. As the disease progresses, it affects the mesolimbic dopaminergic system, which projects to the ventral striatum. The ventral striatum projects to cortical areas involved in emotional processing, namely the anterior cingulate cortex and orbitofrontal cortex. Furthermore, postmortem studies have shown significant amygdala atrophy in PD patients, which may be related to disease-related Lewy body pathology. Additionally, depression in PD has been linked to reduced serotonin levels. There are several evidence-based treatments for depression in PD, including at least one randomized controlled study showing positive effects with cognitive behavioral therapy (Dobkin et al., 2011). There are no evidence-based treatments for apathy in PD though behavioral activation techniques are likely to be important.

B. Huntington's Disease

Similar to PD, Huntington's disease (HD) has high rates of depression and apathy. However, apathy often occurs in the context of depression in HD, as opposed to apathy without depression symptoms. Depression rates in HD may be two times that of the general population and comprise up to 50% of individuals with HD. No relationship has been found between depression and disease severity or length of trinucleotide (CAG) repeats in individuals with the disease. Emotional symptoms in HD may be related to basal ganglia pathology, but there is also evidence to suggest that depression may be related to adjustment to a debilitating illness, because the proportion of those endorsing significant depression has been found to actually decrease with disease progression (Paulsen et al., 2005).

C. Dementia

Emotional changes are common across all types of dementia and have significant relationships to both clinical outcome and caregiver burden. Apathy has been associated with Alzheimer's disease, frontotemporal, and vascular dementia. In fact, apathy (rather than depression) is a major risk factor for conversion from mild cognitive impairment to dementia.

1. ALZHEIMER'S DISEASE

AD has been associated with high prevalence rates (>50%) of apathy, irritability, agitation, depression, and anxiety. Apathy is considered to be a major neuropsychiatric component of the disease, with prevalence rates up to 76%. Apathy in AD is associated with

older age, more advanced disease, greater cognitive impairment, and more impairment in activities of daily living. Although depression and apathy are associated in AD according to cross-sectional studies, longitudinal evidence suggests that these are separate processes and that apathy predicts depression (Starkstein, Jorge, & Mizrahi, 2006). Apathy in AD is thought to be due to frontal lobe dysfunction and disruption of basal ganglia circuits. Compared with nonapathetic subjects, apathetic AD patients have been found to have significantly decreased perfusion in the anterior cingulate, the inferior and medial gyrus frontalis, and the orbitofrontal gyrus, as well as increased cortical atrophy in the left anterior cingulated cortex, ventrolateral prefrontal cortex, and orbitofrontal regions.

2. FRONTOTEMPORAL DEMENTIA

Disruption in emotional and social conduct is the hallmark of behavioral (or frontal) variant of frontotemporal dementia (bvFTD), the most common of three frontotemporal dementia (FTD) subtypes. Generally speaking, emotional symptoms in bvFTD are characterized by two not-mutually-exclusive subtypes: apathetic and disinhibited (see Chapter 21, this volume, for more details). Prevalence of apathy in bvFTD has been reported to be between 60 % and 90% of patients, and disinhibition has been reported in 68% (Levy, Miller, Cummings, Fairbanks, & Craig, 1996). Both apathy and disinhibition are more common in FTD than in AD, whereas AD has higher depression rates. Disruption of emotion and social behavior in bvFTD is likely related to the vast frontal lobe pathology associated with the disease. One study linked both apathy and disinhibition to hypometabolism in the orbitofrontal cortex (Peters et al., 2006), whereas another linked atrophy of the dorsolateral prefrontal cortex to apathetic symptoms and atrophy of medial temporal limbic structures to symptoms of disinhibition (Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008).

3. VASCULAR DEMENTIA/WHITE MATTER DISEASE

Vascular dementia and white matter disease have been repeatedly associated with depression in late life (see Chapter 24, this volume). As such, the term *vascular depression* was coined to describe individuals who meet criteria for clinically significant depression and also have cardiovascular and cerebrovascular disease or major risk factors (e.g., diabetes, hypertension, heart disease, obesity). Approximately 3.4% of Americans can be defined as having vascular depression, and one of five of those with major depression also had the presence of cerebrovascular disease (González, Tarraf, Whitfield, & Gallo, 2012). It is hypothesized that vascular depression results from disruption of cortico–subcortical limbic circuitry. Although a relationship between depression and white matter hyperintensities

has been consistently reported, the relationship between depression and vascular disease (i.e., the direction of the casual relationship) is less clear (cf. Culang-Reinlieb et al., 2011).

