Clinical Handbooks in Neuropsychology

William B. Barr
Chris Morrison *Editors*

Handbook on the Neuropsychology of Epilepsy

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For KBM—in recognition of all the sacrifices he has made for me.
To CNB—my wife and my love.

Preface

Epilepsy is a prevalent condition affecting approximately 1 % of the general population with approximately 30 % of those individuals suffering from refractory seizures. While medical management of seizures and other symptoms (e.g., mood and behaviors) is most common, a significant number of these individuals can also benefit from various neurosurgical interventions. The cognitive, behavioral, and emotional effects of this condition and associated etiological comorbidities can be as debilitating as those caused by ongoing seizures. As a result, clinical neuropsychologists have become key members of medical teams that evaluate and treat patients with epilepsy. In fact, for the past 50 years, neuropsychologists have played an integral role in epilepsy surgical management teams with the goal of helping to reduce the risk for postoperative deficits in language and memory, as well as in developing treatment plans for cognitive, behavioral, and mood issues that may be present before and/or after medical/surgical interventions.

As neuropsychological services are needed to meet established standards of care in a specialized epilepsy treatment setting, neurology and neurosurgery teams are increasingly turning to their local neuropsychology colleagues to engage their services in the context of developing new epilepsy care centers and surgical programs. Over the years we have been contacted by many neuropsychology and medical colleagues who have found themselves transitioning into these new settings and being asked to join the assessment and treatment decision-making process (including type and extent of surgery) of individuals with epilepsy. The conceptualization and development of this book was in part generated from such requests.

While doctoral-level practitioners can be highly skilled in clinical neuropsychology, the issues, procedures, and special considerations within the epilepsy population are unique in some respects and even a well-trained neuropsychologist will need some supplementary education and training to function optimally in this setting and to provide the best care possible to this population. Dedicated training to obtain fluency in the issues and skills needed to serve this patient group is often obtained within the context of an epilepsy center-based postdoctoral fellowship and/or under the supervision of an experienced neuropsychologist within an established comprehensive epilepsy center. That said, such training is not always available and/or practical. For example, the established neuropsychologist who has been

asked to expand their role within a new epilepsy program at their center cannot leave their paid position for prolonged training at another clinic. The current volume is written with these issues in mind and with the goals of outlining the range of services provided by neuropsychologists in specialized epilepsy centers and serving as an accessible, introductory "how-to" guide.

Given this "skills-based" goal, the format of the book is a radical departure from traditional literature reviews and aggregate data style papers and chapters that are available on the neuropsychology of epilepsy. In the chapters that follow detailed descriptions, reviews of the recent literature, and clinical vignettes, as well as concrete recommendations on how to conduct specialized procedures, are provided. The information contained in this book will also be useful to more veteran practitioners who want to know the "latest information" on neuropsychological practice involving patients with epilepsy. These advanced readers will be able to obtain a quick review of the research literature on these procedures in addition to "inside tips" from practitioners with years of experience in conducting these tests.

Neurologists and other medical professionals involved in the care of patients with epilepsy will also find this book to be helpful. Many medical practitioners consider the work of clinical neuropsychologists in their settings to be somewhat "mysterious." This book attempts to change this perception by making the details of neuropsychological practice more accessible. While medical professionals might be familiar with some of the research findings relevant to neuropsychological procedures in epilepsy patients, they are not likely to have been exposed to more "inside knowledge" on how neuropsychologists actually perform these procedures. The information provided in this book will help inform neurologists in charge of running epilepsy centers on the tasks required of neuropsychologists before making offers of employment. Added knowledge on these procedures will also enhance other professionals' ability to understand and better appreciate the information provided in neuropsychological reports.

The organization and content of this volume emphasizes working with adults aged 20–55 (those most often considered for surgery) as well as the presurgical special procedures that can involve evaluation of cognition, mood, and behavior. In Section I, Neuropsychological Assessment Across the Lifespan, the chapters provide an overview of neuropsychological assessment in patients with epilepsy with separate attention to how and why evaluations are performed in children and in older adults. Seizures often occur for different reasons in children as compared to older individuals and the influence of medical and surgical treatments, methods of assessment, reasons for referral, and types of recommendations needed are often unique at these ends of the age spectrum.

Section II focuses on evaluation of the epilepsy surgical candidate wherein there is an obvious role for the clinical neuropsychologist. However, many of the procedures covered in this section also apply to patients undergoing neurosurgery for focal lesions, such as brain tumors or vascular malformations, where there may be perturbation of cerebral cortex en route to the lesion and/or cortex may be affected by surgical removal of the lesion itself. The section opens with a review of the purposes of neuropsychological testing in this context, including efforts to identify seizure localization/lateralization, estab-

lish a presurgical baseline, predict surgical outcome, and provide outcome markers that can be useful in clinical research. There is review of common methods for assessing various domains of functioning with elaboration on the typical neuropsychological test findings in the most common populations of epilepsy surgery patients. Importantly, there is also a review of many of the potential confounds to neuropsychological test data as well as a case vignette to highlight the process and integration of cognitive data for rendering a neuropsychological opinion of relevance to the surgical team.

The subsequent chapters within Section II review various specialized procedures associated with presurgical evaluations. Functional techniques such as fMRI and MEG, are becoming more widely used clinically to identify language lateralization. Research to understand how these methods can be used to characterize the functional integrity of specific brain regions, such as hippocampal support of memory functioning, is burgeoning with some promising data emerging. In Chaps. 8 and 9 the reader is presented with the basics for understanding fMRI and MEG as well as the methods for cognitive testing that can be integrated into these protocols.

Though functional imaging techniques are becoming more widely available, there continue to be many centers that use the Wada procedure in at least a subset of surgical candidates to identify language dominance and memory functionality in each of the hemispheres. This "deactivation" procedure remains the gold standard for obtaining select types of information. Chapter 5 provides an overview of the Wada procedure and the various methods for performing the test, calculating outcome variables, and clinically interpreting the scores. The Medical College of Georgia protocol is used to take the reader through an example of how the procedure might be conducted.

When we have been contacted by neuropsychologists and neurologists at other hospitals, the Wada procedure and electrocortical mapping of language eloquent cortex are the two procedures that we have been asked to provide education and training on the most frequently. The challenge here is that these procedures are the least amenable to learning via textbook study and are the least standardized in terms of assessment of cognition and behavior. In an attempt to operationalize mapping of language eloquent cortex as much as possible, Chap. 6 provides an overview of the procedure, details for understanding how to conduct the procedure, and common methods used for assessing various aspects of language functioning. The overall structure of this chapter and the case example within are probably the most "manualized" in organization of all the chapters in this volume.

While there is an obvious role of structural imaging in the presurgical work-up, this procedure less commonly has a direct role for neuropsychology. That said, highlights within Chap. 7 include how variables obtained from structural imaging are being used in combination with cognitive and behavioral data to better understand functional neuroanatomy. Given the complexity of the brain, this area of research will continue long into the future and the critical role of the neuropsychologist in developing, applying, modifying, repeating, and interpreting cognitive and behavioral measures will remain important in facilitating high-quality and well-controlled research in this area.

Section III takes the reader through a few of the special topics and populations that the clinician will need to be familiar with when working with an epilepsy population. The chapters address the very high frequency of psychiatric comorbidity in epilepsy patients as well as psychiatric conditions/behaviors that may be confused with seizures. Clinical neuropsychologists need to be well versed in assessing mood issues, personality disorders, conversion disorders, and behavioral and pharmacological treatments for psychiatric features in a person with an epilepsy syndrome and/or with conversion, psychogenic nonepileptic seizures. Clinical neuropsychologists, with their understanding of functional neuroanatomy as it relates to cognition AND mood (i.e., that mood disorders in these individuals can be reactive and/or the result of the underlying epilepsy), as well as their training in psychopathology and psychological interventions are uniquely positioned to assist in evaluation and treatment planning.

The epilepsy population is extremely diverse in terms of cognitive ability and level of adaptive functioning. Because about a third of epilepsy patients can be fairly well controlled with one medicine, a clinical neuropsychologist may encounter very high functioning individuals with advanced education, challenging vocations, and well-controlled seizures. These individuals can present with cognitive complaints, perceived cognitive changes, and/or other emotional/adjustment factors related or unrelated to their neurological condition. In contrast, other patients may be cognitively devastated by their epilepsy syndrome and the underlying brain abnormality(ies) that produce their seizures (e.g., tuberous sclerosis, migrational abnormalities, complex epilepsy syndromes). When first confronted with extremely low functioning individuals, the neuropsychologist might not immediately appreciate how a neuropsychological evaluation could be of value to the treatment team. Chapters 13 and 14 address issues related to assessing individuals at these extremes of functioning to highlight the special considerations in these evaluations and the modifications in testing approach that the neuropsychologist might make.

Finally, performing neuropsychological assessments in multicultural, multilingual, and/or non-English speaking individuals is a challenge ubiquitous to the field neuropsychology and not unique to the epilepsy population. However, because individuals may travel from different regions, even different countries, to obtain care at a specialized clinic, practitioners in a tertiary care epilepsy center may encounter a higher proportion individuals whose language and/or cultural background is disparate from that of the neuropsychological test items and test normative samples we have available. Thus considerable caution and limitations to interpretation of data are warranted. In the final chapter of this volume, special considerations in assessing ethnically and linguistically diverse populations are discussed. While the content of this chapter is heavily weighted to assessment of Spanish speakers (or bilingual Spanish/English speakers), the general principles regarding the assessment process and application of available assessment tools to a person of a different linguistic and cultural background remain relevant.

New York, NY, USA

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Neuropsychological Assessment of Patients with Epilepsy

1

William B. Barr

Introduction

Neuropsychological assessment provides essential and unique information for diagnosing and managing patients with epilepsy. While the goal of most medical and neurological approaches is naturally to cease or reduce seizures, the symptoms most commonly associated with epilepsy, neuropsychology focuses more on understanding and measuring disorders of cognition and behavior associated with epilepsy and using this information to aid in diagnosis and treatment planning.

Neuropsychology provides, in many ways, the most comprehensive approach to evaluating the patient with epilepsy by allowing the clinician to integrate medical, developmental, and social factors in coming to an understanding of how these factors influence cognitive and behavioral functioning. With its occurrence in an estimated 1 % of the population, epilepsy is a relatively common disorder that is seen on a frequent basis by most neuropsychologists in practice settings. Clinical neuropsychologists also play important roles in epilepsy specialty centers by providing information that is useful for diagnosis, outlining functional strengths and weaknesses, and tracking the effects of various treatments.

The goal of this chapter is to introduce the reader to many of the general issues relevant to neuropsychology as it applies to assessment of patients with epilepsy. It will begin with a brief review of epilepsy and seizures and will continue with a description of neuropsychological assessment of general adult patients (ages, 20–55) who are evaluated in a medical or neurological setting. Chapters focusing on neuropsychological assessment of patients from other age groups and those evaluated in a surgical and other settings will follow in this volume.

Background

Seizures and Epilepsy

Epilepsy is a condition defined by both a combination of recurrent seizures and alterations in behavior (Engel & Pedley, 2008). It is important to establish a basic understanding of epilepsy and the seizures characterizing the disorder. Epilepsy is a heterogeneous condition characterized by multiple seizure types. It is quite prevalent, with statistics indicating that its occurrence is as common as breast cancer and other medical conditions receiving much more publicity. Among neurological conditions, it is more prevalent multiple sclerosis, muscular dystrophy, cerebral palsy, and Parkinson's disease combined. Public

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understanding of epilepsy remains poor despite its prevalence. Much of this is the result of continuing stigma associated with epilepsy, dating back to centuries old misconceptions about associations between seizures and supernatural phenomena, including demonic possession. Medical professionals and patient advocacy groups have worked hard together to remove much of the stigma associated with epilepsy.

The diagnosis of epilepsy is based on clinical criteria, including the presence of recurring seizures, with the neurophysiological basis of the seizures confirmed through neurodiagnostic testing. Electroencephalography (EEG) is generally considered the "gold standard" for diagnosing epilepsy. Neurologists trained in EEG are able to identify the presence of epilepsy through analysis of characteristic waveforms associated with seizures. Information from the EEG can also be useful in localizing the onset of the seizures. Additional information is often provided through structural brain imaging using computed tomographic (CT) or magnetic resonance (MR) technology, with the latter known as providing the most detailed information regarding neuroanatomic abnormalities associated with seizures. Functional brain imaging with single photon emission computed tomography (SPECT), positron emission tomography (PET), or functional MRI (fMRI) can also provide useful information regarding reductions in localized blood flow and/or metabolism associated with the location of the seizure focus. Interested readers can go to Chaps. 7 and 8 for more information about those modalities.

It is important to remember, however, that epilepsy is defined as a condition by its recurring seizures. There are a number of situations, such as in acute drug intoxication or CNS infection, where one might develop a single seizure, but not have epilepsy. Seizures in patients with epilepsy may manifest in various forms. The terms used to describe different types of seizures can be confusing at times, given the fact that many patients and even some health care professionals persist in using outdated terms such as *petit mal* or *grand mal* to describe variants of seizure activity. Use of these older terms obscures many of the important etiologic, symptomatic, and neuroanatomic characteristics of seizures and should be avoided altogether.

Our understanding of epilepsy and seizures is forever changing, due to ongoing developments in science and technology. The International League Against Epilepsy (ILAE) is a multidisciplinary group of health care professionals that has been responsible for providing some standardization to the terms that are used across the world for characterizing seizures and various epilepsy syndromes. In the year 2010, the ILAE provided an important update and revision to the concepts and terminology used for classification of seizures and epilepsies (Berg et al., 2010). A listing of the revised classification of seizures is provided in Table 1.1.

In the 2010 ILAE classification, one finds the well-known distinction between generalized seizures and focal seizures, differing in the characteristics of their underlying seizure networks, which are known to be bilaterally distributed in the case of generalized seizures and more localized in focal seizures. Generalized seizures can include tonic–clonic seizures, which is the most obvious and dramatic symptom of epilepsy, in addition to more subtle types of generalized seizures such as absence attacks and myoclonic seizures, which are seen mostly in childhood epilepsy syndromes.

Terms such as "simple" and "complex" partial seizures have been dropped from the new classi-

Table 1.1 Classification of seizures—ILAE revised (2010)

Generalized seizures
Tonic–clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Unknown
Epileptic spasms

fication as a result of common misuse or misunderstanding of those terms. The current classification makes much less specification regarding focal seizures, placing more emphasis on describing these seizures based on features that are most useful for a given purpose. The symptomatic characteristics of focal seizures are varied and reflect functional characteristics associated with the brain region from which they originate. For this reason, neuropsychologists and other professionals interested in the study of behavior have shown a marked interest in focal epilepsy and its tendency to provide a "window" into underlying brain mechanisms.

Focal seizures often begin with an aura, which commonly reflects the anatomic origin of the initial site of abnormal brain activity. Seizures originating in temporal or limbic zones will often be preceded by onset of a visceral feeling or behavioral manifestations involving cognition or emotion. For example, seizures originating from the hippocampus are commonly characterized by mnestic changes, such as the well-known déjà vu phenomenon whereas those involving the amygdala might have more of an affective component, such as the subjective feeling of fear. Auras emanating from more posterior brain regions might involve somatosensory or visual changes associated with parietal or occipital regions respectively. Details regarding these auras provide valuable information about the localization of the seizure onset in addition to helpful clues about the nature of the functional impairment that might exist when the individual is not having seizures.

The evolution of focal seizures can be varied in nature, with the variability reflecting the track of abnormal electrical activity through a complex neural network involving subcortical and cortical brain regions. Some seizures will not evolve beyond the level of the aura, which makes them brief and simple in their characteristics. Other focal seizures will spread into a generalized tonic–clonic convulsion. In between these extremes, seizures will involve varying changes in consciousness, which are often difficult to characterize. In some cases, individuals are totally aware of their surroundings. In other cases, individuals might experience changes in consciousness accompanied by behaviors that seem out of their control. These behavioral "automatisms" have formed the basis of much debate on the role of consciousness in behavior, both from a medical and legal perspective. Table 1.2 includes a summary of terms that are now used to describe the range of impairment associated with focal seizures. Neuropsychologists are urged to become familiar with the terminology from this table as a starting point for providing a full clinical description of the phenomena reported by their patients.

Epilepsy Syndromes

In the past, clinicians evaluating and treating patients with epilepsy focused primarily on seizure types and EEG abnormalities when classifying various forms of epilepsy. With technological developments in brain imaging and molecular genetics, clinicians now focus more on characterizing epilepsy syndromes, which now extend beyond the disorder's electroclinical characteristics. A listing of the syndrome recognized by the ILAE is provided in Table 1.3. Neuropsychologists working with epilepsy patients are encouraged to be well acquainted with these syndromes.

Table 1.2 Descriptors of focal seizures according to degree of impairment during seizure—ILAE Revised (2010)

Without impairment of consciousness or awareness with observable motor or autonomic components. This roughly corresponds to the concept of "simple partial seizure." "Focal motor" and "autonomic" are terms that may adequately convey this concept depending on the seizure manifestations.
Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary.
With impairment of consciousness or awareness. This roughly corresponds to the concept of complex partial seizure. "Dyscognitive" is a term that has been proposed for this concept.
Evolving to a bilateral, convulsive seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term "secondarily generalized seizure."

Table 1.3 Electroclinical syndromes and other epilepsies—ILAE Revised (2010)

Electroclinical syndromes arranged by age at onset
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Febrile seizures plus (FS+) (can start in infancy)
Panayiotopoulos syndrome
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BECTS)
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
Late onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Lennox–Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau–Kleffner syndrome (LKS)
Childhood absence epilepsy (CAE)
Adolescence—Adult
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
Less specific age relationship
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
Distinctive constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion–hemiplegia–epilepsy
Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Benign neonatal seizures (BNS)
Febrile seizures (FS)

A full discussion of the pediatric epilepsy syndromes is beyond the scope of the current discussion. Excellent reviews of this material are provided in Chaps. 2 and 12. However, from the perspective of a neuropsychologist working with adults with epilepsy, it is important to remember that many forms of the disorder are developmental in nature, meaning that patients seen as adults might have experienced one of these developmental syndromes during childhood. This is particularly true for adults with focal epilepsy beginning in childhood secondary to perinatal stroke, brain tumor, traumatic brain injury, or any one of a number of causes of localized brain disturbance. It is important to recognize that cognitive deficits in these early onset cases will appear different from those in cases where seizures develop in adulthood. In other cases, epilepsy syndromes resulting from genetic or

metabolic causes will be exhibited in adults as causes of intellectual disability. It is clear that the scope of the neuropsychological evaluation will be affected by specific characteristics and needs of the patient.

Most pediatric epilepsy syndromes characterized by the presence of absence or myoclonic seizures do not extend into the adult years. There are, however, some important exceptions. Juvenile myoclonic epilepsy (JME) is a form of epilepsy developing in adolescence or early adulthood characterized by bilateral repetitive myoclonic jerks occurring predominately in the upper extremities. These are, in many cases, accompanied by generalized tonic–clonic seizures and possibly absence attacks. While the condition is considered a form of generalized epilepsy, neuropsychological studies find that affected patients exhibit a pattern of neuropsychological test performance characterized by intellectual functioning within the average range and deficits in executive functions including planning, concept formation, and verbal fluency (Piazzini, Turner, Vignoli, Canger, & Canevini, 2008). More generalized patterns of neuropsychological dysfunction have been identified in patients with idiopathic generalized epilepsy (Shehata & Bateh Ael, 2009). There is now interest in determining whether there are, in fact, structural brain abnormalities in patients with generalized epilepsies that might provide an explanation as to why some forms, such as JME, show more localized patterns of neuropsychological dysfunction.

Neuropsychologists working with epilepsy patients should become very familiar with focal epilepsy syndromes as these are seen in more than half (60 %) of patients with epilepsy and are those most often referred for assessment of cognitive functioning. Temporal lobe epilepsy is the most well known and frequent of the focal epilepsy syndromes, occurring in approximately 70–90 %. Most of these patients demonstrate an onset of seizures emanating from the medial temporal lobe region, involving structures such as the hippocampus and amygdala. This form of the disorder, often referred to as mesial temporal lobe epilepsy (P. D. Williamson et al., 1993), is often seen in individuals with a history of febrile convulsions, auras of a visceral nature, and seizures beginning in the first decade of life. Hippocampal sclerosis, a condition characterized by gliosis and atrophy of the hippocampus, is the most common pathological feature. Patients with temporal lobe seizures originating from a more lateral neocortical onset often have auras involving illusory auditory or visual phenomena in addition to more complex behavioral automatisms (Pacia et al., 1996). The cause of epilepsy in these cases is varied with etiologies ranging from brain tumors, cortical dysplasia, to head trauma.

From a neuropsychological standpoint, patients with mesial temporal lobe epilepsy are known to have intact intelligence with particular deficits in word finding and memory retention (B. P. Hermann, Seidenberg, Schoenfeld, & Davies, 1997). Memory deficits in these patients are believed to result from a primary disruption of consolidation processes secondary to the hippocampal pathology. These patients are thought to differ on a neuropsychological basis from patients with lateral temporal lobe seizures, who are thought to exhibit more difficulty with memory encoding in addition to a more pronounced impairment in naming skills (Hamberger, Seidel, Goodman, Perrine, & McKhann, 2003).

Frontal lobe epilepsy is the second most frequently observed form of focal epilepsy. Seizures in patients with frontal lobe seizures include a combination of unusual movements and/or vocalizations often accompanied by abnormal motor activity (Patrikelis, Angelakis, & Gatzonis, 2009). Like temporal lobe epilepsy, one encounters seizures manifested specifically by changes in awareness or consciousness, previously referred to as complex partial seizures. Differentiating patients with frontal lobe epilepsy from those with temporal lobe epilepsy based on neuropsychological testing has proven more difficult than what was suggested by the early literature (Barr & Goldberg, 2003; B. P. Hermann, Wyler, & Richey, 1988; Milner, 1964). However, there is now published evidence indicating that

patients with frontal lobe epilepsy exhibit more impairment in motor programming and deficits on tests of response inhibition (Helmstaedter, Gleibner, Zentner, & Elger, 1998).

Seizure localization in posterior cortical regions is much less common than those originating from the temporal and frontal lobes. Given the infrequency of the posterior cortical epilepsies they are often lumped into a general classification of "extratemporal seizures." Seizures originating from the occipital lobe are characterized by visual auras, eye blinking, alterations in consciousness, and motor phenomena (Jobst et al., 2010). Those with an onset in the parietal lobe are often accompanied by somatosensory phenomena but little else that is specific to a disruption of that part of the brain (P. D. Williamson et al., 1992). Deficits in attention and processing speed are seen in some patients with occipital lobe seizures, but neuropsychological evidence of disruption of higher or visuoperceptual or language functions associated with focal seizures originating from the posterior cortex is mixed (Guerrini et al., 1997).

It is important to remember that focal epilepsy can be the result of any one of a number of different pathological processes. Brain tumor is the second most frequent cause of seizures. Stroke is another common cause of epilepsy with seizures known to develop at a higher rate following embolic events and from cerebrovascular events involving the middle cerebral artery. While neuropsychological profiles in patients with seizures resulting from one of these conditions are clearly influenced by lesion location, one must also consider the influence of seizure variables, medication effects, and other medical and emotional characteristics of the patient (Morrison & Nakhutina, 2007).

Treatment of Epilepsy

Nearly every patient with an established diagnosis of epilepsy will undergo some form of medication management with antiepileptic drugs (AEDs). While these drugs are known to be effective in reducing seizures through effects on neuronal irritability, they also have a simultaneous effect on neuronal excitability, which has the potential to reduce cognitive efficiency. Many of the most commonly used AEDs, their indications, and their effects on cognition are listed in Table 1.4. There is an interesting history to some of the older drugs, where their effectiveness for reducing seizures was identified "accidentally" in laboratory studies with animal models. While these drugs are known to be effective in treating multiple types of seizures in humans, they are also known to have significant effects on cognition, which was not a focus of study when the use of these drugs was first initiated. As a result, many of the newer AEDs were developed with the goal of modulating alternative neuronal mechanisms with the ultimate goal of improving seizure reduction with minimal effects on cognition.

Many patients require treatment with more than one AED to achieve adequate seizure control. Clinicians prescribing these medications must consider the balance between the need to minimize seizure recurrence and the desire to reduce side effects as polypharmacy is the number one treatment factor known to affect cognitive functioning (Loring, Marino, & Meador, 2007). Surprisingly little is known about the profile of cognitive side effects associated with specific AEDs. Most of this is the result of the

Table 1.4 Cognitive side effects of antiepileptic drugs (AEDs)

	Epilepsy type	Cognitive effects
Older AEDs		
Phenobarbital	Generalized, focal	Significant
Phenytoin	Focal, generalized	Moderate
Carbamazepine	Focal	Moderate
Sodium valproate	Generalized, focal	Moderate
Newer AEDs		
Felbatol	Focal	Mild
Lamotrigine	Generalized, focal	Mild
Vigabatrin	Focal, generalized	Mild
Gabapentin	Focal	Mild
Topiramate	Focal, generalized	Moderate
Tiagabine	Focal	Mild
Oxcarbazepine	Focal, generalized	Mild
Zonisamide	Focal	Mild
Levetiracetam	Focal, generalized	Mild

multitude of methodological challenges one faces when attempting to conduct controlled studies on AEDs in patient samples (Kwan & Brodie, 2001). Some of this has been the result of a failure of neuropsychology, as a field, to agree upon a set of measures to evaluate cognitive functions in randomized controlled drug trials, much in the manner that the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) is used in Alzheimer's disease studies (Mohs et al., 1997).

What is known from existing research is that the newer drugs have less severe side effects than the older drugs. It is generally known that phenobarbital is the drug with the most potent cognitive side effects. Based on the older literature, it has generally been assumed that other drugs, such as phenytoin and carbamazepine, have more moderate level effects on attention, processing speed, and memory retrieval. At one point, investigators were arguing whether these drugs' influence on processing speed was the primary result of attentional or motoric factors (Dodrill, 1975, 1992; Trimble & Thompson, 1983).

Findings on newer AEDs have shown more generalized effects on cognitive functioning. Many note that some drugs, such as lamotrigine, have only minor CNS side effects in addition to some "alerting" properties associated with beneficial effects on mood (Kwan & Brodie, 2001; Loring et al., 2007). Topiramate, an extremely effective antiepileptic agent, is the one among the newer drugs that stands out as having differential effects than the other newer drugs. Patients taking this drug have been described as having more effects on cognition than other drugs with additional effects reported on executive functions and language skills including naming and verbal fluency. It has been demonstrated that these effects can be reduced with careful titration and minimal dosing, when possible (Loring, Williamson, Meador, Wiegand, & Hulihan, 2011).

In practice, neuropsychologists need to recognize that patients with epilepsy will require variable levels and types of medications to control their seizures. Some patients tend to report more cognitive side effects than others. In counseling patients receiving medication management, one should emphasize that, based on results of experimental studies, the AED effects on cognition are known to be minimal. The clinician should also inform them that the initial cause of the epilepsy and the ongoing effects of seizures are likely to be exerting an effect on their cognition and that their subjective sense of attention or memory disturbance is not likely to be caused solely by the drugs they are taking. They also need to be reminded that while the drugs are known to have some side effects, these are likely to be minimal in comparison to the decline in cognitive functioning that would potentially result if one were to discontinue medication management altogether, which would lead to uncontrolled seizures in many patients taking AEDs and the possibility of a steady decline in cognitive functioning.

While most patients with epilepsy achieve adequate seizure control with AED treatment, there remain a substantial number who become "drug-resistant," which is defined as a failure following an appropriate trial of two (or more) appropriately used medications. It is now estimated that 30–40 % of patients will eventually become refractory to treatment, defined by medical terms (Kwan, Schachter, & Brodie, 2011). One must also consider a number of other factors when determining whether an individual has reached a treatment refractory state. One of these involves whether the patient has "socially disabling" seizures, which are seizures that reach a point where they have a marked detrimental effect on one's lifestyle. It is important to recognize that some patients, possibly in the context of intellectual disability, can tolerate the occurrence of daily seizures, if they are residing in a safe and supportive environment. Other patients, such as those working in professional roles or with family responsibilities, might not be able to tolerate one seizure per year without sustaining a substantial disruption on their lives. It is important to realize that cognitive functioning, as assessed through neuropsychological testing, can provide significant information in helping to determine whether patients are achieving optimal treatment of their seizures.

There are a number of alternatives to drug treatment for epilepsy, although most are used in combination with drugs in the majority of cases.

Surgery is the most well known of these treatments, with results demonstrating that significant relief from seizures can be obtained in approximately 70 % of patients undergoing surgical resection of the epileptic focus (Wiebe, Blume, Girvin, Eliasziw, & Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group, 2001). However, it is recognized that there is risk to decline in verbal memory and naming following these procedures, with greater levels of impairment observed in those undergoing left side surgery (Sherman et al., 2011). More details about the neuropsychological aspects of epilepsy surgery can be found in Chap. 4. Vagal nerve stimulation is another one of the other available nondrug treatments involving surgical placement of a programmable pulse generator in the patient's chest. While the efficacy of this treatment is considered somewhat modest, there have been some suggestions that it has less of an effect on cognitive functioning with possible improvement seen in some patients. Information about cognitive functions associated with some of the newer epilepsy treatments such as electrical or pharmacological stimulation is currently limited.

Neuropsychological Assessment

Clinical neuropsychologists are considered essential members of the interdisciplinary teams found at most epilepsy centers. In fact, guidelines established by the National Association of Epilepsy Centers consider doctoral level neuropsychologist among the staff members recommended for staffing at all Level 3 and 4 epilepsy specialty centers (NAEC Guidelines, 2010). The guidelines encourage neuropsychologists working in these settings to have postdoctoral training in neuropsychology with specific experience in using neuropsychological tests for evaluation of epilepsy surgery along with a background in interpreting results of intracarotid amobarbital procedures (Wada Tests).

Neuropsychologists play a number of important roles in an epilepsy center by virtue of the unique training they have received. While many associate neuropsychologists with assessment services, the role they play in specialized epilepsy centers often extends far beyond testing. As found in many clinical settings, neuropsychologists are valued for their ability to integrate information obtained through various sources. As a result, they are often the only clinicians present on the team who are in a position to provide a comprehensive and balanced description of the patient based on their medical, cognitive, emotional, and psychosocial characteristics. Neuropsychologists are also able to provide valuable input to the treatment team by taking into account unique characteristics of the patient's social and cultural background when making clinical recommendations.

There are numerous reasons to conduct a neuropsychological assessment on a patient with epilepsy. Some of these recommended by the NAEC are listed in Table 1.5. While most attention is typically based on assessment for epilepsy surgery (see Chap. 4), there are many other questions that can be addressed by performing neuropsychological testing on a patient with epilepsy.

Neuropsychological assessment is often requested in situations when there is a need to know a patient's particular strengths and weaknesses. This knowledge will be put to use in different ways depending on the patient's age and the context of their daily activities. For example, a student in college might need this information to receive academic accommodations while another patient might benefit from receiving

Table 1.5 Guidelines for neuropsychological services: National Association of Epilepsy Centers (NAEC, 2010)

1. Comprehensive neuropsychological test batteries for:
(a) Evaluation of cerebral dysfunction for vocational and rehabilitative services.
(b) Localization of cerebral dysfunction in evaluation for epilepsy surgery.
(c) Basic assessment of characterological and psychopathological issues.
2. An established referral arrangement for comprehensive management of psychogenic nonepileptic events.
3. Clinical psychological services for assessment and basic treatment of emotional disorders associated with chronic epilepsy.

information from testing to guide vocational planning. Other patients complaining of cognitive difficulties will appear for testing with the goal of verifying whether their subjective sense of memory or concentration impairment is "real" and finding if there is a way that something can be done to reduce it.

Evaluations by neuropsychologists are also commonly obtained when the treatment team desires input on cognition to help in making a differential diagnosis. This information might come in handy when there is a need to determine whether a geriatric patient's reported memory disturbance is related more to the influence of ongoing seizures or to the effects of an underlying neurodegenerative process such as Alzheimer's disease. In other cases, testing can be useful in monitoring effects of nonsurgical treatments such as the side effects of medications.

While neuropsychological assessment of a patient with epilepsy generally focuses on evaluation of cognitive functions it is important to recognize that clinicians working in epilepsy centers also play a role in addressing mental health issues. As listed in Table 1.5, neuropsychologists often play a significant role in evaluating and treating patients with psychological nonepileptic seizures (PNES) and other types of psychiatric disorders. Details regarding these types of evaluations are provided in Chaps. 9 and 11.

Clinical Interview

Many consider the neuropsychologist's clinical interview to be the most important component of the assessment process. In many cases, it is the opportunity for the clinician to obtain a direct description of symptoms and important historical elements while observing the patient's behavior in an open-ended condition. The Russian neuropsychologist, A.R. Luria, emphasized the "preliminary conversation" as the point where the clinician develops initial theories about the patient and his or her condition that will guide the choice of assessment procedures (Luria, 1966). The interview often serves as the time when the clinician arrives at a set of relevant hypotheses that will either be confirmed or disconfirmed through the results of formal testing. In a patient with epilepsy, the clinical interview provides an occasion for the neuropsychologist to pose questions directly to the patient regarding the characteristics of their seizures in addition to how the seizures affect their cognitive and behavioral functioning.

Before considering the elements of a clinical interview with an epilepsy patient, it is useful to present a model for understanding how epilepsy affects behavior and cognition. In a comprehensive review published in 1984, Bruce Hermann and Steven Whitman provided a model for understanding epilepsy's effects on behavior and personality, which can be adapted easily to explain cognitive factors (B. P. Hermann & Whitman, 1984). The model conceptualizes behavior in patients with epilepsy as influenced by various effects, beginning with brain-related factors, such as the initial cause of the epilepsy or the effects of seizures. Secondly, one must consider treatment effects, particularly the influence of AEDs and surgery. Lastly, one needs to acknowledge that various "non-brain" variables will affect behavior, including social variables and the effects of mood. Figure 1.1 provides a depiction of the relative contributions of these various factors. Characterizing the effects of these three variables on cognition can be very helpful to clinicians when attempting to integrate information relevant to the assessment and when providing feedback to patients regarding the effects of the epilepsy on their attention and memory functioning.

When beginning the interview, the neuropsychologist should start with a description of the nature and purposes of the testing. The examinee must have the ability to provide informed consent to proceed with the evaluation, consistent with the ethical principles of the American Psychological Association (APA, 2002). During this point of the evaluation process, the examiner should be in a position to address any questions the patient might have about the testing or their condition and life in general. It is also important to inform the patient that a report will be prepared and will be sent to

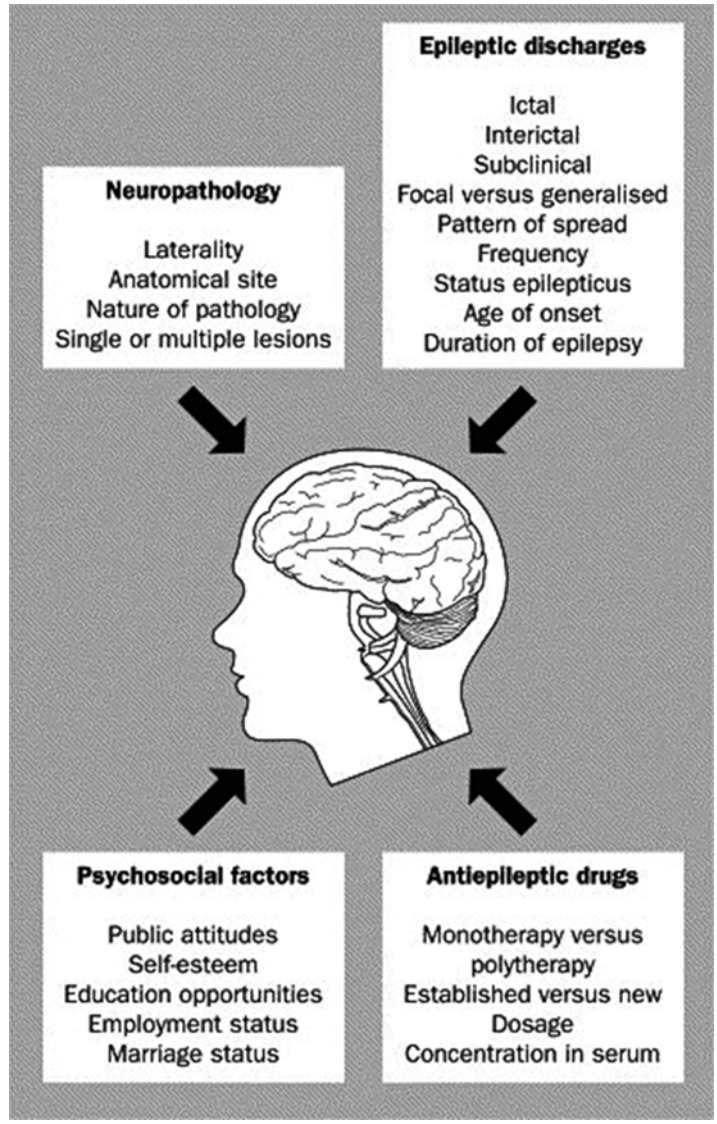

Fig. 1.1 Factors contributing to cognitive and behavioral impairment in epilepsy (from Kwan & Brodie, 2001. Reproduced with permission)

the referring party. One might also ask whether the report should be sent to any other parties and what arrangements will be made to provide direct feedback to the patient regarding the final results.

The information-gathering portion of the interview should begin with the patient's subjective description of their symptoms and how the symptoms affect their daily lives. Based on research findings, we know that approximately 70 % of patients with epilepsy experience a subjective disturbance of memory, making this the most common cause for a referral for neuropsychological assessment (Thompson & Corcoran, 1992). However, the clinician should always remember that patients and referral sources are not psychologists and, as a result of a lack of knowledge, may refer to cognitive difficulties more generally as memory difficulties in cases when attention or executive functions are the actual domains that are affected. One will encounter many cases where a patient with epilepsy will complain of memory difficulties and it is discovered that their major problem is more consistent with impairment in executive functions such as organization

or planning. A guided description of the patient's symptoms and the context in which they arise will provide the neuropsychologist with valuable insights into the presenting problem.

After coming to an understanding of the patient's cognitive complaints it is important to turn to their seizure history. To begin with, it is important to have a good idea of when the seizures began. While this might be assumed to be when the patient first came to medical attention, that is not likely to be the exact point when the seizures first appeared. Many patients will describe unusual experiences occurring during their lifetime that, in retrospect, were likely to have been the effects of focal seizures, long before they received medical treatment. It also helps to differentiate when in life the patient developed habitual seizures, as opposed to other types of seizures that had appeared at some point during their lifetime. In this context, it is important, for example, to determine whether a patient ever experienced a febrile seizure during infancy or early childhood (<3 years), which is known to be a strong risk factor for mesial temporal epilepsy in a patient presenting later in life with a history of focal seizures.

At some point, the interview will turn to the patient's own description of their seizures. It is often useful to obtain these descriptions in spite of the fact that the medical record might contain detailed information on their seizure history. As in other contexts, it is often good to go back to the original source for a full description. Coming to an understanding of the patient's subjective account of the seizure, as opposed to what others have told them, will help the interviewer determine to what degree consciousness is affected during the seizure and whether there are any specific subjective phenomena that might provide clues to localization. Negative information, such as the patient claiming to be totally amnestic for the seizures, can also be extremely helpful, as it has been shown that those who are amnestic for seizure activity are more likely to experience bitemporal abnormalities on EEG (Palmini, Gloor, & Jones-Gotman, 1992).

A number of studies over the past 40 years have examined the effects that various seizure variables have on neuropsychological test performance. From a neuropsychological perspective it is important to estimate the age of onset of the epilepsy, as it is known that an onset of seizures early in life will have a more generalized and detrimental effect on test performance (Dikmen, Matthews, & Harley, 1975; Elger, Helmstaedter, & Kurthen, 2004). In terms of seizure type, it is clear that generalized tonic–clonic seizures provide a greater impact on neuropsychological functioning than other types of focal seizures (Dodrill, 1986). It is also important to determine whether the patient has ever experienced *status epilepticus*, a condition characterized by prolonged or clustered seizures, which is known to provide a significant long-term disruption to memory and other functions in some patients (Dodrill & Wilensky, 1990).

Patients often have a difficult time quantifying the frequency and severity of their seizures. While many are asked to keep a diary on their seizure activity, these are often found to be inaccurate as a result of the fact that some patients are not aware that a seizure has occurred and, without the help of a reliable collateral informant, might not be able to specify how many seizures they are having with any acceptable degree of reliability. While it is clear that having frequent seizures is not good for one's cognitive functioning, it is not totally clear how "seizure burden," a concept designed to capture a combination of seizure type and frequency, affects performance on neuropsychological testing. Further research on this topic is clearly needed.

A good clinical interview will also address the etiology of the epilepsy, as this is likely to have a major impact on neuropsychological functioning, independent of the effects of seizures. This should start with a detailed neurodevelopmental history, beginning with details on the patient's birth and early maturation. This will include information regarding the age at which the patient began walking and talking. One will also want to learn details of the patient's school history and whether there was any evidence of learning disability (LD) or attention deficit hyperactivity disorder (ADHD) identified by parents, school, or medical personnel. Information regarding the patient's favorite subjects in school, or those subjects they disliked

immensely, has the potential of providing valuable input to cognitive deficits that might have originated in childhood. It is also important to learn about the patient's social development, in terms of their ability to establish friendships and peer relationships. One might also ask if they remember being bullied or excluded from activities as a result of their seizures.

In patients with a history of focal seizures, it is important to obtain medical information on the causative factor, as this will also have a likely impact on neuropsychological functioning. In those patients with a history of brain tumor, one should understand when symptoms of the tumor first appeared and whether that coincided with the onset of epilepsy. One must also know the pathological type and grade of the tumor in addition to whether any surgery has been performed. In cases of traumatic brain injury (TBI), it is necessary to gain information on the nature of the initial injury, including whether there was a loss of consciousness, post-traumatic amnesia, or coma. One must come to an understanding of the overall severity of the injury, as it is clear that epilepsy will occur much more frequently following a severe level of TBI as opposed to mild TBI (Lowenstein, 2009). Neuropsychologists will also need to obtain details regarding illness and onset of seizures in patients with epilepsies resulting from infectious and other medical causes.

One must always remember that a patient with epilepsy is first and foremost a person living their life who will face the same medical, psychological, and social factors that affect all other individuals undergoing a neuropsychological evaluation. The clinician must be in a position to determine whether there are any ongoing medical factors, such as hypertension, hypercholesterolemia, diabetes, or cardiac abnormalities that might affect the patient's neuropsychological functioning. One must know whether the patient has undergone any type of surgical procedure, whether or not it is related to treatment for epilepsy. It is important to have information on the full regimen of medications the patient is taking. While the cognitive side effects of AEDs are reviewed above, one must also determine whether the patient is taking any other medications for other physical illnesses or ailments with a potential for similar side effects. The interviewer should be aware if there is a family history of epilepsy or any other types of family based neurological or neuropsychiatric disorders. As with any evaluation, the clinician should determine whether there is any history of alcohol or drug abuse.

Patients with epilepsy are known to have a higher rate of mental illness than the general population. This topic is covered in detail in Chap. 9. It is estimated that approximately 30 % of patients with epilepsy will encounter depression at some point in their lives (Kanner, 2013). A substantial number of patients with epilepsy also experience anxiety disorders. Clinicians should ask whether the patient has ever been under any form of psychological or psychiatric treatment. The neuropsychologist will need to conduct a detailed assessment of mood disorder symptoms during the clinical interview and should be in a position to refer for psychiatric treatment, if indicated. While seen more rarely, one should also be on the lookout for the presence of psychotic symptoms, either emerging in the context of seizure clusters or occurring totally independent of seizure activity.

It is helpful to learn details about the patient's social background. One might ask questions on where they were born and raised. At this point, one can get information about the family background, including the number of siblings. It is often helpful to know details about family members and their educational and occupational backgrounds. As a result of the condition and its effects on cognition and education, some patients with epilepsy may be prone to feeling as if they have achieved less than others in their family, which can have an effect on them from a psychosocial perspective.

It is very important for the neuropsychologist to have a full understanding of the patient's cultural background before proceeding with the evaluation. One must know first whether English is the patient's native language. The vast majority of neuropsychological tests used in North America are developed and normed in English.

When planning the evaluation, it is important to understand whether or not the patient can complete the testing with the use of standard instruments, or whether testing in their native language will be required. More detailed discussion of this issue is provided in Chap. 14. Secondly, it is known that patients' and families' understanding and perception of illness and seizures varies widely among cultures. Neuropsychologists, by virtue of their specialized training, are in a position to recognize many of these factors and integrate them into their evaluation and interpretation of the test findings.

Turning back to the patient, it is helpful to learn details about their educational history. One will also want to obtain a detailed occupational history with emphasis on how seizures and cognitive effects were expressed during the course of the individual's employment and how employers, supervisors, and coworkers reacted to these issues. It is often helpful to break down the patient's workday and activities to determine if any workplace accommodations are warranted if supported by the neuropsychological test findings.

Finally, one will want to know details about the patient's home and social life. Asking about who is living with the patient in their current home environment is a good way to address relationship issues without any ties to traditional values. It is important to understand the quality of relationships and how these individuals react and support the patient in terms of their epilepsy. At this point, one might also obtain information about the patient's interests and their daily activities. One might also query on how seizures and/or cognitive issues affect their ability to perform and enjoy these activities.

Neuropsychological Testing

Background on Testing

While the specific roles that clinical neuropsychologists will play in each epilepsy center might vary, their responsibilities will almost always include neuropsychological assessment as a primary function. It is important to remember that the process of neuropsychological assessment is rather broad and encompasses test selection, interpretation of the data, and integrating the findings with clinical information obtained from other sources. One must not confuse the assessment process with that of test administration, which is clearly an important component of the overall assessment process, but requires less extensive training with heavy reliance on procedural guidelines provided in test manuals.

It is recognized that professional preparation for practice in neuropsychological assessment requires extensive coursework and clinical training in neuropsychology and knowledge about epilepsy syndromes and effects of seizures and treatments on cognitive functions. In terms of education and training, this typically requires a doctoral degree in professional psychology (e.g., Ph.D. or Psy.D.), clinical training in generic clinical psychology, and 2 years of postdoctoral training in clinical neuropsychology.

Practice in clinical neuropsychology requires a professional license in psychology, consistent with local state or provincial laws. The scope of knowledge and skills required for effective practice in clinical neuropsychology, with its focus on the study of the science of psychology, statistical methods, and psychometrics, is distinctly different from the education and training obtained in receipt of a typical medical degree or in other health care fields, which do not include a comparable level of education in any of these topics. It is becoming more and more common for clinical neuropsychologists to obtain board certification (e.g., ABCN) to formally document their training and proficiency. Commensurate with the medical model and the expectations made of our physician colleagues, obtaining board certification is highly recommended for those planning to work in comprehensive epilepsy centers.

Results from professional surveys indicate that over 50 % of neuropsychologists utilize ancillary staff, such as graduate school trainees or technicians, to administer neuropsychological tests under their direct supervision (Sweet, Meyer, Nelson, & Moberg, 2011). Results of a survey conducted on neuropsychologists practicing specifically in epilepsy centers indicate that 63 % employ technicians to assist with test administration

(Djordjevic & Jones-Gotman, 2011). The process is analogous to that of a radiologist who interprets images produced from the work of a technician rather than obtaining the images directly. The professional component lies in the interpretation and communication of the results, rather than from collecting the data. This practice, when used by neuropsychologists, is recognized legislatively in nearly every state and is reimbursed by third-party payers across the country including the Centers for Medicare and Medicaid Services (CMS) with specific Current Procedural Terminology (CPT) codes (e.g., CPT code 96119). Interested readers can obtain further details about the use of technicians in neuropsychological testing through published statements provided by professional organizations including Division 40 of the APA (APA Division 40, 1991), the National Academy of Neuropsychology [NAN, (Puente, Adams, Barr, Bush, & N. P. P. Committee, 2006)], and the American Academy of Clinical Neuropsychology (AACN, 1999).

Neuropsychological tests provide an empirically based method for evaluating and measuring cognition and behavior. Successful use of these tests requires adherence to standardized administration guidelines and the proper use of psychometric and normative principles when interpreting the results. The guidelines for neuropsychological services provided in Table 1.5 above include general reasons for administering test batteries. However, from a purely empirical basis, the information provided by standardized testing is most useful in advising the treatment team regarding three basic questions: (1) has there been a general decline in the patient's level of intellectual functioning, (2) are there weaknesses or impairments in specific aspects of cognitive functioning, and (3) has there been a relevant and identifiable change in performance or functioning on testing performed between Time 1 and Time 2?

Clinicians treating patients with epilepsy are very interested in knowing whether a given patient is experiencing any form of cognitive decline that can be attributed to the epilepsy or seizures. Results from longitudinal studies indicate that a progressive pattern of cognitive decline can be identified in adults with epilepsy with duration of illness appearing to be the most reliable predictor of its occurrence (Seidenberg, Pulsipher, & Hermann, 2007). More detailed information about this issue can be found in Chap. 3. Scores from neuropsychological testing naturally provide the optimal data for addressing this issue. Empirical documentation of cognitive decline can be provided by demonstrating a statistically rare discrepancy between current test performance and measures used to estimate expected "premorbid" levels of functioning or through demonstrating on repeat testing that the interval change in test scores exceeds what is expected by "chance" or as a result of "practice effects." Clinicians using neuropsychological tests to address these questions must therefore be adept at using psychometric principles for interpreting base rates of discrepancy between test scores and formal statistical methods for assessing changes in test scores over time.

Based on contents of the clinical descriptive literature, we are well aware that patients with epilepsy can exhibit "normal" levels of intellectual functioning while experiencing specific deficits in cognitive areas such as attention, executive functions, and/or memory. However, identifying specific weaknesses in cognitive functioning in a valid and reliable manner through neuropsychological testing can be a challenge to even the most seasoned clinical neuropsychologist. When using a comprehensive battery of tests, one must be very careful to avoid making a Type I statistical error resulting from erroneously identifying a deficit based on what might be statistically "chance" findings. The field of neuropsychology has been paying more attention to this issue in recent years with an increasing number of published papers demonstrating the frequency of "abnormal" test scores found in healthy control samples who have completed neuropsychological testing (Binder, Iverson, & Brooks, 2009; Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008). Neuropsychologists working in epilepsy centers must be aware of these base rates of abnormal test findings and exercise care when reviewing a sheet of scores from a neuropsychological test battery by making sure that a sufficient number of

scores are in the abnormal range and that the pattern of abnormal scores fit some reasonable conception of an identifiable cognitive deficit.

One of the most powerful uses of neuropsychological testing is to identify the presence of cognitive changes over time. Making inferences from changes in test scores obtained over two or more evaluations provides information that is useful for measuring treatment effects from medication and/or surgery and, as discussed above, can be helpful in identifying changes associated with a pattern of cognitive decline. Neuropsychologists working in the field of epilepsy have been at the forefront of developing empirical methods for assessing interval change. Valuable information from a pioneering set of studies performed in the 1990s has been used to determine "normal" patterns of change over time in samples of epilepsy patients using a variety of different tests (Chelune, Naugle, Luders, & Awad, 1991; B. P. Hermann et al., 1996). Data from these studies, combined with empirical methods for assessing change, such as the reliable change index (RCI) and standardized regression-based (SRB) methods, have provided the field with a statistically rigorous methodology for assessing change associated with drug treatment, surgery, and other factors (Barr, 2002). Neuropsychologists are encouraged to use this information when assessing changes in their patients.

Neuropsychological Test Battery

There is no universally accepted approach to conducting a neuropsychological assessment in epilepsy patients or in those with any other clinical condition. Over the years, methodological approaches to neuropsychological testing have fluctuated between an emphasis on purely empirical or quantitative methods, such as that which is characterized by use of a fixed-standardized approach such as the *Halstead-Reitan Neuropsychological Test Battery* (*HRNB*) (Reitan & Wolfson, 1985) and an emphasis on purely flexible approach using clinical or qualitative methods, such as what might be found using the *Boston Process Approach* (Kaplan, 1988) to assessment. However, according to recent surveys, a more hybrid approach to assessment is now used by the majority of practicing neuropsychologists, characterized by what is termed as a flexible battery of tests, chosen for use with specific patient groups. This approach is based on the use of a core battery of tests with various patient groups supplemented by adding or subtracting certain tests from the battery depending on characteristics and needs of the patient. This is the approach recommended for use when evaluating patients with epilepsy.

A neuropsychological test battery for epilepsy, based significantly on use of measures from the HRNB, was developed by Carl Dodrill in the 1980s (Dodrill, 1978). However, based on results from experimental studies on cognition in epilepsy, most clinicians evaluating patients with epilepsy using a flexible battery of tests for assessment of adults are encouraged to include measures of general intelligence, attention, executive functions, language, and memory. There is currently no universally accepted battery of tests. Common with traditions in neuropsychology, individuals from various centers tend to use tests that are most familiar to them based on a number of scientific and nonscientific factors including the preference of their clinical supervisors. This has led to differences in test usage based on the regional location of the epilepsy center. There are efforts in the field of neuropsychology to phase out the tendency to choose tests based on comfort level in favor of selecting a set of measures that has been validated for clinical decision-making through empirical research (Chelune, 2010).

Clinicians aiming to develop a clinical test battery are often informed by learning which tests are used by their colleagues. Several surveys of neuropsychological test usage among clinicians have been published (Rabin, Barr, & Burton, 2005), including some conducted on neuropsychologists working in specialized epilepsy centers. Djordjevic and Jones-Gotman (2011) conducted a recent survey from 75 respondents working in epilepsy centers spanning across 17 countries, with the majority (65 %) of them from North America. The results of the survey are listed in Table 1.6. The findings demonstrate that, on average, the duration of neuropsychological

Table 1.6 Summary of survey of neuropsychological test usage among neuropsychologists working in specialized epilepsy centers (Djordjevic & Jones-Gotman, 2011)

Domain	Most use (>50 %)	Many use (20–50 %)
Intelligence		WAIS/WASI
Attention	WAIS Digit Span	Letter-Number Sequencing
	WAIS Digit Symbol	WMS Spatial Span
	Trail making Test	
Executive	WCST	Stroop
	Letter Fluency (COWAT)	
	Category Fluency	
Motor	Grooved Pegboard	Finger Tapping
		Motor Strength
Language	Boston Naming Test	Token Test
	WAIS Vocabulary	WRAT
Visuospatial	WAIS Block Design	Judgment of Line Orientation
	WAIS Picture Completion	Facial Recognition Test
	Rey Complex Figure Copy	
Memory	WMS	RAVLT
	Rey Complex Figure Recall	CVLT
Mood		BDI
		BAI
Personality		MMPI
		PAI

BAI Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *COWAT* Controlled Oral Word Association Test, *CVLT* California Verbal Learning Test, *MMPI* Minnesota Multiphasic Personality Inventory, *PAI* Personality Assessment Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *WCST* Wisconsin Card Sorting Test, *WAIS* Wechsler Adult Intelligence Scale, *WASI* Wechsler Abbreviated Scale of Intelligence, *WMS* Wechsler Memory Scale, *WRAT* Wide Range Achievement Test

evaluations performed in epilepsy centers is 5.6 h. The number of tests administered varies widely, with a range from 12 to 56 tests considered part of a "standard" battery. Neuropsychologists across the globe are in general agreement about the domains of functioning assessed in patients with epilepsy and the type of core battery that is used, although there is certainly evidence that many centers continue to use their own specific choice of tests for many applications.

The lack of a standardized battery of neuropsychological tests has posed a problem for epilepsy investigators attempting to conduct large-scale multicenter investigations of cognition or medication side effects. Recent recommendations for a standardized set of tests have been made by a subcommittee of the National Institute of Neurological Disorders and Stroke (NINDS) of the Common Data Elements (CDE) Project in Epilepsy (Loring, Lowenstein, et al., 2011). The aim of this group was to produce a battery of tests that would enable some form of standardized data collection to facilitate direct comparisons across studies and to enable data pooling in NINDS-funded studies. The committee chose tests with the goal of capturing relevant areas of cognitive functioning across a variety of epilepsy syndromes. Tests were more likely to be included if there was evidence of widespread use in epilepsy studies and if the test is in the public domain. A listing of the recommended CDE battery is provided in Table 1.7.

There is surprisingly little information regarding the use of cognitive test batteries in patients with epilepsy. While measures such as the Woodcock-Johnson battery (WJR-III) (Woodcock, McGrew, & Mather, 2001) have been used in children with epilepsy, there is little information on the use of this measure in adults, in spite of there being ample norms for this group. Investigators from the United Kingdom have demonstrated some success using the Adult Memory and Information Processing Battery (AMIPB) (Baxendale, Thompson, & Duncan, 2008; Baxendale, Thompson, Harkness, & Duncan, 2006), a set of tests including speeded cancellation tests and measures of verbal and nonverbal memory. There is little information on the value of using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998) or the Neuropsychological Assessment Battery (NAB) (Stern & White, 2003) in patients with epilepsy in spite of growing use of these batteries in North America.

In spite of the entry of computer tests into the market, only a few studies have reported the use of these batteries with epilepsy patients (Witt, Alpherts, & Helmstaedter, 2013). Hoppe and

Table 1.7 Epilepsy common data elements: recommended neuropsychological instruments—adult (16+ years old) (Loring, Lowenstein et al., 2011)

Domain	Test
General IQ Estimation	American National Adult Reading Test (AmNART)
Formal IQ Testing[a]	Wechsler Adult Intelligence Scale (WAIS-IV)
	Wechsler Abbreviated Scale of Intelligence (WASI)
Executive Function	Trail making A and B
	Wisconsin Card Sorting Test (WCST-64)
Motor Speed	Grooved Pegboard
Language	Boston Naming Test (BNT)
	Controlled Oral Word Association Test (COWAT)
	Animal Naming
Verbal Memory	Rey Auditory Verbal Learning Test (AVLT)

[a]Either WAIS-IV or WASI is recommended

colleagues demonstrated "fair" to "good" diagnostic utility of computerized measures in comparison to established neuropsychological tests. Based on initial investigations examining the reliability and validity of computerized tests, there is a long way to go before there will be any evidence that such measures have any diagnostic advantage over traditional neuropsychological tests (Hoppe, Fliessbach, Schlegel, Elger, & Helmstaedter, 2009).

Intellectual Functioning

As mentioned above, measuring and tracking cognitive decline is one of the most important functions a neuropsychologist plays in a comprehensive epilepsy center. Assessment of intellectual functioning is therefore an essential component of the neuropsychological test battery. Administering a measure of intelligence provides one of the most sensitive means of tracking cognitive functions primarily as a result of the fact that these tests provide composite scores that are the most reliable measures found within the test battery. Furthermore, these batteries provide assessment of a number of different functional domains that can be compared statistically, based on the fact that they are co-normed and provide means for assessing individual strengths and weaknesses through comprehensive statistical methods.

One of the most important issues encountered in the context of a neuropsychological evaluation is whether or not the patient has experienced any limitation in general intellectual functioning secondary to epilepsy or any other causes. Standardized tests of intelligence are generally used for this purpose with the Wechsler Adult Intelligence Scale (WAIS), now in its fourth edition (WAIS-IV) (Wechsler, 2008), as the most commonly used of these tests. Recent editions of the WAIS have moved from a previous focus on intelligence quotient (IQ) scores to analysis of four cognitive composite scores, which is more consistent with results of factor analytic research on intelligence. This allows clinicians to examine and measure factors that are more relevant to the effects of various clinical disorders. There is a rather large literature on the use of the various Wechsler scales in patients with epilepsy, providing a rationale for standard use with that population.

While the WAIS also provides valuable information for specific diagnostic purposes, such as the identification of intellectual disability (ID), there is evidence that its use in epilepsy centers has declined over the years (Djordjevic & Jones-Gotman, 2011). Some clinicians might prefer the use of other tests, such as the Stanford Binet Intelligence Scales, now in their fifth revision (SB5) (Roid, 2003), for evaluation of those patients with IQ scores falling below 70. When addressing the issue of ID, the clinician needs to be sure to take into account all of the issues relevant to that diagnosis, as spelled out by definition provided by the American Association of Intellectual and Developmental Disabilities (AAIDD) (A. T. C. Committee & Schalock, 2007). In adults with possible ID it is often helpful to supplement the IQ testing with assessment of adaptive functioning through either interview (e.g., Vineland Adaptive Behavior Scale-II) (Sparrow, Cicchetti, & Balla, 2006) or questionnaire (Adaptive Behavior Assessment Scale—ABAS-II) (Harrison & Oakland, 2003) techniques.

There are a number of other measures of intelligence that are available, although much less is known about their validity and clinical utility in evaluating cognitive functions in patients with epilepsy. Some criticize the Wechsler scales as taking too long to administer. Some measures designed to provide IQ estimates in a relatively short period of time, including the Shipley-Hartford Scale (Shipley, 1940), have been available for many years but have not been widely used in patients with epilepsy. Dodrill (1981) demonstrated that the Wonderlic Test of Intelligence (Wonderlic, 2004) can be used effectively for rapid assessment of intelligence in epilepsy patients. A number of shorter forms of the WAIS, including the abbreviation methods recommended by Kaufman (Kaufman & Lichtenberger, 2005), have been used in some studies as well as the Wechsler Abbreviated Scale of Intelligence (WASI-II), which is the short form developed by publishers of the WAIS (Wechsler, 2011). While norms for adults are available for other tests, such as the Woodcock Johnson Tests of Cognitive Abilities (WJ3) (Woodcock et al., 2001) and the Reynolds Intelligence Screening Tests (RIST) (Kamphaus & Reynolds, 2003), these measures do not appear to be used commonly in adults with epilepsy. In some cases, where native language might be an issue tests such as the Raven Standard Progressive Matrices (RSPM) (Raven, Raven, & Court, 1998) or Test of Nonverbal Intelligence (TONI-4) (Brown, Sherbenou, & Johnson, 2010) can be used for assessment of intelligence through nonverbal means.

Up until 20 years ago, neuropsychologists would address the issue of cognitive decline through informal "historical" means comparing IQ scores to estimations of intelligence vaguely defined by the individual's demographic, educational, and occupational backgrounds (Vanderploeg & Schinka, 1995). More recently, a number of actuarial methods have been developed for this purpose. Some of these involve use of statistical regression techniques, where various demographic indices can be inserted into an equation to arrive at predicted WAIS IQ scores (Barona, Reynolds, & Chastain, 1984). There are also a number of performance-based indices where indices of vocabulary or oral reading are used (e.g., WTAR, TOPF) (Pearson Assessment, 2009) or the North American version of the National Adult Reading Test (NART) (Blair & Spreen, 1989), either alone or in combination with demographic indices, to arrive at estimates of IQ scores. To date, while these methods have been demonstrated to be of use in identifying the degree of cognitive decline observed in clinical samples of dementia or traumatically brain injured patients, no studies have validated their use in patients with cognitive impairment secondary to epilepsy.

Attention and Processing Speed

Most discussions on the neuropsychology of attention begin with the topic of attention span, which is typically assessed through the Digit Span subtest from one of the Wechsler scales (Wechsler, 2008). Scores from this subtest are generally combined with the score from the Arithmetic subtest to comprise with Working Memory Index (WMI). While scores on the WMI are reduced in some patients, performances on digit span tasks, both forward and backward, are generally preserved in patients with epilepsy, similar to what is seen in many other clinical populations (Wilde et al., 2001).

There are no indications that Digit Span performance is affected appreciably by either drug effects or the ongoing influence of uncontrolled seizures. The claims from clinical folklore, that forward and backward span tasks assessed different neuropsychological processes, have not been supported through empirical study of patients with epilepsy (Bowden, Petrauskas, Bardenhagen, Meade, & Simpson, 2013). While interest in the spatial span analog of the digit span subtest was generated through early studies by Milner and Corsi (Milner, 1968), there has been little evidence that addition of a spatial span task adds any novel information about cognitive functioning or cerebral localization in routine assessment of epilepsy patients (Piekema et al., 2007).

Patients with epilepsy commonly demonstrate decrements in processing speed, defined primarily through performance on paper-pencil tests.

Reduced scores are commonly observed on the Digit Symbol and Symbol Search subtests from the Wechsler scales, both of which comprise the Processing Speed Index (PSI). Low scores on these tests can be attributed to a combination of different factors, including medication effects and more generalized effects of seizures and brain dysfunction. Clinicians should keep in mind that signs of reduced processing speed can also be observed on other neuropsychological tests, including many tests of executive function, such as Part A of the Trail Making Test (Reitan & Wolfson, 1985), the initial trials of the Stroop Color Naming Test (Golden, 1978), and on measures of verbal and visual fluency.

On an interesting historical note, neuropsychologists should be aware that the paradigm for the Continuous Performance Test (CPT) commonly associated with evaluations of patients with ADHD was initially developed for assessment of attentional lapses in patients with epileptic seizures (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). While one can argue that use of the CPT might provide additional data to diagnose ADHD in an adult with epilepsy, the evidence is that these measures are used on a routine basis in only 13 % of epilepsy centers (Djordjevic & Jones-Gotman, 2011) and that epilepsy patients, as a whole, demonstrate minimal signs of impairment on these measures (Fleck, Shear, & Strakowski, 2002). Studies using experimental computerized tasks have demonstrated decrements in reaction time in epilepsy patients, particularly in studies of medication side effects (Witt et al., 2013). However, neuropsychologists have apparently been reluctant to include computerized assessment of reaction time, processing speed, or vigilance into their routine test batteries, as only 5 % indicate usage of these tests on a routine basis (Djordjevic & Jones-Gotman, 2011).

Executive Functions

The term executive functions is commonly used to describe a wide range of psychological constructs, including initiation, sequencing, organization, and planning. Most neuropsychologists will agree that evaluation of executive functions is an important component to the clinical test battery for evaluation of epilepsy patients, although in practice one sees that only a limited number of tests are used on a regular basis. The Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) and measures of verbal fluency are the measures most commonly used in epilepsy centers (Djordjevic & Jones-Gotman, 2011). The WCST is commonly utilized as a measure of problem solving and set shifting while the verbal fluency measures are used for evaluation of initiation, particularly in reference to left hemisphere functions. While the results of pioneering studies by Milner (1964) demonstrated that low levels of performance on these tests could be used to identify patients with frontal lobe seizures, more recent studies have demonstrated that performance decrements are also common in patients with epileptic foci localized in other regions (Barr & Goldberg, 2003; B. P. Hermann et al., 1988).

There are a number of other tests that are useful for evaluating executive functions in patients with epilepsy. Impairments in mental rigidity and higher-order sequencing are commonly identified through poor performance on Part B of the Trail Making Test. The Stroop Color Naming Test (Golden, 1978) can be useful for identifying difficulties with impulsivity or response inhibition. While there had been suggestions that verbal fluency tests, such as the COWAT, could be combined with measures of figural fluency [e.g., Ruff Figural Fluency Test (Ruff, 1988)] to help lateralize frontal lobe dysfunction, the empirical evidence to support this practice appears mixed (Suchy, Sands, & Chelune, 2003).

Many clinicians have now turned to the Delis Kaplan Executive Function System (DKEFS) (Delis, Kaplan, & Kramer, 2001) versions of many executive function measures as a result of its inclusion of co-normed instrument across a wide age spectrum. While the research literature on use of the DKEFS in assessment of epilepsy patients is limited, there are suggestions that many of these measures can be used successfully in patients with frontal and temporal lobe seizures (McDonald, Delis, Norman, Tecoma, & Iragui, 2005; McDonald, Delis, Norman, Wetter,

et al., 2005). While the use of executive functioning questionnaires can be useful for identifying daily functioning in some patients, there remains little published research supporting the use of measures, such as the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) or Frontal Systems Behavior Scale (FrSBE) (Grace & Malloy, 2001), for evaluating patients with epilepsy.

Motor and Sensory Functions

It is important to include a comprehensive assessment of handedness when assessing motor functions in patients with epilepsy. An association between hand preference patterns and underlying patterns of brain organization has been demonstrated in numerous studies (Sveller et al., 2006). The Edinburgh Handedness Inventory (Oldfield, 1971) is a ten-item instrument that provides an effective means of measuring hand preference patterns on a continuum by computing a laterality quotient range from +100 (totally right handed) to −100 (totally left handed). Location on this continuum has been demonstrated to correlate with degree of language lateralization (Isaacs, Barr, Nelson, & Devinsky, 2006). Knowing whether a patient exhibits a pattern of left or mixed-handedness can be extremely helpful when interpreting unusual combinations of verbal and nonverbal performance in patients with epilepsy, as deficits in perceptual tasks secondary to the "crowding effects" are known to exist in patients with right hemisphere language representation (Loring et al., 1999).

The Grooved Pegboard Test is included in many neuropsychological test batteries as the sole measure of motor functions, owing to its demonstrated sensitivity to detecting general effects of brain dysfunction. This test is currently used by more than 60 % of neuropsychologists practicing in specialized epilepsy centers (Djordjevic & Jones-Gotman, 2011). Based on published research studies, patients with epilepsy exhibit relative decrements on this test in comparison to healthy controls (Kupke & Lewis, 1985). Greater levels of impairment are generally seen in patients with more severe forms of epilepsy. Performance on the Grooved Pegboard Test has also been demonstrated to be a measure that is sensitive to detecting psychomotor slowing associated with antiepileptic drug treatment (Meador, Loring, Huh, Gallagher, & King, 1990). Additional measures of motor functioning, such as the Finger Tapping Test and Hand Dynamometer, can also be added to the neuropsychological test battery to determine the presence of consistent lateralized performance decrements, although these tests have been shown to be less sensitive to detecting subtle motor deficits in this population (Klove & Matthews, 1966).

Neuropsychologists have paid much less attention to a formal assessment of somatosensory functions in patients with epilepsy with only 16 % reporting that they evaluate these functions on a routine basis (Djordjevic & Jones-Gotman, 2011). A formal evaluation of a wide range of somatosensory tasks, including manual extinction, graphesthesia, finger gnosis, and stereognosis, can be accomplished through the use of the Reitan-Klove Sensory Perceptual Examination (Reitan & Wolfson, 1985). Evaluation of these functions can be helpful when the examiner wants to go beyond assessment of motor functions for assessment of lateralized symptoms or when there is a suspected focus in parietal regions adjacent to the post-central gyrus.

Language

Neuropsychologists commonly begin their assessment of language functions in patients with epilepsy by examining the profile of performance on the Wechsler scales. Weaknesses in language skills can be identified through relative decrements on the Verbal Comprehension Index (VCI) relative to other scales, which correspond in some cases to more widespread deficits in academic skills such as reading and spelling. Further screening of those academic skills can be accomplished quickly with a screening measure such as the Wide Range Achievement Test (WRAT) (Wilkinson & Robertson, 2006) or in a more comprehensive fashion with the Wechsler Individual Achievement Test (WIAT-III) (NCS Pearson, 2009).

For analysis of more specific language functions, neuropsychologists will often turn their attention to scores from the subtests comprising the VCI score, most notably Vocabulary. In terms of adding specific language tests to the battery, most will include the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), which has demonstrated to be a sensitive indicator of language dysfunction in patients with left temporal lobe seizures (B. P. Hermann et al., 1999; Loring et al., 2008). There has also been recent interest in assessment of naming in relation to auditory descriptors, which is reported to be a more sensitive indicator than visual naming as a result of its reliance on a more widespread network of representation in left hemisphere language zones (Hamberger et al., 2003).

Additional information about language fluency and semantic retrieval can be identified through analysis of performances on verbal fluency tests, such as the COWAT and the Animal Naming Test. To complete the most thorough evaluation of language, one would add tests of sentence repetition and comprehension. The Token Test is commonly used for the latter. Administration of complete language batteries such as the Multilingual Aphasia Examination (MAE) (Benton & Hamsher, 1978) or the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983) is generally reserved for those patients showing frank signs of aphasia during the interview or on simple mental status testing.

Visual Perceptual and Spatial Skills

Neuropsychologists exhibit a natural interest in evaluating a broad category of visual, spatial, and constructive skills that are typically given one of a number of hybrid names, such as visuospatial or visuoconstructive functions. In spite of years of study, our understanding of these skills and their relationship to underlying brain function in epilepsy and most other neurological conditions is not well developed. Most neuropsychologists working in epilepsy centers begin their assessment of these skills with use of the Wechsler subtests (Wechsler, 2008). Identification of differentially low scores on the Perceptual Reasoning Index (PRI) from the WAIS can be helpful in identifying weaknesses in perceptual functions that are potentially the result of a disruption of right hemisphere functions. This can be followed up with further analysis of performance on any one of a number of other more specific tests.

Based on survey results (Djordjevic & Jones-Gotman, 2011), more than 20 % of neuropsychologists in epilepsy centers commonly use the tests of Judgment of Line Orientation (JLO) and Facial Recognition Test (FRT) developed by Benton and colleagues for more detailed evaluation of right hemisphere functions in patients with epilepsy (Benton, Hamsher, Varney, & Spreen, 1983). Both tests, used in combination, can be helpful in identifying lesions affecting either the dorsal (where) or ventral (what) perceptual streams described in the posterior cortex in the 1980s (Ungerleider & Mishkin, 1982). While studies have shown that patients with temporal lobe epilepsy do not typically exhibit impairments on the FRT prior to surgery, they do exhibit declines on that test following surgery, consistent with the effects of a disruption of the ventral stream (B. P. Hermann, Seidenberg, Wyler, & Haltiner, 1993). Low scores on the JLO, theoretically affecting the dorsal stream, have been demonstrated in patients with epilepsy localized in more posterior brain regions (Guerrini et al., 1997).

While measures of visual construction are a standard component of most neuropsychological test batteries, interpretation of performance decrements can be problematic, owing to the multifactorial nature of these tasks. Determining the core deficit on these tasks will often require analysis of scores from measures of executive functions and motor skills to determine the degree to which the decrement is associated with efferent factors as opposed to purely perceptual factors. Survey results indicate that the majority of neuropsychologists working in epilepsy centers include the WAIS Block Design subtest (79 %) and copy of a complex figure (68 %) in their test batteries (Djordjevic & Jones-Gotman, 2011). It is important to remember that much about the mechanisms underlying dysfunction on these tests can be identified through a careful analysis of the process by which the patient proceeds with his or

her construction of the figure or design (Kaplan, 1988; Swenson, Bettcher, Barr, Campbell-Marsh, & Libon, 2013). Patients with disturbances of the left hemisphere will commonly make errors with perceptual details while those with right hemisphere disturbance are prone to making more globally based errors, affecting the larger contour of the figure (Barr, 2003).

Learning and Memory

Memory is a primary area of concern for most patients with epilepsy, with over 70 % reporting subjective concerns about their memory functions at any given time (Thompson & Corcoran, 1992). Examination of memory skills thus becomes one of the major purposes of the neuropsychological evaluation and a thorough assessment of these skills requires observation of a patient's performance on a range of different types of memory tasks. To accomplish this, most neuropsychological batteries will include tests of rote learning, using lists of individual words or word pairs to study learning skills and retention. Many will also use story recall tasks for evaluation of larger units of learning and retention. Inclusion of tests of nonverbal memory, using learning and recall of figures and designs, is still common, although questions about the validity of that practice have been raised over the years due to a lack of empirical data supporting the use of these tests.

Most neuropsychologists will agree that verbal list-learning tasks provide extremely valuable information on the degree and type of memory impairment observed in patients with epilepsy. Useful information about the nature of encoding can be determined through analysis of the initial learning trials while details about retention and retrieval can be discerned through analysis of delayed recall and recognition trials. There is, however, a lack of consensus on which test to use. Survey results (Djordjevic & Jones-Gotman, 2011) indicate that the majority of clinicians working in epilepsy centers use either the Rey Auditory Verbal Learning Test (RAVLT—40 %) (Schmidt, 1996) or the California Verbal Learning Test (CVLT—31 %) (Delis, Kramer, Kaplan, & Ober, 2000). While the CVLT is alleged to provide the clinician more detailed information about the underlying processes involved in learning and recall, results of empirical studies indicate that the RAVLT is actually more sensitive to the effects of left hemisphere dysfunction (Loring et al., 2008). The remaining centers appear to use a combination of other tasks, including selective reminding measures, or lists of words meeting specific language and/or normative needs for the population served at that center.

Neuropsychologists continue to find the Paired Associates and Logical Memory subtests from the WMS helpful for evaluation of memory skills in patients with epilepsy, with evidence that these measures remain in use in nearly 50 % of the surveyed centers (Djordjevic & Jones-Gotman, 2011). Many argue that inclusion of paired associate learning tasks provides a useful adjunct to the information obtained from list-learning tests with suggestions that these tests might even be more sensitive to the effects of hippocampal dysfunction than other tests (Rausch & Crandall, 1982). The Logical Memory subtest, in turn, is alleged to provide a more ecologically valid measure than the rote memory tasks. There is also evidence that a decline in performance on delayed memory versus immediate memory trials provides a valid and sensitive measure reflecting consolidation impairment, particularly in patients with left temporal lobe epilepsy (Delaney, Rosen, Mattson, & Novelly, 1980).

Inclusion of tests of "nonverbal" memory remains common in most neuropsychological test batteries, based on Milner's (1967) early description of dual "material-based" memory systems involving the left and right hemispheres. While empirical support for the relationship between verbal memory impairment and dysfunction in the left temporal lobe has been strong, there is little support for the existence of specific deficits in nonverbal memory in patients with right temporal lobe impairment (Barr et al., 1997; Kneebone, Lee, Wade, & Loring, 2007). Based on these findings, the recommendation from an NIH panel was to omit nonverbal memory tests from inclusion of the Common Data Elements test battery for evaluation of patients with epilepsy (see Table 1.7) (Loring, Lowenstein, et al., 2011).

Survey results indicate that, in spite of the empirical findings, neuropsychologists continue to use measures of figural reproduction in their test batteries, nonetheless, with most including the Rey Complex Figure Test (RCFT—65 %) and a lesser amount using the Visual Reproduction subtest (21 %) from the WMS (Djordjevic & Jones-Gotman, 2011). The results of a large-scale study on 757 patients demonstrated that neither of these tests is useful for lateralizing the hemispheric location of memory dysfunction in temporal lobe epilepsy patients before surgery (Barr et al., 1997). However, there are suggestions from other studies indicating that useful information can be obtained from the RCFT when more qualitatively based scoring systems are used (Barr, 2003). The challenge becomes whether there is value added by going through the rigorous process of using one of the many qualitative systems developed for scoring these figures. Many have now turned to a basic subjective phenomenal analysis of the figure, determining whether it shows qualitative signs, such as fragmentation or spatial errors, associated with right hemisphere dysfunction.

Some neuropsychologists have reported success using figural learning tests, with procedures that are analogous to the verbal list-learning paradigms, using groups of geometric designs presented over multiple trials instead of words (Helmstaedter, Pohl, Hufnagel, & Elger, 1991; Jones-Gotman et al., 1997). Patients with right temporal lobe seizures have been observed to perform poorly across the initial learning trials but do not typically show impairment on the delayed recall trial (Jones-Gotman et al., 1997). These findings suggest that individuals with right temporal lobe dysfunction might exhibit a qualitatively different type of impairment in learning and memory than what is seen in patients with left temporal lobe dysfunction. The challenge has been that most of the published data on figural list-learning tests are based on measures that are not widely available to other clinicians and investigators. Attempts to replicate these findings with commercially available tests, such as the Brief Visuospatial Memory Test-Revised (BVMT-R), have been unsuccessful (Barr, Morrison, Zaroff, & Devinsky, 2004).

In a continuing search for a valid test of nonverbal memory, there have been some positive findings from use of facial memory tests, although the results from these studies, too, have been mixed. Findings from studies using the Facial Recognition subtest of the Recognition Memory Test (Warrington, 1984) have been positive in studies performed in the United Kingdom (Baxendale, 1997), but these findings have not been replicated in North America (B. P. Hermann, Connell, Barr, & Wyler, 1995; Kneebone, Chelune, & Luders, 1997). Results from studies using the Facial Recognition subtest from the WMS have also been mixed (Wilde et al., 2001), while there have been more positive results using other tests (Barr, 1997). Further work in developing valid tests for assessment of nonverbal memory is clearly needed.

Performance Validity Testing

There has been an increasing trend in the field of neuropsychology to include tests of validity, effort, and response bias when administering a clinical test battery. A distinction is now made between performance validity tests (PVTs), which are measures designed to evaluate the validity of cognitive test performance, and symptom validity tests (SVTs), which are scales used to evaluate the validity and response biases in relation to symptom reporting (Larrabee, 2012). In terms of PVTs, neuropsychologists distinguish between the use of free-standing measures such as the Test of Memory Malingering (TOMM) (Tombaugh, 1996) or Victoria Symptom Validity Test (VSVT) (Slick et al., 1997) and embedded measures obtained from tests that are included routinely in the test battery, such as the Reliable Digit Span (RDS) (Greiffenstein, Baker, & Gola, 1994) or recognition trials from the RAVLT and CVLT (Lu, Rogers, & Boone, 2007).

While inclusion of PVTs and SVTs is now considered routine in forensic applications where rates of malingering are estimated in the range of 40 %, the question is whether these tests need to be used routinely in clinical settings, where the estimated rate of invalid performance is less than 10 % (Mittenberg, Patton, Canyock, & Condit, 2002). Based on survey results, PVTs are used by less than 7 % of neuropsychologists working in

epilepsy centers in spite of the fact that there are studies demonstrating that rates of invalid test performance exceeding 20 % on single tests (Djordjevic & Jones-Gotman, 2011). However, the rates of failure on multiple tests are shown to be much lower, with failures on two or more tests seen in less than 5 % (Cragar, Berry, Fakhoury, Cibula, & Schmitt, 2006).

The highest rates of test failure in epilepsy samples are seen in studies using the VSVT where failure rates exceeding 20 % have been reported (Cragar et al., 2006; Loring, Lee, & Meador, 2005). It has been suggested that this test might yield a high false positive rate in this population due to its dependence on IQ and working memory skills, which are known to be reduced in epilepsy samples relative to the general population (Keary et al., 2013). Similarly, false positives were also identified in another study using the Word Memory Test (Drane et al., 2006; Green, 2003), suggesting that PVTs in this population are not limited to identification of potential malingering, but can be useful for identifying invalid test performance secondary to low intelligence, amnesia, or increased seizures (Drane et al., 2006). Failure rates on the Test of Memory Malingering (TOMM) are reported to be less than 3 % in patients with epilepsy (Cragar et al., 2006).

Results from other studies have suggested that increased rates of PVT failure are seen in patients with diagnoses of PNES, with failure rates in the range of 30–50 % (Drane et al., 2006). Again the increased rates observed in these samples might not necessarily be the result of outright malingering, but rather a result of somatization and other psychological processes related to the expression of seizures in that group (D. J. Williamson, Holsman, Chaytor, Miller, & Drane, 2012).