D. Epilepsy

Depression and anxiety are common in epilepsy. An estimated 60% of individuals with epilepsy have a clinical diagnosis of depression or anxiety (Hecimovic, Goldstein, Sheline, & Gilliam, 2003). These emotional problems are likely a result of both structural and functional neuropathological changes as a part of the disease, psychosocial factors, and treatment side effects. Although anxiety or fear auras are associated with temporal lobe epileptic seizures before and during seizure activity, both anxiety and depression also occur independent of actual seizure activity and are associated with more localized (temporal and frontal) as opposed to generalized epilepsy. This is likely due to involvement of limbic structures in the mesial temporal lobe, such as the amygdala and hippocampus. Furthermore, treatment of epilepsy can result in emotional side effects. Anticonvulsant therapy side effects include irritability and mood lability, in addition to cognitive slowing. If anterior temporal lobectomy is performed to control seizures, one might expect emotional changes due to the removal of surrounding limbic tissue such as the amygdala and hippocampus, although reports on the effect of surgery on mood and anxiety changes have been mixed and may vary depending on lateralization (Hixson & Kirsch, 2009).

E. TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) can result in both acute and chronic changes in emotionality. Acutely, after a person has lost consciousness or is being weaned off of sedation, the brain's arousal centers begin to come online first, which can result in agitation and irritability. Initial agitation typically resolves as the recovery process continues, but there can be long-term emotional effects of mild-to-severe TBI, such as apathy (estimated 42% in severe TBI), irritability (estimated 37% in severe TBI), dysphoria/depressed mood (estimated 29% in severe TBI), disinhibition (estimated 28% in severe TBI), and agitation (estimated 24% in severe TBI; see Chapter 10, this volume, and Ciurli, Formisano, Bivona, Cantagallo, & Angelelli, 2011). Chronic emotional changes in TBI are likely a result of frontal lobe damage. The orbitofrontal cortex, an important limbic structure in the prefrontal cortex for emotion regulation, is often damaged by closed head injury. Closed head injury can also result in white matter shearing that disrupts cortico–subcortical circuitry important in

emotional functioning. Another point for consideration is that, frequently, individuals with mild TBI report a greater number of symptoms compared with those with moderate-to-severe TBI, but the difference in symptom count is eliminated when controlling for posttraumatic stress (in veterans), because these conditions are often comorbid (see Belanger, Kretzmer, Vanderploeg, & French, 2010).

F. FOCAL HEMISPHERIC LESIONS

Depending on the location, severity, and recovery period, large vessel strokes can result in numerous emotional changes such as emotional blunting, irritability, depression, and lack of emotional awareness. There are some neuroanatomical principles with respect to emotion that are useful in considering potential emotional disruption following stroke. Damage to the right hemisphere, as in the case of right middle cerebral artery (MCA) stroke, is more likely to result in deficits in emotional perception, emotional flattening, and emotional awareness. Damage to the left hemisphere, as in the case of left MCA stroke, is more strongly associated with acute agitation and catastrophic reaction and increased rates of depression (Heilman et al., 2012). The likelihood of depression seems directly related to the anterior extent of the lesion within the left hemisphere.

V. CONCLUSION

This chapter provided a brief overview of the some of the complexities that may be involved in assessing patients for neurologically based emotional/mood changes. To fully appreciate these complexities, the neuropsychologist should have firm grounding in neuroanatomical principles, a keen understanding of differential diagnosis as it pertains to general psychiatric disorders, knowledge of various diseases and disorders that can affect neural circuitries of emotion in the brain, and an appreciation of the types of emotional behaviors that might emerge with neurologically based disorders. Although the typical neuropsychological exam generally involves administration of one or two standard mood questionnaires, such information may not be sufficient to capture the breadth and range of changes that may emerge with perturbations of emotion-related neural circuitries. Because different aspects of emotional behavior can become unraveled with neurologic disease, we believe that it is important to take a multicomponential approach to emotion assessment. This does not necessarily involve extra time or additional measures with every patient, but awareness when extra measures are important and necessary to help with diagnosis and treatment.

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Chapter 27

Greg J. Lamberty and Anita H. Sim

Somatic Symptom Disorders

Neuropsychological assessment always involves a process of differential diagnosis that includes consideration of numerous general health and personality factors. In recent years a good deal of attention has been paid to Somatoform Disorders, as originally described in the *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition* (*DSM–III;* American Psychiatric Association, 1980). However, clinical presentations involving the experience of multiple physical symptoms without a clear medical cause have been the focus of research since at least the mid-19th century. Further, clinicians have been interested in such patients for hundreds of years (Lamberty, 2008). Attributions regarding the causes of such symptoms have varied widely, but the basic belief that the symptoms are psychological in nature has remained the dominant view.