Taken together, the suggestion is to include routine administration of at least one free-standing PVT (e.g., TOMM or WMT) in the neuropsychological test battery in addition to utilizing data from one or more of the embedded measures (e.g., RDS or CVLT-II). However, it is important for clinicians to remember that failures on these tests seen in epilepsy patients evaluated in a clinical setting will not necessarily indicate the presence of malingering, but may identify other clinical factors, such as the effects of seizures, that would signal the presence of potentially invalid test findings.

Mood and Personality

It is well known that increased rates of psychiatric disturbance are observed in patients with epilepsy as compared to the general population. Screening for disturbances in mood and personality is thus a key component to neuropsychological evaluations performed in this population. While most well-trained neuropsychologists learn to identify the presence of many psychiatric conditions through interview techniques and observational methods, it is often useful to include self-report as part of the neuropsychological test battery to obtain more objective data to support those conclusions.

Nearly a third of patients with epilepsy will experience a depressive episode in their lifetime, making this the most common psychiatric comorbidity encountered in patients with epilepsy (Kanner, 2013). In the majority of these cases, the patients will also exhibit clinically relevant features of anxiety. Survey results indicate that approximately 50 % of neuropsychologists working in epilepsy centers use a self-report symptom inventory to screen for underlying depressive and anxiety disorders (Djordjevic & Jones-Gotman, 2011). The majority of these centers report use of the Beck Depression Inventory (Beck, Steer, & Brown, 1996) and Beck Anxiety Inventory (Beck, 1993). There are indications that depression and anxiety might be manifested in qualitatively different manner in patients with epilepsy, leading some investigators to develop specialized measures for assessment of mood disorder in this population (Kanner et al., 2012). The Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) is one such measure, consisting of six items designed to provide a more sensitive assessment of depressive symptoms in epilepsy by avoiding overlap with symptoms that could potentially be the result of medication side effects (Kessler et al., 1996).

More comprehensive evaluations of mood and personality are performed by clinicians at nearly

one-third of epilepsy centers, with most including either the Minnesota Multiphasic Personality Inventory (MMPI) (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1990) or the Personality Assessment Inventory (PAI) (Morey, 1991) as part of their routine test battery. One of the major advantages to using these more comprehensive measures is that they naturally include a number of validity scales that enable them to serve as SVTs by helping identify patients that might be overreporting or underreporting symptoms. These measures also go beyond assessment of depression and anxiety, providing a means for the neuropsychologist to potentially identify other psychiatric conditions, particularly those involving the presence of underlying thought disorder.

Many clinicians are moving towards the use of the Minnesota Multiphasic Personality Inventory-2, Restructured Format (MMPI-2-RF), which is a shortened and newly validated version of the older instrument (Ben-Porath & Tellegan, 2008). This version of the test includes a number of the newer validity scales, such as the Symptom Validity Scale (FBS-r) and Response Bias Scale (RBS) that have been demonstrated to be useful in identifying invalid test profiles in epilepsy patients as well as in other clinical samples (Nelson, Hoelzle, Sweet, Arbisi, & Demakis, 2010; Wygant et al., 2010). This test also provides a means for identifying underlying psychotic or behavioral disorders through analysis of newly developed superordinate scales, including the Thought Dysfunction (THD) and Behavioral/Externalizing Dysfunction (BXD) scales. It is important to remember, however, that certain interpretive strategies need to be employed when interpreting this and all other versions of the MMPI as some of the symptoms associated with seizures might serve to inflate scales associated with somatic (RC1) or bizarre (RC8) symptoms. The test has also been shown to be very helpful in identifying patients with PNES (Locke et al., 2010).

There have been prior attempts to develop "epilepsy-specific" measures to screen for psychopathology in this population. In the 1980s, Dodrill and colleagues (Dodrill, Batzel, Queisser, & Temkin, 1980) developed the Washington Psychosocial Seizure Inventory (WPSI), which was a 132-item questionnaire designed to identify various difficulties in emotional, interpersonal, and vocational adjustment, in addition to other factors including family background, financial status, adjustment to seizures, and medical management. The WPSI never gained wide acceptance or usage in spite of a number of papers demonstrating its empirical utility. The Bear-Fedio Personality Inventory (Bear & Fedio, 1977) was another inventory developed to measure the temporal lobe personality that had been described by Geschwind and others (Waxman & Geschwind, 1975). However, that scale never gained wide acceptance due to its lack of empirical validity and inability to distinguish personality factors in patients with epilepsy from those observed in other clinical samples (Devinsky & Najjar, 1999).

During the 1990s attention turned from assessment from the development of measures to assess quality of life (QOL) in patients with epilepsy. The ultimate goal was to provide a means of evaluating treatment effects by moving beyond assessment of frequency into more meaningful aspects of an individual's life and experience. The result was the development of a number of Quality of Life in Epilepsy Instruments (QOLIE) (Devinsky et al., 1995). These instruments include a number of epilepsy-specific items such as seizure severity, fear of having a seizure, the associated loss of control over one's life, cognitive and behavioral dysfunction, social limitations and stigma, sexual functioning, driving restrictions, and medication side effects. The QOLIE-89 is the longest and most commonly used of these instrument. The QOLIE-31 and QOLIE-10 are both shorter instruments derived from the larger form that are useful for screening QOL in conjunction with other instruments. Survey results indicate that these instruments are used routinely in approximately 30 % of epilepsy centers (Djordjevic & Jones-Gotman, 2011).

Interpreting and Reporting Test Results

The major task following completion of the neuropsychological test battery is to score the test protocols, interpret them, and communicate the

results to the patient, referral source, and other health care professionals. Scoring the test protocols is a rather straightforward process, with detailed criteria typically specified in test manuals. Most manuals also contain normative information that will suffice for interpretation of the test data in most cases. However, there are some instances when the neuropsychologist might want to obtain more detailed normative information relative to a demographically matched sample. In those cases, he or she is encouraged to utilize the *Comprehensive Norms for an Expanded Halstead-Reitan Battery* developed by Heaton and colleagues (2004) and supplemental material for WAIS-IV interpretation (Brooks, Holdnack, & Iverson, 2011). Use of those norms will also facilitate profile interpretation by placing test scores on a common metric with co-normed instruments. Neuropsychologists are known to vary across patients and tests in the criteria they set to identify "impairment," with definitions of abnormally low scores often ranging from −1 SD to −2 SDs below the normative mean. There is a movement in the field of neuropsychology to make clinicians aware of the possibility of identifying impairment by "chance" when numerous test scores are analyzed. The reader is encouraged to consult papers providing tables and interpretive guidelines that will enable them to reduce the probability of making a Type I error regarding identification of cognitive impairment when analyzing test profiles (Binder et al., 2009; Schretlen et al., 2008).

Moving on to profile interpretation, this chapter has provided some background on the tests and methods used to evaluate a range of different cognitive domains. As mentioned, impairments in attention, executive functions, and memory will be observed most often in patients with epilepsy, owing to the combined effects of neural systems involved in propagation of seizures, medication, and other factors. Individuals working in epilepsy settings should be prepared to identify neuropsychological profiles in patients with idiopathic generalized (Shehata & Bateh Ael, 2009), mesial-temporal (B. P. Hermann et al., 1997), and lateral temporal (Pacia et al., 1996) lobe syndromes, as outlined earlier in the chapter. They should also be aware of the set of empirically derived "cognitive phenotypes" identified by Hermann and Seidenberg (B. Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007) through cluster analytic techniques. These investigators found statistical support for three groups using cluster analytic techniques, based on distinct neuropsychological test, clinical, and structural imaging data. The first was a group with minimal cognitive impairment. The second included a group with specific impairment in the domain of memory and the third involved a group with combined impairment in memory, executive functions, and processing speed. Knowledge of these empirically validated profiles can be extremely useful in guiding the interpretive process when integrating test data from an individual patient. The clinician's knowledge and training in brain-behavior relationships will influence their ability to identify relevant profiles not meeting any of these typical patterns, which in some cases may reflect the effects of dysfunction in extra-temporal brain regions.

Results of the neuropsychological examination are typically summarized in a written report. The scope and length of the report will vary widely across settings. There is a movement, in general, for neuropsychologists to reduce the length of their reports, which might vary from a one-page length to over 30 pages across centers (Donders, 2001a, 2001b). There is no set standard or limit with regard to page length. The ultimate length of a report will depend on the degree to which the clinician summarizes the medical and neurological history. In many epilepsy settings, only minor details about seizures and their onset are required, as this information is commonly summarized in great detail in neurological notes and other sources. In most cases, the neuropsychologist might want to focus on providing more detail on psychosocial factors, including the patient's education, occupation, and home life, which are often not specified in great detail in other medical records. In some settings, the neuropsychological report might also be the only place where details about the patient's psychiatric and emotional state are provided. Details regarding other aspects of the patient's medical

history will be outlined to the degree that is necessary for interpretation of the test findings. For example, reports for patients with a history of traumatic brain injury will require some detail regarding the nature and functional outcome of that injury. In contrast, reporting of other medical factors, such as those placing the patient at risks for the metabolic syndrome (e.g., hypertension, diabetes, and hypercholesterolemia), only need be provided in list form.

There are also wide variations in the degree to which neuropsychologists report the neuropsychological test findings. Some provide a simple paragraph-length summary of the entire protocol, while others provide detailed summaries of various cognitive domains assessed through the test battery, with specific information about performance on each test (Donders, 2001a). Again, the degree to which the clinician provides this detail will vary across setting. However, it is known that many physicians prefer to hear the neuropsychologist's bottom-line account of the test findings and often ignore many of the details provided in the test results section. There are variations in the degree to which neuropsychologists report specific test scores. Some reports will include selected test scores embedded in the body of the report, while others will include summary tables of scores from specific tests (e.g., Wechsler scales) or the entire test battery. Another approach is to omit test scores from the report entirely, while making them available in summary sheet form in the event that another neuropsychologist needs them for interpretation of change on a subsequent report.

All neuropsychological test reports should conclude with a concise summary section, containing a brief review of the findings, an outline of the final interpretation, and the final conclusions. This is the most important section of the report, which reflects the ultimate work product, where the clinician has provided a final integration of results from the interview, record review, and test findings. The summary section should include specific information to directly address the referral question. This will commonly include details about the presence or absence of cognitive decline, observed strengths and weaknesses, and how these results relate to the presence of seizures, medication, and underlying brain functions and/or to other relevant medical or psychiatric factors. In some settings, a written description of these factors will suffice. In other settings, a formal diagnosis will be required. In terms of the DSM-V (APA, 2013), clinicians evaluating patients will be commonly using the diagnosis Mild Neurocognitive Dysfunction due to Another Medical Condition (331.83; Epilepsy, 345.90) to characterize the diagnosis reached through administration of the neuropsychological test battery.

The neuropsychological test report will generally conclude with recommendations, which will again vary widely by setting. In some settings, recommendations from the neuropsychologist regarding further medical work-up, including EEG and MRI, can be helpful, although these same recommendations will often not be appropriate in a specialized epilepsy center, where it can be assumed that the referring epileptologist has addressed these issues in a competent manner. One needs to keep in mind what recommendations can be drawn from the neuropsychological evaluation that will be unique to the care of the patient in comparison to those recommendations originating from more medically oriented evaluations. In some settings, the neuropsychologist might be the primary clinician who is identifying the need for further psychiatric and/or psychological care through initiation of psychopharmacological and/or psychotherapeutic interventions. The neuropsychologist is most often the primary clinician utilized for identification and documentation of a patient's need for accommodations in school or the workplace secondary to the effects of cognitive dysfunction. Results from the testing will also be used to determine the patient's need for any form of cognitive remediation. Further information regarding psychological treatments for patients with epilepsy can be found in Chap. 10. Finally, the neuropsychological recommendations should address if or when the patient will need to return for follow-up testing to monitor or assess any changes over time secondary to a progression of disease or to the effects of treatment.

Preparation of the written report will often be followed by providing more specific feedback directly to the patient. Many neuropsychologists prefer to provide this feedback in a personalized manner through a formally scheduled session with the patient and his or her family. While this is often done in person, there are certain circumstances such as distance that will dictate performing this session by telephone. In an effort to become more "consumer friendly," neuropsychologists have worked very hard on developing and improving the feedback process and the patient's experience of the entire testing process (Postal & Armstrong, 2013). There has been a growing emphasis on using the feedback session for therapeutic purposes, using some of the techniques developed in a style of motivational interviewing (Gorske & Smith, 2009). The feedback appointment should begin with an opportunity to address the patient's perceptions of the testing process and their thoughts about their test performance. This can be followed by the clinician's systematic review of the test findings and conclusions. A review of recommendations will often be provided in the context of further exploration of the patient's responses to the test results.

The written report provides the most common means to communicate the assessment results to the referral source. However, some clinicians will prefer to receive an additional brief communication through telephone or some other HIPAA compliant form of transmission where there is an opportunity for other questions to be addressed. It is important for the neuropsychologist to know these preferences when cultivating their referral sources. In epilepsy specialty centers, the staff neuropsychologists are often asked to present the assessment results at a multidisciplinary treatment meeting. In these settings, the clinician will often need to keep in mind the unique contributions offered by the neuropsychological evaluation, and how this is often the only means of communicating the factors that are unique to the patient as a person and how these will influence the developing treatment plan. The challenge is to reduce what is often very rich material into a few brief sentences that will be absorbed effectively by those working in other professions.

Case Example

This chapter will conclude with a case example highlighting many of the issues and procedures described in this chapter. The patient is a 29-year-old right-handed woman with a history of complex partial seizures dating back to childhood. She was referred for a neuropsychological evaluation as part of a comprehensive outpatient evaluation for assessment of reported difficulties with memory and word finding. The examination was performed in the outpatient department of a large comprehensive epilepsy center located in an academic medical center.

According to the history that was obtained, the patient's first witnessed seizure occurred in adolescence when her father saw her experience an event while she was watching television. However, the patient reported having similar previous events since early childhood (i.e., 6 or 7 years of age), but assumed that they were a normal occurrence that everyone experienced. With regard to current semiology, the patient typically has an aura (i.e., feeling of deja vu) followed by a brief period of altered consciousness during which she is generally unable to understand or respond to others. Despite this, she can still often execute purposeful tasks (e.g., stop at a red light when walking, continue running on a treadmill). Seizures can also include oral automatisms and repetitive right hand fist clenching, with events generally lasting a few minutes.

The patient reported that lack of sleep, stress, alcohol use, and missing medication dosages all provoke events. The patient has experienced two lifetime secondarily generalized seizures related to these precipitating factors. Despite good medication compliance more recently, she has been experiencing several seizures occurring in a cluster (i.e., over the course of a day or 2) approximately every 4–6 weeks. Her typical events are characterized as complex partial seizures. She was taking lamotrigine at the time of the neuropsychological evaluation.

Video-EEG performed within months of the neuropsychological evaluation captured four seizures, including "one complex partial seizure

with secondary generalization arising from the left posterior quadrant, one complex partial seizure arising from the left frontotemporal region," and "two complex partial seizures arising from the left hemisphere [which could not be localized]." An early MRI of the brain reportedly indicated left mesial temporal sclerosis. However, additional MRI studies performed subsequently were interpreted as normal.

The patient reported some mild and chronic memory difficulties. She described herself as a "forgetful" person in general, noting that her family and friends would characterize her as such, if asked. Specifically, she noted trouble recalling smaller details of past events. In addition, she felt that her memory difficulties had worsened somewhat over time. The patient reported word finding difficulties as well, noting that it takes her a few moments to recall peoples' names and words more generally.

This patient had been informed by her neurologist that she might be a surgical candidate at some time in the future, but she expressed a desire to delay any decisions for surgery while making a decision to start a family.

With regard to her birth and early developmental history, no delivery complications or delays in achievement of developmental milestones were reported. The patient experienced febrile convulsions at 8 months related to an illness (*roseola*), which included a generalized tonic–clonic event lasting 30–45 min followed by a brief right hemiparesis. She reported that, at the time of the assessment, she was in good physical health, with no significant medical problems. She denied any prior history of concussion, head injury, surgical intervention, or substance abuse.

The patient did not report a history of psychological difficulties and has never sought psychotherapeutic treatment. There is no family history of memory disorder or psychiatric problems. Both parents are alive and in good health. The patient's father is left-handed. She grew up in a large northeastern city where she lived with her parents and three sisters. She is Caucasian, from a Polish-American background, and English is her first and only language. She currently lives in a large northeast metropolitan region with her husband. The patient reported doing well in school, experiencing no learning difficulties. She obtained a Bachelor of Arts degree from a small northeastern university. She currently works as a product representative for a large pharmaceutical industry firm.

The neuropsychological test results are listed in Table 1.8. The test findings indicated that her general level of intellectual functioning was in the high average range. Higher-order verbal reasoning abilities, visuospatial skills, attention, and most aspects of executive function were all areas of strength. Word finding deficits were clearly documented, in addition to relative weaknesses in verbal memory, more specifically related to memory retention or retrieval. No mood-related difficulties were endorsed on self-report inventories. However, some internalizing behaviors were evident on the MMPI-2-RF, with evidence of a mild focus on somatic symptoms.

The test findings demonstrated that the patient is a bright woman with an average level of intelligence and some specific weaknesses in verbal memory and word finding. The resulting test profile was rather consistent with the effects of left temporal lobe epilepsy, which was compatible with the reported findings from EEG and imaging studies. There was no evidence of any underlying mood disorder, but there was evidence of a mild focus on somatic symptoms, which could warrant a referral for psychotherapeutic intervention. The patient did exhibit some mild cognitive deficit and was provided with an opportunity to request appropriate accommodations in the workplace, which she declined, indicating that she felt that she was holding her own on the job. She was offered a referral to one of the university's ongoing memory enhancement groups. She was informed that records from the neuropsychological evaluation would be kept on file in the event that they are needed for future reference.

Table 1.8 Neuropsychological test scores

Demographics: 29 year old Caucasian female with 16 years of formal education. Complex partial seizures diagnosed in adolescence. Experiences clusters of seizures every 4		
TOPF, Estimated FSIQ =		
WAIS-IV	**Standard Score (SS)**	**Demographic *T*-Score**
– Verbal Comprehension Index (VCI)	115	55
– Perceptual Reasoning Index (PRI)	113	55
– Working Memory Index (WMI)	111	53
– Processing Speed Index (PSI)	102	46
– General Abilities Index (GAI)	115	56
– Full Scale Intelligence Quotient (FSIQ)	113	53
WAIS-IV Digit Span, *T*-Score = 56 – Forward, raw = 10, ss = 9 – Backward, raw = 11, ss = 13 – Sequenced, raw = 13, ss = 16 Trail making Test – Trails A, raw = 16, *T* = 63 – Trails B, raw = 49, *T* = 46 Stroop Color Naming Test – Word, raw = 96, *T* = 44 – Color, raw = 82, *T* = 53 – Color-Word, raw = 50, *T* = 55 Ruff Figural Fluency Test (RFFT) – Unique Designs = 95, *T* = 51 – Perseverations = 5, *T* = 47 Controlled Oral Word Association Test (COWAT) – Raw Score = 55, *T* = 55 WCST-64 – Categories, raw = 4 – Errors, raw = 9, *T* = 58 – Perseverative Errors, raw = 7, *T* = 47		**Rey Auditory Verbal Learning Test (RAVLT)** – Total Learning (5-Trials), raw = 51, *T* = 51 – **Delayed Recall, raw = 7/15, *T* = 34** – Recognition (Hits/FP), Hits = 15, FP = 0 WMS-IV Logical Memory – LMI, raw = 22, *T* = 41 – LMII, raw = 21, *T* = 43 Rey Complex Figure – Copy Trial = 34.5, WNL – 30-min recall = 21, *T* = 43 WMS-IV Visual Reproduction – VRI, raw = 37, *T* = 43 – VRII, raw = 27, *T* = 44 Test of Memory Malingering (TOMM) – Trial 1, raw score = 47/50 correct – Trial 2, raw score = 50/50 correct
Boston Naming Test – **Raw Score = 51, *T* = 36** Animal Naming Test Raw Score = 22, *T* = 41		Beck Depression Inventory (BDI-II) – raw score = 3 Beck Anxiety Inventory (BAI) – raw score = 5 MMPI-2-RF – Validity Scales—L-r, F-r, and K-r, <60 • FBS, *T* = 57 • RBS, *T* = 59 – Clinical Profile • EID, *T* = 74 • RC1, *T* = 72

Conclusions

Epilepsy is a neurological disorder that is unique as a result of its relatively high rate of cognitive and behavioral disorders. It has been established over the years that neuropsychological testing is valuable to the care of patients with epilepsy, providing information that is unique to what is obtained using EEG, brain imaging, and other diagnostic methods. Clinical neuropsychologists are now considered key members of the specialized treatment team. Those entering positions in comprehensive epilepsy centers will need to have background knowledge on the heterogeneity of seizures, various epilepsy syndromes, and the effects of treatment. Neuropsychological assessment strategies will focus on evaluation of attention, executive functions, and memory, which are the skills most often affected in patients with

epilepsy. The assessment will also extend to a formal evaluation of mood and behavior with standardized methods.

The neuropsychologist's primary aim is to establish how the deficits identified in cognition and behavior relate to other clinical information relevant to the patient's seizures and their underlying cause. The goal of this opening chapter was to provide the reader with a general overview of epilepsy and the important role of neuropsychological assessment as it relates to this population. The reader is now invited to obtain more specific clinical information regarding the neuropsychology of epilepsy in the chapters following.

References

A. T. C. Committee, & Schalock, R. L. (2007). The renaming of mental retardation: Understanding the change to the term intellectual disability. *Intellectual and Developmental Disabilities, 45*, 116–124.

AACN. (1999). American Academy of Clinical Neuropsychology policy on the use of non-doctoral-level personnel in conducting clinical neuropsychological evaluations. *The Clinical Neuropsychologist, 13*, 385.

APA. (2002). Ethical principles of psychologists and code of conduct. *American Psychologist, 57*, 1060–1073.

APA. (2013). *Diagnostic and statistical manual of mental disorders—Fifth edition (DSM-V)*. Washington, DC: American Psychiatric Association.

APA Division 40. (1991). Recommendations for education and training of nondoctoral personnel in clinical neuropsychology. *The Clinical Neuropsychologist, 5*, 20–23.

Barona, A., Reynolds, C. R., & Chastain, R. (1984). A demographically based index of premorbid intelligence for the WAIS-R. *Journal of Consulting and Clinical Psychology, 52*, 885–887.

Barr, W. B. (1997). Examining the right temporal lobe's role in nonverbal memory. *Brain and Cognition, 35*(1), 26–41.

Barr, W. B. (2002). Neuropsychological testing for assessment of treatment effects: Methodologic issues. *CNS Spectrums, 7*(4), 300–302, 304–306.

Barr, W. B. (2003). Assessment of temporal lobe epilepsy using the Rey-Osterrieth Complex Figure Test. In J. A. Knight & E. F. Kaplan (Eds.), *The handbook of Rey-Osterrieth Complex Figure usage: Clinical and research applications*. Odessa, FL: Psychological Assessment Resources.

Barr, W. B., Chelune, G. J., Hermann, B. P., Loring, D. W., Perrine, K., Strauss, E., … Westerveld, M. (1997). The use of figural reproduction tests as measures of nonverbal memory in epilepsy surgery candidates. *Journal of the International Neuropsychological Society, 3*, 435–443.

Barr, W. B., & Goldberg, E. (2003). Pitfalls in the method of double dissociation: Delineating the cognitive functions of the hippocampus. *Cortex, 39*, 153–157.

Barr, W. B., Morrison, C., Zaroff, C., & Devinsky, O. (2004). Use of the Brief Visuospatial Memory Test-Revised (BVMT-R) in neuropsychological evaluation of epilepsy surgery candidates. *Epilepsy & Behavior, 5*(2), 175–179. doi:10.1016/j.yebeh.2003.12.010.

Baxendale, S. (1997). The role of the hippocampus in recognition memory. *Neuropsychologia, 35*, 591–598.

Baxendale, S., Thompson, P., Harkness, W., & Duncan, J. (2006). Predicting memory decline following epilepsy surgery: A multivariate approach. *Epilepsia, 47*(11), 1887–1894. doi:10.1111/j.1528-1167.2006.00810.x.

Baxendale, S., Thompson, P. J., & Duncan, J. S. (2008). Improvements in memory function following anterior temporal lobe resection for epilepsy. *Neurology, 71*(17), 1319–1325. doi:10.1212/01.wnl.0000319699.04265.fd.

Bear, D. M., & Fedio, P. (1977). Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Archives of Neurology, 34*, 454–467.

Beck, A. T. (1993). *Beck anxiety inventory (BAI)*. San Antonio, TX: Psychological Corporation.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck depression inventory—Second edition (BDI-II)*. San Antonio, TX: Psychological Corporation.

Ben-Porath, Y. S., & Tellegan, A. (2008). *MMPI-2-RF: Manual for administration scoring and interpretation*. Minneapolis, MN: University of Minnesota Press.

Benton, A. L., & Hamsher, K. S. (1978). *Multilingual aphasia examination manual*. Iowa City: University of Iowa.

Benton, A. L., Hamsher, K. S., Varney, N. R., & Spreen, O. (1983). *Contributions to neuropsychological assessment: A clinical manual*. New York, NY: Oxford University Press.

Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., van Emde Boas, W., … Scheffer, I. E. (2010). Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia, 51*(4), 676–685. doi:10.1111/j.1528-1167.2010.02522.x.

Binder, L. M., Iverson, G. L., & Brooks, B. L. (2009). To err is human: "Abnormal" neuropsychological scores and variability are common in healthy adults. *Archives of Clinical Neuropsychology, 24*(1), 31–46. doi:10.1093/arclin/acn001.

Blair, J. R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. *The Clinical Neuropsychologist, 3*, 129–136.

Bowden, S. C., Petrauskas, V. M., Bardenhagen, F. J., Meade, C. E., & Simpson, L. C. (2013). Exploring the dimensionality of digit span. *Assessment, 20*(2), 188–198. doi:10.1177/1073191112457016.

Brooks, B. L., Holdnack, J. A., & Iverson, G. L. (2011). Advanced clinical interpretation of the WAIS-IV and WMS-IV: Prevalence of low scores varies by level of

intelligence and years of education. *Assessment, 18*(2), 156–167. doi:10.1177/1073191110385316.

Brown, L., Sherbenou, R. J., & Johnson, S. K. (2010). *Test of nonverbal intelligence, Fourth edition (TONI-4)*. Austin, TX: PRO-ED.

Butcher, J. N., Dahlstrom, W. G., Graham, J. R., Tellegen, A. M., & Kaemmer, B. (1990). *MMPI-2: Minnesota multiphasic personality inventory—2. Manual for administration and scoring*. Minneapolis, MN: University of Minnesota Press.

Chelune, G. J. (2010). Evidence-based research and practice in clinical neuropsychology. *The Clinical Neuropsychologist, 24*(3), 454–467. doi:10.1080/13854040802360574.

Chelune, G. J., Naugle, R. I., Luders, H., & Awad, I. A. (1991). Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. *Neurology, 41*(3), 399–404.

Cragar, D. E., Berry, D. T., Fakhoury, T. A., Cibula, J. E., & Schmitt, F. A. (2006). Performance of patients with epilepsy or psychogenic non-epileptic seizures on four measures of effort. *The Clinical Neuropsychologist, 20*(3), 552–566. doi:10.1080/13854040590947380.

Delaney, R. C., Rosen, A. J., Mattson, R. H., & Novelly, R. A. (1980). Memory function in focal epilepsy: A comparison of non-surgical, unilateral temporal lobe and frontal lobe samples. *Cortex, 16*, 103–117.

Delis, D. C., Kaplan, E., & Kramer, J. (2001). *Delis-Kaplan executive function system: Examiner's manual*. San Antonio, TX: Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California verbal learning test* (2nd ed.). San Antonio, TX: The Psychological Corporation.

Devinsky, O., & Najjar, S. (1999). Evidence against the existence of a temporal lobe epilepsy personality syndrome. *Neurology, 53*(5 Suppl. 2), S13–S25.

Devinsky, O., Vickrey, B. G., Cramer, J., Perrine, K., Hermann, B., Meador, K., & Hays, R. D. (1995). Development of the quality of life in epilepsy inventory. *Epilepsia, 36*(11), 1089–1104.

Dikmen, S., Matthews, C. G., & Harley, J. P. (1975). The effect of early versus late onset of major motor epilepsy upon cognitive-intellectual performance. *Epilepsia, 16*, 73–81.

Djordjevic, J., & Jones-Gotman, M. (2011). Inquiry on assessments across epilepsy centers in different countries. In C. Helmstaedter, B. Hermann, M. Lassonde, P. Kahane, & A. Arzimanoglou (Eds.), *Neuropsychology in the care of people with epilepsy*. Montrouge, FR: John Libbey Eurotext.

Dodrill, C. B. (1975). Diphenylhydantoin serum levels, toxicity, and neuropsychological performance in patients with epilepsy. *Epilepsia, 16*(4), 593–600.

Dodrill, C. B. (1978). A neuropsychological battery for epilepsy. *Epilepsia, 19*, 611–623.

Dodrill, C. B. (1981). Rapid evaluation of intelligence in adults with epilepsy. *Epilepsia, 21*, 359–367.

Dodrill, C. B. (1986). Correlates of generalized tonic-clonic seizures with intellectual, neuropsychological, emotional, and social function in patients with epilepsy. *Epilepsia, 27*(4), 399–411.

Dodrill, C. B. (1992). Problems in the assessment of cognitive effects of antiepileptic drugs. *Epilepsia, 33*(Suppl. 6), S29–S32.

Dodrill, C. B., Batzel, L. W., Queisser, H. R., & Temkin, N. (1980). An objective method for the assessment of psychological and social problems among epileptics. *Epilepsia, 21*, 123–135.

Dodrill, C. B., & Wilensky, A. J. (1990). Intellectual impairment as an outcome of status epilepticus. *Neurology, 40*(5 Suppl. 2), 23–27.

Donders, J. (2001a). A survey of report writing by neuropsychologists, I: General characteristics and content. *The Clinical Neuropsychologist, 15*(2), 137–149. doi:10.1076/clin.15.2.137.1893.

Donders, J. (2001b). A survey of report writing by neuropsychologists, II: Test data, report format, and document length. *The Clinical Neuropsychologist, 15*(2), 150–161. doi:10.1076/clin.15.2.150.1902.

Drane, D. L., Williamson, D. J., Stroup, E. S., Holmes, M. D., Jung, M., Koerner, E., … Miller, J. W. (2006). Cognitive impairment is not equal in patients with epileptic and psychogenic nonepileptic seizures. *Epilepsia, 47*(11), 1879–1886. doi:10.1111/j.1528-1167.2006.00611.x.

Elger, C. E., Helmstaedter, C., & Kurthen, M. (2004). Chronic epilepsy and cognition. *The Lancet. Neurology, 3*(11), 663–672. doi:10.1016/s1474-4422(04)00906-8.

Engel, J., & Pedley, T. A. (2008). Introduction: What is epilepsy? In J. Engel (Ed.), *Epilepsy: A comprehensive textbook*. Philadelphia, PA: Lippincott, Williams, & Wilkins.

Fleck, D. E., Shear, P. K., & Strakowski, S. M. (2002). A reevaluation of sustained attention performance in temporal lobe epilepsy. *Archives of Clinical Neuropsychology, 17*, 399–405.

Golden, C. (1978). *Stroop color and word test*. Wood Dale, IL: Stoelting Company.

Goodglass, H., & Kaplan, E. (1983). *The assessment of aphasia and related disorders*. Philadelphia, PA: Lee & Febiger.

Gorske, T. T., & Smith, S. R. (2009). *Collaborative therapeutic neuropsychological assessment*. New York, NY: Springer Science + Business Media, LLC.

Grace, J., & Malloy, P. (2001). *Frontal systems behavior scale: Professional manual*. Lutz, FL: Psychological Assessment Resources.

Green, P. (2003). *Green's word memory test for windows: User's manual*. Edmonton, AL: Green's Publishing.

Greiffenstein, M. F., Baker, W. J., & Gola, T. (1994). Validation of malingered amnesia measures with a large clinical sample. *Psychological Assessment, 6*, 218–224.

Guerrini, R., Dubeau, F., Dulac, O., Barkovich, A. J., Kuzniecky, R., Fett, C., … Andermann, F. (1997). Bilateral parasagittal parietooccipital polymigrogyria and epilepsy. *Annals of Neurology, 41*, 65–73.

Hamberger, M. J., Seidel, W. T., Goodman, R. R., Perrine, K., & McKhann, G. M. (2003). Temporal lobe

stimulation reveals anatomic distinction between auditory naming processes. *Neurology, 60*(9), 1478–1483.
Harrison, P. L., & Oakland, T. (2003). *Adaptive behavior assessment system—Second edition (ABAS-II)*. San Antonio, TX: The Psychological Corporation.
Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin card sorting test manual: Revised and expanded*. Odessa, FL: Psychological Assessment Resources, Inc.
Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2004). *Revised comprehensive norms for and expanded Halstead-Reitan battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults professional manual*. Lutz, FL: Psychological Assessment Resources.
Helmstaedter, C., Gleibner, U., Zentner, J., & Elger, C. E. (1998). Neuropsychological consequences of epilepsy surgery in frontal lobe epilepsy. *Neuropsychologia, 36*(4), 333–341.
Helmstaedter, C., Pohl, C., Hufnagel, A., & Elger, C. E. (1991). Visual learning deficits in nonresected patients with right temporal lobe epilepsy. *Cortex, 27*, 547–555.
Hermann, B. P., Connell, B., Barr, W. B., & Wyler, A. R. (1995). The utility of the Warrington Recognition Memory Test for temporal lobe epilepsy: Pre- and postoperative results. *Journal of Epilepsy, 8*, 139–145.
Hermann, B. P., Perrine, K., Chelune, G. J., Barr, W., Loring, D. W., Strauss, E., …. Westerveld, M. (1999). Visual confrontation naming following left anterior temporal lobectomy: A comparison of surgical approaches. *Neuropsychology, 13*(1), 3–9.
Hermann, B., Seidenberg, M., Lee, E. J., Chan, F., & Rutecki, P. (2007). Cognitive phenotypes in temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 13*(1), 12–20. doi:10.1017/S135561770707004X.
Hermann, B. P., Seidenberg, M., Schoenfeld, J., Peterson, J., Leveroni, C., & Wyler, A. R. (1996). Empirical techniques for determining the reliability, magnitude, and pattern of neuropsychological change after epilepsy surgery. *Epilepsia, 37*(10), 942–950.
Hermann, B. P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology, 54*, 369–376.
Hermann, B. P., Seidenberg, M., Wyler, A., & Haltiner, A. (1993). Dissociation of object recognition and spatial localization abilities following temporal lobe lesions in humans. *Neuropsychology, 7*, 343–350.
Hermann, B. P., & Whitman, S. (1984). Behavioral and personality correlates of epilepsy: A review, methodological critique, and conceptual model. *Psychological Bulletin, 95*, 451–497.
Hermann, B. P., Wyler, A. R., & Richey, E. T. (1988). Wisconsin Card Sorting Test performance in patients with complex partial seizures of temporal-lobe origin. *Journal of Clinical and Experimental Neuropsychology, 10*(4), 467–476. doi:10.1080/01688638808408253.
Hoppe, C., Fliessbach, K., Schlegel, U., Elger, C. E., & Helmstaedter, C. (2009). NeuroCog FX: Computerized screening of cognitive functions in patients with epilepsy. *Epilepsy & Behavior, 16*, 298–310.
Isaacs, K. L., Barr, W. B., Nelson, P. K., & Devinsky, O. (2006). Degree of handedness and cerebral dominance. *Neurology, 66*(12), 1855–1858. doi:10.1212/01.wnl.0000219623.28769.74.
Jobst, B. C., Williamson, P. D., Thadani, V. M., Gilbert, K. L., Holmes, G. L., Morse, R. P., … Roberts, D. W. (2010). Intractable occipital lobe epilepsy: clinical characteristics and surgical treatment. *Epilepsia, 51*(11), 2334–2337. doi:10.1111/j.1528-1167.2010.02673.x.
Jones-Gotman, M., Zatorre, R. J., Olivier, A., Andermann, F., Cendes, F., Staunton, H., … Wieser, H. G. (1997). Learning and retention of words and designs following excision from medial or lateral temporal lobe structures. *Neuropsychologia, 35*, 963–973.
Kamphaus, R. W., & Reynolds, C. R. (2003). *Reynolds intellectual screening test (RIST)*. Lutz, FL: Psychological Assessment Resources.
Kanner, A. M. (2013). The treatment of depressive disorders in epilepsy: What all neurologists should know. *Epilepsia, 54*(Suppl. 1), 3–12. doi:10.1111/epi.12100.
Kanner, A. M., Schachter, S. C., Barry, J. J., Hersdorffer, D. C., Mula, M., Trimble, M., … Gilliam, F. (2012). Depression and epilepsy, pain and psychogenic nonepileptic seizures: Clinical and therapeutic perspectives. *Epilepsy & Behavior, 24*(2), 169–181. doi:10.1016/j.yebeh.2012.01.008.
Kaplan, E. (1988). A process approach to neuropsychological assessment. In T. Boll & B. K. Bryant (Eds.), *Clinical neuropsychology and brain function: Research, measurement, and practice* (pp. 125–167). Washington, DC: American Psychological Association.
Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test*. Philadelphia, PA: Lea and Febiger.
Kaufman, A. S., & Lichtenberger, E. O. (2005). *Assessing adolescent & adult intelligence* (3rd ed.). Hoboken, NJ: John Wiley & Sons.
Keary, T. A., Frazier, T. W., Belzile, C. J., Chapin, J. S., Naugle, R. I., Najm, I. M., & Busch, R. M. (2013). Working memory and intelligence are associated with Victoria symptom validity test hard item performance in patients with intractable epilepsy. *Journal of the International Neuropsychological Society, 19*(3), 314–323. doi:10.1017/S1355617712001397.
Kessler, R., Nelson, C., McGonagle, K., Liu, J., Swartz, M., & Blazer, D. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: Results from the U.S. National Comorbidity Survey. *The British Journal of Psychiatry, 30*, 17–30.
Klove, H., & Matthews, C. G. (1966). Psychometric and adaptive abilities in epilepsy with differential etiology. *Epilepsia, 7*, 330–338.
Kneebone, A. C., Chelune, G. J., & Luders, H. O. (1997). Individual patient prediction of seizure lateralization in temporal lobe epilepsy: A comparison between neuropsychological memory measures and the Intracarotid

Amobarbital Procedure. *Journal of the International Neuropsychological Society, 3*(2), 159–168.

Kneebone, A. C., Lee, G. P., Wade, L. T., & Loring, D. W. (2007). Rey Complex Figure: Figural and spatial memory before and after temporal lobectomy for intractable epilepsy. *Journal of the International Neuropsychological Society, 13*(4), 664–671. doi:10.1017/S1355617707070828.

Kupke, T., & Lewis, R. (1985). WAIS and neuropsychological tests: Common and unique variance within an epileptic population. *Journal of Clinical and Experimental Neuropsychology, 7*(4), 353–366. doi:10.1080/01688638508401269.

Kwan, P., & Brodie, M. J. (2001). Neuropsychological effects of epilepsy and antiepileptic drugs. *The Lancet, 357*(9251), 216–222.

Kwan, P., Schachter, S. C., & Brodie, M. J. (2011). Drug-resistant epilepsy. *The New England Journal of Medicine, 365*, 919–926.

Larrabee, G. J. (2012). Performance validity and symptom validity in neuropsychological assessment. *Journal of the International Neuropsychological Society, 18*, 1–7.

Locke, D. E., Kirlin, K. A., Thomas, M. L., Osborne, D., Hurst, D. F., Drazkowski, J. F., … Noe, K. H. (2010). The Minnesota Multiphasic Personality Inventory-2-Restructured Form in the epilepsy monitoring unit. *Epilepsy & Behavior, 17*(2), 252–258. doi:10.1016/j.yebeh.2009.12.004.

Loring, D. W., Lee, G. P., & Meador, K. J. (2005). Victoria symptom validity test performance in non-litigating epilepsy surgery candidates. *Journal of Clinical and Experimental Neuropsychology, 27*(5), 610–617. doi:10.1080/13803390490918471.

Loring, D. W., Lowenstein, D. H., Barbaro, N. M., Fureman, B. E., Odenkirchen, J., Jacobs, M. P., … Stout, A. (2011). Common data elements in epilepsy research: development and implementation of the NINDS epilepsy CDE project. *Epilepsia, 52*(6), 1186–1191. doi:10.1111/j.1528-1167.2011.03018.x.

Loring, D. W., Marino, S., & Meador, K. J. (2007). Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychology Review, 17*(4), 413–425. doi:10.1007/s11065-007-9043-9.

Loring, D. W., Strauss, E., Hermann, B. P., Barr, W. B., Perrine, K., Trenerry, M. R., … Bowden, S. C. (2008). Differential neuropsychological test sensitivity to left temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 14*, 394–400.

Loring, D. W., Strauss, E., Hermann, B. P., Perrine, K., Trenerry, M. R., Barr, W. B., … Meador, K. J. (1999). Effects of anomalous language representation on neuropsychological performance in temporal lobe epilepsy. *Neurology, 53*(2), 260–260. doi:10.1212/wnl.53.2.260.

Loring, D. W., Williamson, D. J., Meador, K. J., Wiegand, F., & Hulihan, J. (2011). Topiramate dose effects on cognition: A randomized double-blind study. *Neurology, 76*(2), 131–137. doi:10.1212/WNL.0b013e318206ca02.

Lowenstein, D. H. (2009). Epilepsy after head injury: An overview. *Epilepsia, 50*(Suppl. 2), 4–9. doi:10.1111/j.1528-1167.2008.02004.x.

Lu, P. H., Rogers, S. A., & Boone, K. B. (2007). Use of standard memory tests to detect suspect effort. In K. B. Boone (Ed.), *Assessment of Feigned cognitive impairment: A neuropsychological perspective*. New York, NY: The Guilford Press.

Luria, A. R. (1966). *Higher cortical functions in man*. New York, NY: Basic Books.

McDonald, C. R., Delis, D. C., Norman, M. A., Tecoma, E. S., & Iragui, V. J. (2005). Discriminating patients with frontal-lobe epilepsy and temporal-lobe epilepsy: Utility of a multilevel design fluency test. *Neuropsychology, 19*(6), 806–813. doi:10.1037/0894-4105.19.6.806.

McDonald, C. R., Delis, D. C., Norman, M. A., Wetter, S. R., Tecoma, E. S., & Iragui, V. J. (2005). Response inhibition and set shifting in patients with frontal lobe epilepsy or temporal lobe epilepsy. *Epilepsy & Behavior, 7*(3), 438–446. doi:10.1016/j.yebeh.2005.05.005.

Meador, K. J., Loring, D. W., Huh, K., Gallagher, B. B., & King, D. W. (1990). Comparative cognitive effects of anticonvulsants. *Neurology, 40*, 391–394.

Milner, B. (Ed.). (1964). *Some effects of frontal lobectomy in man*. New York, NY: McGraw-Hill.

Milner, B. (Ed.). (1967). *Brain mechanisms suggested by studies of temporal lobes*. New York, NY: Grune & Stratton.

Milner, B. (1968). Disorders of memory after brain lesions in man. *Neuropsychologia, 6*, 175–179.

Mittenberg, W., Patton, C., Canyock, E. M., & Condit, D. (2002). Base rates of malingering and symptom exaggeration. *Journal of Clinical and Experimental Neuropsychology, 24*, 1094–1102.

Mohs, R. C., Knopman, D., Petersen, R. C., Ferris, S. H., Ernesto, C., Grundman, M., … The Alzheimer's Disease Cooperative Study. (1997). Development of cognitive instruments for use in clinical trials of antidementia drugs: Additions to the Alzheimer's Disease Assessment Scale that broaden its scope. *Alzheimer Disease and Associated Disorders, 11*(S2), S13–S21.

Morey, L. C. (1991). *Personality assessment inventory professional manual*. Odessa, FL: Psychological Assessment Resources.

Morrison, C. E., & Nakhutina, L. (2007). Neuropsychological features of lesion-related epilepsy in adults: An overview. *Neuropsychology Review, 17*(4), 385–403. doi:10.1007/s11065-007-9044-8.

National Association of Epilepsy Centers (NAEC) (2010) *Guidelines for Essential Services, Personnel, and Facilities in Specialized Epilepsy Centers*. Minneapolis, MN.

NCS Pearson. (2009). *Wechsler individual achievement test—Third edition (WIAT-III)*. San Antonio, TX: NCS Pearson.

Nelson, N. W., Hoelzle, J. B., Sweet, J. J., Arbisi, P. A., & Demakis, G. J. (2010). Updated meta-analysis of the MMPI-2 symptom validity scale (FBS):

Verified utility in forensic practice. *The Clinical Neuropsychologist, 24*(4), 701–724. doi:10.1080/13854040903482863.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinborough inventory. *Neuropsychologia, 9*, 97–113.

Pacia, S. V., Devinsky, O., Perrine, K., Ravdin, L., Luciano, D., Vazquez, B., & Doyle, W. (1996). Clinical features of neocortical temporal lobe epilepsy. *Annals of Neurology, 40*, 724–730.

Palmini, A. I., Gloor, P., & Jones-Gotman, M. (1992). Pure amnestic seizures in temporal lobe epilepsy. *Brain, 115*, 749–769.

Patrikelis, P., Angelakis, E., & Gatzonis, S. (2009). Neurocognitive and behavioral functioning in frontal lobe epilepsy: A review. *Epilepsy & Behavior, 14*(1), 19–26. doi:10.1016/j.yebeh.2008.09.013.

Pearson Assessment. (2009). *Advanced clinical solutions for the WAIS-IV/WMS-IV*. San Antonio, TX: Pearson.

Piazzini, A., Turner, K., Vignoli, A., Canger, R., & Canevini, M. P. (2008). Frontal cognitive dysfunction in juvenile myoclonic epilepsy. *Epilepsia, 49*(4), 657–662. doi:10.1111/j.1528-1167.2007.01482.x.

Piekema, C., Fernandez, G., Postma, A., Hendriks, M. P., Wester, A. J., & Kessels, R. P. (2007). Spatial and non-spatial contextual working memory in patients with diencephalic or hippocampal dysfunction. *Brain Research, 1172*, 103–109. doi:10.1016/j.brainres.2007.07.066.

Postal, K., & Armstrong, K. (Eds.). (2013). *Feedback that sticks: The art of communicating neuropsychological assessment results*. New York, NY: Oxford University Press.

Puente, A. E., Adams, R. L., Barr, W. B., Bush, S., & N. P. P. Committee. (2006). The use, education, training and supervision of neuropsychological test technicians (psychometrists) in clinical practice: Official statement of the National Academy of Neuropsychology. *Archives of Clinical Neuropsychology, 21*, 837–839.

Rabin, L. A., Barr, W. B., & Burton, L. A. (2005). Assessment practices of clinical neuropsychologists in the United States and Canada: A survey of INS, NAN, and APA Division 40 members. *Archives of Clinical Neuropsychology, 20*(1), 33–65. doi:10.1016/j.acn.2004.02.005.

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology, 20*, 310–319.

Rausch, R., & Crandall, P. H. (1982). Psychological status related to surgical control of temporal lobe seizures. *Epilepsia, 23*, 191–202.

Raven, J., Raven, J. C., & Court, J. H. (1998). *Manual for Raven's progressive matrices and vocabulary scales, Section 1*. San Antonio, TX: Harcourt Assessment.

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan neuropsychological test battery. Theory and clinical interpretation*. New York, NY: Hemisphere.

Roid, G. H. (2003). *Stanford-Binet intelligence scales, Fifth edition (SB5)*. Itasca, IL: Riverside Publishing.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology, 20*, 343–350.

Ruff, R. M. (1988). *Ruff figural fluency test administration manual*. San Francisco, CA: Neuropsychological Resources.

Schmidt, M. (1996). *Rey auditory and verbal learning test: A handbook*. Los Angeles, CA: Western Psychological Services.

Schretlen, D. J., Testa, S. M., Winicki, J. M., Pearlson, G. D., & Gordon, B. (2008). Frequency and bases of abnormal performance by healthy adults on neuropsychological testing. *Journal of the International Neuropsychological Society, 14*, 436–445.

Seidenberg, M., Pulsipher, D. T., & Hermann, B. (2007). Cognitive progression in epilepsy. *Neuropsychology Review, 17*(4), 445–454. doi:10.1007/s11065-007-9042-x.

Shehata, G. A., & Bateh Ael, A. (2009). Cognitive function, mood, behavioral aspects, and personality traits of adult males with idiopathic epilepsy. *Epilepsy & Behavior, 14*(1), 121–124. doi:10.1016/j.yebeh.2008.08.014.

Sherman, E. M., Wiebe, S., Fay-McClymont, T. B., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., … Jette, N. (2011). Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia, 52*(5), 857–869. doi:10.1111/j.1528-1167.2011.03022.x.

Shipley, W. (1940). A self-administering scale for measuring intellectual impairment and deterioration. *Journal of Psychology, 9*, 371–377.

Slick, D. J., Tan, J. E., Strauss, E., Mateer, C. A., Harnadek, M., & Sherman, E. (1997). *Manual for the Victoria symptom validity test*. Odessa, FL: Psychological Assessment Resources.

Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2006). *Vineland adaptive behavior scales—Second edition (Vineland-II)*. San Antonio, TX: Pearson.

Stern, R. A., & White, T. (2003). *NAB administration, scoring, and interpretation manual*. Lutz, FL: Psychological Assessment Resources.

Suchy, Y., Sands, K., & Chelune, G. J. (2003). Verbal and nonverbal fluency performance before and after seizure surgery. *Journal of Clinical and Experimental Neuropsychology, 25*(2), 190–200. doi:10.1076/jcen.25.2.190.13640.

Sveller, C., Briellmann, R. S., Saling, M. M., Lillywhite, L., Abbott, D. F., Masterson, R. A. J., & Jackson, G. D. (2006). Relationship between language laterlization and handedness in left-hemisphere partial epilepsy. *Neurology, 67*, 1813–1817.

Sweet, J. J., Meyer, D. G., Nelson, N. W., & Moberg, P. J. (2011). The TCN/AACN 2010 "salary survey": Professional practices, beliefs, and incomes of U.S. neuropsychologists. *The Clinical Neuropsychologist, 25*(1), 12–61. doi:10.1080/13854046.2010.544165.

Swenson, R., Bettcher, B. M., Barr, W. B., Campbell-Marsh, M., & Libon, D. J. (2013). Visuoconstructive test performance and process approach application: Block design, object assembly, and the Rey-Osterrieth complex figure. In L. Ashendorf, R. Swenson, & D. J. Libon (Eds.), *The Boston process approach to neuropsychological assessment: A practitioner's guide*. New York, NY: Oxford University Press.

Thompson, P. J., & Corcoran, R. (1992). Everyday memory failures in people with epilepsy. *Epilepsia, 33*(Suppl. 6), S18–S20.

Tombaugh, T. N. (1996). *TOMM: Test of memory malingering*. North Tonawanda, NY: Multi-Health Systems.

Trimble, M. R., & Thompson, P. J. (1983). Anticonvulsant drugs, cognitive function, and behavior. *Epilepsia, 24*(S1), S55–S63.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior*. Cambridge, MA: MIT Press.

Vanderploeg, R. D., & Schinka, J. A. (1995). Predicting WAIS-R IQ premorbid ability: Combining subtest performance and demographic variable predictors. *Archives of Clinical Neuropsychology, 10*, 225–239.

Warrington, E. K. (1984). *Recognition memory test*. Berkshire: NFER-Nelson.

Waxman, S. G., & Geschwind, N. (1975). The interictal behavior syndrome of temporal lobe epilepsy. *Archives of General Psychiatry, 32*, 1580–1586.

Wechsler, D. (2008). *Wechsler adult intelligence scale—Fourth edition (WAIS-IV)*. San Antonio, TX: Pearson.

Wechsler, D. (2011). *Wechsler abbreviated scale of intelligence—Second edition (WASI-II)*. San Antonio, TX: Pearson.

Wiebe, S., Blume, W. T., Girvin, J. P., Eliasziw, M., & Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. (2001). A randomized, controlled trial of surgery for temporal lobe epilepsy. *The New England journal of medicine, 345*, 311–318.

Wilde, N., Strauss, E., Chelune, G. J., Loring, D. W., Martin, R. C., Hermann, B. P., … Hunter, M. (2001). WMS-III performance in patients with temporal lobe epilepsy: Group differences and individual classification. *Journal of the International Neuropsychological Society, 7*(7), 881–891.

Wilkinson, G. S., & Robertson, G. J. (2006). *Wide range achievement test—Fourth edition (WRAT-4)*. Lutz, FL: Psychological Assessment Resources.

Williamson, P. D., Boon, P. A., Thadani, V. M., Darcey, T. M., Spencer, D. D., Spencer, S. S., … Mattson, R. H. (1992). Parietal lobe epilepsy: Diagnostic considerations and results of surgery. *Annals of Neurology, 31*, 193–201.

Williamson, P. D., French, J., Thadani, V. M., Kim, J. H., Novelly, R. A., Spencer, S. S., … Mattson, R. H. (1993). Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. *Annals of Neurology, 34*, 781–787.

Williamson, D. J., Holsman, M., Chaytor, N., Miller, J. W., & Drane, D. L. (2012). Abuse, not financial incentive, predicts non-credible cognitive performance in patients with psychogenic non-epileptic seizures. *The Clinical Neuropsychologist, 26*(4), 588–598. doi:10.1080/13854046.2012.670266.

Wilson, B. A., Alderman, N., Burgess, P. W., Emslie, H., & Evans, J. J. (1996). *Behavioural assessment of the dysexecutive syndrome (BADS)*. London: Thames Valley Test Company.

Witt, J. A., Alpherts, W., & Helmstaedter, C. (2013). Computerized neuropsychological testing in epilepsy: Overview of available tools. *Seizure, 22*(6), 416–423. doi:10.1016/j.seizure.2013.04.004.

Wonderlic, I. (2004). *Wonderlic personnel test & scholastic level exam users's manual*. Libertyville, IL: Wonderlic.

Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III (WJ3)*. Itasca, IL: Riverside Publishing.

Wygant, D. B., Sellbom, M., Gervais, R. O., Ben-Porath, Y. S., Stafford, K. P., Freeman, D. B., & Heilbronner, R. L. (2010). Further validation of the MMPI-2 and MMPI-2-RF Response Bias Scale: Findings from disability and criminal forensic settings. *Psychological Assessment, 22*(4), 745–756. doi: 10.1037/a0020042.

Evaluation of Children and Adolescents with Epilepsy

2

William S. MacAllister and Elisabeth M.S. Sherman

Introduction and Comments on General Intellectual Function

Children with epilepsy have a range of cognitive ability, from profound global impairment to superior skills. Nevertheless, cognitive and behavioral difficulties have a higher base rate in children with epilepsy than in healthy children, and in some children, cognitive difficulties may predate first seizure (Fastenau et al., 2009). For this reason, neuropsychological assessment is helpful in identifying strengths and weaknesses in children with epilepsy, particularly early on in the condition (Fastenau et al., 2009). Appropriate assessment and characterization of cognitive and behavioral strengths and weaknesses may prove beneficial toward planning and tracking medical treatment (e.g., pharmacological, surgical, rehabilitative) and for educational planning (e.g., placement, allocation of educational services in a formal individualized educational plan), toward the goal of helping each child maximize academic and occupational potential.

In most neuropsychological assessments, evaluation of overall intellectual functioning forms the foundation of the test battery. The most frequently employed measures of intelligence are the Wechsler scales (i.e., Wechsler Primary and Preschool Scale of Intelligence—Third Edition [WPPSI-III]; Wechsler, 2002, Wechsler Intelligence Scale for Children—Fourth Edition [WISC-IV]; Wechsler, 2003, or the Wechsler Abbreviated Scale of Intelligence [WASI]; Wechsler, 1999), and these scales have certainly seen the most use in the study of cognition in pediatric epilepsy. Other commonly utilized intelligence measures include the Stanford-Binet—Fifth Edition (Roid, 2003), the Reynolds Intellectual Assessment System (Reynolds & Kamphaus, 2003), the Woodcock-Johnson Cognitive-III (Woodcock, McGrew, & Mather, 2001), and the Kaufman Assessment Battery for Children-2 (Kaufman & Kaufman, 2002).

Though assessment of overall intellectual function is a crucial "first pass" toward understanding the child, it has long been recognized that school performance in children with epilepsy is often lower than what would be predicted based on global measures of intelligence (i.e., IQ scores; Farwell, Dodrill, & Batzel, 1985). In fact, for many children with epilepsy, IQ is

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somewhat lower than that seen in the general population but still within the average range (Bourgeois, Prensky, Palkes, Talent, & Busch, 1983). This being said, intelligence in children with epilepsy has varied across studies. Whereas studies by Camfield suggest that children with epilepsy have IQs similar to the normal population (Camfield et al., 1984), others have more consistently shown that these individuals have IQs that are significantly lower than age-matched peers (O'Leary, Burns, & Borden, 2006; Singhi, Bansal, Singhi, & Pershad, 1992; Smith, Elliott, & Lach, 2002). The differences across studies reflect factors such as the populations studied (e.g., community-based samples versus tertiary care patients).

Several neurological and epilepsy-specific factors may be predictive of lowered IQ and cognitive problems more generally in children with epilepsy. Children with intractable seizures (i.e., drug-resistant epilepsy) often show lower IQ compared to children with milder forms of epilepsy, and this lowered IQ may reflect a combination of regression of skills, cognitive plateauing, or delayed acquisition of skills. Specific antiepileptic drugs (AEDs) may also affect IQ in children, and medication toxicity may produce marked declines in IQ. Overall, the newer-generation medications typically have more favorable side effect profiles than earlier epilepsy drugs. For example, phenobarbital still sees frequent use in very young children/infants presenting to emergency rooms, despite significant cognitive and behavioral side effects, including reducing IQ (Farwell et al., 1990). At the same time, newer AEDs are not free of cognitive side effects; medications such as topiramate and zonisamide, for example, can produce significant cognitive deficit in some individuals. Most AEDs, whether older or newer generation, have dose-dependent side effects which increase with polytherapy and primarily consist of sedation and inhibitory effects, along with behavioral effects such as irritability (Lee, 2010).

A high seizure frequency (Bourgeois et al., 1983; Farwell et al., 1985), multiple seizure types (e.g., generalized tonic-clonic seizures, absences, partial-complex seizures), as well as multiple antiepileptic drugs (Bourgeois et al., 1983; Bulteau et al., 2000; Reynolds, 1983) have all been associated with lower intellectual functioning, but it should be noted that these cannot be disentangled from epilepsy severity. For example, a child with frequent seizures is more likely to be placed on two or more antiepileptic medications than a child with infrequent seizures. Some research has shown that generalized tonic-clonic seizures and complex partial seizures are more likely to result in prominent cognitive dysfunction (Hoie et al., 2005), but subtler interictal, preictal, and postictal effects may also affect cognition.

The age of the child at the onset of seizures is also an important factor to consider, as this has been linked to level of intellectual function across several studies. For example, in a large community sample, an age of onset prior to 5 years was the strongest predictor of lower intelligence (Berg et al., 2008). Similar findings were reported by others (e.g., Farwell et al., 1985; O'Leary et al., 1983; Schoenfeld et al., 1999).

There are also setting-specific factors that should be considered with respect to IQ expectations in children with epilepsy. Those practicing in community settings may see children with less severe epilepsy whose seizures can be managed quite adequately in nonspecialized clinics and general outpatient centers; these children will present with a lower base rate of cognitive disability, with most functioning in the average range. In contrast, clinicians working in hospitals with specialized epilepsy programs will see a broader range of cognitive ability, including a number of children with cognitive impairments, as the children with more complex management issues often present to these specialized centers. Moreover, neuropsychologists working in these settings often evaluate children being considered for surgical interventions. Within this subpopulation, the frequency of children with intellectual disability is considerably higher than in community settings, with many showing intellectual function in the range of mild intellectual disability or lower. This issue is further discussed below.

Though it is commonly held that the side of seizure onset may predict a pattern of performance on IQ measures (e.g., left-sided onset is related to reduced verbal IQ versus right-sided onset predicting lowered performance or nonverbal IQ), this may not be true in most children with epilepsy. In young children with epilepsy, the onset of seizures may coincide with the period of critical language development. It is well established that early cerebral damage may impact the cortical representation of language; whereas a normally developing right-handed child will likely show left-hemisphere language dominance, children with left-hemisphere epilepsy may show functional reorganization, particularly when seizures are secondary to a catastrophic or extensive lesion experienced early in life (e.g., left middle cerebral artery stroke). Accordingly, global measures of verbal and performance/perceptual intelligence may not show lateralized patterns because of neural plasticity/functional reorganization seen in young children with neurologic conditions. In a group of pediatric epilepsy patients for whom language dominance was established via Wada procedure, only about a third of those with typical language organization, and under a quarter of those with atypical language organization, showed noteworthy VIQ/PIQ discrepancies. Of the total sample, side of focus was correctly predicted for only 24 %, with 8 % being incorrectly lateralized. The authors appropriately concluded that a VIQ/PIQ discrepancy alone is not effective in lateralizing the hemisphere of seizure onset (Blackburn et al., 2007).

Epilepsy Syndromes

It is important to appreciate that epilepsy is not a unitary condition, but represents a diverse neurological condition associated with many underlying causes. Accordingly, there is no single neuropsychological profile associated with "epilepsy" in children, and heeding the specific syndrome is important, as cognitive deficits more closely reflect characteristics of the syndrome, rather than seizure or EEG characteristics. As such, prior to evaluating children and adolescents with epilepsy, it is imperative for clinicians to have a working understanding of the cognitive profile seen in specific syndromes such that the evaluation can be planned appropriately, targeting areas of known or suspected deficits. A comprehensive review of specific cognitive profiles associated with childhood epilepsy syndromes is outside the scope of this chapter (see MacAllister & Schaffer, 2007), but some common syndromes seen by neuropsychologists assessing children with epilepsy will be briefly introduced as illustrative examples.

Benign rolandic epilepsy (BRE) is the most common epilepsy syndrome of childhood, representing about 15 % of all childhood seizure disorders (Sidenvall, Forsgren, Blomquist, & Heijbel, 1993), with an onset typically occurring between age 3 and 13 years. Boys are more often affected. Characteristic EEG findings in BRE involve centrotemporal spikes followed by slow waves that tend to be activated by sleep. Seizure semiology commonly involves brief, simple partial, and hemifacial motor seizures that may secondarily generalize. Treatment with antiepileptic medications is not always warranted in BRE, as seizures tend to be infrequent, typically occur at night, and usually spontaneously remit in adolescence (Bourgeois, 2000).

Despite its designation as a "benign" syndrome, neuropsychological impairments often accompany BRE. For example, some studies indicated deficits in language (vocabulary, prosody, phonological awareness, speech, verbal fluency), memory, motor skills, attention, and executive functioning (Croona, Kihlgren, Lundberg, Eeg-Olofsson, & Eeg-Olofsson, 1999; Gunduz, Demirbilek, & Korkmaz, 1999; Northcott et al., 2005). Interestingly, EEG features in BRE may be only minimally associated with neuropsychological function, with no relation seen between cognition and spike burden or laterality (Northcott et al., 2005).

The International League Against Epilepsy specifies three common generalized idiopathic epilepsies of childhood including childhood absence seizures, juvenile absence seizures, and juvenile myoclonic epilepsy. In childhood

absence epilepsy (CAE), onset is typically between age 3 and the teenage years, with girls being more frequently affected (Wirrell, 2003). In juvenile absence epilepsy (JAE), seizures tend to develop in puberty. These syndromes are challenging to differentiate, and studies of absence epilepsies often consider them together. As such, information specific to JAE is limited, though this syndrome is often associated with generalized tonic-clonic seizures upon awakening (Loiseau, Duche, & Pedespan, 1995). Further, myoclonic seizures are present in 15 % of cases, which also makes this syndrome difficult to distinguish from juvenile myoclonic epilepsy (JME; Reutens & Berkovic, 1995).

Overall, neuropsychological findings in CAE suggest that visual spatial and visual memory functions are more affected than verbal functions. One study of children with CAE showed that these individuals had lower full-scale IQs than matched controls (Pavone et al., 2001), though 81 % had scores in the average range. Patients showed poorer visual spatial skills, nonverbal memory, and delayed recall in comparison to controls, with verbal skills and verbal memory being less affected (Pavone et al., 2001). These findings were generally commensurate with later work on generalized idiopathic epilepsies (Jambaque, Dellatolas, Dulac, Ponsot, & Signoret, 1993; Nolan et al., 2003).

JME, the most common primary generalized epilepsy syndrome in adolescence, usually has an onset between age 12 and 18 and requires lifelong AED treatment. This syndrome is associated with myoclonic jerks of the neck, shoulders, and arms (Janz, 1985), and many also have generalized tonic-clonic seizures and absences (Asconape & Penry, 1984). JME patients show difficulty on tests of executive functioning, including mental flexibility and concept formation (Devinsky et al., 1997; Holmes, Quiring, & Tucker, 2010; Pulsipher et al., 2009). A study of 50 JME patients showed more extensive deficits; patients had poorer attention, inhibition, working memory, processing speed, and mental flexibility, in addition to difficulties with verbal and visual memory, naming, and verbal fluency (Pascalicchio et al., 2007).

As with adults with epilepsy, children frequently present with focal epilepsy syndromes. Temporal lobe epilepsy is among the most frequently occurring epilepsy syndromes in both adults and children. In children, temporal lobe epilepsy typically has an onset in the school age years and, with a younger onset, cognitive outcomes are often poorer and such children are at a high risk for learning disabilities (Jambaque et al., 1993; Williams et al., 1996). Given the onset in the temporal lobes, it is not surprising that the most prominent neuropsychological deficits are in memory, which may be seen even in the presence of average IQ. However, impairments are often broader, and as in other epilepsies, factors such as age of seizure onset and seizure frequency contribute to greater neuropsychological impairment (Hermann & Seidenberg, 2002; Hermann et al., 2002). Children with TLE may also present with executive function deficits (Guimaraes et al., 2007; Rzezak et al., 2007, 2009) and attention impairments (Dunn & Kronenberger, 2005; Schubert, 2005). Further, language deficits, such as poor naming and reduced vocabulary, have been seen in children with left-sided temporal lobe epilepsy (Jambaque et al., 1993).

Frontal lobe epilepsies are also seen in children and are often caused by cortical dysplasia, tumors, vascular lesions, trauma, or genetic factors. Unfortunately, frontal lobe epilepsies are often refractory to conventional treatments and are associated with frequent seizures that tend to propagate and generalize (Bancaud & Talairach, 1992; Lawson et al., 2002). Pediatric frontal lobe epilepsy may be associated with executive functioning problems such as difficulties with planning, impulse control, temporal orientation, sequencing, categorization, mental flexibility, and verbal reasoning (Auclair, Jambaque, Dulac, LaBerge, & Sieroff, 2005; Culhane-Shelburne, Chapieski, Hiscock, & Glaze, 2002; de Guise et al., 1999; Hernandez et al., 2002; Lendt et al., 2002; Parisi et al., 2010; Patrikelis, Angelakis, & Gatzonis, 2009; Perez, Davidoff, Despland, & Deonna, 1993; Riva, Saletti, Nichelli, & Bulgheroni, 2002).

Occipital lobe epilepsies account for between 6 and 8 % of focal epilepsies (Manford, Hart, Sander, & Shorvon, 1992) and are more common in children than in adults (Sveinbjornsdottir & Duncan, 1993). Neuropsychological findings in pediatric occipital lobe epilepsy are inconsistent. One study recently demonstrated that children with occipital lobe epilepsy performed more poorly than controls on measures of intellectual functioning, with PIQ being particularly affected (Gulgonen, Demirbilek, Korkmaz, Dervent, & Townes, 2000). Another study found VIQ to be low relative to controls, with no difference found between patients and controls on PIQ (Germano et al., 2005). In both of these studies, however, the children with epilepsy showed poor performances across many other neuropsychological domains, including attention, memory, visuospatial skills, language skills, and motor skills.

The epileptic encephalopathies refer to a group of severe epilepsy syndromes that often include deterioration of sensory and motor skills. Each tends to include frequent seizures and/or prominent interictal activity (Nabbout & Dulac, 2003). Moreover, in all there is a regression of cognitive development or a failure to attain developmental milestones, and as such the long-term outcomes are quite guarded. A complete discussion of each of the epileptic encephalopathies is outside the scope of this chapter, but the most well known are introduced briefly below (i.e., West syndrome, Lennox-Gastaut, Landau-Kleffner syndrome).

West syndrome, with its onset in infancy, is characterized by infantile spasms, psychomotor deterioration, and hypsarrhythmia on EEG. The syndrome may be caused by neurological insult (e.g., infection or hypoxia-ischemia), cortical malformations, neurocutaneous syndrome (e.g., tuberous sclerosis complex, Sturge-Weber syndrome), genetic disorders, or an inborn error of metabolism (Wirrell, Farrell, & Whiting, 2005), though a third of cases are idiopathic (Nabbout & Dulac, 2003). Early signs of cognitive deficit involve reduced social contact (Guzzetta, 2006). About 80 % of individuals with West syndrome present with intellectual disability, but those with idiopathic West syndrome may have a better outcome (Guzzetta, 2006; Koo, Hwang, & Logan, 1993; Matsumoto et al., 1981). Lennox-Gastaut is a rare syndrome with an estimated incidence 1–2 per 100,000 children (Cowan, 2002) with an age of onset between 2 and 8 years of age (Wirrell et al., 2005), though many have a prior history of infantile spasms. The syndrome usually results from focal, multifocal, or diffuse brain dysfunction arising from diverse etiologies (e.g., malformation, perinatal stroke), but idiopathic cases are seen that usually have an older age at onset (Nabbout & Dulac, 2003). In Lennox-Gastaut syndrome, both tonic and akinetic seizures are seen, and EEG shows slow generalized spike-and-wave discharges. The outcome for these children is usually poor, with over 90 % showing mental retardation (Cowan, 2002). Moreover, intellectual functioning may further deteriorate as these children age (Oguni, Hayashi, & Osawa, 1996). Earlier onset (i.e., below age 3) and a history of infantile spasms are associated with poorer outcomes. In some, vagus nerve stimulation can improve seizure frequency and may also result in some degree of cognitive improvement. However, it is not clear if such gains are maintained over time (Majoie et al., 2001; Majoie, Berfelo, Aldenkamp, Renier, & Kessels, 2005).

Though fewer than 1 % of childhood epilepsies are characterized by continuous spike and waves during slow-wave sleep (Kramer et al., 1998), these syndromes have received a fair amount of attention due to the dramatic effects on neuropsychological functioning. In this group, partial and generalized seizures are seen at the onset, and EEG shows generalized spike-wave discharges that may occupy more than 85 % of slow-wave sleep (Camfield & Camfield, 2002). The age of onset is usually between 5 and 7 years (McVicar & Shinnar, 2004), and though most had normal development prior to onset, preexisting neurological abnormalities are reported in about a third. Overall intellectual functioning, language skills, spatial orientation, motor skills, and behavior are all adversely affected (Tassinari et al., 2000). The most well-studied disorder associated with continuous spike and waves dur-

ing slow-wave sleep is Landau-Kleffner syndrome (i.e., acquired epileptic aphasia), which includes severe language regression at onset, involving profound deficits in comprehension (often referred to as an auditory agnosia), though it usually progresses to involve expressive language deficits as well (Landau & Kleffner, 1957; Rotenberg & Pearl, 2003). Clinical seizures are present in only about 80 % of children with Landau-Kleffner syndrome and are not necessary to make the diagnosis.

Evaluation of Specific Cognitive Domains

Attention and Executive Functions

As with most neurologic populations, attention and executive function deficits are quite common in childhood epilepsy. As such, a comprehensive neuropsychological evaluation must include assessment of these skills, especially considering the fact that attentional and executive function deficits often lead to considerable academic underachievement. In epilepsy, attentional impairment is secondary to several factors, including the underlying brain pathology, which causes both the cognitive deficits and seizures, as well as the seizures themselves (causing preictal, ictal, and postictal symptomology). Moreover, interictal EEG phenomena often results in disrupted attention as many antiepileptic medication side effects. It should also be noted that certain seizure types (e.g., absence seizures) have, as their primary manifestation, a behavioral arrest which may be behaviorally indistinguishable from inattention. It should not be surprising that, given the above, attention deficit/hyperactivity disorder (ADHD) is quite common in children with epilepsy.

For example, in a study of 175 children and adolescents with various seizure types, 42 % of adolescents and 58 % of children were in the "at-risk" range for attention problems on the Child Behavior Checklist (CBCL), and 25 % adolescents and 37 % of children fell in the "clinical" range. Categorical classifications on the Child and Adolescent Symptom Inventories indicated that 11.4 % had possible ADHD-combined subtype, 44 % had possible ADHD-inattentive subtype, and 2.3 % had ADHD-hyperactive subtype. The inattentive subtype of ADHD was more common in children with epilepsy; in children with developmental ADHD, the combined subtype (with features of both inattention and hyperactivity) is far more common. Further, girls with epilepsy may be more likely to show attention problems. Epilepsy-related variables (e.g., seizure type, location of onset) were not significant predictors of ADHD symptoms (Dunn, Austin, Harezlak, & Ambrosius, 2003).

Hermann et al. (2007) evaluated the rate, subtype, and clinical correlates of ADHD in children with idiopathic epilepsy recruited from neurology clinics in the Midwestern United States. Results were similar to prior findings, indicating that ADHD is more common in children with epilepsy than controls (31.5 % versus 6.4 %). Again, the inattentive subtype was more common (52.1 %) than hyperactive (13.1 %), combined subtypes (13.1 %), or ADHD—not otherwise specified (17.4 %). Notably, the symptoms of ADHD predated onset of epilepsy in 82 % of cases, and those with ADHD and epilepsy showed poorer performance across most neuropsychological tasks, with motor/psychomotor speed and executive functioning (e.g., response inhibition, mental flexibility, working memory, etc.) often being affected. Epilepsy variables, such as specific syndrome, medications, age of onset, and duration of epilepsy, did not predict ADHD diagnosis. Given the high likelihood of ADHD in children with epilepsy, a competent neuropsychological evaluation should heed the guidelines set forth by the American Academy of Pediatrics to appropriately diagnose ADHD. These guidelines suggest that the clinician must assess the formal DSM-IV criteria through evidence obtained from both parents and teachers, including information regarding the age of onset, duration of symptoms, and degree of functional impairment (American Academy of Pediatrics, 2000).

"Executive functions," mediated by a network of neuroanatomical circuits involving the prefrontal cortex and its connections (Miller &

Cummings, 2007; Stuss & Knight, 2002), refer to higher-order cognitive functions such as planning, inhibition, set shifting, self-monitoring, organization, working memory, and initiating and sustaining motor and mental activity. Assessment of executive dysfunction in children with epilepsy is important both because of the high rate of such problems in clinical samples and the fact that executive deficits predict poorer quality of life in children. In particular, the constellation of executive dysfunction, low adaptive level, high medication load, and a history of drug-resistant epilepsy contributes significantly to the risk of poor quality of life in children with epilepsy (Sherman, Slick, & Eyrl, 2006). Executive dysfunction is associated with earlier age of epilepsy onset and higher seizure frequency (Hoie, Mykletun, Waaler, Skeidsvoll, & Sommerfelt, 2006), as well as with school performance problems (Hoie et al., 2006). Further, long-term functional difficulties associated with executive dysfunction include behavioral disturbance, social difficulties, and reduced educational and occupational attainment (Baron, 2004; Lezak, 2004).

Executive problems are seen in a number of childhood epilepsies, including frontal lobe epilepsy, temporal lobe epilepsy (see above), idiopathic absence epilepsy (Vuilleumier, Assal, Blanke, & Jallon, 2000), childhood absence epilepsy (Caplan, Siddarth, Stahl, Lanphier, Vona, Gurbani, et al., 2008), and benign rolandic epilepsy (Nicolai, Aldenkamp, Arends, Weber, & Vles, 2006). Children with mild epilepsy (i.e., recent onset, well controlled with medication, normal IQ) tend to have poorer executive functioning than healthy children (Parrish et al., 2007). At the more severe end of the epilepsy spectrum, 40–50 % of children seen in tertiary settings present with clinically significant problems with executive functioning (Rzezak et al., 2007; Slick, Lautzenhiser, Sherman, & Eyrl, 2006). Accurately synthesizing the literature on executive dysfunction in epilepsy requires remaining aware of ascertainment biases, which influence the rate of cognitive deficits in epilepsy; as indicated above, children from tertiary centers often have the highest rates of cognitive and behavioral problems, and those from community settings, the lowest. On the other hand, only recently in the pediatric epilepsy literature have executive functions been systematically assessed. Consequently, some earlier studies on neuropsychological functioning in children with epilepsy may not have reported executive deficits simply because these were not assessed.

There are a number of well-known paradigms that have been used in children with epilepsy and in other clinical groups to assess executive functions. The most well known is the Wisconsin Card Sorting Test (WCST; Kongs, Thompson, Iverson, & Heaton, 2000), a test that measures conceptual reasoning and ability to shift mental set. In one pediatric study involving tertiary-center temporal lobe patients, the WCST had the highest sensitivity among executive functioning tests (77 %; including 50 % for Trail Making B and 26–40 % for fluency tasks; Rzezak et al., 2009). The highest executive dysfunction detection was when the WCST was used in combination with at least one other executive functioning test (94 %).

Although continuous performance tests (CPTs), such as the Test of Variables of Attention (Greenberg, 1988), Conners' Continuous Performance Test II (Conners, 2004), and the Integrated Visual and Auditory Continuous Performance Test (Sandford & Turner, 1995), are typically considered sustained attention paradigms, all also involve an inhibition component that requires the child to resist impulsive responding over time. Because these tasks also measure reaction time, continuous performance tasks allow for the measurement of multiple neuropsychological domains. These tasks are also generally well validated in terms of sensitivity and validity in clinical groups (Riccio & Reynolds, 2001; Riccio, Reynolds, & Lowe, 2001). In our experience, CPTs are especially sensitive to subtler forms of inattention, impulsivity, and executive dysfunction, likely because they are not administered through direct one-to-one interaction. Instead, the child works independently on a computer and must maintain a goal-directed, focused stance in order to perform well. CPTs are also typically longer than

many executive functioning tasks, which may mitigate the novelty effect that sometimes masks executive difficulties.

Fluency tasks are also a classic method for detecting initiation, effortful search, and organization problems evident in the verbal and visual modality. Word fluency tasks require the child to spontaneously provide lists of specific words (starting with a certain letter) or of specific exemplars (from a given category such as animals), within a given timeframe. The analogous nonverbal tasks are design fluency tests, which require generation of novel designs under time constraints. Both the word fluency and design fluency have been relatively well studied in adults with epilepsy (e.g., Martin et al., 2000; Suchy, Sands, & Chelune, 2003). Fluency tasks are part of the standard battery in most epilepsy centers assessing children, though its sensitivity to laterality in children remains to be empirically determined. In one study, approximately 26–40 % of children with temporal lobe epilepsy from a tertiary care center had impaired scores on categorical fluency tasks (Rzezak et al., 2009).

The Rey Complex Figure Test (Rey, 1941), although primarily considered a visual memory test, includes a copy trial that can provide information on organization skills in the visual modality, in addition to visual spatial ability, discussed below. Usually, the comparison to performance on a simpler visual design copying task, such as the Beery-Buktenica visuomotor integration test (VMI; Beery & Beery, 2006), can inform as to whether deficits are primarily organizational or reflect a more fundamental problem with visuospatial or visuomotor skills. Other tasks sensitive to age-dependent expression of executive deficits include the Stroop, Trail Making Test, Tower of London, Contingency Naming Test, and Twenty Questions Test (Jacobs, Harvey, & Anderson, 2007; Rzezak et al., 2007, 2009; Strauss, Sherman, & Spreen, 2006). Many of these basic paradigms have been used as inspiration for executive functioning tests in comprehensive batteries such as the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001) and NEPSY-II (Korkman, Kirk, & Kemp, 2007; for review, see Brooks, Sherman, & Strauss, 2009) and have also been used to assess executive functioning in children with epilepsy (Bender, Marks, Brown, Zaroff et al. 2007; Parrish et al., 2007).

It is well established that performance-based tests of attention and executive functions are not always sensitive to dysfunction by virtue of being administered in a structured, quiet, one-on-one testing environment that reduces the need for self-initiated organization and problem-solving (Strauss et al., 2006). Therefore, specialized questionnaires completed by family members and teachers to assess attention and executive functioning in daily life are useful. To assess attention (with consideration of formal diagnostic criteria for ADHD), indices such as the SNAP-IV (Swanson, Schuck, Mann, et al., 2001), Conners' Scales (Conners, 2001), or other similar DSM-IV-oriented scales are useful, though more general rating scales that assess attention in addition to other psychological factors are also frequently employed (e.g., CBCL; Achenbach, 1991); Behavior Assessment System for Children-2 (BASC-2; Reynolds & Kamphaus, 2004) and these latter scales have utility in pediatric epilepsy (Bender, Auciello, Morrison, MacAllister, & Zaroff, 2008). Considering executive functions per se, the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is increasingly used in the neuropsychological assessment of children with epilepsy. The BRIEF shows sensitivity to executive deficits in children with severe epilepsy (Slick et al., 2006), as well as in children with recent-onset epilepsy with good seizure control (Parrish et al., 2007). A version also exists for preschoolers (BRIEF-P; Gioia, Espy, & Isquith, 2003), which is particularly welcome because reliable performance-based measures of executive functioning designed for this age group for clinical use are lacking.

Ideally, the detection of attention and executive deficits is the first step toward treatment. To date, there have been no studies aimed at improving executive deficits per se in children with epilepsy, but there are a few studies demonstrating successful pharmacological treatment of ADHD in chil-

dren with epilepsy, some finding improvements in quality of life after treatment (e.g., Yoo et al., 2009). There are also guidelines for treating physicians on how to balance AED treatment with pharmacological treatment of ADHD symptoms (Parisi et al., 2010). When assessing children with epilepsy, the neuropsychologist should include recommendations on treatments aimed explicitly at improving executive dysfunction such as referral for consideration of stimulant medication and behavioral interventions. In addition, many parent and teacher resources aimed at children with primary ADHD (e.g., Barkley, 2000) are useful for children with epilepsy.

Learning and Memory

Memory deficits are common in children with epilepsy. Further, it has been shown that memory is more disrupted in children with complex partial seizures than other seizure types because these seizures tend to arise from temporal and frontotemporal zones, areas associated with memory and learning. However, generalized epilepsy syndromes such as CAE and BRE may also be associated with memory problems, including poorer memory for nonverbal information in comparison to verbal information (Pavone et al., 2001; Pinton et al., 2006). Notably, a 2001 study did not show differences in memory performance across seizure types (Williams et al., 2001). Given the high base rate of memory problems in epilepsy and the importance of memory in the acquisition of knowledge, a thorough assessment of memory skills is crucial. Hermann, Seidenberg, & Bell (2002) demonstrated progressive cognitive decline (including memory and intellectual functioning) in children with temporal lobe epilepsy, with the decline being associated with epilepsy duration. The authors posited that temporal lobe epilepsy affects a negative impact on brain structure, setting into motion a cascade of cognitive deficits related to reduced cognitive reserve and continuing seizures (Hermann, Seidenberg, & Bell, 2002).