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I. DEFINITION/CLASSIFICATION

Historically, all previous editions of the *DSM* included descriptions of disorders that involved the reporting of physical complaints or symptoms that were presumably psychological in nature: 1952 (I), 1969 (II), 1980 (III), 1994 (IV), and 2000 (IV–TR). In the first *DSM* (American Psychiatric Association, 1952), the diagnosis of conversion reaction was used in a manner similar to that originally described by Freud. That is, emotional distress too difficult to process directly was "converted" to physical symptoms representative of underlying conflicts. In the second edition (*DSM–II;* American Psychiatric Association, 1968) hysterical neuroses included both dissociative and conversion varieties, with conversion retaining the characteristics described in *DSM–I*. In the *DSM–III* (American Psychiatric Association, 1980), the diagnostic category of Somatoform Disorders was proposed to account for a range of presumably more specific conditions that all involved the reporting and experience of troubling physical symptoms. The inclusion of somatization disorder (aka Briquet's syndrome) in *DSM–III* was an historical acknowledgment of the work of Briquet (1859) whose extensive monograph on patients with hysteria became the descriptive standard for these complex patients.

Although the *DSM–III* was a more descriptive and empirically oriented departure from the psychoanalytic formulations of psychiatry's past, the somatoform disorders category was unique in that it explicitly invoked a purely psychological etiology. This forced a dualistic view of these disorders in an increasingly biologically oriented psychiatry and relegated the diagnoses to an arguably less-consequential status where researchers were concerned. In addition, patients quickly came to understand that a diagnosis of a somatoform disorder meant that their problems were not real or were simply "all in their head." Rather than facilitating communication and appropriate treatment, the diagnoses often led to alienation. Finally, many of the diagnostic criteria outlined from *DSM–III* forward simply did not reflect what was being seen in typical clinical settings.

As it became clear that the Somatoform Disorders category had limited clinical utility, researchers began to view the number, nature, and severity of symptoms as indicators of potential clinical relevance. On the symptom-oriented end of the spectrum, there was interest in medically unexplained symptoms (MUS; Binder & Campbell, 2004), whereas a more syndrome-oriented approach involved the description of various functional somatic syndromes (FSS; Barsky & Borus, 1999). These approaches generally facilitated more relevant clinical research, as newer criteria and definitions were based on what was seen in clinical settings. The reality was that there was little relevance to *DSM*-based criteria, so the task became how to better understand

complex patient presentations that often involved physical complaints, distress, and preoccupation with illness or disease. For these reasons and others, many researchers and clinicians called for substantial revisions or abandonment of the *DSM* Somatoform Disorders category altogether (Engel, 2006; Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005; Noyes, Stuart, & Watson, 2008; Voigt et al., 2010).

The *DSM–5* (American Psychiatric Association, 2013) has revised the criteria for Somatic Symptom Disorders. As suggested above, the many concerns expressed about the Somatoform Disorders category resulted in a considerably modified set of diagnoses and criteria (see Table 27.1). Most notably, there is less emphasis on specific symptoms as diagnostic of a disorder and more attention to the report of symptoms that were distressing, involved preoccupation with symptoms, and resulted in problematic behaviors related to the symptoms.

Table 27.1. Changes in DSM Criteria for Somatic Symptom Disorders

DSM–IV–TR **(American Psychiatric Association, 2000)**	***DSM–5***
Somatoform Disorders	Somatic Symptom and Related Disorders
Somatization Disorder	Somatic Symptom Disorder
Hypochondriasis (predominant somatic symptoms)	
Undifferentiated Somatoform Disorder	
Pain Disorder	
Conversion Disorder	Conversion Disorder (Functional Neurological Symptoms Disorder)
Hypochondriasis (predominant anxiety)	Illness Anxiety Disorder
Other disorders	Other disorders
Factitious Disorder	Factitious Disorder
No specific diagnostic category	No specific diagnostic category
Psychological factors affecting medical condition	Psychological factors affecting medical condition

As indicated in Table 27.1, Somatic Symptom and Related Disorders (SSD) is put forth as the replacement for the *DSM–IV* category of Somatoform Disorders. Previously, the disorders (i.e., Somatization Disorder, Undifferentiated Somatoform Disorder, Hypochondriasis, and Pain Disorder) in this category focused on physical symptoms and a patient's distorted thinking related to the symptoms. In the new scheme, the criteria are more basic. Criterion A requires one or more somatic symptoms that cause significant distress or disruption, whereas Criterion B requires excessive thoughts, feelings, and behaviors related to the Criterion A symptoms. Criterion C specifies that the symptoms must have been present for more than 6 months. Finally, a Predominant Pain variant allows pain complaints to be substituted for the Criterion A symptoms. For all of the *DSM–5* SSD diagnoses, the suggestion that observed symptoms are psychological in origin is no longer present.