The issue of material specificity of memory deficits is an ongoing debate in the empirical literature. Classically, verbal memory deficits have been associated with left-hemisphere dysfunction, whereas memory for visually presented information is suggestive of right-hemisphere pathology. However, the material specificity of memory deficits in childhood epilepsy has been variable across studies. Generally speaking, much of the empirical evidence suggests that children with memory deficits may show more general cognitive impairment, though those with left-sided temporal lobe epilepsy may perform particularly poorly. This should not seem all that surprising given that an early memory deficit will result in difficulties in the acquisition of knowledge, which will lead to lower overall abilities.

The hypothesis that memory in epilepsy exhibits material specificity (i.e., that left-sided seizures are associated with verbal memory problems and right-sided seizures with visual memory problems) has a long history in the epilepsy literature. For example, in a study by Fedio and Mirsky (1969), children with left temporal lobe epilepsy showed poor retention of verbal information, but both immediate and delayed nonverbal memory was intact. Conversely, children with right temporal lobe epilepsy showed the opposite pattern; these children had impaired recall for nonverbal memory items (Fedio & Mirsky, 1969). Similar results were reported by Jambaque et al. (1993) though the left temporal lobe epilepsy group studied here was lower functioning than the right temporal lobe group overall. However, numerous other studies have failed to show such differences in children (e.g., Camfield et al., 1984; Engle & Smith, 2010; Helmstaedter & Elger, 2009), with researchers essentially finding no difference between visual and verbal memory between left and right temporal lobe epilepsy groups. Of note, a recent study of children with temporal lobe epilepsy demonstrated that children with mesial temporal involvement had lower memory skills than those with lateral involvement. In this group, facial recognition tasks differentiated left and right temporal lobe epilepsies, with the latter showing poorer performance, but other memory tasks were not helpful in determining side of

epilepsy onset (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007). Moreover, a recent study indicated that though lateralization of seizure focus was not associated with verbal versus visual memory deficits, the laterality influenced the correlation between attention- and material-specific memory (Engle & Smith, 2010).

Variable findings across studies may reflect psychometric issues to some extent but also may be due to the fact that children may show less hemispheric specialization than adults. Further, early damage or disruption of maturational processes of the left hemisphere may be associated with functional reorganization, with the right hemisphere subsuming some aspects of linguistic processing, which likely explains why some studies report lower functioning overall in children with left temporal lobe epilepsy (Jambaque et al., 1993). It has also been suggested that the rapid spread of seizures from one temporal lobe results in dysfunction in both hippocampi, regardless of the side of seizure origin, thus muddying the material specificity of results. There are numerous instruments available to assess memory in children, with several older instruments undergoing revisions that have significantly improved their psychometric properties. The CVLT-C has been frequently utilized in the study of neurologic illness in children and has shown sensitivity to memory impairment in children with epilepsy as well (e.g., Williams et al., 2001). As in adult studies, the Rey-Osterrieth Complex Figure has been utilized in the study of visual memory deficits in childhood epilepsy (Schouten, Hendriksen, & Aldenkamp, 2009). Many pediatric neuropsychologists prefer using co-normed batteries of memory tests so that visual and verbal memory can be directly compared. The past decade has seen the revisions of several such batteries, including the Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2; Sheslow & Adams, 2003), and the Test of Memory and Learning, Second Edition (TOMAL-2; Reynolds & Voress, 2007). Prior research has shown the sensitivity of the WRAML (original version) to deficits in childhood epilepsy (Giordani et al., 2006). The NEPSY-II Edition also includes verbal and visual memory tests, including a task of memory for faces, which again may be of particular importance when evaluating memory deficits in the presence of a right-hemisphere onset. Facial memory tasks are also seen in batteries such as the Children's Memory Scale (Cohen, 1997), the TOMAL-2 (Reynolds & Kamphaus, 2004), and the KABC-2 (Kaufman & Kaufman, 2002), a larger cognitive battery that extends down to the preschool age.

Language

One of the most dramatic examples of language deficits in the context of pediatric epilepsy is the Landau-Kleffner Syndrome, which has, as its primarily manifestation, an auditory agnosia followed by receptive (and later expressive) language regression. However, as indicated above, subtler language deficits can be seen in other epilepsy syndromes. For example, naming and vocabulary deficits are often seen in children with left-sided temporal lobe epilepsy (Jambaque et al., 1993), and earlier onset is often associated with developmental language problems. However, in other children, language problems may arise or remit depending on epilepsy-related factors. For example, a sample of young children with left frontal simple partial seizures was followed longitudinally. Results suggested dissociations between language comprehension and expressive language. Specifically, comprehension gradually improved, reaching average performance by age 7. In contrast, expressive skills remained poorer (Cohen & Le Normand, 1998). Volkl-Kernstock, Bauch-Prater, Ponocny-Seliger, and Feucht (2009) described a sample of children with benign rolandic epilepsy that showed impairments in receptive language, expressive speech, and expressive vocabulary. An important finding in this study was that after remission of the seizure disorder, language deficits were no longer seen in this group.

Caplan, Siddarth, et al. (2009) commented on the paucity of research conducted on children

with epilepsy and normal intellectual function. Interestingly, their study, which included 183 children with either generalized or partial seizures, a quarter of the younger children, a third of the intermediate-aged children, and over half of the adolescent group, showed language deficits in comparison to their age-matched peers. Their findings were interpreted to suggest an "age-related rise" in the vulnerability to language deficits. In a 2008 study of 69 children with absence seizures, nearly half showed language deficits despite, on average, normal IQ (Caplan et al., 2008).

It is also important to recognize the fact that language skills, such as phonological awareness, are the underpinnings of competent reading ability, and such skills have been shown to be deficient in many children with epilepsy (Vanasse, Beland, Carmant, & Lassonde, 2005). Language-based learning disabilities are therefore more prevalent in children with epilepsy than in the general population and more prominent in some kinds of epilepsy versus others. For example, reading deficits are more prevalent in children with temporal lobe epilepsy compared to children with idiopathic generalized epilepsy and benign rolandic epilepsy (Chaix et al., 2006).

The assessment of language is therefore an important consideration in the comprehensive evaluation of neurocognitive functioning in pediatric epilepsy. The astute clinician will note apparent receptive and expressive language deficits in casual conversation, and the ability to understand verbal instructions during other neuropsychological tasks may be initial evidence of receptive language deficits, if present. Moreover, clinicians should pay close attention to the quality of verbal utterances during casual discourse, paying special attention to the rate, rhythm/prosody of speech, articulation, and the quality of grammatical and syntactical constructions. Certain subtests often routinely administered during assessment of intellectual functioning provide excellent opportunities to observe the latter; for example, the Vocabulary, Similarities, and Comprehension subtests of the WISC-IV allow observation of verbal expression under semi-structured conditions and may serve as the initial foundational screening of language on which a more comprehensive evaluation may be built. Measures of confrontation naming may prove important, such as the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and Expressive One Word Vocabulary Test, Third Edition (Brownell, 2000), as well as measures of verbal initiation and fluency reviewed above. Examples of letter fluency and semantic fluency are available in several batteries with developmentally appropriate normative data, such as the DKEFS (Delis et al., 2001) and the NEPSY-II (Korkman et al., 2007).

If a more comprehensive evaluation of language is deemed necessary based on parent and/or teacher concerns or clinician impressions during screening, several comprehensive language batteries are commercially available. The Test of Language Development and Test of Adolescent Language (Newcomer & Hammil, 1988) have shown sensitivity to language deficits in pediatric epilepsy (Caplan, Siddarth, et al., 2009) offering assessment of vocabulary, syntax, and phonology. School systems often have familiarity with the Clinical Evaluation of Language Fundamentals (CELF)—4th Edition (Semel, Wiig, & Secord, 2003), which provides a comprehensive evaluation of receptive and expressive language abilities. Earlier versions of the CELF have been employed in prior studies; for example, in a sample of children with stroke, those with comorbid epilepsy showed greater language deficits on the CELF-Revised (Ballantyne, Spilkin, & Trauner, 2007). The CELF-IV also provides indices of phonological awareness, which is a foundational skill for competent reading. Other measures of phonological awareness include subtests from the NEPSY-II (Korkman et al., 2007) or the Comprehensive Test of Phonological Processing (Wagner, Torgesen, & Rashotte, 1999). The latter may be particularly important when language-based learning disabilities are suspected, which again are more prevalent in individuals with epilepsy than in the general population.

Visuospatial and Visuomotor Skills

In surveying the extant literature on cognition in pediatric epilepsy, it becomes readily apparent that visual spatial skills have received fairly sparse attention in comparison to other cognitive domains. This may relate to the fact that deficits in domains such as attention or memory are more likely to manifest as problems in the child's day-to-day life. Nevertheless, research clearly suggests that children with epilepsy may show visuospatial and motor deficits.

Occipital-parietal areas are crucial in the processing of visuospatial information. This said, as indicated above, neuropsychological findings in pediatric occipital lobe epilepsy have been inconsistent with some studies suggesting PIQ deficits (Gulgonen et al., 2000) and others showing poorer VIQ (Germano et al., 2005). Deficits in visuospatial skills have also been demonstrated in other seizure types as well. For example, in a sample of children with benign rolandic epilepsy, deficits were seen in spatial orientation and spatial memory, and deficits were not associated with side of epilepsy focus (Volkl-Kernstock, Willinger, & Feucht, 2006). In a study employing the NEPSY in children with various epilepsy types, some showed deficits on visuospatial processing tasks. Specifically, 15 % of children showed deficits on the Design Copy subtest, a task of graphomotor construction, and 16 % showed impairment on the "Arrows" subtest, a motor-free spatial perception task. Of the subtests within the NEPSY battery, the task most sensitive to impairment was the Visuomotor Precision subtest, a complex task of visual perception, speed, attention, and motor control; 73 % were impaired on this task (Bender, Marks, Brown, Zach, Zaroff et al. 2007). In a study of children with localization-related epilepsy, a temporal onset was associated with poorer copy of the Rey-Osterrieth Complex Figure (Schouten et al., 2009). Numerous studies have demonstrated deficits in fine motor control in children with epilepsy (e.g., Giordani et al., 2006), and it should be noted that certain antiepileptic medications may produce a tremor and motor slowing as a side effect, which may complicate the assessment of visuomotor skills (see Loring, Marino, & Meador, 2007).

Numerous instruments are available for the assessment of visuospatial and visuomotor skills in children. As indicated, studies have shown that the PIQ (and/or perceptual reasoning) subtests of the Wechsler scales have shown sensitivity to such deficits (Gulgonen et al., 2000). The Beery VMI (Beery & Beery, 2006), a graphomotor task, is perhaps one of the most frequently employed tasks by pediatric neuropsychologists to assess these skills. The NEPSY battery includes an analogous task (i.e., Design Copy) that has shown sensitivity to visuospatial dysfunction in childhood epilepsy (Zach, et al., 2007). Similarly, other NEPSY subtests assess visual spatial skills that do not involve a motor component (e.g., Arrows) and have been successfully used in this population (Bender, Marks, Brown, Zach, et al., 2007). It should also be noted that other more "classic" neuropsychological tasks that were initially designed for use in adults, such as the Rey-Osterrieth Complex Figure (Rey, 1941) and Judgment of Line Orientation test (Benton, Varney, & Hamsher, 1978), have pediatric norms available and may be used in children. To assess fine manual dexterity, many pediatric neuropsychologists employ the Purdue Pegboard, which has shown sensitivity to motor skills deficits in childhood epilepsy. The grooved pegboard is another option for such assessment (Mathews & Klove, 1964). It is recommended that the assessment of visual spatial skills in children with epilepsy employs both motor tasks and pure perceptual tasks that will not be adversely affected by poor motor control.

Mood and Quality of Life

Unfortunately, mood disorders are fairly common in pediatric epilepsies, and for this reason, a comprehensive neuropsychological evaluation should involve assessment of the child's mental health. A review of depression and anxiety disorders in pediatric epilepsy was recently published (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009), and readers are referred there for a more

comprehensive discussion, but major findings will be discussed here. In studies of pediatric epilepsy, the prevalence rates of psychological challenges vary quite widely due to methodological issues, including how mood disorders were assessed (e.g., self-report forms, parent-report forms versus clinical interview). In a population-based survey of mental health problems in children with epilepsy completed by Davies, Heyman, and Goodman (2003), over 16 % of children had noteworthy mental health problems. Another study employed a more comprehensive interview of psychiatric problems (e.g., the Kiddie Schedule for Affective Disorders and Schizophrenia [KSADS]) and found that 12 % of children with complex partial seizures had anxiety or depression, and 13 % of those with childhood absence epilepsy had anxiety and/or depression. Importantly, suicidal ideation was also reported in many of these children (Ott et al., 2001).

With respect to factors that predict mental health problems, gender effects have been seen in some studies. For example, one study showed that girls with epilepsy were more often depressed than boys (Dunn, Austin, & Huster, 1999). Some have shown that seizure frequency may be related to mood (Oguz, Kurul, & Dirik, 2002), and others have shown that children with epilepsy and associated intellectual disability may show more severe mood disorders (Buelow et al., 2003; Davies et al., 2003). Psychiatric problems may also be related to antiepileptic medication use. One study, for example, reported a high rate of depression in children treated with phenobarbital in comparison to those treated with carbamazepine (Brent, Crumrine, Varma, Allan, & Allman, 1987); depression subsided when phenobarbital was discontinued (Brent, Crumrine, Varma, Brown, & Allan, 1990). An extremely noteworthy finding is that of children having significant mental health problems; only a third may receive proper treatment for such difficulties (Caplan, Sagun, et al., 2005).

The impact of having a child with epilepsy also places considerable strain on a family. The degree of impact is related to several key factors, including the severity of the epilepsy, how complicated the medical management is, the restrictions placed on child and family as a result of the illness, and the innate coping skills of family members and the resources afforded to them (see Camfield, Breau, & Camfield, 2001). As many as 50 % of mothers of children with epilepsy are at risk for psychiatric difficulties such as clinical depression (Ferro & Speechley, 2009; Wood, Sherman, Hamiwka, Blackman, & Wirrell, 2008). The total impact that epilepsy has on a family has been shown to relate to factors such as cognitive problems, neurologic complications, as well as variables such as age of onset, frequency of seizures, medications, and the frequency of visits to the doctor. Other studies have examined the impact of epilepsy on social competence and peer relations. One study, for example, showed that lower IQ and externalizing behaviors are related to poorer social competence (Caplan, Sagun, et al., 2005).

Quality of life is increasingly important in the assessment of the impact of illness in people with medical conditions. Health-related quality of life (HRQOL) refers to a rating of subjective well-being as it relates to the impact of a medical condition on physical functioning, psychological functioning, social functioning, and behavioral functioning. Factors such as low IQ, low adaptive functioning, psychosocial difficulties, high seizure frequency, intractability, polydrug therapy, long-standing epilepsy duration, parental maladjustment, low family income, and older age tend to be associated with lower HRQOL in children with epilepsy (Buelow et al., 2003; Devinsky et al., 1999; Miller, Palermo, & Grewe, 2003; Sabaz, Cairns, Lawson, Bleasel, & Bye, 2001; Sabaz et al., 2003; Sherman et al., 2002; Sillanpaa, Haataja, & Shinnar, 2004).

Several epilepsy-specific HRQOL instruments have been validated for use in children and adolescents. Some examples include the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE, Sabaz et al., 2000), the Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-48; Cramer et al., 1999), the Impact of Childhood Neurologic Disability Scale (ICND; Camfield, Breau, & Camfield, 2003), and the HRQOL in children with epilepsy (Ronen,

Streiner, Rosenbaum, & Canadian Pediatric Epilepsy Network, 2003). Generic instruments that can be used across medical conditions are also useful, such as the PedsQL (Varni, Seid, & Rode, 1999). Not all instruments meet psychometric, reliability, and validity standards for all purposes, however; for a more detailed review of HRQOL instruments for use in epilepsy, see Cowan and Baker (2004) and Eiser and Morse (2001).

As in any population, the assessment of psychological factors in pediatric epilepsy begins with a thorough clinical interview that assesses mood and affect, appetite, sleep disturbance, as well as family and peer relationships. In the context of a full neuropsychological evaluation, which in itself is extremely time intensive, screening for psychological difficulties may suffice, and several broadband scales are available for these purposes. The most frequently employed measures are the Child Behavior Checklist (Achenbach, 1991) and the Behavior Assessment System for Children, 2nd Edition (Reynolds & Kamphaus, 2004). Recent research in children with epilepsy has demonstrated that these two instruments are strongly intercorrelated (Bender et al., 2008). It is also important to note that these forms have parallel forms for self-report, parent report, and teacher report. These are important in order to assess the child's function across multiple settings, as each person viewing the child sees him or her in a unique setting that may inform the overall clinical picture. This may also be of particular importance as the children and adolescents themselves may show a tendency to minimize problems. Self-report indices have also proven helpful in clinical assessment. For example, short self-report inventories such as the Manifest Anxiety Scales (Reynolds & Richmond, 1978) and the Child Depression Inventory (Kovacs, 1985) have been used in several studies of children with epilepsy (Baki et al., 2004; Caplan, Siddarth, et al., 2005).

In some cases, a more structured assessment of psychological functioning may be warranted. Instruments such as the KSADS (Kaufman, Birmaher, Brent, et al., 1997), a formalized semi-structured clinical interview for psychological disorders for the purposes of rendering formal DSM-IV diagnoses, may be appropriate; this instrument is often considered to be the "gold standard" for the assessment of DSM-IV disorders and has been used successfully in many research studies of psychiatric disturbance in children with epilepsy (e.g., Caplan, Siddarth, et al., 2005). However, as this instrument is fairly labor intensive if the full interview is completed, routine use in a busy clinical practice is not always practical or necessary, but it should be noted that prior work suggests that full KSADS interview will identify more children with psychological problems than will screening instruments such as the CBCL (Ott et al., 2001).

The Role of the Pediatric Neuropsychologist in the Presurgical Evaluation

Within the context of a pediatric epilepsy presurgical evaluation, the neuropsychological assessment must meet several needs, including addressing questions regarding cognitive risks and benefits of surgery, determining the concordance of the cognitive profile with imaging and other investigations which may point to the possibility of abnormal function outside areas identified by EEG and imaging, identifying any additional investigations needed to inform surgical decision-making (e.g., language mapping, Wada exam), and addressing psychosocial and school-based needs. Further, the neuropsychologist helps families understand the nature of their child's cognitive strengths and weaknesses, which can alleviate frustration and help families develop realistic expectations with regard to behavior, schooling, and family adjustment.

At its core, the function of the presurgical neuropsychological evaluation is to determine the neuropsychological risks and benefits of undergoing a specific surgical procedure. Practically speaking, there are no clear guidelines on how this is accomplished in children. However, there are several key concepts inherent to the presurgical evaluation of patients with

epilepsy. First, a risk/benefit analysis rests on assessing two main components: the adequacy of the to-be-resected tissue and the functional reserve capacities of the non-resected tissue (Chelune, 1995). Specifically, the neuropsychological capabilities of the tissue that will be resected informs clinicians of the likelihood of declines after surgery (i.e., higher functional adequacy means the surgery may remove functional tissue, which may lead to deficits after surgery), whereas cognitive recovery depends on the capacity of the brain circuits that will remain postsurgically. In general, children with high cognitive reserve (e.g., high IQ), discrete focal lesions (e.g., unilateral mesial temporal sclerosis), and no factors that may hinder plasticity (e.g., a high likelihood of seizure freedom after surgery) will have a higher potential for reorganization and compensation for deficits than those with low reserve, extensive or multifocal lesions, and factors that hinder plasticity (e.g., a likelihood of continuing seizures after surgery). The clinician should consider factors that affect neuropsychological outcome, such as age at epilepsy onset, age at surgery, type of underlying abnormality, side of resection, and likelihood of ongoing seizures after surgery, all of which are prognostic factors for cognitive recovery, compensation, and reorganization of function (Elger, Helmstaedter, & Kurthen, 2004; Helmstaedter & Kockelmann, 2006; Hermann & Loring, 2008). At the same time, it is important to emphasize that children may show a potential for recovery of functions both ipsilateral and contralateral to the surgical site that is greater than that of adult patients (Gleissner, Sassen, Schramm, Elger, & Helmstaedter, 2005). Other pragmatic aspects of evaluating patients with epilepsy such as ictal and interictal effects on cognition during testing and antiepileptic medication load at the time of testing (Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003) should be documented, as these may affect the validity of the findings. Ideally, the surgical work-up will be followed by a postsurgical assessment, typically conducted 1 year after surgery, to help identify cognitive recovery, rule out further decline, and assist with ongoing treatment planning.

The presurgical test battery should have several features: (1) it should be comprehensive enough for the purposes of surgical decision-making, (2) it should show utility in detecting common cognitive and behavioral problems specific to children with severe epilepsy, and (3) it should include measures that show sensitivity and responsiveness to treatment effects, be they surgical or pharmacological. It is important to recognize that the neuropsychological profile of children with epilepsy often reflects the additive effects of the underlying neurological condition from which seizures arise (e.g., perinatal stroke, cortical dysplasia), on which are superimposed the cognitive effects of antiepileptic drugs, seizure activity, interictal discharges, and pre- and postictal cognitive alterations. For these reasons, the neuropsychological profile of children with epilepsy, particularly those seen as part of a presurgical evaluation, may best be considered a current "snapshot," rather than as a stable and enduring estimate of cognition; surgical candidates are *by definition* assessed when all other treatments have failed, often while on several antiepileptic drugs at maximum dosages, and when seizures are at their worst in frequency or intensity. Accordingly, cognitive disruption caused by seizures and medication side effects may be at their peak when children are assessed presurgically.

Finally, at the time of the evaluation, the exact seizure focus and the exact surgical approach that will be offered to the patient may be unknown. For example, an outpatient EEG might indicate left temporal discharges, which on further investigations (e.g., inpatient video EEG, intracranial monitoring, etc.) actually represent secondary spread from a distant focus. Consequently, the neuropsychological evaluation should be comprehensive and flexible enough to allow the neuropsychologist to address issues pertinent to different kinds of resections, should the surgical plan change after the evaluation is completed.

As in other evaluations, determination of the child's IQ typically comprises the first step in the presurgical evaluation. Although the choice of IQ measure is up to the clinician, the vast majority of

research on intellectual function in pediatric epilepsy has employed Wechsler tests (see above). In our experience, the high base rate of children with cognitive disabilities and the need to document these for school and community programming justify the use of full IQ batteries rather than short forms, though these decisions must be balanced against practical considerations, including the fact that some evaluations are conducted during inpatient EEG monitoring in less-than-optimal testing conditions with children who may not be able to participate in lengthy testing sessions. Adequately measuring IQ is particularly important in surgical candidates because declines in cognition may indicate that seizures are worsening or the presence of medically critical situations such as nonconvulsive status epilepticus or medication toxicity, all of which require immediate review by the treating epileptologist. Other children may exhibit lags in development resulting from frequent seizures or from an underlying neurodevelopmental condition, which can be detected by tracking IQ over time. In our experience, approximately 1/3 to ½ of children evaluated for epilepsy surgery have a cognitive disability (i.e., IQ below 70 with associated adaptive function deficits).

The most crucial domains assessed during presurgical evaluations are language and memory due to the large impact deficits these domains may cause. In adults, verbal memory declines are commonly reported side effects of temporal lobe surgery, with base rates of between 30 and 50 % in left-sided surgeries (Engman, Andersson-Roswall, Svensson, & Malmgren, 2004; Stroup et al., 2003). Visual memory deficits may not be as consistently reported with right temporal lobectomy but do occur with similar incidence in some series (Dulay et al., 2009).

A comprehensive surgical battery should also include measures of expressive and receptive language. In adults, declines on naming tasks after left temporal lobe surgery range between 20 and 50 % (Davies, Risse, & Gates, 2005; Schwarz, Pauli, & Stefan, 2005), consistent with the dominant temporal lobe's role in naming and receptive language in most right-handed individuals.

Other important domains to assess are attention and executive functions. Although deficits in these functions may have a high base rate in surgical candidates including children with epileptic foci outside the frontal lobe (Guimaraes et al., 2007; Rzezak et al., 2009), improvements in these functions may follow surgery (Kim, Lee, Yoo, Kang, & Lee, 2007; Martin et al., 2000). Visuospatial testing is also critical, and assessment of children undergoing posterior resections should include screening for attentional and visuo-constructional problems, including neglect (Gleissner, Kuczaty, Clusmann, Elger, & Helmstaedter, 2008; Luerding, Boesebeck, & Ebner, 2004). Assessing motor skills is also important to determine the presence of lateralized difficulties but also for measuring the impact of AEDs.

A surgical battery should further provide a comprehensive coverage of psychosocial function that allows for screening for the most common psychiatric comorbidities in pediatric epilepsy, namely, ADHD, anxiety, and depression (Pellcock, 2004). A surgical battery should include an adaptive functioning scale to help determine the presence of cognitive disability, another highly prevalent condition in children with intractable seizures, and because adaptive skills may change over time (Berg et al., 2004). Ideally, the battery should include an assessment of health-related quality of life using scales that have been validated in pediatric epilepsy, to help determine the functional impact of surgery on daily functioning on the child and family.

Neuropsychologists working in epilepsy surgery centers should have some expertise in evaluating very low-functioning children who may be "untestable" using standardized face-to-face measures. At times, evaluations of this sort will consist of a parent interview, behavioral observations and non-standardized testing, and a small battery of standardized questionnaires/structured interviews for assessing adaptive functioning, such as the Adaptive Behavior Assessment System-II (Harrison & Oakland, 2003) or Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984). Although the value of assessing "untestable" children may

have been questioned in the past, parents and treating physicians frequently appreciate the insights these evaluations bring to understanding the child's condition, as well as the extra services that can be advocated for by documenting the degree of cognitive and language delay in the neuropsychological evaluation. Standardized questionnaires of adaptive function and quality of life also serve as a benchmark for measuring improvements after surgery in children whose severe cognitive and behavioral challenges preclude standardized testing.

One of the most important aspects of the neuropsychological assessment is providing information to the family that will help guide them in decision-making regarding their child's epilepsy surgery. Oddly, there is very little information in the literature on how this should be accomplished. In our experience in providing feedback to families, there are three broad areas to cover: (1) the child's neuropsychological functioning overall, with a discussion of specific strengths and weaknesses; (2) the factors presumed to underlie any cognitive problems, including the location of the lesion based on imaging and EEG findings and the combined impact of seizures and AEDs on cognition; (3) surgical risks and benefits from a cognitive and psychosocial standpoint; and finally, (4) implications of test results for school programming and home. In most cases, the main risks that need to be discussed with families are the possibility of declines in language and/or declines in memory, particularly declines in verbal memory since this is the deficit that may have the greatest impact on academics.

Importantly, the costs of *not* proceeding to surgery should also be discussed with the family. Risks of this kind can rarely be conclusively determined on an individual basis (unless the child has a clear risk factor for cognitive decline, such as repeated and uncontrollable bouts of status epilepticus), but the family should be informed of factors relevant to the child's future cognitive prognosis, including the possibility of cognitive plateauing or decline with continued uncontrolled seizures, an established risk in chronic epilepsy (Elger et al., 2004; Helmstaedter & Elger, 2009). Unfortunately, with continuing chronic seizures in childhood, the outlook for psychological adjustment and quality of life is poor, and this includes educational, social, marital, and occupational functioning (Elger et al., 2004; Helmstaedter et al., 2003; Sherman, 2009; Sillanpaa et al., 2004). The family must then determine, with the assistance of the treatment team, whether surgery and its attendant risk of cognitive changes is an acceptable risk in light of the possibility of better seizure control.

Determining language dominance is an important component of the presurgical evaluation because surgical approaches will differ based on whether surgery occurs in the dominant or non-dominant hemisphere and whether the surgery may involve eloquent cortex. In children, the probability of atypical speech increases with seizure onset before age 6, left-sided seizure focus, extra-temporal seizures, and left-handedness (Saltzman-Benaiah, Scott, & Smith, 2003). In addition, over half of children with left-hemisphere lesions and seizure onset before age 6 show atypical language lateralization that is unrelated to the type of pathology underlying the epilepsy, be it developmental (e.g., cortical dysplasia, tuberous sclerosis), acquired (e.g., mesial temporal sclerosis, encephalitis), or tumor related (Kadis et al., 2009).

Techniques for determining language dominance range in terms of invasiveness, sensitivity, and spatial resolution. Such techniques include handedness, dichotic listening, fMRI, Wada testing, and language mapping, discussed here in order of increasing invasiveness. Readers are referred to other sources for further information on these and other techniques for mapping cognitive functions, such as MEG (Papanicolaou et al., 2004) and near infrared spectroscopy (Gallagher et al., 2007).

Determining handedness provides an initial "ball-park" estimate of language dominance. Because the vast majority of right-handers are left-hemisphere dominant, left-handedness (without a family history of sinistrality) may be a red flag for atypical language dominance but will in no way provide a definitive estimate of which

hemisphere subserves language. For example, although the base rate of atypical language dominance is much higher in left-handed people with epilepsy, 50 % of these left-handers nevertheless have left-hemisphere language dominance, and less than 10 % will have full right-hemisphere language dominance (Lee, 2010). Handedness can be inferred with interview and unstructured observation or determined via a standardized lateral dominance examination involving manipulation of real objects.

Dichotic listening tasks have a long history in the determination of language dominance (Strauss et al., 2006). However, they too are not definitive, as lesion affects peripheral hearing impairments, and speech-processing problems may complicate interpretation of results (Fernandes, Smith, Logan, Crawley, & McAndrews, 2006; Gramstad, Engelsen, & Hugdahl, 2003).

fMRI paradigms to assess language have become a standard in many centers. Semantic decision tasks, verbal fluency, sentence generation, and listening to sentences have been used successfully with children in fMRI paradigms (Hertz-Pannier et al., 2000). The disadvantages of fMRI are that widespread circuits may be activated which may make it difficult to identify crucial language zones against a more generalized language network for surgical planning, which is where language mapping may be of particular utility. For this reason, fMRI language paradigms are used principally to determine which hemisphere subserves language but are less useful for determining with precision the exact demarcation lines of language zones in the surgical field. fMRI requires children who are sufficiently testable and old enough to cooperate with the fMRI testing procedure, which may include relatively lengthy sessions of immobility. Because many children being considered for epilepsy surgery have intellectual disability or behavioral disorders, such techniques are not feasible for all children.

Cortical stimulation of language areas (language mapping or electrocortical stimulation mapping) permits a precise localization of language-dependent cortical zones and provides a more fine-grained localization than fMRI or Wada testing. Research on language mapping in children is more limited than in adults but indicates that language mapping may have low sensitivity to identification of language-critical sites in children younger than 8–10 years (Ojemann, Berger, Lettich, & Ojemann, 2003; Schevon et al., 2007), although some report success with children as young as 2 years of age (Duchowny et al., 1996; Ojemann et al., 2003). Children also show greater variability in language sites compared to adults (Ojemann et al., 2003). Reduced efficacy of mapping in younger children has been attributed to immature myelination, which requires higher stimulation thresholds (Schevon et al., 2007). Intraoperative mapping can be accomplished in awake children during a craniotomy, but this is typically reserved for higher-functioning, older children, and some centers conduct only extra-operative mapping in children. Extra-operative language mapping can be conducted in even very young or behaviorally challenged patients, although the resolution of the subdural grid may not be as high as mapping that uses stimulation points chosen by the surgeon during an awake craniotomy (Ojemann et al., 2003).

Extra-operative language mapping is typically carried out by the neuropsychologist and neurologist at bedside using a variety of stimuli and paradigms to assess language functions. Although many paradigms are used across centers, the procedure typically includes testing of language comprehension (e.g., following simple commands, sentence completion tasks), confrontation naming, and continuous speech. Before mapping, it is crucial that baseline testing be undertaken to identify a series of items that can be performed error free; results from the neuropsychological assessment are often very useful in gearing these items to the child's capacities. Because many children feel lethargic or uncomfortable during the intracranial monitoring period, language mapping is often carried out in several short sessions using generous praise and reinforcements. For more in-depth discussions of language mapping, see Lee (2010) or Chap. 5.

Wada testing (i.e., the intracarotid amobarbital procedure) is a deactivation procedure during

which one of the cerebral hemispheres is anaesthetized in order to test the language and memory capacity of the contralateral hemisphere. As such, it provides a "reversible surgery" simulation and can be used for predicting patients who may be at risk of amnesia postsurgery. Although an in-depth discussion of the history, rationale, and limitations of the Wada test is beyond the scope of this chapter (see Chap. 4), the routine use of this procedure has been increasingly questioned, and some centers no longer administer the Wada to all surgical candidates (Baxendale, Thompson, & Duncan, 2008a, 2008b; Kubu, Girvin, McLachlan, Pavol, & Harnadek, 2000). Wada testing may have reduced sensitivity in children compared to adults (Jansen et al., 2002), particularly under age 10, and may cause obtundation in some (Schevon et al., 2007). However, Wada testing has been used successfully in children as young as 2 and in very cognitively impaired children to identify language dominance, though memory testing is more difficult to assess in younger children (Jansen et al., 2002).

Conclusions

The neuropsychological assessment of children and adolescents with epilepsy is a complex undertaking. The competent clinician will have knowledge of the cognitive deficits associated with specific epilepsy syndromes to provide an adequate assessment of cognitive skills that mirrors known or suspected areas of difficulty in a given child. Moreover, a skilled clinician must be aware of various factors associated with cognitive deficits in children with epilepsy, as well as of tasks sensitive to neuropsychological strengths and weaknesses in order to provide accurate and helpful treatment recommendations. Furthermore, those working in specialized epilepsy centers must demonstrate expertise in specialized procedures such as cortical mapping and tools for determining language dominance and have skills in determining the cognitive risks and benefits of surgery for individual children as part of a comprehensive presurgical evaluation. Appropriate assessment and characterization of cognitive and behavioral strengths and weaknesses as part of the neuropsychological assessment of children with epilepsy is beneficial for planning and tracking medical treatment (pharmacological, surgical, and rehabilitative) and for educational planning, toward the goal of helping each child maximize academic and occupational potential.

References

Achenbach, T. M. (1991). *Manual for the child behavior checklist*. Burlington: Department of Psychiatry, University of Vermont.

American Academy of Pediatrics. (2000). Clinical practice guideline: Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. American Academy of Pediatrics. *Pediatrics, 105*(5), 1158–1170.

Asconape, J., & Penry, J. K. (1984). Some clinical and EEG aspects of benign juvenile myoclonic epilepsy. *Epilepsia, 25*(1), 108–114.

Auclair, L., Jambaque, I., Dulac, O., LaBerge, D., & Sieroff, E. (2005). Deficit of preparatory attention in children with frontal lobe epilepsy. *Neuropsychologia, 43*(12), 1701–1712.

Baki, O., Erdogan, A., Kantarci, O., Akisik, G., Kayaalp, L., & Yalcinkaya, C. (2004). Anxiety and depression in children with epilepsy and their mothers. *Epilepsy & Behavior, 5*(6), 958–964.

Ballantyne, A., Spilkin, A., & Trauner, D. (2007). Language outcome after perinatal stroke: Does side matter? *Child Neuropsychology, 13*(6), 494–509.

Bancaud, J., & Talairach, J. (1992). Clinical semiology of frontal lobe seizures. *Advances in Neurology, 57*, 3–58.

Barkley, R. A. (2000). *Taking charge of ADHD: The complete authoritative guide for parents*. New York, NY: Guilford.

Baron, I. (2004). *Neuropsychological evaluation of the child*. New York, NY: Oxford University Press.

Baxendale, S., Thompson, P. J., & Duncan, J. S. (2008a). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: An international survey. *Epilepsia, 49*(4), 715–720. discussion 720–725.

Baxendale, S. A., Thompson, P. J., & Duncan, J. S. (2008b). Evidence-based practice: A reevaluation of the intracarotid amobarbital procedure (Wada test). *Archives of Neurology, 65*(6), 841–845.

Beery, K. E., & Beery, N. A. (2006). *The Beery Buktenica developmental test of visual-motor integration—Fifth edition: Administration, scoring, and teaching manual*. Minneapolis, MN: NCS Pearson.

Bender, H. A., Auciello, D., Morrison, C., MacAllister, W. S., & Zaroff, C. M. (2008). Comparing the

convergent validity and clinical utility of the BASC-PRS and CBCL in children with epilepsy. *Epilepsy & Behavior, 13*, 237–242.

Bender, H. A., Marks, B. C., Brown, E. R., Zach, L., & Zaroff, C. M. (2007). Neuropsychologic performance of children with epilepsy on the NEPSY. *Pediatric Neurology, 36*(5), 312–317.

Bender, H. A., Marks, B. C., Brown, E., & Zaroff, C. M. (2007). The clinical utility of the NEPSY in assessing young children with epilepsy. *Pediatric Neurology, 36*, 312–317.

Benton, A. L., Varney, N. R., & Hamsher, K. D. (1978). Visuospatial judgment: A clinical test. *Archives of Neurology, 35*, 364–367.

Berg, A. T., Langfitt, J. T., Testa, F. M., Levy, S. R., DiMario, F., Westerveld, M., et al. (2008). Global cognitive function in children with epilepsy: A community-based study. *Epilepsia, 49*(4), 608–614.

Berg, A. T., Smith, S. N., Frobish, D., Beckerman, B., Levy, S. R., Testa, F. M., et al. (2004). Longitudinal assessment of adaptive behavior in infants and young children with newly diagnosed epilepsy: Influences of etiology, syndrome, and seizure control. *Pediatrics, 114*(3), 645–650.

Blackburn, L. B., Lee, G. P., Westerveld, M., Hempel, A., Park, Y. D., & Loring, D. W. (2007). The verbal IQ/Performance IQ discrepancy as a sign of seizure focus laterality in pediatric patients with epilepsy. *Epilepsy & Behavior, 10*(1), 84–88.

Bourgeois, B. F. (2000). Drug treatment of benign focal epilepsies of childhood. *Epilepsia, 41*(8), 1057–1058.

Bourgeois, B. F., Prensky, A. L., Palkes, H. S., Talent, B. K., & Busch, S. G. (1983). Intelligence in epilepsy: A prospective study in children. *Annals of Neurology, 14*(4), 438–444.

Brent, D. A., Crumrine, P. K., Varma, R. R., Allan, M., & Allman, C. (1987). Phenobarbital treatment and major depressive disorder in children with epilepsy. *Pediatrics, 80*(6), 909–917.

Brent, D. A., Crumrine, P. K., Varma, R., Brown, R. V., & Allan, M. J. (1990). Phenobarbital treatment and major depressive disorder in children with epilepsy: A naturalistic follow-up. *Pediatrics, 85*(6), 1086–1091.

Brooks, B. L., Sherman, E. M., & Strauss, E. (2009). Test review: NEPSY-II: A developmental neuropsychological assessment, second edition. *Child Neuropsychology, 16*, 80–101.

Brownell, R. (2000). *Expressive one-word picture vocabulary test—Third edition manual*. Novato, CA: Academic Therapy Publications.

Buelow, J. M., Austin, J. K., Perkins, S. M., Shen, J., Dunn, D. W., & Fastenau, P. S. (2003). Behavior and mental health problems in children with epilepsy and low IQ. *Developmental Medicine and Child Neurology, 45*(10), 683–692.

Bulteau, C., Jambaque, I., Viguier, D., Kieffer, V., Dellatolas, G., & Dulac, O. (2000). Epileptic syndromes, cognitive assessment and school placement: A study of 251 children. *Developmental Medicine and Child Neurology, 42*(5), 319–327.

Camfield, C., Breau, L., & Camfield, P. (2001). Impact of pediatric epilepsy on the family: A new scale for clinical and research use. *Epilepsia, 42*(1), 104–112.

Camfield, C., Breau, L., & Camfield, P. (2003). Assessing the impact of pediatric epilepsy and concomitant behavioral, cognitive, and physical/neurologic disability: Impact of childhood neurologic disability scale. *Developmental Medicine and Child Neurology, 45*(3), 152–159.

Camfield, P., & Camfield, C. (2002). Epileptic syndromes in childhood: Clinical features, outcomes, and treatment. *Epilepsia, 43*(Suppl 3), 27–32.

Camfield, P. R., Gates, R., Ronen, G., Camfield, C., Ferguson, A., & MacDonald, G. W. (1984). Comparison of cognitive ability, personality profile, and school success in epileptic children with pure right versus left temporal lobe EEG foci. *Annals of Neurology, 15*(2), 122–126.

Caplan, R., Levitt, J., Siddarth, P., Wu, K. N., Gurbani, S., Sankar, R., et al. (2009). Frontal and temporal volumes in childhood absence epilepsy. *Epilepsia, 50*(11), 2466–2472.

Caplan, R., Sagun, J., Siddarth, P., Gurbani, S., Koh, S., Gowrinathan, R., et al. (2005). Social competence in pediatric epilepsy: Insights into underlying mechanisms. *Epilepsy & Behavior, 6*(2), 218–228.

Caplan, R., Siddarth, P., Gurbani, S., Hanson, R., Sankar, R., & Shields, W. D. (2005). Depression and anxiety disorders in pediatric epilepsy. *Epilepsia, 46*(5), 720–730.

Caplan, R., Siddarth, P., Stahl, L., Lanphier, E., Vona, P., Gurbani, S., et al. (2008). Childhood absence epilepsy: Behavioral, cognitive, and linguistic comorbidities. *Epilepsia, 49*(11), 1838–1846.

Caplan, R., Siddarth, P., Vona, P., Stahl, L., Bailey, C., Gurbani, S., et al. (2009). Language in pediatric epilepsy. *Epilepsia, 50*(11), 2397–2407.

Chaix, Y., Laguitton, V., Lauwers-Cances, V., Daquin, G., Cances, C., Demonet, J. F., et al. (2006). Reading abilities and cognitive functions of children with epilepsy: Influence of epileptic syndrome. *Brain & Development, 28*(2), 122–130.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology, 10*(5), 413–432.

Cohen, M. (1997). *The children's memory scale*. San Antonio, TX: The Psychological Corporation.

Cohen, H., & Le Normand, M. (1998). Language development in children with simple-partial left-hemisphere epilepsy. *Brain and Language, 64*(3), 409–422.

Conners, C. K. (2001). *Conners' rating scales: Revised*. North Tonawanda, NY: Multi-Health Systems.

Conners, C. K. (2004). *Conners' CPT II continuous performance test II*. North Tonawanda, NY: Multi-Health Systems.

Cowan, L. D. (2002). The epidemiology of the epilepsies in children. *Mental Retardation and Developmental Disabilities Research Reviews, 8*(3), 171–181.

Cowan, J., & Baker, G. A. (2004). A review of subjective impact measures for use with children and adolescents with epilepsy. *Quality of Life Research, 13*(8), 1435–1443.

Cramer, J. A., Westbrook, L. E., Devinsky, O., Perrine, K., Glassman, M. B., & Camfield, C. (1999). Development of the quality of life in epilepsy inventory for adolescents: The QOLIE-AD-48. *Epilepsia, 40*(8), 1114–1121.

Croona, C., Kihlgren, M., Lundberg, S., Eeg-Olofsson, O., & Eeg-Olofsson, K. E. (1999). Neuropsychological findings in children with benign childhood epilepsy with centrotemporal spikes. *Developmental Medicine and Child Neurology, 41*(12), 813–818.

Culhane-Shelburne, K., Chapieski, L., Hiscock, M., & Glaze, D. (2002). Executive functions in children with frontal and temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 8*(5), 623–632.

Davies, S., Heyman, I., & Goodman, R. (2003). A population survey of mental health problems in children with epilepsy. *Developmental Medicine and Child Neurology, 45*(5), 292–295.

Davies, K. G., Risse, G. L., & Gates, J. R. (2005). Naming ability after tailored left temporal resection with extraoperative language mapping: Increased risk of decline with later epilepsy onset age. *Epilepsy & Behavior, 7*(2), 273–278.

de Guise, E., del Pesce, M., Foschi, N., Quattrini, A., Papo, I., & Lassonde, M. (1999). Callosal and cortical contribution to procedural learning. *Brain, 122*(Pt 6), 1049–1062.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan executive function system (DKEFS): Examiner's manual*. San Antonio, TX: The Psychological Corporation.

Devinsky, O., Gershengorn, J., Brown, E., Perrine, K., Vazquez, B., & Luciano, D. (1997). Frontal functions in juvenile myoclonic epilepsy. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 10*(4), 243–246.

Devinsky, O., Westbrook, L., Cramer, J., Glassman, M., Perrine, K., & Camfield, C. (1999). Risk factors for poor health-related quality of life in adolescents with epilepsy. *Epilepsia, 40*(12), 1715–1720.

Duchowny, M., Jayakar, P., Harvey, A. S., Resnick, T., Alvarez, L., Dean, P., et al. (1996). Language cortex representation: Effects of developmental versus acquired pathology. *Annals of Neurology, 40*(1), 31–38.

Dulay, M. F., Levin, H. S., York, M. K., Mizrahi, E. M., Verma, A., Goldsmith, I., et al. (2009). Predictors of individual visual memory decline after unilateral anterior temporal lobe resection. *Neurology, 72*(21), 1837–1842.

Dunn, D. W., Austin, J. K., Harezlak, J., & Ambrosius, W. T. (2003). ADHD and epilepsy in childhood. *Developmental Medicine and Child Neurology, 45*(1), 50–54.

Dunn, D. W., Austin, J. K., & Huster, G. A. (1999). Symptoms of depression in adolescents with epilepsy. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(9), 1132–1138.

Dunn, D., & Kronenberger, W. (2005). Childhood epilepsy, attention problems, and AD/HD: Review and practical considerations. *Seminars in Pediatric Neurology, 12*, 222–2228.

Eiser, C., & Morse, R. (2001). A review of measures of quality of life for children with chronic illness. *Archives of Disease in Childhood, 84*(3), 205–211.

Ekinci, O., Titus, J. B., Rodopman, A. A., Berkem, M., & Trevathan, E. (2009). Depression and anxiety in children and adolescents with epilepsy: Prevalence, risk factors, and treatment. *Epilepsy & Behavior, 14*(1), 8–18.

Elger, C. E., Helmstaedter, C., & Kurthen, M. (2004). Chronic epilepsy and cognition. *Lancet Neurology, 3*(11), 663–672.

Engle, J. A., & Smith, M. L. (2010). Attention and material-specific memory in children with lateralized epilepsy. *Neuropsychologia, 48*(1), 38–42.

Engman, E., Andersson-Roswall, L., Svensson, E., & Malmgren, K. (2004). Non-parametric evaluation of memory changes at group and individual level following temporal lobe resection for pharmacoresistant partial epilepsy. *Journal of Clinical and Experimental Neuropsychology, 26*(7), 943–954.

Farwell, J. R., Dodrill, C. B., & Batzel, L. W. (1985). Neuropsychological abilities of children with epilepsy. *Epilepsia, 26*(5), 395–400.

Farwell, J. R., Lee, Y. J., Hirtz, D. G., Sulzbacher, S. I., Ellenberg, J. H., & Nelson, K. B. (1990). Phenobarbital for febrile seizures—Effects on intelligence and on seizure recurrence. *The New England Journal of Medicine, 322*(6), 364–369.

Fastenau, P. S., Johnson, C. S., Perkins, S. M., Byars, A. W., deGrauw, T. J., Austin, J. K., et al. (2009). Neuropsychological status at seizure onset in children: Risk factors for early cognitive deficits. *Neurology, 73*(7), 526–534.

Fedio, P., & Mirsky, A. F. (1969). Selective intellectual deficits in children with temporal lobe or centrencephalic epilepsy. *Neuropsychologia, 7*, 287–300.

Fernandes, M. A., Smith, M. L., Logan, W., Crawley, A., & McAndrews, M. P. (2006). Comparing language lateralization determined by dichotic listening and fMRI activation in frontal and temporal lobes in children with epilepsy. *Brain and Language, 96*(1), 106–114.

Ferro, M. A., & Speechley, K. N. (2009). Depressive symptoms among mothers of children with epilepsy: A review of prevalence, associated factors, and impact on children. *Epilepsia, 50*(11), 2344–2354.

Gallagher, A., Theriault, M., Maclin, E., Low, K., Gratton, G., Fabiani, M., et al. (2007). Near-infrared spectroscopy as an alternative to the Wada test for language mapping in children, adults and special populations. *Epileptic Disorders, 9*(3), 241–255.

Germano, E., Gagliano, A., Magazu, A., Sferro, C., Calarese, T., Mannarino, E., et al. (2005). Benign

childhood epilepsy with occipital paroxysms: Neuropsychological findings. *Epilepsy Research, 64*(3), 137–150.

Gioia, G. A., Espy, K. A., & Isquith, P. K. (2003). *Behavior rating inventory of executive function: Preschool version*. Lutz, FL: Psychological Assessment Resources.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *Behavior rating inventory of executive function: Professional manual*. Lutz, FL: Psychological Assessment Resources.

Giordani, B., Caveney, A. F., Laughrin, D., Huffman, J. L., Berent, S., Sharma, U., et al. (2006). Cognition and behavior in children with benign epilepsy with centrotemporal spikes (BECTS). *Epilepsy Research, 70*(1), 89–94.

Gleissner, U., Kuczaty, S., Clusmann, H., Elger, C. E., & Helmstaedter, C. (2008). Neuropsychological results in pediatric patients with epilepsy surgery in the parietal cortex. *Epilepsia, 49*(4), 700–704.

Gleissner, U., Sassen, R., Schramm, J., Elger, C. E., & Helmstaedter, C. (2005). Greater functional recovery after temporal lobe epilepsy surgery in children. *Brain, 128*(Pt 12), 2822–2829.

Gonzalez, L. M., Anderson, V. A., Wood, S. J., Mitchell, L. A., & Harvey, A. S. (2007). The localization and lateralization of memory deficits in children with temporal lobe epilepsy. *Epilepsia, 48*(1), 124–132.

Gramstad, A., Engelsen, B. A., & Hugdahl, K. (2003). Left hemisphere dysfunction affects dichotic listening in patients with temporal lobe epilepsy. *The International Journal of Neuroscience, 113*(9), 1177–1196.

Greenberg, L. M. (1988). *T.O.V.A. continuous performance test*. Los Alamitos, CA: Universal Attention Disorders.

Guimaraes, C. A., Li, L. M., Rzezak, P., Fuentes, D., Franzon, R. C., Augusta Montenegro, M., et al. (2007). Temporal lobe epilepsy in childhood: Comprehensive neuropsychological assessment. *Journal of Child Neurology, 22*(7), 836–840.

Gulgonen, S., Demirbilek, V., Korkmaz, B., Dervent, A., & Townes, B. D. (2000). Neuropsychological functions in idiopathic occipital lobe epilepsy. *Epilepsia, 41*(4), 405–411.

Gunduz, E., Demirbilek, V., & Korkmaz, B. (1999). Benign rolandic epilepsy: Neuropsychological findings. *Seizure, 8*(4), 246–249.

Guzzetta, F. (2006). Cognitive and behavioral outcome in West syndrome. *Epilepsia, 47*(Suppl 2), 49–52.

Harrison, P. L., & Oakland, T. (2003). *Adaptive behavior assessment system manual* (2nd ed.). San Antonio, TX: Harcourt Assessment.

Helmstaedter, C., & Elger, C. E. (2009). Chronic temporal lobe epilepsy: A neurodevelopmental or progressively dementing disease? *Brain, 132*(Pt 10), 2822–2830.

Helmstaedter, C., & Kockelmann, E. (2006). Cognitive outcomes in patients with chronic temporal lobe epilepsy. *Epilepsia, 47*(Suppl 2), 96–98.

Helmstaedter, C., Kurthen, M., Lux, S., Reuber, M., & Elger, C. E. (2003). Chronic epilepsy and cognition: A longitudinal study in temporal lobe epilepsy. *Annals of Neurology, 54*(4), 425–432.

Hermann, B., Jones, J., Dabbs, K., Allen, C. A., Sheth, R., Fine, J., et al. (2007). The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. *Brain, 130*(Pt 12), 3135–3148.

Hermann, B. P., & Loring, D. W. (2008). Improving neuropsychological outcomes of epilepsy surgery. *Epilepsy & Behavior, 13*(1), 5–6.

Hermann, B., & Seidenberg, M. (2002). Neuropsychology and temporal lobe epilepsy. *CNS Spectrums, 7*(5), 343–348.

Hermann, B., Seidenberg, M., Bell, B., Rutecki, P., Sheth, R., Ruggles, K., et al. (2002). The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. *Epilepsia, 43*(9), 1062–1071.

Hermann, B. P., Seidenberg, M., & Bell, B. (2002b). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research, 135*, 429–438.

Hernandez, M. T., Sauerwein, H. C., Jambaque, I., De Guise, E., Lussier, F., Lortie, A., et al. (2002). Deficits in executive functions and motor coordination in children with frontal lobe epilepsy. *Neuropsychologia, 40*(4), 384–400.

Hertz-Pannier, L., Lehericy, S., Cordoliani, Y., Le Bihan, D., Marsault, C., & Brunelle, F. (2000). Brain functional MRI: Physiological, technical, and methodological bases, and clinical applications. [IRM fonctionnelle cerebrale: bases physiologiques, techniques et methodologiques, et applications cliniques]. *Journal de Radiologie, 81*(6 Suppl), 717–730.

Hoie, B., Mykletun, A., Sommerfelt, K., Bjornaes, H., Skeidsvoll, H., & Waaler, P. E. (2005). Seizure-related factors and non-verbal intelligence in children with epilepsy. A population-based study from western Norway. *Seizure, 14*(4), 223–231.

Hoie, B., Mykletun, A., Waaler, P. E., Skeidsvoll, H., & Sommerfelt, K. (2006). Executive functions and seizure-related factors in children with epilepsy in western Norway. *Developmental Medicine and Child Neurology, 48*(6), 519–525.

Holmes, M. D., Quiring, J., & Tucker, D. M. (2010). Evidence that juvenile myoclonic epilepsy is a disorder of frontotemporal corticothalamic networks. *NeuroImage, 49*(1), 80–93.

Jacobs, R., Harvey, A. S., & Anderson, V. (2007). Executive function following focal frontal lobe lesions: Impact of timing of lesion on outcome. *Cortex, 43*(6), 792–805.

Jambaque, I., Dellatolas, G., Dulac, O., Ponsot, G., & Signoret, J. L. (1993). Verbal and visual memory impairment in children with epilepsy. *Neuropsychologia, 31*(12), 1321–1337.

Jansen, F. E., Jennekens-Schinkel, A., Van Huffelen, A. C., Van Veelen, W. M., Van Rijen, C. P., Alpherts, W. C., et al. (2002). Diagnostic significance of Wada procedure in very young children and children with

developmental delay. *European Journal of Paediatric Neurology, 6*(6), 315–320.

Janz, D. (1985). Epilepsy with impulsive petit mal (juvenile myoclonic epilepsy). *Acta Neurologica Scandinavica, 72*(5), 449–459.

Kadis, D. S., Kerr, E. N., Rutka, J. T., Snead, O. C., III, Weiss, S. K., & Smith, M. L. (2009). Pathology type does not predict language lateralization in children with medically intractable epilepsy. *Epilepsia, 50*(6), 1498–1504.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test* (2nd ed.). Philadelphia, PA: Lea and Febiger.

Rau, U., Flynn, C., Moreci, et al. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980–988.

Kaufman, A. S., & Kaufman, N. L. (2002). *Kaufman assessment battery for children, second edition*. Circle Pines, MN: American Guidance Service.

Kim, C. H., Lee, S. A., Yoo, H. J., Kang, J. K., & Lee, J. K. (2007). Executive performance on the Wisconsin card sorting test in mesial temporal lobe epilepsy. *European Neurology, 57*(1), 39–46.

Kongs, S. K., Thompson, L. L., Iverson, G. L., & Heaton, R. K. (2000). *Wisconsin card sorting test—64 card version*. Lutz, FL: Psychological Assessment Resources.

Koo, B., Hwang, P. A., & Logan, W. J. (1993). Infantile spasms: Outcome and prognostic factors of cryptogenic and symptomatic groups. *Neurology, 43*(11), 2322–2327.

Korkman, M., Kirk, U., & Kemp, S. N. (2007). *NEPSY-II: A developmental neuropsychological assessment*. San Antonio, TX: The Psychological Corporation.

Kovacs, M. (1985). The children's depression, inventory (CDI). *Psychopharmacology Bulletin, 21*(4), 995–998.

Kramer, U., Nevo, Y., Neufeld, M. Y., Fatal, A., Leitner, Y., & Harel, S. (1998). Epidemiology of epilepsy in childhood: A cohort of 440 consecutive patients. *Pediatric Neurology, 18*(1), 46–50.

Kubu, C. S., Girvin, J. P., McLachlan, R. S., Pavol, M., & Harnadek, M. C. (2000). Does the intracarotid amobarbital procedure predict global amnesia after temporal lobectomy? *Epilepsia, 41*(10), 1321–1329.

Landau, W. M., & Kleffner, F. R. (1957). Syndrome of acquired aphasia with convulsive disorder in children. *Neurology, 7*(8), 523–530.

Lawson, J. A., Cook, M. J., Vogrin, S., Litewka, L., Strong, D., Bleasel, A. F., et al. (2002). Clinical, EEG, and quantitative MRI differences in pediatric frontal and temporal lobe epilepsy. *Neurology, 58*(5), 723–729.

Lee, G. (2010). *Neuropsychology of epilepsy and epilepsy surgery*. New York, NY: Oxford University Press.

Lendt, M., Gleissner, U., Helmstaedter, C., Sassen, R., Clusmann, H., & Elger, C. E. (2002). Neuropsychological outcome in children after frontal lobe epilepsy surgery. *Epilepsy & Behavior, 3*(1), 51–59.

Lezak, M. (2004). *Neuropsychological assessment* (4th ed.). New York, NY: Oxford University Press.

Loiseau, P., Duche, B., & Pedespan, J. M. (1995). Absence epilepsies. *Epilepsia, 36*(12), 1182–1186.

Loring, D. W., Marino, S., & Meador, K. J. (2007). Neuropsychological and behavioral effects of antiepilepsy drugs. *Neuropsychology Review, 17*(4), 413–425.

Luerding, R., Boesebeck, F., & Ebner, A. (2004). Cognitive changes after epilepsy surgery in the posterior cortex. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*(4), 583–587.

MacAllister, W. S., & Schaffer, S. G. (2007). Neuropsychological deficits in childhood epilepsy syndromes. *Neuropsychology Review, 17*(4), 427–444.

Majoie, H. J., Berfelo, M. W., Aldenkamp, A. P., Evers, S. M., Kessels, A. G., & Renier, W. O. (2001). Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: Clinical results, neuropsychological effects, and cost-effectiveness. *Journal of Clinical Neurophysiology, 18*(5), 419–428.

Majoie, H. J., Berfelo, M. W., Aldenkamp, A. P., Renier, W. O., & Kessels, A. G. (2005). Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure, 14*(1), 10–18.

Manford, M., Hart, Y. M., Sander, J. W. A. S., & Shorvon, S. D. (1992). The national general practice study of epilepsy: The syndromic classification of the international league against epilepsy applied to epilepsy in a general population. *Archives of Neurology, 49*(8), 801–808.

Martin, R. C., Sawrie, S. M., Edwards, R., Roth, D. L., Faught, E., Kuzniecky, R. I., et al. (2000). Investigation of executive function change following anterior temporal lobectomy: Selective normalization of verbal fluency. *Neuropsychology, 14*(4), 501–508.

Mathews, C. G., & Klove, K. (1964). *Instruction manual for the adult neuropsychology test battery*. Madison, WI: University of Wisconsin Medical School.

Matsumoto, A., Watanabe, K., Negoro, T., Sugiura, M., Iwase, K., Hara, K., et al. (1981). Infantile spasms: Etiological factors, clinical aspects, and long term prognosis in 200 cases. *European Journal of Pediatrics, 135*(3), 239–244.

McVicar, K. A., & Shinnar, S. (2004). Landau-kleffner syndrome, electrical status epilepticus in slow wave sleep, and language regression in children. *Mental Retardation and Developmental Disabilities Research Reviews, 10*(2), 144–149.

Miller, B. L., & Cummings, J. L. (2007). *The human frontal lobes: Functions and disorders*. New York, NY: Guilford Press.

Miller, V., Palermo, T. M., & Grewe, S. D. (2003). Quality of life in pediatric epilepsy: Demographic and disease-related predictors and comparison with healthy controls. *Epilepsy & Behavior, 4*(1), 36–42.

Nabbout, R., & Dulac, O. (2003). Epileptic encephalopathies: A brief overview. *Journal of Clinical Neurophysiology, 20*(6), 393–397.

Newcomer, P. L., & Hammil, D. (1988). *Test of language development-2*. Austin, TX: Pro-Ed.

Nicolai, J., Aldenkamp, A. P., Arends, J., Weber, J. W., & Vles, J. S. (2006). Cognitive and behavioral effects of nocturnal epileptiform discharges in children with benign childhood epilepsy with centrotemporal spikes. *Epilepsy & Behavior, 8*(1), 56–70.

Nolan, M. A., Redoblado, M. A., Lah, S., Sabaz, M., Lawson, J. A., Cunningham, A. M., et al. (2003). Intelligence in childhood epilepsy syndromes. *Epilepsy Research, 53*(1–2), 139–150.

Northcott, E., Connolly, A. M., Berroya, A., Sabaz, M., McIntyre, J., Christie, J., et al. (2005). The neuropsychological and language profile of children with benign rolandic epilepsy. *Epilepsia, 46*(6), 924–930.

Oguni, H., Hayashi, K., & Osawa, M. (1996). Long-term prognosis of lennox-gastaut syndrome. *Epilepsia, 37*(Suppl 3), 44–47.

Oguz, A., Kurul, S., & Dirik, E. (2002). Relationship of epilepsy-related factors to anxiety and depression scores in epileptic children. *Journal of Child Neurology, 17*(1), 37–40.

Ojemann, S. G., Berger, M. S., Lettich, E., & Ojemann, G. A. (2003). Localization of language function in children: Results of electrical stimulation mapping. *Journal of Neurosurgery, 98*(3), 465–470.

O'Leary, S. D., Burns, T. G., & Borden, K. A. (2006). Performance of children with epilepsy and normal age-matched controls on the WISC-III. *Child Neuropsychology, 12*(3), 173–180.

O'Leary, D. S., Lovell, M. R., Sackellares, J. C., Berent, S., Giordani, B., Seidenberg, M., et al. (1983). Effects of age of onset of partial and generalized seizures on neuropsychological performance in children. *Journal of Nervous and Mental Disease, 10*, 624–629.

Ott, D., Caplan, R., Guthrie, D., Siddarth, P., Komo, S., Shields, W. D., et al. (2001). Measures of psychopathology in children with complex partial seizures and primary generalized epilepsy with absence. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(8), 907–914.

Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., et al. (2004). Magnetocephalography: A noninvasive alternative to the Wada procedure. *Journal of Neurosurgery, 100*(5), 867–876.

Parisi, P., Verrotti, A., Paolino, M. C., Urbano, A., Bernabucci, M., Castaldo, R., et al. (2010). Headache and cognitive profile in children: A cross-sectional controlled study. *The Journal of Headache and Pain, 11*(1), 45–51.

Parrish, J., Geary, E., Jones, J., Seth, R., Hermann, B., & Seidenberg, M. (2007). Executive functioning in childhood epilepsy: Parent-report and cognitive assessment. *Developmental Medicine and Child Neurology, 49*(6), 412–416.

Pascalicchio, T. F., de Araujo Filho, G. M., da Silva Noffs, M. H., Lin, K., Caboclo, L. O., Vidal-Dourado, M., et al. (2007). Neuropsychological profile of patients with juvenile myoclonic epilepsy: A controlled study of 50 patients. *Epilepsy & Behavior, 10*(2), 263–267.

Patrikelis, P., Angelakis, E., & Gatzonis, S. (2009). Neurocognitive and behavioral functioning in frontal lobe epilepsy: A review. *Epilepsy & Behavior, 14*(1), 19–26.

Pavone, P., Bianchini, R., Trifiletti, R. R., Incorpora, G., Pavone, A., & Parano, E. (2001). Neuropsychological assessment in children with absence epilepsy. *Neurology, 56*(8), 1047–1051.

Pellcock, J. M. (2004). Understanding co-morbidities affecting children with epilepsy. *Neurology, 62*(5 Suppl 2), S17–S23.

Perez, E. R., Davidoff, V., Despland, P. A., & Deonna, T. (1993). Mental and behavioral deterioration in children with epilepsy and CSWS: Acquired epileptic frontal syndrome. *Developmental Medicine and Child Neurology, 35*, 661–674.

Pinton, F., Ducot, B., Motte, J., Arbues, A. S., Barondiot, C., Barthez, M. A., et al. (2006). Cognitive functions in children with benign childhood epilepsy with centrotemporal spikes (BECTS). *Epileptic Disorders, 8*(1), 11–23.

Pulsipher, D. T., Seidenberg, M., Guidotti, L., Tuchscherer, V. N., Morton, J., Sheth, R. D., et al. (2009). Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. *Epilepsia, 50*(5), 1210–1219.

Reutens, D. C., & Berkovic, S. F. (1995). Idiopathic generalized epilepsy of adolescence: Are the syndromes clinically distinct? *Neurology, 45*(8), 1469–1476.

Rey, A. (1941). L'examen psychologique dans les sac d'encephalopathie traumatique [psychological examination of traumatic encephalopathy]. *Archives de Psychologie, 29*, 286–340.

Reynolds, E. H. (1983). Mental effects of antiepileptic medication: A review. *Epilepsia, 24*(Suppl 2), S85–S95.

Reynolds, C. R., & Kamphaus, R. W. (2003). *Reynolds intellectual assessment scales*. Lutz, FL: PAR.

Reynolds, C. R., & Kamphaus, R. W. (2004). *Behavior assessment system for children* (2nd ed.). Circle Pine, MN: American Guidance Service.

Reynolds, C., & Richmond, B. (1978). What I think and feel: A revised measure of children's manifest anxiety. *Journal of Abnormal Child Psychology, 6*, 271–280.

Reynolds, C. R., & Voress, J. K. (2007). *Test of memory and learning* (2nd ed.). Austin, TX: ProEd.

Riccio, C. A., & Reynolds, C. R. (2001). Continuous performance tests are sensitive to ADHD in adults but

lack specificity. A review and critique for differential diagnosis. *Annals of the New York Academy of Sciences, 931*, 113–139.

Riccio, C. A., Reynolds, C. R., & Lowe, P. A. (2001). *Clinical application of continuous performance tests: Measuring attention and impulsive responding in children and adults*. New York, NY: John Wiley & Sons.

Riva, D., Saletti, V., Nichelli, F., & Bulgheroni, S. (2002). Neuropsychologic effects of frontal lobe epilepsy in children. *Journal of Child Neurology, 17*(9), 661–667.

Roid, G. H. (2003). *Stanford-Binet intelligence scales—Fifth edition*. Itasca, IL: Riverside Publishing.

Ronen, G. M., Streiner, D. L., Rosenbaum, P., & Canadian Pediatric Epilepsy Network. (2003). Health-related quality of life in children with epilepsy: Development and validation of self-report and parent proxy measures. *Epilepsia, 44*(4), 598–612.

Rotenberg, J., & Pearl, P. L. (2003). Landau-Kleffner syndrome. *Archives of Neurology, 60*(7), 1019–1021.

Rzezak, P., Fuentes, D., Guimaraes, C. A., Thome-Souza, S., Kuczynski, E., Guerreiro, M., et al. (2009). Executive dysfunction in children and adolescents with temporal lobe epilepsy: Is the Wisconsin card sorting test enough? *Epilepsy & Behavior, 15*(3), 376–381.

Rzezak, P., Fuentes, D., Guimaraes, C. A., Thome-Souza, S., Kuczynski, E., Li, L. M., et al. (2007). Frontal lobe dysfunction in children with temporal lobe epilepsy. *Pediatric Neurology, 37*(3), 176–185.

Sabaz, M., Cairns, D., Bleasel, A., Lawson, J., Grinton, B., Scheffer, I., et al. (2003). The health-related quality of life of childhood epilepsy syndromes. *Journal of Paediatrics and Child Health, 39*(9), 690–696.

Sabaz, M., Cairns, D. R., Lawson, J. A., Bleasel, A. F., & Bye, A. M. (2001). The health-related quality of life of children with refractory epilepsy: A comparison of those with and without intellectual disability. *Epilepsia, 42*(5), 621–628.

Sabaz, M., Cairns, D. R., Lawson, J. A., Nheu, N., Bleasel, A. F., & Bye, A. M. (2000). Validation of a new quality of life measure for children with epilepsy. *Epilepsia, 41*(6), 765–774.

Saltzman-Benaiah, J., Scott, K., & Smith, M. L. (2003). Factors associated with atypical speech representation in children with intractable epilepsy. *Neuropsychologia, 41*(14), 1967–1974.

Sandford, J. A., & Turner, A. (1995). *Manual for the integrated visual and auditory continuous performance test*. Richmond, VA: Brain Train.

Schevon, C. A., Carlson, C., Zaroff, C. M., Weiner, H. J., Doyle, W. K., Miles, D., et al. (2007). Pediatric language mapping: Sensitivity of neurostimulation and Wada testing in epilepsy surgery. *Epilepsia, 48*(3), 539–545.

Schoenfeld, J., Seidenberg, M., Woodard, A., Hecox, K., Inglese, C., Mack, K., et al. (1999). Neuropsychological and behavioral status of children with complex partial seizures. *Developmental Medicine and Child Neurology, 41*(11), 724–731.

Schouten, D., Hendriksen, J. G. M., & Aldenkamp, A. (2009). Performance of children with epilepsy on the Rey-Osterrieth complex figure test: Is there an effect of localization or lateralization? *Epilepsy Research, 83*(2–3), 184–189.

Schubert, R. (2005). Attention deficit disorder and epilepsy. *Pediatric Neurology, 32*(1), 1–10.

Schwarz, M., Pauli, E., & Stefan, H. (2005). Model based prognosis of postoperative object naming in left temporal lobe epilepsy. *Seizure, 14*(8), 562–568.

Semel, E., Wiig, E. H., & Secord, W. A. (2003). *Clinical evaluation of language fundamentals* (4th ed.). San Antonio, TX: The Psychological Corporation.

Sherman, E. M. (2009). Maximizing quality of life in people living with epilepsy. *The Canadian Journal of Neurological Sciences, 36*(Suppl 2), S17–S24.

Sherman, E. M., Slick, D. J., Connolly, M. B., Steinbok, P., Camfield, C., Eyrl, K. L., et al. (2002). Validity of three measures of health-related quality of life in children with intractable epilepsy. *Epilepsia, 43*(10), 1230–1238.

Sherman, E. M., Slick, D. J., & Eyrl, K. L. (2006). Executive dysfunction is a significant predictor of poor quality of life in children with epilepsy. *Epilepsia, 47*(11), 1936–1942.

Sheslow, D., & Adams, W. (2003). *Wide range assessment of memory and learning, second edition administration and technical manual*. Wilmington, DE: Wide Range.

Sidenvall, R., Forsgren, L., Blomquist, H. K., & Heijbel, J. (1993). A community-based prospective incidence study of epileptic seizures in children. *Acta Paediatrica, 82*(1), 60–65.

Sillanpaa, M., Haataja, L., & Shinnar, S. (2004). Perceived impact of childhood-onset epilepsy on quality of life as an adult. *Epilepsia, 45*(8), 971–977.

Singhi, P. D., Bansal, U., Singhi, S., & Pershad, D. (1992). Determinants of IQ profile in children with idiopathic generalized epilepsy. *Epilepsia, 33*(6), 1106–1114.

Slick, D. J., Lautzenhiser, A., Sherman, E. M., & Eyrl, K. (2006). Frequency of scale elevations and factor structure of the behavior rating inventory of executive function (BRIEF) in children and adolescents with intractable epilepsy. *Child Neuropsychology, 12*(3), 181–189.

Smith, M. L., Elliott, I. M., & Lach, L. (2002). Cognitive skills in children with intractable epilepsy: Comparison of surgical and nonsurgical candidates. *Epilepsia, 43*(6), 631–637.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland adaptive behavioral scales*. Circle Pines, MN: American Guidance Service.

Strauss, S., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York, NY: Oxford University Press.

Stroup, E., Langfitt, J., Berg, M., McDermott, M., Pilcher, W., & Como, P. (2003). Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology, 60*(8), 1266–1273.

Stuss, D. T., & Knight, R. T. (2002). *Principles of frontal lobe function*. New York, NY: Oxford University Press.

Suchy, Y., Sands, K., & Chelune, G. J. (2003). Verbal and nonverbal fluency performance before and after seizure surgery. *Journal of Clinical and Experimental Neuropsychology, 25*(2), 190–200.

Sveinbjornsdottir, S., & Duncan, J. S. (1993). Parietal and occipital lobe epilepsy: A review. *Epilepsia, 34*(3), 493–521.

Swanson, J., Schuck, S., Mann, M., Carlson, C., Hartman, K., Sergeant, J., & McCleary, R. (2006). Categorical and dimensional definitions and evaluations of symptoms of ADHD: The SNAP and SWAN Rating Scales. *University of California, Irvine*.

Tassinari, C. A., Rubboli, G., Volpi, L., Meletti, S., d'Orsi, G., Franca, M., et al. (2000). Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clinical Neurophysiology, 111*(Suppl 2), S94–S102.

Vanasse, C. M., Beland, R., Carmant, L., & Lassonde, M. (2005). Impact of childhood epilepsy on reading and phonological processing abilities. *Epilepsy & Behavior, 7*(2), 288–296.

Varni, J. W., Seid, M., & Rode, C. A. (1999). The PedsQL: Measurement model for the pediatric quality of life inventory. *Medical Care, 37*(2), 126–139.

Volkl-Kernstock, S., Bauch-Prater, S., Ponocny-Seliger, E., & Feucht, M. (2009). Speech and school performance in children with benign partial epilepsy with centro-temporal spikes (BCECTS). *Seizure, 18*(5), 320–326.

Volkl-Kernstock, S., Willinger, U., & Feucht, M. (2006). Spacial perception and spatial memory in children with benign childhood epilepsy with centro-temporal spikes (BCECTS). *Epilepsy Research, 72*(1), 39–48.

Vuilleumier, P., Assal, F., Blanke, O., & Jallon, P. (2000). Distinct behavioral and EEG topographic correlates of loss of consciousness in absences. *Epilepsia, 41*(6), 687–693.

Wagner, R. K., Torgesen, J. K., & Rashotte, C. A. (1999). *The comprehensive test of phonological processing: Examiner's manual*. Austin, TX: Pro-Ed.

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. New York, NY: Psychological Corporation.

Wechsler, D. (2002). *Wechsler primary and preschool scale of intelligence—Third edition*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2003). *Wechsler intelligence scale for children—Fourth edition*. New York, NY: The Psychological Corporation.

Williams, J., Phillips, T., Griebel, M. L., Sharp, G. B., Lange, B., Edgar, T., et al. (2001). Patterns of memory performance in children with controlled epilepsy on the CVLT-C. *Child Neuropsychology, 7*(1), 15–20.

Williams, J., Sharp, G., Bates, S., Griebel, M., Lange, B., Spence, G. T., et al. (1996). Academic achievement and behavioral ratings in children with absence and complex partial epilepsy. *Education and Treatment of Children, 19*(2), 143–152.

Wirrell, E. C. (2003). Natural history of absence epilepsy in children. *The Canadian Journal of Neurological Sciences, 30*(3), 184–188.

Wirrell, E., Farrell, K., & Whiting, S. (2005). The epileptic encephalopathies of infancy and childhood. *The Canadian Journal of Neurological Sciences, 32*(4), 409–418.

Wood, L. J., Sherman, E. M., Hamiwka, L. D., Blackman, M. A., & Wirrell, E. C. (2008). Maternal depression: The cost of caring for a child with intractable epilepsy. *Pediatric Neurology, 39*(6), 418–422.

Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III tests of cognitive abilities*. Itasca, IL: Riverside Publishing.

Yoo, H. K., Park, S., Wang, H. R., Lee, J. S., Kim, K., Paik, K. W., et al. (2009). Effect of methylphenidate on the quality of life in children with epilepsy and attention deficit hyperactivity disorder: And open-label study using an osmotic-controlled release oral delivery system. *Epileptic Disorders, 11*(4), 301–308.

Geriatric Patients with Epilepsy

3

Jessica Chapin and Richard Naugle

Introduction

Elderly patients with epilepsy share many characteristics with their younger cohort, but there are important differences between these groups that are relevant for the neuropsychologist working with older adults. Elderly patients with epilepsy have unique risk factors for comorbidities and complications that put them at increased risk of neurocognitive sequelae. The medical, cognitive, and psychosocial characteristics of this group often result in different referral questions and approaches for the development of clinical hypotheses, selection of tests, interpretation of results, and provision of recommendations.

Because the prevalence and incidence of epilepsy are greatest in those over age 60, neuropsychologists who conduct evaluations with adults with epilepsy are likely to be asked to assess these patients. It is also important for neuropsychologists conducting dementia evaluations to understand the interface between dementia and epilepsy because of the overlap in symptoms between, and co-occurrence of, these two disorders.

This chapter provides the clinician seeing elderly patients information about the presentation of epilepsy in this population, including characteristics of epilepsy, cognitive functioning, psychosocial considerations, and treatment alternatives. This is followed by practical considerations when completing a neuropsychological evaluation with an elderly epilepsy patient, including interview, test selection, result interpretation, and recommendations. Finally, a case is presented that illustrates these unique considerations in an elderly patient with epilepsy.

In this chapter, "elderly" will be used to indicate individuals aged 60 years and older. We acknowledge that this is a fairly young point at which to start applying this descriptor, but this age range is not completely arbitrary, since the incidence of unprovoked epilepsy sharply increases after age 60 (Hauser, Annegers, et al., 1993), and age-related physiological changes that complicate pharmacokinetics and pharmacodynamics of antiepileptic drugs (AEDs) are often evident by age 65. Incidence of relevant medical comorbidities such as stroke increases after about age 55 years (Thorvaldsen, Asplund, et al., 1995). Studies on older adults in the literature generally define the elderly as over 55 or 60. Because of the above findings, and to maintain consistency with existing literature, this chapter defines the elderly as those aged 60 and older unless stated otherwise.

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Background

Prevalence and Incidence of Epilepsy in Elderly Patients

Epilepsy has an increased prevalence and incidence in elderly patients, as suggested by studies from several countries (e.g., de la Court, Breteler, et al., 1996; Hauser, Annegers, et al., 1991; Wallace, Shorvon, et al., 1998). Data from the Rochester Epidemiology Project collected from 1935 to 1984 revealed a relatively high incidence of "unprovoked" epilepsy (i.e., recurrent seizures with no identified immediate precipitant) during the first year of life (82/100,000) that declined throughout childhood and remained generally low until it started rising again at age 55–60, peaking in those aged 75 years and older (139/100,000; Hauser, Annegers, et al., 1993; Hauser, Annegers, et al., 1996). See Fig. 3.1 for a graphical representation of these results. Likewise, *prevalence* of active epilepsy steadily increased over adulthood and reportedly affected approximately 1 % of the population over 75 years of age (de la Court, Breteler, et al., 1996; Hauser, Annegers, et al., 1996). Because older individuals make up the most rapidly growing sector of the population in the industrialized world, the number of elderly people with epilepsy will continue to rise.

Unique Characteristics of Epilepsy in Elderly Patients

Types of Seizures

While the incidence of both focal and generalized unprovoked epilepsy increases in older adults, the most dramatic increase is in focal epilepsy (Hauser, Annegers, et al., 1993). In those over age 65, focal seizures with alteration of consciousness are the most frequent seizure type (48 %), followed by generalized (29 %) and focal seizures without alteration of consciousness (13 %) (Hauser, 1992). In elderly patients with chronic rather than new-onset epilepsy, seizures may become briefer and less elaborate over time, and generalized tonic-clonic seizures may become less frequent or even disappear (Tinuper, Provini, et al., 1996). Whereas focal seizures most often arise from the temporal lobe in the general population, these seizures in elderly patients often originate from extratemporal or frontal regions frequently affected by stroke (Ramsay, Rowan, et al., 2004).

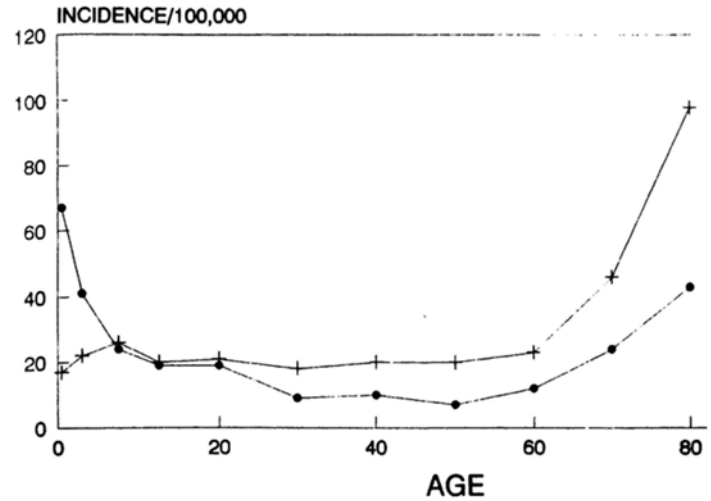

Fig. 3.1 Age-specific incidence of generalized-onset (*solid circles*) and partial-onset (*plus signs*) unprovoked epilepsies based on data collected in the Rochester Epidemiology Project from 1935 to 1984 (Hauser et al., 1993) Used with permission from *Epilepsia*

Etiology of Seizures

Cerebrovascular disease is the most common non-idiopathic etiology of new-onset epilepsy in those aged 65 and older, accounting for 28 % of cases (Hauser, Annegers, et al., 1993). Approximately 20 % of cases were attributed to degenerative diseases, and less than 5 % were related to CNS tumors, trauma, or infection. Etiology remains unknown in 25–50 % (Hauser, Annegers, et al., 1993; Ramsay, Rowan, et al., 2004). See Fig. 3.2 for a comparison of etiologies of newly diagnosed epilepsy across the life span.