It is interesting to note that the other disorders in the SSD category do not involve the presence of significant somatic symptoms. These include Illness Anxiety Disorder, Factitious Disorder, and Psychological Factors Affecting Medical Condition. These disorders involve worrying about and/or complaining about symptoms but not actually experiencing them. Whether or not these changes in the diagnostic approach to such patients result in improved accuracy, it will be a positive development if they facilitate appropriate disposition and treatment.

II. FUNCTIONAL NEUROANATOMY

If *DSM* criteria are used as a basis for the diagnosis of a somatoform disorder, it should be clear that there is little or no evidence of neuroanatomical underpinnings for the various somatoform disorders. Most efforts to date have yielded inconsistent results or have been hampered by methodological limitations, such as small sample sizes, inadequate control of comorbid conditions, and nonrandom patient selection. As an example, it is not uncommon for a patient to be diagnosed with fibromyalgia by one provider and then be given a diagnosis of chronic fatigue syndrome (CFS) by another. The considerable overlap in symptoms among the various somatoform disorders has diminished the reliability and specificity of any pathological findings as well. Similarly, symptom overlap with other psychiatric disorders has confounded neuroimaging studies. Hsu et al. (2009) found, for instance, that fibromyalgia patients with affective disturbance demonstrated a reduction in gray/white matter volume compared with healthy controls. However, this difference disappeared when comparing fibromyalgia patients without affective disturbance,

suggesting that affective disturbance rather than fibromyalgia contributed to the gray matter volume reduction. The authors noted that, unlike previous investigations that controlled only for major depression, their study included generalized anxiety and dysthymia as potential confounds that could likely account for the different results. Similarly, a study of male veterans with psychogenic nonepiletic seizures found that they were more likely to have not only normal brain magnetic resonance imaging and neurological examinations than those with epileptic seizures but also greater levels of chronic pain, anxiety, and posttraumatic stress disorder (Dworetzky et al., 2005).

III. NEUROPSYCHOLOGICAL EVALUATION

The preferred approach to neuropsychological evaluation of somatoform disorders is to conduct a general examination of neuropsychological abilities, as opposed to investigating specific cognitive deficits (Lamberty, 2008). As noted in the previous section, the rationale for such an approach is based on the lack of definitive neuropathology underlying these disorders, as well as the nonspecific or equivocal nature of symptoms as described below.

It is essential to utilize methods that increase assurance that the information obtained from or about the patient is objective. In addition to standard neurocognitive ability measures, the neuropsychological assessment of somatoform disorders should include

- a review of available outside records,
- a comprehensive clinical interview,
- behavioral observations,
- an assessment of personality functioning, and
- an assessment of symptom/performance validity.

When reviewing external records, it is important to consider the expertise of the specific provider in dealing with the condition of interest. For instance, in cases of mild head injury, it is not uncommon for providers who are not well-versed in traumatic brain injury (TBI) to render a diagnosis of "severe TBI" based on the patient's current reporting of symptoms, as opposed to the acute injury characteristics. Research has also shown that primary care providers often fail to detect mood disorders (e.g., Garrard et al., 1998), which can result in an incomplete understanding of the patient's clinical picture and limit the utility of those records. Any inconsistencies between records and the patient's self-report or clinical presentation should also be noted and can prove to be clinically significant. Although in most routine clinical cases, clinicians often rely on the patient to provide relevant background information, obtaining written records, such as school transcripts and work records, is ideal whenever possible

(Board of Directors, 2007). Written records can help provide information on premorbid functioning and enhance the predictive accuracy of the assessments. Obtaining written records is particularly important in forensic and medico-legal cases, given that the potential for dissimulation may be stronger, and the neuropsychologist will benefit from reviewing as much information about the past and present functioning of the individual as possible.

As it is not uncommon for referrals to lack significant records, the clinical interview often serves as the primary source of information about the patient's somatic concerns. Making note of the coherence between patients' self-report of symptoms during the interview and their behavioral presentation assists in evaluating the objective nature of their complaints. For instance, individuals who describe their pain intensity as 10 out of 10, yet do not demonstrate any pain behaviors (e.g., shifting in their chair, grimacing, rubbing painful spots) during the course of a multiple-hour evaluation may raise reasonable suspicions about the accuracy of their self-report and the potential for symptom distortion. Similarly, obtaining detailed information about the patient's subjective cognitive limitations can be helpful, particularly when they are then compared with the objective findings (Lamberty & Nelson, 2012).

Clinicians should be aware that it is not uncommon for patients to inaccurately recall salient childhood events and past medical history and to underreport traumatic events (Binder & Campbell, 2004). Consistent with the well-established "good old days" bias, patients can also have a tendency to minimize their premorbid mental health history and view themselves as having been healthier in the past relative to their current state. Current mental health concerns can be minimized or denied as well. Obtaining medical and mental health records can help mitigate these effects.