Diagnostic Complications

Diagnosing epilepsy in elderly patients can be complicated, and there is increased risk of both over- and underdiagnosis in this group. It is important for neuropsychologists conducting evaluations with older adults to keep this in mind, since presenting symptoms may reflect undiagnosed seizures. Older adults who presented with tonic-clonic seizures were correctly diagnosed 66.7 % of the time, although only 25.4 % of those with focal seizures without alteration of consciousness received an initial correct diagnosis (as described in Ramsay, Rowan, et al. (2004)). In patients with TIAs or strokes, the diagnosis of seizures was almost always delayed. It took an average of 1.7 years before correct diagnosis was made in this sample. This diagnostic difficulty is based, in part, on the limited knowledge of seizure semiology in the elderly, the reduced frequency of interictal discharges, the variety of EEG patterns seen, and the increased incidence of other conditions that may mimic seizures in this population (Van Cott, 2002). Further, it may be difficult to understand the presence or characteristics of spells in elderly individuals because patients are often more socially isolated (i.e., are more likely to live alone, be unemployed, have fewer social activities) and may have more memory problems than their younger cohort.

Because seizures tend to originate from extratemporal foci more often among elderly patients, they are less likely to exhibit the typical clinical manifestations characteristic of temporal lobe seizures (Ramsay & Pryor, 2000). Seizure symptoms are often nonspecific and may include altered mentation, staring, unresponsiveness, blackouts, and auras of dizziness (Ramsay &

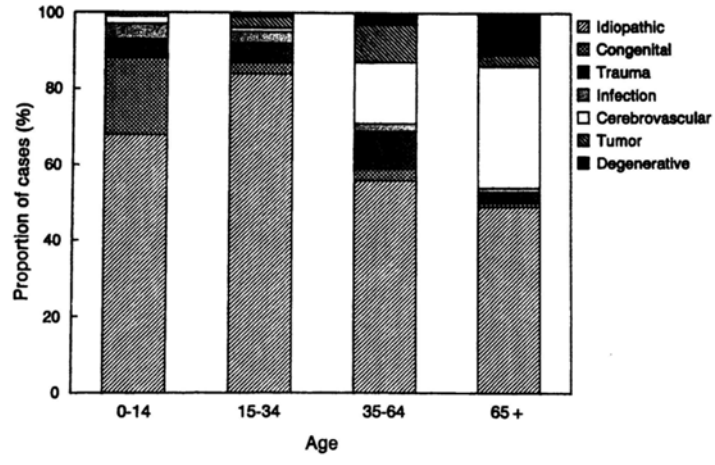

Fig. 3.2 Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups, including idiopathic/cryptogenic category. Area: idiopathic (*gray cross-hatched*), congenital (*dashed*), trauma (*dotted*), trauma (*widely dotted*), infection (*hatched*), cerebrovascular (*closely dotted*), tumor (*black*), degenerative (*light cross-hatch*)

Pryor, 2000). Postictal confusion may persist for several days in older patients, compared to minutes in younger patients (Cloyd, Hauser, et al., 2006; Sheth, Drazkowski, et al., 2006).

These nonspecific symptoms make seizures more difficult to diagnose based on description alone. Several types of disorders or events may mimic seizures in elderly patients. Focal seizures with alteration of consciousness may be mistaken for TIAs or other cardiovascular disease, syncope, dementia, arrhythmias, or fluctuations in blood pressure or blood sugar levels (Sheorajpanday & De Deyn, 2007). The most common initial diagnoses in patients in the VACS 428 study whose diagnoses were later confirmed as epilepsy included altered mental status (41.8 %), confusion (37.5 %), blackout spells (29.3 %), and syncope (16.8 %) (Brodie & Kwan, 2005; Ramsay, Rowan, et al., 2004). See Table 3.1 for the primary differential diagnosis of seizures in elderly patients.

Status epilepticus (SE) often presents with no convulsive activity in elderly patients and may appear simply as confusion or minimal motor movements. In a prospective study, nonconvulsive SE was diagnosed in 16 % of elderly patients presenting with confusion of unknown origin (Baxendale, 1998). Thus, SE may go undiagnosed for several days in ambulatory elderly patients with ictal confusion (Sheth, Drazkowski, et al., 2006). This is concerning since even after it is treated, SE can result in persistent cognitive dysfunction. Further, SE is more common and has a higher morbidity rate in elderly patients (DeLorenzo, Hauser, et al., 1996).

Finally, further complicating an epilepsy diagnosis, EEG is less sensitive and specific for epilepsy in elderly patients (Brodie & Kwan, 2005). Absence of interictal epileptiform activity on routine EEG does not rule out the diagnosis, since its presence decreases with age and only occurs in 35 % of patients with preexisting epilepsy (mean age = 65) and 26 % of elderly patients with new-onset seizures (mean age = 70) (Drury & Beydoun, 1998). Conversely, benign EEG changes are associated with normal aging and have the potential to be misinterpreted as indicating a seizure tendency (Van Cott, 2002). Therefore, video-EEG monitoring may be valuable in establishing the diagnosis (Brodie & Kwan, 2005; McBride, Shih, et al., 2002; Van Cott, 2002).

Table 3.1 Main differential diagnosis of seizures in elderly patients

Neurological
– Transient ischemic attack
– Transient global amnesia
– Migraine
– Restless leg syndrome
– Dyskinesia
Cardiovascular
– Vasovagal syncope
– Orthostatic hypotension
– Cardiac arrhythmias
– Structural heart disease
– Carotid sinus syndrome
Endocrine/metabolic
– Hypoglycemia
– Hypocalcemia
– Hypomagnesemia
Sleep disorders
– Obstructive sleep apnea
– Narcolepsy
– Rapid eye movement sleep disorders
– Hypnic jerks
Psychological
– Nonepileptic psychogenic seizures

Adapted from (Brodie & Kwan, 2005)

Cognition in Elderly Patients with Epilepsy

Effect of Age on Cognition in Epilepsy

Epilepsy is associated with cognitive impairment, the cause of which is often multifactorial and may include underlying seizure etiology, ictal and interictal neuronal discharges, AED side effects, and psychosocial confounds (Kwan & Brodie, 2001). This is no different in elderly patients with epilepsy (Caramelli & Castro, 2005) and several factors may increase the risk of cognitive dysfunction in this group.

First, there is a subset of elderly patients with epilepsy who have had epilepsy for many years. There is evidence for greater cognitive morbidity when epilepsy has been long-standing (Helmstaedter, Kurthen, et al., 2003; Hermann, Seidenberg, et al., 2006).

Second, even "healthy" aging is associated with decreased processing speed and fluid intelligence, likely resulting from neurophysiological changes including loss of synapses, neurons, neurotransmitters, and neuronal networks (Fillit, Butler, et al., 2002). Furthermore, normal aging often results in mild levels of cerebral atrophy, ventricular enlargement, hippocampal atrophy, and deposition of beta-amyloid peptide and neurofibrillary tangles (Smith & Rush, 2006). The presence of epilepsy potentially exacerbates these changes.

Third, both aging and epilepsy have been associated with increased incidence of dementia and other disorders and lifestyle factors that can cause cognitive dysfunction (Hermann, Seidenberg, et al., 2008b). Compared to population-based controls, individuals with epilepsy had an increased relative risk of being diagnosed with Alzheimer's disease at least 1 year *after* epilepsy diagnosis, with relative risk values ranging from 1.2 to 4.0 (Breteler, van Duijn, et al., 1991). Hermann (2008b) makes a compelling case that chronic epilepsy has been associated with several risk factors for poorer cognitive aging. As a group, those with chronic epilepsy have greater vascular risk factors, including more ischemic heart disease, hypertension, heart failure, diabetes, and cerebrovascular disease (Gaitatzis, Carroll, et al., 2004; Tellez-Zenteno, Matijevic, et al., 2005). This may be partially attributable to side effects (e.g., metabolic disorders, increased homocysteine) associated with select AEDs such as valproic acid and enzyme-inducing medications (Hamed & Nabeshima, 2005; Isojarvi, Rattya, et al., 1998; Luef, Waldmann, et al., 2004; Ono, Sakamoto, et al., 1997; Pylvanen, Knip, et al., 2003; Schwaninger, Ringleb, et al., 2000; Sheth, 2004). Elderly patients with epilepsy who had no preexisting cerebrovascular disease were at 2.89 times the risk of experiencing a first ever stroke compared to an elderly control group (Cleary, Shorvon, et al., 2004). Epilepsy has also been associated with increased inflammatory markers, both through the effects of seizures themselves (Vezzani & Granata, 2005) as well as AED effects (Verrotti, Basciani, et al., 2001). Finally, Hermann (2008) describes lifestyle factors which are both associated with poor cognitive aging and epilepsy, including decreased social networks and physical activity (Bjorholt, Nakken, et al., 1990; Nakken, 1999).

Although the above factors raise concern that elderly patients with epilepsy may be at greater risk of cognitive dysfunction than younger patients with epilepsy or older individuals without epilepsy, there has been little research published in this area. Older adults with chronic epilepsy performed more poorly across most cognitive measures compared to healthy older controls, both in a sample of medically intractable patients (Martin, Griffith, et al., 2005) and a sample in which 63 % were successfully controlled with medications (Piazzini, Canevini, et al., 2006). Griffith and colleagues (2006) found that memory deficits in older adults with chronic epilepsy were similar to deficits in patients with amnestic mild cognitive impairment, and the patients with epilepsy had greater difficulty on measures of executive functioning. Further suggestive of memory impairment in this group, elderly patients with chronic epilepsy did not demonstrate practice effects on a measure of verbal memory at 2–3-year follow-up compared to healthy elderly controls tested over the same interval (Griffith, Martin, et al., 2007), suggesting that elderly epilepsy may be associated with failure to learn compared to healthy elderly subjects.

Although these studies support cognitive morbidity associated with epilepsy in elderly patients, no study has directly investigated if this cognitive dysfunction is any greater than that experienced in younger adults with epilepsy, and evidence for accelerated cognitive decline associated with epilepsy in older adults is mixed. A recent cross-sectional study by Helmstaedter and Elger (2009)

suggested *against* accelerated deterioration of episodic memory with older age in patients with TLE. Examination of verbal learning and memory in 1,156 patients with TLE and 1,000 controls over the life span revealed that the slow linear decline in verbal learning exhibited by normal controls after age 25 was mirrored in patients with TLE (although at a much lower level). Thus, although the TLE group had a lower level of performance, the rate of decline was the same between the groups. There was no relative decrease in memory in the TLE group compared to controls with advancing age. However, although patients ranged in age from 6 to 70 years, most were 50 years and younger, with only 17 patients over 60 years of age.

Conversely, there are other data supporting the possibility of age-accelerated cognitive decline in select patients with epilepsy. Another cross-sectional study by this same group suggested an age-accelerated decline in the retention of auditory information in preoperative patients who had temporal lobe epilepsy not confined to mesial temporal sclerosis (e.g., normal imaging or other lesions such as tumor) (Helmstaedter, Reuber, et al., 2002). Further, in a longitudinal study, Hermann et al. (2006) found that older age was one of the several predictors of decline in simple and complex psychomotor speed, but not other cognitive domains including memory, relative to expected values over a 4-year period in patients with chronic temporal lobe epilepsy. However, patients were relatively young in both of the above studies, with the average age in the low 30s.

In summary, there are several unique risk factors for cognitive morbidity in older adults with epilepsy. The few published studies examining the relationships among epilepsy, aging, and cognition suggest that older adults with epilepsy have more cognitive dysfunction than older adults without epilepsy and younger adults with epilepsy. It is unclear if this is due to additive or interactive effects of epilepsy and aging. However, most participants in these studies have been under 60 years old. More research is needed to determine the relationship between epilepsy and cognition as patients reach older age when the above comorbidities are more likely to start showing effects.

Epilepsy and Dementia

There is evidence for a bidirectional relationship between epilepsy and dementia. It is well established that those with dementia are at increased risk of developing epilepsy, and there is also some evidence that those with epilepsy may be at increased risk of developing dementia. Patients with dementia have a five- to tenfold increase in risk of seizures (Hesdorffer, Hauser, et al., 1996). Most of this research has been conducted in Alzheimer's disease (AD), although there are a few studies reporting the presence of seizures in dementia with Lewy bodies (Weiner, Hynan, et al., 2003) and Creutzfeldt-Jakob disease (Marchiori, Yasuda, et al., 1996). It is estimated that between 10 and 22 % of patients with AD will experience at least one seizure (Mendez & Lim, 2003). The incidence of seizures increases with the severity of the dementia (Hesdorffer, Hauser, et al., 1996; McAreavey, Ballinger, et al., 1992; Mendez & Lim, 2003), with seizure onset often 7 years after dementia diagnoses (Mendez, Catanzaro, et al., 1994). However, seizures can begin at any time during the course of the illness (Hauser, Morris, et al., 1986), even as early as 3 months after diagnosis (Hesdorffer, Hauser, et al., 1996). The mechanism causing seizures in Alzheimer's disease remains unknown, but suspected factors include the accumulation of amyloid-β plaques, neurofibrillary tangles, selective loss of inhibitory neurons, comorbid vascular lesions, and excessive neuronal cell loss in hippocampal and parietal cortices (Forstl, Burns, et al., 1992; Mendez, Catanzaro, et al., 1994; Mendez & Lim, 2003). The onset of seizures has been associated with a faster progression of cognitive and functional impairment in patients with AD (Volicer, Smith, et al., 1995).

There is also evidence that those with epilepsy may be at increased risk of developing a progressive dementia. Breteler et al. (1991) reviewed four studies that examined the relative risk of a subsequent diagnosis of Alzheimer's disease in those with an epilepsy diagnosis. Diagnoses were

based on interview with an informant in three studies and medical record review in the other. Compared to population-based controls, individuals with epilepsy had an increased relative risk of being diagnosed with AD at least 1 year after epilepsy diagnosis (relative risk values ranging from 1.2 to 4.0). The reason for the increased risk of subsequent AD diagnosis in those with epilepsy is unknown, although data from this study suggested that cumulative effects of long-standing seizures did not appear to be a factor in the development of dementia. The greatest risk for a diagnosis of AD was in patients who had epilepsy less than 10 years (relative risk = 2.4) versus 10 years or more (relative risk = 1.4). Alternatively, seizures may represent early pathological dementia-related changes in these patients, or the presence of both seizures and dementia may reflect shared risk factors. In a follow-up study, Breteler et al. (1995) found that patients diagnosed with epilepsy had a relative risk of 1.5 for being diagnosed with dementia over the next 8 years compared to other hospital patients. In an investigation of all patients diagnosed with probable AD by a neurologist over a 6-year period, 6.8 % had a history of epilepsy and/or were taking AEDs at the time of diagnosis (Lozsadi & Larner, 2006). In half of these cases, seizure onset occurred at about the same time as the onset of cognitive decline, with no identified acute cause of the seizures identified. Data from the Canadian Study on Health and Aging found that a diagnosis of epilepsy in those aged 65 years and older had a relative risk of 1.56 for being diagnosed with dementia over the next 5 years compared to community-dwelling controls without epilepsy, although this did not meet statistical significance (Carter, Weaver, et al., 2007).

Another way to determine whether epilepsy increases the risk of dementia is to compare brain tissue from epilepsy patients with tissue from patients and unaffected, age-matched controls. Mackenzie and Miller (1994) compared the number and location of senile plaques in temporal lobe tissue from epilepsy patients and normal controls. The age-related incidence of senile plaques was significantly higher in epilepsy patients. However, no patient showed any evidence of dementia on cognitive testing, and no other AD-related pathology was identified. Postoperative follow-up (mean 3.7 years, range 2–7) of the ten patients with senile plaques revealed no clinical suggestion of dementia, suggesting that the senile plaques were not associated with dementia or cognitive deterioration for at least several years (Mackenzie, McLachlan, et al., 1996). Overall, these findings suggest that TLE is associated with increased formation of senile plaques, but these plaques do not have an apparent effect on cognition, including the development of dementia.

Psychosocial Considerations in Elderly Patients with Epilepsy

Epilepsy can have profound effects on mood, anxiety, and quality of life (QOL). Elderly patients may be particularly vulnerable to these symptoms because they often live alone and may have additional physical and cognitive vulnerabilities that put them at increased risk for loss of independence.

The concern for worse QOL in the elderly compared to younger patients with epilepsy has not been born out in research findings. Comparisons between QOL measures in the elderly and younger adults suggest similar QOL in these groups (Baker, Jacoby, et al., 2001; Laccheo, Ablah, et al., 2008) or that older patients may even cope better with epilepsy than middle-aged peers (Pugh, Copeland, et al., 2005). A potential confounding factor is that QOL measures are generally developed and normed for those under 65 years of age. When Martin and colleagues (2005) gave a group of community-dwelling elderly adults a blank paper to list their concerns regarding living with epilepsy, results were similar in content to concerns voiced by younger epilepsy patients and included driving/transportation (64 %), medication side effects (64 %), personal safety (39 %), AED costs (29 %), employment (26 %), social embarrassment (21 %), and memory loss (21 %). Thus, the elderly with epilepsy may not have worse

perceived QOL than younger patients but do report lower QOL than the general population (Laccheo, Ablah, et al., 2008) or older adults without epilepsy (McLaughlin et al. 2008).

Depression and anxiety rates are higher in patients with epilepsy in general, and this has been shown to extend to the elderly with epilepsy (Haut, Katz, et al., 2009). Further, many elderly people have been found to suffer from "subsyndromal" depression, in which they report significant depressive symptomatology but fail to meet formal diagnostic criteria for major depression (Strober & Arnett, 2009). Mental health disorders can be more difficult to diagnose in elderly patients with a neurological disorder compared to younger, otherwise healthy, individuals due to several factors including atypical presentation, difficulty distinguishing between symptoms of the mental health disease and epilepsy, and lack of assessment tools developed specifically for this population (Strober & Arnett, 2009). Nevertheless, it is often the responsibility of the neuropsychologist to determine whether or not a patient has a mental health disorder that requires treatment. It is important to understand unique characteristics of the presentation and treatment of mental health problems in the elderly with epilepsy. It has been suggested that depression in elderly individuals may present with more weight loss and fewer feelings of worthlessness and guilt than younger people (Frey, 2007), and depressive symptoms in patients with epilepsy may present as intermittent irritability, lack of energy, anxiety, and somatic symptoms such as pain (i.e., interictal dysphoric disorder). Many of the commonly used self-report inventories for depression do not have established cutoff scores for identifying depression in the elderly with epilepsy, although a recent review of depression assessment in the elderly with neurological disorders summarized the recommended cutoff scores for common measures when used with neurological populations (Strober & Arnett, 2009). The atypical presentation of depression in the elderly with epilepsy heightens the importance of a thorough clinical interview of the patient's symptoms and lack of strict adherence to formal diagnostic criteria.

There is also little known about the most effective treatment for depression and other mental health disorders in the elderly with epilepsy. Cognitive behavioral and interpersonal are two therapy modalities that have received the most empirical support for treatment of depression (Barlow, 2001), although these studies have not specifically examined the elderly with epilepsy. Referral to a psychiatrist with specialized knowledge in treating emotional distress in those with epilepsy is often very helpful. The patient's AED regimen should also be examined, since select AEDs have been associated with adverse mood side effects, most notably those such as phenobarbital, primidone, vigabatrin, topiramate, and levetiracetam (Frey, 2007). Finally, stressing medication compliance is especially important in this group, since depressed elderly medical patients were found to be less compliant with medications than nondepressed elderly medical patients (Carney, Freedland, et al., 1995).

Treatment of Epilepsy in Elderly Patients

AEDs

Epilepsy is more frequently controlled with AEDs in patients aged 65 years and over compared to younger patients (Mohanraj & Brodie, 2006). After starting AEDs for newly diagnosed epilepsy, approximately 80 % of patients aged 65 years and older remained seizure-free at 1-year follow-up (Brodie & Kwan, 2005).

Unfortunately, elderly patients are also generally more susceptible to the adverse effects of drugs than younger patients. Overall, AED side effects are more pronounced in elderly patients, there are more adverse drug interactions, and risk of toxicity is greater (Sheorajpanday & De Deyn, 2007). It is important for the neuropsychologist to be aware of situations in which AEDs may be contributing to cognitive deficits. Adverse side effects are more likely to occur with the specific AEDs described below, fast dose escalation rates, high doses, and polypharmacy (Sheorajpanday et al. 2007).

Despite these concerns, elderly individuals are underrepresented in AED clinical trials, and much of the information about AEDs used in elderly patients is derived from studies with younger adults (Beghi, Savica, et al., 2009). The few data available suggest that greater cognitive side effects of AEDs in elderly patients may be associated with polypharmacy (Griffith, Martin, et al., 2006; Piazzini, Canevini, et al., 2006) and old generation AEDs (Massimiliano, Rodolfo, et al., 2009). In addition, although cognitive side effects of topiramate have not been specifically examined in the elderly with epilepsy, there is reason to suspect that it carries cognitive risk based on the side effects seen in studies not restricted to the elderly (Sommer & Fenn, 2010).

Research has supported the effectiveness and tolerability of lamotrigine (LTG) and gabapentin (GBP) in elderly patients. Randomized controlled trials that have specifically recruited elderly patients found that LTG and/or GBP resulted in less early termination compared to carbamazepine (CBZ) with similar efficacy (Brodie, Overstall, et al., 1999; Rowan, Ramsay, et al., 2005; Saetre, Perucca, et al., 2007). An exception to this is one study that found no significant difference in effectiveness and tolerability of LTG and CBZ in elderly patients, although there were trends for greater tolerability of LTG and greater seizure-free rates of CBZ (Saetre, Perucca, et al., 2007). Several additional studies also found a good tolerability profile for, and effectiveness of, LTG in patients aged 60 or 65 and older (Arif, Buchsbaum, et al., 2010; Ferrendelli, French, et al., 2003; Giorgi, Gomez, et al., 2001; Mauri Llerda, Tejero, et al., 2005). Treatment guidelines from the International League Against Epilepsy state that, in focal epilepsies in elderly patients, LTG and GBP should be considered for initial monotherapy due to the available efficacy and effectiveness data (Glauser, Ben-Menachem, et al., 2006). Not all evidence is convergent on the superiority of LTG and GBP in elderly patients, however. A recent survey of patients aged 65–90 found no differences in adverse effects between LTG, CBZ, and sodium valproate (Brodie & Stephen, 2007), and Saetre et al. (2010) found that neither LTG nor CBZ caused significant changes in health-related quality of life. Other medications have not received as extensive study in the elderly with epilepsy, although oxcarbazepine appeared promising regarding tolerability in patients 65 years and older (Kutluay, McCague, et al., 2003).

Surgery

Epilepsy remains intractable to medications in approximately 20 % of elderly patients (Mohanraj & Brodie, 2006). Surgery is a successful treatment option for many patients with medically intractable epilepsy, and a recent study demonstrated similar rates of seizure outcome (i.e., Engel classes I and II) after temporal lobectomy with pathologically confirmed hippocampal sclerosis in those 50 and older (i.e., 95.2 %) compared with those under age 50 (i.e., 90.3 %) at follow-up approximately 10 years later. However, there has been some hesitancy to provide surgical treatment to elderly patients (Acosta, Vale, et al., 2008; Grivas, Schramm, et al., 2006; Sirven, Malamut, et al., 2000), in part due to concerns that surgery may exacerbate age-related cognitive decline (Grivas, Schramm, et al., 2006; Sirven, Malamut, et al., 2000).

The extent to which concern is warranted for poor cognitive outcome from surgery in elderly patients is unknown. Cross-sectional studies raise the possibility that temporal lobe surgery may accelerate memory decline with increasing age (Helmstaedter, Reuber, et al., 2002; Rausch, Kraemer, et al., 2003). Helmstaedter et al. (2002) found age-accelerated decline in postoperative verbal learning scores in patients after anterior temporal lobectomy compared to controls. This effect was not present in preoperative scores, in which age regression was similar to controls, suggesting that standard anterior temporal lobectomy has worse memory outcome for older individuals. However, there are sederal careats. First, age-related memory decline was specific to patients who underwent standard anterior temporal lobectomy for TLE that was not confined to mesial temporal sclerosis (e.g., normal imaging or other lesions such as tumor), as age-accelerated memory decline was not found in the

selective amygdalohippocampectomy group with MTS. Second, older patients may have had a later age of epilepsy onset and longer duration of epilepsy, both of which were correlated with poorer memory, so results may, at least in part, reflect these factors. Finally, the average age of subjects in that study was 30 years, with no patient aged 60 or older. Similarly, Rausch et al. (2003) found that patients showed increasing deviation from age-corrected normative data on episodic auditory memory tests both 1 year and ~12 years after left temporal lobectomy. However, patients were rather young in this study as well, with an average age of 40 years at the long-term follow-up.

Two studies have been published to date that directly compare cognitive outcome in older versus younger patients after surgery for epilepsy. Both found that the older adults did not demonstrate greater memory declines than younger adults. Sirven et al. (2000) found no difference in memory change between 17 older (approximate age range 50–66) and 180 younger (approximate age range 18–49 years) patients before and after temporal lobectomy. Similarly, Grivas et al. (2006) did not find significant differences in memory changes between 34 older adults (approximate age range 50–71) and 359 younger adults (age <50 years) before and after temporal lobectomy. However, there was a trend for greater decline in postoperative auditory memory performance in the eight patients over 60 years of age than in those under 60 years of age.

Further, elderly patients appear to be at greater risk of cognitive decline after major surgery in general compared to younger adults, even when the surgery does not involve the heart or brain. A well-designed study by Monk and colleagues (2008) found that although about 31–40 % of non-demented adult patients experience cognitive dysfunction (i.e., deficits in episodic memory, executive functioning, and processing speed compared to control group) at hospital discharge with no difference between those who are young adult, middle aged, or elderly, the elderly patients were at significantly higher risk of cognitive deficits 3 months after surgery compared to young adults or middle-aged patients, as well as elderly controls. While prevalence of cognitive dysfunction in the younger groups returned to the levels of age-matched controls at 3 months after surgery (i.e., young adults 5.7 % and middle aged 5.6 %), the prevalence of cognitive dysfunction in the elderly group was significantly higher (12.7 %). Additional predictors of cognitive dysfunction at 3-month follow-up included cognitive dysfunction at hospital discharge, increased age, history of cerebral vascular accident with no residual impairment, and years of education. These results are similar to those of another similar large-scale study (Moller, Cluitmans, et al., 1998). Thus, older age appears to be a risk factor for cognitive dysfunction after major surgery in general.

In summary, the elderly may be at increased risk of postoperative cognitive decline after any major surgery. Regarding cognitive risk associated specifically with surgery for epilepsy, preliminary cross-sectional data suggest that anterior temporal lobectomy may accelerate age-related memory decline in patients with pathology other than MTS, although this increased cognitive risk for elderly patients has not been born out in direct comparisons of memory decline in older versus younger adults. However, the few available studies in this area have been limited by a small sample size of older patients, with few if any of the samples composed of those over age 60 years.

Methods

Role of the Neuropsychologist Assessing Elderly Patients with Epilepsy

There are several different reasons why a neuropsychologist may be asked to conduct an evaluation of an elderly patient with epilepsy. Referral questions can include those typical of a younger adult with epilepsy, such as characterizing the

impact of seizures, AEDs, or surgery on cognition; obtaining a baseline of cognitive functioning by which to measure any changes in the future (e.g., after surgery, AED changes, or ongoing seizures); and providing insight into the level of cognitive functioning in order to help estimate functional abilities. Additionally, in the elderly with epilepsy, it may be important to determine whether or not the patient appears to be experiencing a comorbid progressive neurodegenerative process. Any neuropsychological evaluation for an elderly patient with epilepsy should take into account the unique etiology, cognitive considerations, psychosocial functioning, and treatment implications of this group that are outlined above.

Neuropsychologists are often asked to evaluate the cognitive functioning and comment on the potential etiology of deficits in elderly patients with episodes of confusion, memory complaints, and changes in behavior in the absence of epilepsy. It is important to be mindful of the possibility that seizures may be occurring in these patients presenting with rather nonspecific symptoms. Since there is a great deal of overlap between symptoms of dementia and epilepsy, careful history taking and evaluation of any focal area(s) of neurocognitive deficit are key features of the examination in order to determine whether seizures are a potential etiology that deserve further neurological investigation.

Appointment Scheduling

Elderly patients with epilepsy may require slight modifications of the assessment procedure. Obtaining a collateral report is particularly important when conducting a neuropsychological evaluation of elderly patients with epilepsy due to possible difficulty describing seizure-related details and unawareness of cognitive symptoms, particularly in the case of suspected progressive dementias. Elderly patients may become fatigued more quickly during testing, and a shorter battery is often required. Alternatively, in some settings, testing could be broken up into multiple sessions. It may be helpful to structure testing so that measures within a specific cognitive domain are spaced throughout the evaluation to avoid an entire domain being affected by fatigue towards the end of a testing session, as well as maximizing the chance of getting a variety of cognitive domains assessed even if the patient has to discontinue before the end of the evaluation. Scheduling testing for the morning is often preferred, since evidence suggests that older adults perform better on cognitive tasks in the morning than in the afternoon (Hasher, Chung, et al., 2002).

Interview

In addition to obtaining standard background information in a neuropsychological interview, when assessing the elderly with epilepsy, it is even more important to gain a complete and detailed understanding of the history of onset and progression of cognitive, behavioral, and mood symptoms and how these overlay any changes in seizures, AEDs, other medications and medical problems, and other relevant life events (e.g., retirement, death of a spouse). The information obtained in the interview is often the most valuable data for establishing a list of possible etiologies for subjective or objective cognitive impairment. Common etiologies of cognitive dysfunction to consider include:

- Acute and chronic effects of seizures
- AED or other medication side effects
- Progressive dementia
- Cerebrovascular disease
- Head trauma
- Sleep problems
- Emotional distress
- Other medical comorbidities, including any known cause of epilepsy

Cerebrovascular etiology or comorbid disease should be considered in all elderly patients with epilepsy, since cerebrovascular disease accounts for about one third of newly diagnosed cases of epilepsy in elderly patients. Furthermore, elderly patients with epilepsy are at a higher risk of

experiencing a first ever stroke than the elderly without epilepsy (Cleary, Shorvon, et al., 2004). Similarly, evaluations should consider the presence of possible progressive dementias, since about 12 % of newly diagnosed cases of epilepsy in elderly patients are attributed to degenerative disorders, and some evidence suggests that epilepsy increases the risk of developing AD (Breteler, van Duijn, et al., 1991). Other conditions affecting cognition in older adults not listed above also need to be considered as comorbid conditions, although they are not necessarily associated with epilepsy specifically. These include, but of course are not limited to, Parkinson disease, normal-pressure hydrocephalus, hypothyroidism, vitamin B12 deficiency, thiamine deficiency, and sleep breathing disorders. Finally, it is also particularly important to assess activities of daily living, since this is helpful in differential diagnosis and forming recommendations.

Test Selection

General Considerations

Neuropsychological evaluation of any elderly patient requires special considerations. There are limited normative data on many common neuropsychological measures for people of advanced age, although this has improved over the past decade. Test selection should take into careful account the robustness of the norms for older adults. The MOANS and MOAANS studies in particular provide good normative data for individuals between the ages of 56 and 95 (e.g., Ivnik, Malec, et al., 1996; Lucas, Ivnik, et al., 2005). Increased frequency of motor and sensory deficits in this population requires understanding any limitations of the patient and adapting tests appropriately. For example, grooved pegboard performance may be affected by peripheral injury, and results would not reflect brain dysfunction per se. Unique mood, quality of life, and functional issues in elderly patients suggest the use of specific questionnaires developed for this population. Consideration should be given to measures targeting cognitive symptoms specific to common medical comorbidities in this population, such as dementia and cardiovascular disease, even if not directly related to the referral question to help track possible changes in the future (e.g., inclusion of a dementia screening measure). Finally, as in any neuropsychological evaluation, test selection should take into account the specific referral question. In the epilepsy population, measures to help localize and lateralize dysfunction should be included. Considerations for interpreting data in the context of the common referral questions listed above are addressed in the below section "Reporting the Findings."

Domains Assessed

Based on the issues listed above, recommended tests are listed in Table 3.2. This is not meant to be an all-inclusive list of useful tests, nor is this meant to suggest that all tests need to be administered. Rather, this list is provided as a core of select measures useful in the elderly epilepsy population and could be modified based on the specific referral question, the clinician's preliminary impression, and any restrictions posed by a patient such as fatigue or sensory/motor problems.

Some clinicians may prefer to use the Wechsler Fourth Editions rather than the older versions of these measures. At the time of this writing, research regarding the applicability of the newer measures in this population was not available.

Reporting the Findings

Characterize Results

As in a typical neuropsychological report, a good first step is to describe the cognitive profile of strengths and weaknesses. Emotional, personality, and functional data should also be reviewed, including the results of depression and anxiety rating scales, personality questionnaires, quality of life ratings, and activities of daily living scales. Report whether or not cognitive or behavioral/emotional impairment exists, and if so, the nature of the impairment (e.g., affected cognitive domain(s) and severity). If relevant, report the extent to which results are lateralizing or localizing.

Table 3.2 Recommended tests for neuropsychological assessment of elderly patients with epilepsy

Attention and working memory
– Digit Span (WAIS-III/WMS-III)
– Spatial Span (WMS-III)
– Arithmetic (WAIS-III)[a]
Processing speed
– Oral Symbol Digit Modalities Test
– Trails A[b]
– Digit Symbol Coding (WAIS-III)[a]
Motor
– Finger tapping
– Grooved pegboard
Language
– Reading subtest from the Wide Range Achievement Test—Fourth Edition
– Boston Naming Test[b]
– Verbal fluency: Categories[b] and CFL[b]
– Token Test[b]
Visuospatial/constructional skills
– Rey-Osterrieth Complex Figure. If figure may be too difficult, the Greek cross may be substituted
– Clock Drawing Test
– Judgment of Line Orientation[b]
– Picture Completion (WAIS-III)[a]
Executive functioning
– Trails B[b]
– Wisconsin Card Sorting Test
– Similarities (WAIS-III)[a]
– Stroop[b]
Memory
– Logical Memory (WMS-III)
– Rey's Auditory-Verbal Learning Test[b]
– Brief Visual Memory Test
Dementia screening
– Dementia Rating Scale—II (includes orientation items)[b]
Mood/QOL/ADL
– Quality of Life in Epilepsy Inventories (i.e., QOLIE-89 Devinsky, Vickrey, et al., 1995; QOLIE-31, Cramer, Perrine, et al., 1998). These are freely available online at http://www.rand.org/health/surveys_tools/qolie/
– Questionnaires to determine ability to manage the basic and instrumental activities of daily living
– Measure of psychological variables including as depression, such as the Neurological Disorders Depression Inventory for Epilepsy (Gilliam, Barry, et al., 2006); anxiety; and motivation

[a]WAIS-III subtests to be used to calculate Full-Scale IQ (Donnell et al., 2007)

[b]MOANS norms available

Address Referral Questions

Providing Differential Diagnosis for Cognitive Symptoms

The referral questions often include, either explicitly or implicitly, discussion of the etiology of objective and/or subjective cognitive impairment. This requires integration of information obtained from a variety of sources including interview with the patient and a collateral source, medical history including brain imaging, behavioral observations, and test scores. Potential etiologies discussed above should be considered. Differential diagnosis will often depend on the reported onset and progression of cognitive problems or lack thereof, corroboration from imaging data, and cognitive profile.

Evaluating for a comorbid progressive neurodegenerative process may be difficult. No study to date has attempted to establish measures differentiating diagnoses of epilepsy and progressive dementia. Griffith et al. (2006) found that older patients with epilepsy demonstrated reduced executive functioning and similar memory performance compared to patients with amnestic mild cognitive impairment. Factors helpful in diagnosing a progressive dementia versus cognitive impairment due to epilepsy include the onset and progression of cognitive symptoms and the patient's neurocognitive profile of strengths and weaknesses, and how these overlap with their onset, progression, and type of epilepsy or epilepsy treatments compared to the characteristic profile of progressive dementias. However, cognitive dysfunction in epilepsy is not always focal, even in the case of a focal epilepsy (Hermann & Seidenberg, 2002). If the reported onset and progression of cognitive difficulties or the pattern of subjective or objective cognitive-behavioral symptoms are not sufficient to distinguish the etiology, serial assessment may be required to differentiate the cause of the symptoms.

Characterizing the Impact of Epilepsy on Cognition

Epilepsy, particularly when chronic, has been associated with cognitive dysfunction. Several variables have been associated with increased

cognitive impairment, primarily in temporal lobe epilepsy. While not all studies have found similar results, the most commonly reported variables of note include younger age of onset, longer duration of epilepsy, smaller hippocampal and total brain volume, poor seizure control, involvement of the dominant lobe, history of generalized tonic-clonic seizures, and lower baseline IQ (Glosser, Cole, et al., 1997; Hermann, Seidenberg, et al., 2002; Hermann, Seidenberg, et al., 2006; Oyegbile, Dow, et al., 2004; Strauss, Loring, et al., 1995; Thompson & Duncan, 2005). Again, the extent of corroborating evidence between seizure localization data (e.g., EEG, MRI) and the onset, static, or progressive course and pattern of neurocognitive strengths and weaknesses can provide evidence for or against seizures being a primary etiology of cognitive dysfunction.

Determining AED Cognitive Side Effects

As noted above, AEDs carry risk for cognitive side effects. Determining the contribution of various medications to any given patient's cognitive dysfunction requires a careful review of the timing of medication changes (the introduction and discontinuation of medications, changes in dosages, and speed with which changes are made) and the onset or exacerbation of cognitive complaints. Overlooking the possibility that medications are responsible for some cognitive inefficiencies potentially precludes the effective treatment of those symptoms by modifying the medication regimen.

Assessing Risk of Cognitive Decline After Surgical Resection

As reviewed above, there have been limited data addressing the potential for increased risk of postoperative cognitive decline due to advanced age. The available data suggest a cautious approach is prudent, but there are no direct data to suggest that advanced age alone is a strong contraindication for surgery from a cognitive standpoint. Rather, in the absence of strong evidence in either direction, the unique risk factors should be examined for each individual patient, including the well-established predictors of memory decline, including dominant mesial temporal resection, normal imaging, and later age of seizure onset, as well as risk factors associated with major surgeries in general that have emphasized the importance of cerebral reserve (i.e., education and previous cerebrovascular injury; Monk, Weldon, et al., 2008). There is indirect evidence from Helmstaedter and colleagues (2002) that selective amygdalohippocampectomy may carry less age-associated cognitive risk than standard anterior 2/3 temporal lobectomy for temporal lobe epilepsy, but this requires further study.

Recommendations

Recommendations will obviously be made on an individualized basis, but there are several that deserve special consideration among elderly patients with epilepsy.

Modification of Activities

Reduction in activities and functional assistance may be warranted based on the interview, medical history, and examination results. An occupational therapy assessment of specific functional capacities may be helpful to determine if modifications in the patient's activities are required. Basic safety concerns may include confusion regarding medication management, inability to consistently remember to take medications, forgetting to turn off the stove or iron, and wandering/getting lost. Financial issues should be considered, such as the ability to manage the household finances and balance a checkbook. Return to work issues are less common in the elderly, but occasionally arise. Several potential issues must be balanced, including the personal and financial benefits that often accompany continued work with the risk of overexertion that can result in physical and emotional fatigue and further medical/emotional problems, as well as financial risks of losing legitimate disability benefits if the patient fails to perform well and is let go. Gradual reintroduction to the position is often prudent, such as resuming work a few hours per day and increasing the time every few weeks

until they find their optimal schedule. If the seizures are controlled and the patient wants to resume driving, it is important to make sure the patient is cognitively able to drive in a consistently safe fashion and navigate well. To this end, results of the neuropsychological evaluation may suggest that a formal driving evaluation is warranted. Finally, medical decision-making abilities should be considered, as these have been found to be impaired in elderly patients with chronic focal epilepsy, even in those living independently in the community (Bambara, Griffith, et al., 2007).

Review of Medications

A recommendation may be warranted to consider changing AEDs and/or other medications with suspected adverse cognitive or behavioral side effects.

Additional Assistance in Differentiating Potential Etiologies

Understanding the extent and type of any cognitive progression through serial neuropsychological evaluations may be required to delineate etiology of cognitive dysfunction. Other medical referrals may also help to determine etiology, such as a neurological evaluation to determine if brain imaging, additional lab work, or other tests may be appropriate.

In some cases, a patient may be referred without a diagnosis of epilepsy but present with seizure-like symptoms such as unexplained brief episodes of confusion or disorientation. This is particularly relevant for elderly patients, where seizures can be difficult to diagnose but are often treatable with AEDs. As discussed above, only 25 % of elderly individuals with new-onset focal seizures without alteration of consciousness were correctly diagnosed with epilepsy at symptom onset, and it took an average of 18 months to diagnose (Ramsay, Rowan, et al., 2004). Thus, if seizure activity is suspected, referral to an epileptologist or expert neurologist for seizure evaluation is recommended. In addition to a comprehensive neurological workup, they will often order routine serum laboratory tests, neuroimaging (preferably MRI), and EEG. Because interictal epileptiform discharges are less common in older adults (Drury & Beydoun, 1998), if there is strong suspicion of seizures, video-EEG may be warranted. Finally, because of the broad differential diagnoses and common comorbidities, neurologists may order additional tests to rule out other associated problems (e.g., cerebrovascular, cardiac) (Van Cott, 2002).

Improve Quality of Life

Epilepsy is associated with greater impairment in quality of life, increased frequency of depression and anxiety, and decreased social resources (Hermann, Seidenberg, et al., 2008a). Many elderly with newly diagnosed epilepsy and their families may have little knowledge of what epilepsy is, and education about basic facts about epilepsy and its cognitive and mood implications can be empowering. Reassurance that perceptions and treatment of those with epilepsy have changed over the years may be important. There are several excellent online resources for education and online forums specific to seniors with epilepsy:

- Epilepsy Foundation has a section devoted to seniors with epilepsy: senior-specific education about epilepsy, online discussion forum, and information on practical issues of living with epilepsy: http://www.epilepsyfoundation.org/living/seniors/
- This site provides educational information about seniors with epilepsy: http://www.epilepsy.com/info/seniors
- Epilepsy Ontario has a special section for seniors with epilepsy regarding education and practical life issues. The section on support services, however, is targeted mainly to those in Ontario: http://www.epilepsyontario.org/client/EO/EOWeb.nsf/web/Seniors+Living+with+Epilepsy+(kit)
- Many states and cities have local epilepsy groups that can be helpful for locating services for the individual patient.