As feasible, collateral interviews with family or friends can also provide information about problems that are apparent to them and assist in describing the history surrounding the presenting concerns. This information can be especially critical in those instances when an individual minimizes certain symptoms (e.g., depression, anxiety) or neglects to relay important history (e.g., history of trauma/abuse). The clinician should be mindful, however, of the potential role that family and friends can play in a patient's clinical presentation.

A. Cognitive Symptom Validity Measures

Although the impact of effort on neuropsychological test performance has been well-established, focused investigation of effort performance in somatoform disorders outside of disability contexts remains in its nascent stages. Incorporation of cognitive validity measures is essential,

however, given high rates of symptom exaggeration or malingering in FSS, particularly when assessing patients with significant secondary gain issues (Suhr & Spickard, 2007). In a survey of practicing members of the American Academy of Clinical Neuropsychology, for instance, the base rate of cognitive malingering was estimated at 31% in patients with pain/somatoform disorders and 35% in patients with fibromyalgia or chronic fatigue (Mittenberg, Patton, Canyock, & Condit, 2002). Consistent with this estimate, Gervais, Rohling, Green, and Ford (2004) investigated an archival patient database (n = 519) consisting primarily of largely somatoform disability claimants and found that 35% of their sample failed at least one or more symptom validity measures (i.e., Computerized Assessment of Response Bias [Allen, Conder, Green, & Cox, 1997], Test of Memory Malingering [Tombaugh, 1996], or Word Memory Test [Green, Allen, & Astner, 1996]). Studies utilizing the Minnesota Multiphasic Personality Inventory—2 (MMPI–2; Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989) have similarly demonstrated a relationship between cognitive effort test failures and somatic personality configurations (Brauer Boone & Lu, 1999; Larrabee, 1998).

Outside of the disability context, Suhr, Tranel, Wefel, and Barrash (1997) found that somatoform diagnosis had no effect on Digit Span age-corrected scale scores, with the somatoform group obtaining an average score of 8.9 (SD = 3.4). Therefore, although additional data are needed, research conducted to date suggests that disability status, rather than somatoform symptoms per se, may better account for failures on cognitive effort measures.

Although an exhaustive review of the literature is beyond the scope of this chapter, there are several well-established lines of research that neuropsychologists must consider when conceptualizing the neuropsychological profile of a somatizing patient. These include the following (see Binder & Campbell, 2004, and Binder, 2012 for reviews):

- cognitive deficits have high base rates even among "normal" population;
- cognitive complaints are not limited to somatoform disorders, but commonly are endorsed among various other medical or psychological disorders;
- cognitive complaints are strongly correlated with psychological distress; and
- self-report of cognitive complaints does not equate with actual impairments on neuropsychological ability measures.

B. Psychological Assessment

Numerous studies have revealed a robust relationship between psychological disturbance and somatoform disorders. Risk factors for

developing somatoform disorders include trauma (e.g., histories of abuse/rape, combat), certain personality configurations (somatoform, Axis II), female gender, and mood disturbance.

The MMPI–2 (Butcher et al., 1989) is the most widely used measure of personality and psychopathology. Somatoform disorders are primarily associated with dual elevations on Scales 1 (Hypochondriasis) and 3 (Hysteria). If Scale 2 (Depression) is considerably lower than Scales 1 and 3 (Conversion V pattern), then classic conversion symptoms may be present (Graham, 2000). Individuals with a 1-3/3-1 code-type present with a wide variety of vague somatic complaints, which tend to increase in times of stress. They tend to have limited psychological insight into their motivations and prefer medical explanations for their symptoms and reject psychological interpretations (Graham, 2000).

The RC1 Somatic Complaints scale in the MMPI–2–Restructured Form (MMPI–2–RF; Ben-Porath & Tellegen, 2008/2011) was developed to identify individuals who present with an unrealistically large number and type of somatic symptom complaints (Ben-Porath, 2012). The items contained in RC1 include gastrointestinal pain and neurological symptoms that are diagnostic of somatoform disorders, but exclude sexual symptoms. Elevated scores on RC1 have been associated with therapist's ratings of excessive somatic concerns in mental health outpatient samples (Sellbom, Ben-Porath, & Graham, 2006) and with a reliable prediction of a current or lifetime diagnosis of somatoform disorder in military veterans (Simms, Casillas, Clark, Watson, & Doebbeling, 2005). Importantly, although RC1 elevations are sensitive to somatoform symptoms, they are not specific to any one disorder among the somatoform conditions (Ben-Porath, 2012). RC1 elevations have also been associated with effort test failures, but are not recommended as a primary validity scale indicator (Ben-Porath, 2012).

C. Fatigue and Chronic Pain-Related Disorders

Fibromyalgia, CFS, and multiple chemical sensitivities all represent FSS that lack a clearly defined pathophysiological etiology but share a common constellation of pain, fatigue, cognitive complaints, and/or neuropsychiatric features that contribute to disability. To date, neuropsychological studies of these conditions have failed to yield consistent findings and have been hampered by methodological issues, most notably failure to incorporate symptom validity tests. As reviewed by Suhr and Spickard (2007), very few studies of cognitive impairment in fibromyalgia and CFS have controlled for poor effort, and most have neglected to report litigation/disability status of the patient group(s).

This is particularly troubling given that effort accounts for a significant amount of the variance in neuropsychological test scores and high rates of effort test failures are associated with disability status in somatoform samples. When controlling for effort, Suhr (2003) found no significant differences in cognitive performance between fibromyalgia and healthy control/chronic pain groups.

Although some studies have found evidence of neuropsychological deficits associated with these conditions, findings are often scattered among various tests and cognitive domains (Hart, Martelli, & Zasler, 2000) or are better accounted for by other factors such as depression, pain, or fatigue (Suhr, 2003). Based on the Hart et al. (2000) review, Suhr and Spickard (2007) underscored that "for any study finding impairment in a particular neuropsychological construct or with a specific neuropsychological measure, one can find another study that did not find impairment in that construct or with that measure" (p. 261).

Although evidence of neuropsychological impairment is equivocal, it is well-established that these conditions are more common in women (Jason et al., 1999), are often associated with histories of trauma/abuse (Walker et al., 1997), and have significantly high lifetime prevalence rates of mood and anxiety disorders (Walker et al., 1997). It is also well established that patients' subjective cognitive impairments far outweigh any objective evidence of impairment on neuropsychological testing (Binder & Campbell, 2004; Suhr, 2003). Consequently, it is essential that these variables be carefully assessed in the neuropsychological evaluation.

D. Psychogenic Nonepileptic Seizures

Although previous studies have suggested that patients with psychogenic nonepileptic seizures (PNES) demonstrate cognitive deficits akin to those with epileptic seizures (ES; e.g., Wilkus & Dodrill, 1989; Wilkus, Dodrill, & Thompson, 1984), more recent studies utilizing a symptom validity test (SVT) have demonstrated high rates of SVT failures in patients with nonepileptic seizures and have challenged these previously held assumptions. In 2006, Drane and colleagues investigated 166 patients who were referred for video-EEG monitoring for evaluation of their uncontrolled seizures. The patients also underwent neuropsychological testing, which included the Word Memory Test (WMT), a free-standing symptom validity measure. The authors found that patients with PNES were overwhelmingly more likely to fail the WMT ($n = 22$, 51.2%) than the patients with ES ($n = 3$, 8.1%) and that those PNES patients who did pass the WMT significantly outperformed the ES patients on neuropsychological

testing. Patients within the PNES group were also more likely to endorse histories of fibromyalgia and chronic pain (21%–33% of the sample), whereas such endorsement was virtually nonexistent in ES patients. On the basis of these data, the authors concluded that large numbers of patients with PNES produce invalid neuropsychological test scores and, consequently, that past studies investigating cognitive functioning in this population have likely produced distorted findings due to invalid data.

In addition to cognitive effort tests, investigations have also revealed that personality inventories such as the MMPI/MMPI–2 and Personality Assessment Inventory can be helpful in differentiating between ES and PNES patients (Williamson, Drane, & Stroup, 2007), particularly when combined with SVT data. Binder, Kindermann, Heaton, and Salinsky (1998) found that MMPI/MMPI–2 results (particularly elevations on Scales 1 and 2) combined with performance on the Portland Digit Recognition Test (Binder, 1993), a test sensitive to effort and motivation, correctly classified 80% of PNES when compared with ES patients.

IV. TREATMENT, INTEGRATION, COMORBIDITY, AND OTHER ISSUES

Patients are rarely referred for treatment with a sole diagnosis of a somatoform or somatic symptom disorder. Rather, questions emerge in the process of trying to provide appropriate diagnostic services for these complex individuals. It is frequently the case that neuropsychiatric symptoms (e.g., depression, anxiety) are present and treated pharmacologically, though this is mostly symptom based. That there is no clearly indicated treatment for somatoform patients suggests that the *DSM* diagnostic category was never adequate. Most research conducted on the various somatoform diagnoses was not geared toward identifying underlying causes, as it was presupposed that the etiology was "mental" or psychological. Thus, although there was concern in refining diagnostic precision, this did not spark much interest in validating treatments for patients with somatoform presentations. In recent years, this has changed with the realization of the magnitude of how such patients can affect the larger health care system (Barsky, Orav, & Bates, 2005). A brief review of various modalities with somatoform presentations is provided next.

A. Pharmacologic Interventions

Several meta-analytic studies have provided support for the use of antidepressant medications when treating patients with somato-

form symptoms and pain. A meta-analytic review of 94 placebo-controlled studies involving antidepressant treatment of patients with unexplained symptoms revealed a greater than threefold improvement in the report of symptoms relative to those treated with placebo (O'Malley et al., 1999). A smaller meta-analysis of 11 randomized controlled trials examining the effect of antidepressants in treating pain symptoms in somatizing patients showed significantly decreased pain intensity and a moderate-effect size compared with placebo patients (Fishbain, Cutler, Rosomoff, & Rosomoff, 1998). Moderate to large effect sizes for treatment of chronic pain patients with antidepressants were also noted in a meta-analysis of 39 studies (Onghena & Van Houdenhove, 1992). Generally speaking, antidepressants that act on both serotonergic and noradrenergic receptors (tricyclics and serotonin-norepinephrine reuptake inhibitors) may have greater analgesic effects than other antidepressants (Fallon, 2004).

B. Psychotherapy

A host of evidence-based treatments have emerged from the psychotherapy literature over the past 20 or so years, and many of them have shown promise in treating patients with somatic symptom disorders. With increasing pressure to treat patients with fewer sessions, briefer interventions have been emphasized, particularly those that can be used by primary care personnel. Motivational Interviewing is used to facilitate readiness for psychotherapy and significant lifestyle change and is a simple counseling approach that emphasizes meeting patients where they are and encouraging them to explore new ways to improve their life circumstances. It is used increasingly in primary care and has been helpful in preparing patients to make significant behavior change (Rollnick, Miller, & Butler, 2008).

The most widely studied modality for treating patients with somatoform disorders is cognitive behavior therapy (CBT). CBT has been studied extensively across a range of clinical diagnoses and disorders and is generally considered the most widely validated psychotherapy approach. In CBT, patients are directed to examine and challenge dysfunctional thoughts with the goal of changing behavior and mood in a positive way. Kroenke (2007) reviewed randomized controlled trials for patients with prominent somatic complaints (e.g., somatization disorder, MUS, and others) which included 34 studies and nearly 4,000 patients. In 13 of the treatment trials, CBT was used as the primary treatment modality (individual and group formats), with 85% of the studies showing significant improvement in patients. Sumathipala (2007) examined six review articles that included hundreds of somatoform disorder patients

treated with CBT. Overall findings of improved mood, decreased physical complaints, and improved quality of life were noted, as well as greater effectiveness when compared with antidepressant medications. Neither of the reviews used meta-analysis, and readers were cautioned regarding the scarcity of meaningful long-term outcomes. These limitations suggest the need for more prospective studies with broader outcome measures, specifically for patients with primary somatic symptom disorders.

Over the past 30 years, the concept and practice of mindfulness has been increasingly used in medical and mental health settings. John Kabat-Zinn is credited with developing mindfulness-based stress reduction (MBSR), which has been used to treat a range of patients with pain, anxiety, and stress-related disorders (Kabat-Zinn, 1982). Mindfulness-based interventions have developed out of traditional Far Eastern practices that accept that the mind and body are intimately related. Mindfulness-based strategies encourage focused attention and awareness of current states, while assuming a nonjudgmental attitude. This includes the acceptance of both positive and negative emotional and physical states and facilitates the appreciation of the present moment (Kabat-Zinn, 2009). A burgeoning literature supports the benefits of mindfulness-based approaches in managing chronic medical illnesses, including chronic pain, cancer, fibromyalgia, migraine headache, and morbid obesity (Bonadonna, 2003; Carlson, Speca, Faris, & Patel, 2007; Sephton et al., 2007; Veehof, Oskam, Schreurs, & Bohlmeijer, 2011). In addition to MBSR, other psychotherapy approaches incorporate mindfulness techniques and have been used with populations dealing with pain and multiple somatic complaints, most notably Acceptance and Commitment Therapy (ACT; Dahl & Lundgren, 2006; Hayes, Strosahl, & Wilson, 1999).

C. Complementary and Alternative Treatment Approaches

There is considerable overlap between mindfulness approaches and yoga as it is commonly practiced in the West. Yoga involves several mind/body practices, including physical postures, controlled breathing, meditation, and relaxation. It has long been thought that yoga can have positive effects on health and well-being (Nayak & Shankar, 2004). In a recent review on yoga and mindfulness, positive outcomes including reduced symptoms, improved quality of life, and emotional well-being were noted in randomized trials with a range of patient groups with chronic health and somatoform concerns. Importantly, yoga is very adaptive and is well-suited for work with patients with a number of physical limitations.

Although patients with somatic complaints are often disinclined to engage in psychotherapy, the idea of physical exercise is intuitively more sensible and straightforward. An interesting study by Peters, Stanley, Rose, Kaney, and Salmon (2002) involved a randomized controlled trial of aerobic exercise versus stretching in a large sample (n = 228) of primary care patients with MUS. Several measures of health care utilization, medication usage, mood state, and perceived disability were examined before, during, and 6 months after the trial. Both aerobic exercise and stretching groups showed decreased use of medications and fewer primary care visits in the 6-month period following the trials. Results also indicated that the beneficial effects were related to the number of sessions attended. The authors suggested that the outcomes may have been facilitated by social support, resulting in decreased reliance on primary care providers. Although such effects are difficult to parse, it seems clear that patients with somatoform concerns are reluctant to engage in psychotherapy, but tend to improve in general terms with increased activity and socialization.

V. CONCLUSION

The effect of somatoform symptoms on neuropsychological evaluation results is an important consideration in a large proportion of cases referred for assessment (Lamberty, 2008). The neuropsychologist must have an understanding of how such presentations affect test results and how to assess them in a way that will ultimately lead to effective recommendations. Further, an awareness of the range of interventions that are effective or that show promise will assure that neuropsychologists will continue to be consulted in these very complex circumstances.

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Index

About the Editors

Michael W. Parsons, PhD, ABPP, graduated from the University of Virginia and earned his doctoral degree in clinical psychology from the University of Texas at Austin. He completed an internship at the University of Florida/Shands Medical Center and a postdoctoral fellowship in clinical neuropsychology at the Medical College of Wisconsin (MCW). He was on the faculty of MCW briefly before joining the faculty of West Virginia University (WVU) School of Medicine, where he became an associate professor. During his 7 years at WVU, Dr. Parsons directed the clinical psychology internship program and developed a program for clinical functional magnetic resonance imaging (fMRI). He joined the Cleveland Clinic in 2007, serving as Staff in the Section of Neuropsychology with appointments in the Center for Behavioral Health and the Burkhardt Brain Tumor Center.

Dr. Parsons's research has included numerous functional brain imaging studies of processes of learning and memory. His work has included studies of the clinical applications of fMRI. More recently, his research has focused on neuropsychological and neuroimaging studies of clinical conditions, including brain tumor and concussion. He publishes regularly in scholarly journals and presents at scientific conferences. He has participated in studies funded by private foundations, the National Institute of Mental Health, and the Department of Defense. He participates regularly in training at the undergraduate, graduate, and postgraduate levels. His clinical interests include

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Thomas A. Hammeke, PhD, ABPP, graduated summa cum laude from Fort Hays State University and obtained his doctoral degree in clinical psychology from the University of South Dakota. He completed an internship at the Clement J. Zablocki Veterans Affairs Medical Center (VAMC) in Milwaukee and a postdoctoral fellowship in clinical neuropsychology at the Medical College of Wisconsin (MCW). He then joined the faculty in the Department of Neurology at the MCW, where he became a professor and has been the director of the Division of Neuropsychology for 25 years. While there, he also assisted in development and served as the director of training of an American Psychological Association–accredited postdoctoral residency program. He transitioned to the Department of Psychiatry and Behavioral Medicine at MCW in 2010 and became the lead neuropsychologist for the Polytrauma Program at Zablocki VAMC and the preceptor for a postdoctoral residency program in clinical neuropsychology.

Dr. Hammeke has received research grants from the National Academy of Neuropsychology (NAN), American Heart Association of Wisconsin, and NFL Charities, among other organizations and foundations. His research has concentrated on the use of neurocognitive tests and functional imaging techniques in the study of neuropathological conditions, in particular, traumatic brain injury and epilepsy. He has coauthored over 75 peer-reviewed research publications, 25 book chapters, and five books, and has made scientific presentations on his work in North America, Europe, and North Korea. He has served as an associate editor for the *Journal of the International Neuropsychological Society* and on the editorial boards of *Neuropsychology* and *The Clinical Neuropsychologist,* and has done ad hoc research reviews for 11 neuroscience journals and the National Institute for Disability Research and Rehabilitation. He was the founding president of the Association of Postdoctoral Programs in Clinical Neuropsychology, and served as president of the American Psychological Association (APA) Division 40 (Neuropsychology), and the American Board of Clinical Neuropsychology. He is a fellow of APA (Division 40) and NAN. He was honored with the Distinguished Neuropsychologist Award from the American Academy of Clinical Neuropsychology in 2013.