Referral to a psychotherapist, counselor, or psychiatrist may be indicated to address mood and/or behavioral concerns. Consultation with a social worker is often helpful to provide

information regarding community resources such as support groups, job placement services, and other potential services. Finally, referral for occupational or speech therapy can assist in learning skills to compensate for identified cognitive problems.

Case Presentation

Background

Our patient is a 66-year-old, right-handed, African-American, widowed woman with 12 years of formal education. She was referred by her epileptologist as part of a comprehensive evaluation for epilepsy surgery. Her seizures started at age 41 following the birth of her son and were characterized by an aura of a nonspecific "funny feeling" followed by chewing movements and hand automatisms. She was amnestic for these events. Seizures lasted up to a few minutes and were followed by postictal confusion. She typically experienced one to three seizures per day, most days of the week. Seizure frequency had waxed and waned with no obvious change over the past several years, and she had never been seizure-free for more than 1 month since epilepsy onset. However, because she lived alone, seizure frequency was difficult to determine with certainty. She had been taking Carbatrol (800 mg, four times daily) and gabapentin (400 mg, twice daily) and denied experiencing medication side effects. Video-EEG monitoring of AEDs suggested bitemporal seizures, and brain MRI showed left MTS and mild nonspecific white matter lesions. PET showed hypometabolism in the left anterior temporal lobe and mesial temporal structures, as well as mild hypometabolism in the right anterior temporal regions.

When asked about cognitive functioning, the patient described difficulty recalling conversations and remembering to take her medications. She perceived her thinking speed as slowed, and she reported the onset of word-finding difficulties. Her daughter corroborated these changes but at greater severity; she said that her mother frequently repeated herself, her thinking speed had significantly slowed, and she had difficulty making decisions. The patient's daughter said that these problems had progressed over the past 2–3 years and were accompanied by functional impairment; she had lived alone since her husband died 20 years ago, and her daughter had started to help her manage her medications, finances, and appointments. The patient's two daughters checked on her daily. She continued to groom herself and cook independently without obvious difficulty. She was reportedly diagnosed with Alzheimer's disease 2 years earlier by a doctor at an outside hospital, but no additional information about this was available. Her daughter denied any obvious relationship between previous changes in AEDs and cognitive or functional changes.

She worked as a housekeeper for most of her career before retiring several years ago. The patient denied a history of depression or other significant emotional distress, with the exception of an incident 16 years ago in which she seemed confused and left town without the family's knowledge. She was found wading in a river and admitted to a psychiatric hospital. She denied alcohol, tobacco, and recreational drug use.

Medical history is otherwise unremarkable. There is no family history of neurological disorder. Her only medications included Carbatrol and gabapentin.

Neuropsychological Evaluation

Evaluation Results

Behavioral observations were most notable for the patient's difficulty providing a detailed and well-articulated history. She was unable to recall two previous car accidents reported by her daughter or the incident of wandering 16 years earlier, even when prompted by the daughter. She reported that her husband died 4 years ago rather than 20 and said she had six, rather than nine, grandchildren. Word-finding difficulties were noted in casual conversation, and she appeared to process information slowly. She did not initiate conversation with the examiner and, at times, was

unresponsive to questioning. Eye contact was poor and she often sat with her eyes closed. Affect was very flat. She was oriented to the day of week and time of day, but was off on the date by 1 day. She was oriented to the city and state, but not hospital. She often appeared confused during the testing portion of the evaluation and frequently required repetition of task instructions. Her performance on the Token Test was well below expectation; therefore, it is unclear how well she understood task instructions. Although she performed within expectation on a formal effort measure, her poor comprehension and apparent confusion suggested that the current test results may have underestimated her actual level of functioning.

Tests were selected based on several factors, including (1) the presence of adequate normative data for a 66-year-old African-American woman, (2) the nature of her cognitive complaints and suspected epileptogenic focus, (3) the support in the literature regarding prediction of postoperative decline, and (4) the need to maintain core elements of an existing clinical/research battery. Results are presented in Table 3.3.

Summary, Interpretations, and Recommendations

If taken at face value, this patient's assessment was notable in multiple respects. In the context of baseline abilities estimated to have been in the low average to average range, she demonstrated marked language and memory difficulties. Her confrontation naming was particularly poor, attaining only 12/60 words. Memory deficits were characterized by impairment in both auditory and visual memory. Poor performance was also observed on measures of working memory and executive functioning. Conversely, she performed within the expected range on tests of processing and motor speed, simple and complex visuomotor sequencing, and visuospatial intellectual abilities. Some of the typical "hold" indices such as vocabulary and information may have been affected by word-retrieval problems, as scores on these measures were lower than expected based on her education and WRAT-III reading subtest. Her phonemic verbal fluency was better than expected in the context of other language problems observed. She did not report any significant current symptoms of depression. Although the possibility that her confusion and difficulty comprehending task instructions undermined her performance cannot be ruled out, her test performances were consistent with significant cerebral dysfunction.

There are several possible etiologies of the patient's deficits in language, memory, working memory, and executive functioning. It is likely that some of her current impairments are due to many years of frequent seizures. Her cognitive profile was somewhat more complicated than the auditory memory and language deficits often associated with dominant temporal lobe epilepsy. Visual memory was impaired in addition to auditory memory, which could be attributed to nondominant temporal lobe involvement suggested by bitemporal seizures on video-EEG monitoring and PET mild hypometabolism on the right side. The deficits in working memory and executive functioning can also be observed in patients with temporal lobe epilepsy (Hermann & Seidenberg, 2002). However, concern was raised for a progressive neurodegenerative disorder based on her daughter's report of slowly progressive cognitive and functional declines over the past 2–3 years. Importantly, these changes did not appear to correspond to changes in AEDs or obvious changes in her seizure frequency or semiology. Finally, the mild nonspecific white matter lesions noted on MRI may also be contributing to her cognitive deficits, including the more recent progressive declines. It was recommended that other etiologies of cognitive decline be ruled out, such as endocrine/metabolic abnormalities and vitamin deficiency.

Results also raise concern for cognitive decline if she were to undergo surgery, presumably a left temporal lobectomy. Aside from her age and potential progressive dementia, patients with bilateral poor memory and bitemporal seizures and imaging abnormalities are at increased risk of memory problems after surgery (Baxendale, 1998). As discussed above, there is mixed evidence regarding age as a risk factor, but there is some research suggesting that it may be

Table 3.3 Test results for case presentation

Measure		Raw	Standard score[a]
WAIS-III	Full-Scale IQ		75
	Verbal Comprehension Index		74
	Perceptual Organization Index		82
	Working Memory Index		65
	Processing Speed Index		91
	Vocabulary		80
	Similarities		80
	Arithmetic		65
	Digit Span		80
	Information		70
	Letter Number Sequencing		70
	Picture Completion		85
	Digit Symbol		95
	Block Design		90
	Matrix Reasoning		80
	Symbol Search		90
WMS-III	Auditory Immediate		65
	Visual Immediate		78
	Auditory Delayed		64
	Visual Delayed		65
	Auditory Recognition		75
	Logical Memory I	14	65
	Faces I	29	85
	Verbal Paired Associates I	0	70
	Family Pictures I	21	80
	Word List total I	25	95
	Word List learning slope	4	95
	Spatial Span	10	80
	Logical Memory II	2	65
	Faces II	26	75
	Verbal Paired Associates II	0	75
	Family Pictures II	13	70
	Word List long delay	0	80
	Word List recognition	14	65
Trails A[b]		61 (1 error)	95
Trails B[b]		219 (3 errors)	90
Wisconsin Card Sorting Test	Total correct	69	
	Total errors	59	84
	Perseverative errors	26	93
	Categories	0	<1 percentile
	Set failures	3	6–10 percentile
Ruff	Total unique designs (corrected)	32	67
	Error ratio	0.2857	82
Finger tapping	Dominant	29.6	84
	Nondominant	31.8	93
Grooved pegboard	Dominant	113	90

(continued)

Table 3.3 (continued)

Measure		Raw	Standard score[a]
	Nondominant	114	93
Boston Naming Test[b]		12 (1/7 semantic cues; 5/14 phonemic cues)	60
COWAT[b]		30	100
Animal fluency		4	60
Token Test[b]		27	70
WRAT-3	Reading	38	95
Beck Depression Inventory-II		6	"minimal"

[a]Higher standard scores indicate better performance
[b]Based on MOAANS. All other norms are based on the manuals with the exception of Heaton Norms (2008) used for grooved pegboard and finger tapping

associated with further memory decline after temporal lobectomy. Finally, risk to patients with a potential progressive dementia is also unknown, but there is evidence to suggest that those with less cognitive reserve going into surgery may not fare as well as those with more cognitive reserve (Moller, Cluitmans, et al., 1998; Monk, Weldon, et al., 2008). Taken together, these results suggest that the patient was at increased risk for further memory declines following a left, presumably dominant temporal lobectomy.

The patient's cognitive difficulties raised concern about her ability to live independently. In order to ensure her safety, it was recommended that she not use the stove or oven independently and that she receive assistance in managing her medications. Finally, it was recommended that the family begins the discussion of power of attorney for health care and financial decision-making.

Medical Follow-Up

Neurologists disagreed about cognitive and functional surgical risks in the context of an underlying dementia. They recommended social interventions to optimize medication compliance as well as efforts to obtain an accurate description of seizure frequency. Repeat video-EEG monitoring was recommended while on her typical AEDs, so that seizure burden could be estimated and to determine if seizures, while on medication, arise only from the left side.

Results of repeat video-EEG monitoring suggested much more frequent seizures while on AEDs than previously thought (i.e., 3–4 per hour). All arose from the left temporal region. Based on discussions between the epilepsy team, the patient, and her family, it was decided to modify her AEDs to optimize seizure control. If her seizures continued to occur frequently despite further medication trials, surgical options would be considered. One and a half years after these AED changes, the patient has been doing better, with an estimated one to two seizures per week. Social work has followed the patient, who continues to live independently with daily calls and visits from family.

Significance for Neuropsychological Evaluations of the Elderly with Epilepsy

It may be difficult to differentiate progressive dementia and epilepsy etiologies, and much will depend on the onset and progression of cognitive symptoms in relation to seizures, as well as a neurocognitive pattern consistent with that expected for dementia versus where the seizures are thought to arise from. There is no consensus and little data on which to base a decision regarding risk of cognitive and functional decline after

epilepsy surgery in elderly patients with possible progressive dementia. It is often difficult to determine seizure frequency in patients who live alone, and video-EEG monitoring can be helpful in this regard. Finally, it is important to address common psychosocial issues in the elderly with epilepsy, such as ability to living alone, safety concerns including driving, and medical decision-making abilities.

References

Acosta, I., Vale, F., Tatum, W. O., & Benbadis, S. R. (2008). Epilepsy surgery after age 60. *Epilepsy and Behavior, 12*, 324–325.

Arif, H., Buchsbaum, R., Pierro, J., Whalen, M., Sims, J., Resor, S. R., Jr., et al. (2010). Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. *Archives of Neurology, 67*(4), 408–415.

Baker, G. A., Jacoby, A., Buck, D., Brooks, J., Potts, P., & Chadwick, D. W. (2001). The quality of life of older people with epilepsy: Findings from a UK community study. *Seizure, 10*(2), 92–99.

Bambara, J. K., Griffith, H. R., Martin, R. C., Faught, E., Wadley, V. G., & Marson, D. C. (2007). Medical decision-making abilities in older adults with chronic partial epilepsy. *Epilepsy and Behavior, 10*(1), 63–68.

Barlow, D. H. (2001). *Clinical handbook of psychological disorders*. New York, NY: The Guilford Press.

Baxendale, S. (1998). Amnesia in temporal lobectomy patients: Historical perspective and review. *Seizure, 7*(1), 15–24.

Beghi, M., Savica, R., Beghi, E., Nobili, A., & Garattini, L. (2009). Utilization and costs of antiepileptic drugs in the elderly: Still an unsolved issue. *Drugs and Aging, 26*(2), 157–168.

Bjorholt, P. G., Nakken, K. O., Rohme, K., & Hansen, H. (1990). Leisure time habits and physical fitness in adults with epilepsy. *Epilepsia, 31*(1), 83–87.

Breteler, M. M., de Groot, R. R., van Romunde, L. K., & Hofman, A. (1995). Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: A register-based follow-up study. *American Journal of Epidemiology, 142*, 1300–1305.

Breteler, M. M., van Duijn, C. M., Chandra, V., Fratiglioni, L., Graves, A. B., Heyman, A., et al. (1991). Medical history and the risk of Alzheimer's disease: A collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *International Journal of Epidemiology, 20*(Suppl 2), S36–S42.

Brodie, M. J., & Kwan, P. (2005). Epilepsy in elderly people. *BMJ, 331*(7528), 1317–1322.

Brodie, M. J., Overstall, P. W., & Giorgi, L. (1999). Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Research, 37*(1), 81–87.

Brodie, M. J., & Stephen, L. J. (2007). Outcomes in elderly patients with newly diagnosed and treated epilepsy. *International Review of Neurobiology, 81*, 253–263.

Caramelli, P., & Castro, L. H. (2005). Dementia associated with epilepsy. *International Psychogeriatrics, 17*(Suppl 1), S195–S206.

Carney, R. M., Freedland, K. E., Eisen, S. A., Rich, M. W., & Jaffe, A. S. (1995). Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychology, 14*(1), 88–90.

Carter, M. D., Weaver, D. F., Joudrey, H. R., Carter, A. O., & Rockwood, K. (2007). Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia. *Journal of Neurological Sciences, 252*(2), 169–172.

Cleary, P., Shorvon, S., & Tallis, R. (2004). Late-onset seizures as a predictor of subsequent stroke. *Lancet, 363*(9416), 1184–1186.

Cloyd, J., Hauser, W. A., Towne, A., Ramsay, R., Mattson, R., Gilliam, F., et al. (2006). Epidemiological and medical aspects of epilepsy in the elderly. *Epilepsy Research, 68*(Suppl 1), S39–S48.

Cramer, J. A., Perrine, K., Devinsky, O., Bryant-Comstock, L., Meador, K., & Hermann, B. (1998). Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia, 39*(1), 81–88.

de la Court, A., Breteler, M. M. B., Meinardi, H., Hauser, W. A., & Hofman, A. (1996). Prevalence of epilepsy in the elderly: The Rotterdam study. *Epilepsia, 37*(2), 141–147.

DeLorenzo, R. J., Hauser, W. A., Towne, A. R., Boggs, J. G., Pellock, J. M., Penberthy, L., et al. (1996). A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology, 46*(4), 1029–1035.

Devinsky, O., Vickrey, B. G., Cramer, J., Perrine, K., Hermann, B., Meador, K., et al. (1995). Development of the quality of life in epilepsy inventory. *Epilepsia, 36*(11), 1089–1104.

Donnell, A. J., Pliskin, N., Holdnack, J., Axelrod, B., & Randolph, C. (2007). Rapidly-administered short forms of the Wechsler Adult Intelligence Scale-3rd edition. *Archives of Clinical Neuropsychology, 22*(8), 917–924.

Drury, I., & Beydoun, A. (1998). Interictal epileptiform activity in elderly patients with epilepsy. *Electroencephalography and Clinical Neurophysiology, 106*(4), 369–373.

Ferrendelli, J. A., French, J., Leppik, I., Morrell, M. J., Herbeuval, A., Han, J., et al. (2003). Use of levetiracetam in a population of patients aged 65 years and older: A subset analysis of the KEEPER trial. *Epilepsy and Behavior, 4*(6), 702–709.

Fillit, H. M., Butler, R. N., O'Connell, A. W., Albert, M. S., Birren, J. E., Cotman, C. W., et al. (2002). Achieving and maintaining cognitive vitality with aging. *Mayo Clinic Proceedings, 77*(7), 681–696.

Forstl, H., Burns, A., Levy, R., Cairns, N., Luthert, P., & Lantos, P. (1992). Neurologic signs in Alzheimer's disease. Results of a prospective clinical and neuropathologic study. *Archives of Neurology, 49*(10), 1038–1042.

Frey, M. (2007). Psychiatric complications of epilepsy in the geriatric patient: Diagnostic and treatment considerations. In A. B. Ettinger & A. M. Kanner (Eds.), *Psychiatric issues in epilepsy: A practical guide* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Gaitatzis, A., Carroll, K., Majeed, A., & W Sander, J. (2004). The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia, 45*(12), 1613–1622.

Gilliam, F. G., Barry, J. J., Hermann, B. P., Meador, K. J., Vahle, V., & Kanner, A. M. (2006). Rapid detection of major depression in epilepsy: A multicentre study. *Lancet Neurology, 5*(5), 399–405.

Giorgi, L., Gomez, G., O'Neill, F., Hammer, A. E., & Risner, M. (2001). The tolerability of lamotrigine in elderly patients with epilepsy. *Drugs and Aging, 18*(8), 621–630.

Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Chadwick, D., Guerreiro, C., et al. (2006). ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia, 47*(7), 1094–1120.

Glosser, G., Cole, L. C., French, J. A., Saykin, A. J., & Sperling, M. R. (1997). Predictors of intellectual performance in adults with intractable temporal lobe epilepsy. *Journal of International Neuropsychological Society, 3*(3), 252–259.

Griffith, H. R., Martin, R. C., Bambara, J. K., Faught, E., Vogtle, L. K., & Marson, D. C. (2007). Cognitive functioning over 3 years in community dwelling older adults with chronic partial epilepsy. *Epilepsy Research, 74*(2–3), 91–96.

Griffith, H. R., Martin, R. C., Bambara, J. K., Marson, D. C., & Faught, E. (2006). Older adults with epilepsy demonstrate cognitive impairments compared with patients with amnestic mild cognitive impairment. *Epilepsy and Behavior, 8*(1), 161–168.

Grivas, A., Schramm, J., Kral, T., von Lehe, M., Helmstaedter, C., Elger, C. E., et al. (2006). Surgical treatment for refractory temporal lobe epilepsy in the elderly: Seizure outcome and neuropsychological sequels compared with a younger cohort. *Epilepsia, 47*, 1364–1372.

Hamed, S. A., & Nabeshima, T. (2005). The high atherosclerotic risk among epileptics: The atheroprotective role of multivitamins. *Journal of Pharmacological Sciences, 98*(4), 340–353.

Hasher, L., Chung, C., May, C. P., & Foong, N. (2002). Age, time of testing, and proactive interference. *Canadian Journal of Experimental Psychology, 56*(3), 200–207.

Hauser, W. A. (1992). Seizure disorders: The changes with age. *Epilepsia, 33*(Suppl 4), S6–S14.

Hauser, W. A., Annegers, J. F., & Kurland, L. T. (1991). Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia, 32*(4), 429–445.

Hauser, W. A., Annegers, J. F., & Kurland, L. T. (1993). Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia, 34*, 453–468.

Hauser, W. A., Annegers, J. F., & Rocca, W. A. (1996). Descriptive epidemiology of epilepsy: Contributions of population-based studies from Rochester, Minnesota. *Mayo Clinic Proceedings, 71*(6), 576–586.

Hauser, W. A., Morris, M. L., Heston, L. L., & Anderson, V. E. (1986). Seizures and myoclonus in patients with Alzheimer's disease. *Neurology, 36*(9), 1226–1230.

Haut, S. R., Katz, M., Masur, J., & Lipton, R. B. (2009). Seizures in the elderly: Impact on mental status, mood, and sleep. *Epilepsy and Behavior, 14*(3), 540–544.

Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2008). *Revised comprehensive norms for an expanded Halstead-Reitan battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults*. Lutz, FL: PAR.

Helmstaedter, C., & Elger, C. E. (2009). Chronic temporal lobe epilepsy: A neurodevelopmental or progressively dementing disease? *Brain, 132*(Pt 10), 2822–2830.

Helmstaedter, C., Kurthen, M., Lux, S., Reuber, M., & Elger, C. E. (2003). Chronic epilepsy and cognition: A longitudinal study in temporal lobe epilepsy. *Annals of Neurology, 54*(4), 425–432.

Helmstaedter, C., Reuber, M., & Elger, C. C. (2002a). Interaction of cognitive aging and memory deficits related to epilepsy surgery. *Annals of Neurology, 52*(1), 89–94.

Helmstaedter, C., Reuber, M., & Elger, C. C. E. (2002b). Interaction of cognitive aging and memory deficits related to epilepsy surgery. *Annals of Neurology, 52*, 89–94.

Hermann, B., & Seidenberg, M. (2002). Neuropsychology and temporal lobe epilepsy. *CNS Spectrums, 7*(5), 343–348.

Hermann, B. P., Seidenberg, M., Dow, C., Jones, J., Rutecki, P., Bhattacharya, A., et al. (2006a). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of Neurology, 60*(1), 80–87.

Hermann, B. P., Seidenberg, M., Dow, C., Jones, J., Rutecki, P., Bhattacharya, A., et al. (2006b). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of Neurology, 60*, 80–87.

Hermann, B., Seidenberg, M., Sager, M., Carlsson, C., Gidal, B., Sheth, R., et al. (2008). Growing old with epilepsy: The neglected issue of cognitive and brain health in aging and elder persons with chronic epilepsy. *Epilepsia, 49*, 731–740.

Hermann, B. P., Seidenberg, M., & Bell, B. (2002). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research, 135*, 429–438.

Hermann, B., Seidenberg, M., & Jones, J. (2008). The neurobehavioural comorbidities of epilepsy: Can a natural history be developed? *Lancet Neurology, 7*(2), 151–160.

Hesdorffer, D. C., Hauser, W. A., Annegers, J. F., Kokmen, E., & Rocca, W. A. (1996). Dementia and adult-onset unprovoked seizures. *Neurology, 46*(3), 727–730.

Isojarvi, J. I., Rattya, J., Myllyla, V. V., Knip, M., Koivunen, R., Pakarinen, A. J., et al. (1998). Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Annals of Neurology, 43*(4), 446–451.

Ivnik, R. J., Malec, J. F., Smith, G. E., Tangalos, E. G., & Petersen, R. C. (1996). Neuropsychological tests' norms above age 55: COWAT, BNT, MAE Token, WRAT-R Reading, AMNART, STROOP, TMT, and JLO. *The Clinical Neuropsychologist, 10*, 262–278.

Kutluay, E., McCague, K., D'Souza, J., & Beydoun, A. (2003). Safety and tolerability of oxcarbazepine in elderly patients with epilepsy. *Epilepsy and Behavior, 4*(2), 175–180.

Kwan, P., & Brodie, M. J. (2001). Neuropsychological effects of epilepsy and antiepileptic drugs. *Lancet, 357*(9251), 216–222.

Laccheo, I., Ablah, E., Heinrichs, R., Sadler, T., Baade, L., & Liow, K. (2008). Assessment of quality of life among the elderly with epilepsy. *Epilepsy and Behavior, 12*(2), 257–261.

Lozsadi, D. A., & Larner, A. J. (2006). Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 22*(2), 121–124.

Lucas, J. A., Ivnik, R. J., Willis, F. B., Ferman, T. J., Smith, G. E., Parfitt, F. C., et al. (2005). Mayo's Older African Americans Normative Studies: Normative data for commonly used clinical neuropsychological measures. *The Clinical Neuropsychologist, 19*(2), 162–183.

Luef, G. J., Waldmann, M., Sturm, W., Naser, A., Trinka, E., Unterberger, I., et al. (2004). Valproate therapy and nonalcoholic fatty liver disease. *Annals of Neurology, 55*(5), 729–732.

Mackenzie, I. R., McLachlan, R. S., Kubu, C. S., & Miller, L. A. (1996). Prospective neuropsychological assessment of nondemented patients with biopsy proven senile plaques. *Neurology, 46*(2), 425–429.

Mackenzie, I. R., & Miller, L. A. (1994). Senile plaques in temporal lobe epilepsy. *Acta Neuropathologica (Berlin), 87*, 504–510.

Marchiori, P. E., Yasuda, N., Azevedo, H. C., Orfao, M., Callegaro, D., Yamamoto, F. I., et al. (1996). Creutzfeldt-Jakob disease. A survey of 14 patients. *Arquivos de Neuro-Psiquiatria, 54*(4), 577–583.

Martin, R. C., Griffith, H. R., Faught, E., Gilliam, F., Mackey, M., & Vogtle, L. (2005). Cognitive functioning in community dwelling older adults with chronic partial epilepsy. *Epilepsia, 46*, 298–303.

Martin, R., Vogtle, L., Gilliam, F., & Faught, E. (2005). What are the concerns of older adults living with epilepsy? *Epilepsy and Behavior, 7*(2), 297–300.

Massimiliano, B., Rodolfo, S., Beghi, E., Nobili, A., & Garattini, L. (2009). Utilization and costs of antiepileptic drugs in the elderly. *Drugs and Aging, 26*(2), 157–168.

Mauri Llerda, J. A., Tejero, C., Mercade, J. M., Padro, L. L., & Salas Puig, J. (2005). Lamotrigine and epilepsy in the elderly: Observational study of low-dose monotherapy. *International Journal of Clinical Practice, 59*(6), 651–654.

McAreavey, M. J., Ballinger, B. R., & Fenton, G. W. (1992). Epileptic seizures in elderly patients with dementia. *Epilepsia, 33*(4), 657–660.

McBride, A. E., Shih, T. T., & Hirsch, L. J. (2002). Video-EEG monitoring in the elderly: A review of 94 patients. *Epilepsia, 43*(2), 165–169.

McLaughlin, D. P., Pachana, N. A., & McFarland, K. (2008). Stigma, seizure frequency and quality of life: The impact of epilepsy in late adulthood. *Seizure, 17*(3), 281–287.

Mendez, M. F., Catanzaro, P., Doss, R. C., ARguello, R., & Frey, W. H., II. (1994). Seizures in Alzheimer's disease: Clinicopathologic study. *Journal of Geriatric Psychiatry and Neurology, 7*(4), 230–233.

Mendez, M., & Lim, G. (2003). Seizures in elderly patients with dementia: Epidemiology and management. *Drugs and Aging, 20*(11), 791–803.

Mohanraj, R., & Brodie, M. J. (2006). Diagnosing refractory epilepsy: Response to sequential treatment schedules. *European Journal of Neurology, 13*(3), 277–282.

Moller, J. T., Cluitmans, P., Rasmussen, L. S., Houx, P., Rasmussen, H., Canet, J., et al. (1998). Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet, 351*(9106), 857–861.

Monk, T. G., Weldon, B. C., Garvan, C. W., Dede, D. E., van der Aa, M. T., Heilman, K. M., et al. (2008). Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology, 108*(1), 18–30.

Nakken, K. O. (1999). Physical exercise in outpatients with epilepsy. *Epilepsia, 40*(5), 643–651.

Ono, H., Sakamoto, A., Eguchi, T., Fujita, N., Nomura, S., Ueda, H., et al. (1997). Plasma total homocysteine concentrations in epileptic patients taking anticonvulsants. *Metabolism, 46*(8), 959–962.

Oyegbile, T. O., Dow, C., Jones, J., Bell, B., Rutecki, P., Sheth, R., et al. (2004). The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology, 62*(10), 1736–1742.

Piazzini, A., Canevini, M. P., Turner, K., Chifari, R., & Canger, R. (2006). Elderly people and epilepsy: Cognitive function. *Epilepsia, 47*(Suppl. 5), 82–84.

Pugh, M. J., Copeland, L. A., Zeber, J. E., Cramer, J. A., Amuan, M. E., Cavazos, J. E., et al. (2005). The impact of epilepsy on health status among younger and older adults. *Epilepsia, 46*(11), 1820–1827.

Pylvanen, V., Knip, M., Pakarinen, A. J., Turkka, J., Kotila, M., Rattya, J., et al. (2003). Fasting serum

insulin and lipid levels in men with epilepsy. *Neurology, 60*(4), 571–574.

Ramsay, R. E., & Pryor, F. (2000). Epilepsy in the elderly. *Neurology, 55*(5 Suppl 1), S9–S14.

Ramsay, R. E., Rowan, A. J., & Pryor, F. M. (2004). Special considerations in treating the elderly patient with epilepsy. *Neurology, 62*(Suppl 2), S24–S29.

Rausch, R., Kraemer, S., Pietras, C. J., Le, M., Vickrey, B. G., & Passaro, E. A. (2003). Early and late cognitive changes following temporal lobe surgery for epilepsy. *Neurology, 60*(6), 951–959.

Rowan, A. J., Ramsay, R. E., Collins, J. F., Pryor, F., Boardman, K. D., Uthman, B. M., et al. (2005). New onset geriatric epilepsy: A randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology, 64*(11), 1868–1873.

Saetre, E., Perucca, E., Isojärvi, J., & Gjerstad, L. (2007). An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia, 48*(7), 1292–1302.

Schwaninger, M., Ringleb, P., Annecke, A., Winter, R., Kohl, B., Werle, E., et al. (2000). Elevated plasma concentrations of lipoprotein(a) in medicated epileptic patients. *Journal of Neurology, 247*(9), 687–690.

Seaetre, E., Abdelnoor, M., Perucca, E., Taubøll, E., Isojärvi, J., & Gjerstad, L. (2010). Antiepileptic drugs and quality of life in the elderly: Results from a randomized double-blind trial of carbamazepine and lamotrigine in patients with onset of epilepsy in old age. *Epilepsy and Behavior, 17*(3), 395–401.

Sheorajpanday, R. V., & De Deyn, P. P. (2007). Epileptic fits and epilepsy in the elderly: General reflections, specific issues and therapeutic implications. *Clinical Neurology and Neurosurgery, 109*(9), 727–743.

Sheth, R. D. (2004). Metabolic concerns associated with antiepileptic medications. *Neurology, 63*(10 Suppl 4), S24–S29.

Sheth, R. D., Drazkowski, J. F., Sirven, J. I., Gidal, B. E., & Hermann, B. P. (2006). Protracted ictal confusion in elderly patients. *Archives of Neurology, 63*(4), 529–532.

Sirven, J. I., Malamut, B. L., O'Connor, M. J., & Sperling, M. R. (2000). Temporal lobectomy outcome in older versus younger adults. *Neurology, 54*, 2166–2169.

Smith, G., & Rush, B. (2006). Normal aging and mild cognitive impairment. In D. K. Attix & K. A. Welsh-Bohmer (Eds.), *Geriatric neuropsychology*. New York, NY: Guilford.

Sommer, B. R., & Fenn, H. H. (2010). Review of topiramate for the treatment of epilepsy in elderly patients. *Clinical Interventions in Aging, 5*, 89–99.

Strauss, E., Loring, D., Chelune, G., Hunter, M., Hermann, B., Perrine, K., et al. (1995). Predicting cognitive impairment in epilepsy: Findings from the Bozeman epilepsy consortium. *Journal of Clinical and Experimental Neuropsychology, 17*(6), 909–917.

Strober, L. B., & Arnett, P. A. (2009). Assessment of depression in three medically ill, elderly populations: Alzheimer's disease, Parkinson's disease, and stroke. *The Clinical Neuropsychologist, 23*(2), 205–230.

Tellez-Zenteno, J. F., Matijevic, S., & Wiebe, S. (2005). Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia, 46*(12), 1955–1962.

Thompson, P. J., & Duncan, J. S. (2005). Cognitive decline in severe intractable epilepsy. *Epilepsia, 46*(11), 1780–1787.

Thorvaldsen, P., Asplund, K., Kuulasmaa, K., Rajakangas, A. M., & Schroll, M. (1995). Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. *Stroke, 26*(3), 361–367.

Tinuper, P., Provini, F., Marini, C., Cerullo, A., Plazzi, G., Avoni, P., et al. (1996). Partial epilepsy of long duration: Changing semiology with age. *Epilepsia, 37*(2), 162–164.

Van Cott, A. C. (2002). Epilepsy and EEG in the elderly. *Epilepsia, 43*(Suppl 3), 94–102.

Verrotti, A., Basciani, F., Trotta, D., Greco, R., Morgese, G., & Chiarelli, F. (2001). Effect of anticonvulsant drugs on interleukins-1, -2 and -6 and monocyte chemoattractant protein-1. *Clinical and Experimental Medicine, 1*(3), 133–136.

Vezzani, A., & Granata, T. (2005). Brain inflammation in epilepsy: Experimental and clinical evidence. *Epilepsia, 46*(11), 1724–1743.

Volicer, L., Smith, S., & Volicer, B. J. (1995). Effect of seizures on progression of dementia of the Alzheimer type. *Dementia, 6*(5), 258–263.

Wallace, H., Shorvon, S., & Tallis, R. (1998). Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2 052 922 and age-specific fertility rates of women with epilepsy. *Lancet, 352*, 1970–1973.

Weiner, M. F., Hynan, L. S., Parikh, B., Zaki, N., White, C. L., III, Bigio, E. H., et al. (2003). Can Alzheimer's disease and dementias with Lewy bodies be distinguished clinically? *Journal of Geriatric Psychiatry and Neurology, 16*(4), 245–250.

Neuropsychological Evaluation of the Epilepsy Surgical Candidate

4

Daniel L. Drane

Neurosurgical intervention is the primary treatment option for patients with partial epilepsies that are refractory to treatment with antiepileptic drugs (AEDs). The probability that a patient with epilepsy will be successfully treated with an AED greatly diminishes after two drug trial failures (Kwan & Brodie, 2000), and such patients are typically considered for surgical intervention (Kwan et al., 2010). Neuropsychological assessment is an integral component of the surgical management of patients with epilepsy, representing a useful clinical method for identifying optimal surgical candidates and maximizing outcome parameters while serving as a primary research tool. The practice of neuropsychology in the setting of the epilepsy monitoring unit has greatly enriched our understanding of neurocognitive processes and their underlying neural substrates, as this environment provides a unique opportunity to study brain functions in a highly controlled fashion before and after surgical resection. Likewise, the clinical impact of neuropsychology has been profound, as it represents a means to confirm seizure onset, to predict the possible effect of surgical intervention, and to track changes over time. Neuropsychologists are also ideally equipped to explain the potential risks and benefits of surgery to patients, to identify and address comorbid psychiatric issues, and to direct the course of cognitive rehabilitation when necessary following surgery. The goals of the current chapter include elucidating the purpose of neuropsychology in epilepsy surgery, exploring potential difficulties involved in obtaining a valid assessment of the epilepsy patient (e.g., dealing with the possible effects of acute seizure activity or the confounding effect of AEDs), and providing concrete recommendations regarding the selection of tests to achieve both clinical and research goals. A summary of the findings that have been amassed over the years regarding the presurgical confirmation of the seizure focus and postsurgical identification of neurocognitive deficits resulting from surgery is provided. In this context, research regarding the usefulness of neuropsychological results to predict surgical outcome is covered as well, and a clinical vignette is included to highlight several of the central topics.

Role of Neuropsychology in the Evaluation of the Epilepsy Surgical Patient

Neuropsychological assessment can make multiple contributions to the assessment of the epilepsy surgical patient including:

1. *Confirming the lateralization and localization of seizure focus for surgical planning*. While the gold standard of determining

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seizure focus remains the electrophysiological data obtained through video-EEG monitoring, neuropsychological testing provides a useful adjunct for confirming seizure focus. Studies have demonstrated that surgical outcome is better in terms of neurocognitive functioning and seizure freedom when independent sources of data (e.g., neuroimaging, electrophysiology, neuropsychological testing) point to the same probable seizure focus (Holmes, Miles, Dodrill, Ojemann, & Wilensky, 2003; Lineweaver et al., 2006).

2. *Establishing the presurgical neurocognitive and emotional/psychological baseline for the potential surgical candidate*. This allows us to recognize presurgical emotional/psychological factors that may require treatment to improve postsurgical success. Establishing a baseline also makes it possible to recognize change following surgery, allowing for appropriate neurological rehabilitation interventions, education/vocational adjustments, or assistance from social services.
3. *Predicting surgical outcome*. Establishing a presurgical neuropsychological baseline allows us to estimate the risk of potential decline in neurocognitive, functional, emotional, or psychosocial status following surgery. Baseline neuropsychological status is one of several predictors of neurocognitive outcome and the likelihood of achieving seizure freedom. Some have attempted to create formulas for predicting outcome that are based in part on neurocognitive performance.
4. *Providing outcome markers that can be useful in the context of research and program development/evaluation*. The overall goal of epilepsy surgery is to alleviate seizure occurrence while minimizing any secondary neurocognitive, emotional/psychosocial, or physical sequelae of this procedure. Neuropsychological assessment plays a pivotal role in quantifying baseline performance, predicting and evaluating change, and elucidating underlying brain-behavior relationships.

Review of Research Outlining Commonly Observed Pre- and Postsurgical Deficits in Epilepsy Surgical Patients

It is essential that the clinical neuropsychologist has a working knowledge of the commonly observed presurgical deficits in epilepsy patients in order to conduct an optimal evaluation. In this section, commonly observed presurgical deficits are described for each of the major epilepsy surgical populations, including temporal lobe epilepsy, frontal lobe epilepsy, and the posterior cortical epilepsies. Knowledge of the most common postsurgical deficits is also essential in order to select tests that will be useful for monitoring change over time. A summary of findings for each syndrome appears in a table at the end of each section.

Findings in Temporal Lobe Epilepsy (TLE)

Approximately 50 % of patients with epilepsy are believed to experience partial seizures (Williamson, 1987). Among patients diagnosed with complex partial seizures, 70–90 % of patients have seizures arising from the temporal lobe (TL). Patients with mesial temporal sclerosis (MTS), which is neuronal loss and gliotic scarring of the hippocampal formation/mesial TL structures, are typically medication refractory. Individuals with TLE are often ideal candidates for surgical treatment to achieve seizure control (Wiebe, Blume, Girvin, & Eliasziw, 2001).

For many years, the prototypical pattern of deficit in presurgical TLE patients has been described as a material-specific pattern of memory dysfunction (Milner, 1958). More specifically, auditory/verbal memory deficits are often observed in patients with dominant TL seizure onset, while visual memory deficits have been more associated with nondominant TL seizure onset (Blakemore & Falconer, 1967; Jones-

Gotman, 1986; Loring, Lee, Martin, & Meador, 1988; McDonald, Bauer, Grande, Gilmore, & Roper, 2001; Milner, 1968a; Pillon et al., 1999). Neuroimaging studies have bolstered this finding, demonstrating that auditory/verbal and nonverbal stimuli can preferentially activate the left or right MTL, respectively (Golby et al., 2001; Powell et al., 2005). In contrast, other behavioral studies have not found this material-specific pattern (Barr et al., 1997; Pigott & Milner, 1993), and some neuroimaging studies have suggested an interaction between the mesial TLs modulated by specific task demands (Kennepohl, Sziklas, Garver, Wagner, & Jones-Gotman, 2007). Visual memory deficits associated with nondominant hemisphere dysfunction have been particularly difficult to establish. Overall, a material-specific pattern of memory dysfunction can be observed in presurgical TLE patients, which can be useful for confirming seizure focus in the individual patient. However, a variety of confounding factors can obscure this pattern and can lead to divergent findings at both the individual and group level. Emerging research also suggests the material-specific pattern of memory dysfunction model may be affected by other task parameters and disease-related variables. For example, material-specific findings may be easier to detect when examining both learning and recall patterns rather than only examining one-trial learning (Jones-Gotman, Zatorre, Olivier, et al., 1997). Further, material-specific findings may be altered by side of seizure onset (Vannest, Szaflarski, Privitera, Schefft, & Holland, 2008; Weber, Fliessbach, Lange, Kugler, & Elger, 2007), and both TLs may eventually be impacted by a chronic duration of unilateral TLE (Cheung, Chan, Chan, Lam, & Lam, 2006).

Jones-Gotman and colleagues at the Montreal Neurological Institute have suggested that dominant and nondominant presurgical TLE patients may differ in terms of their ability to learn and retain information (Jones-Gotman et al., 1997; Majdan, Sziklas, & Jones-Gotman, 1996). Their data indicated that left TLE patients had minimal difficulty with initial learning for words but demonstrated significant impairment on recall following a delay, while right TLE patients demonstrated impaired learning of abstract designs but recalled what they were able to learn. This pattern represents a possible way that a task paradigm might interact with material-specific findings.

Hermann and colleagues provide evidence that both TLs may eventually be affected in a number of patients by seizures of unilateral TL onset. In one study, they used a cluster analysis to demonstrate that common presurgical neuropsychological profiles may exist for patients with TLE (Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007). Approximately half of their sample did not differ from healthy controls with regard to IQ, perception, primary attention, or immediate memory yet showed mild deficits (no more than 1 SD below the mean of the control sample) on tasks tapping delayed memory, confrontational naming ability, executive control processes (e.g., generative fluency), and cognitive/psychomotor processing speed. These deficits sound reminiscent of the prototypical findings reported over the years, with the exception that these patients showed disruption of both verbal and visual memory functioning. A second group, which comprised another 24 % of the TLE sample, was described as primarily experiencing memory impairment, with immediate and delayed memory scores that were more than 2 SDs below the mean of the control sample. They also displayed mild deficits in all remaining cognitive domains. Finally, the third cluster, including another 29 % of participants, was described as a memory-, executive-, and speed-impaired group and performed more than 2 SDs below controls on all administered measures. The third cluster exhibited the greatest impairment, took the most AEDs, and had the longest duration of epilepsy and greatest MRI volumetric abnormalities. This group also exhibited the worst cognitive course of the three samples. Limitations in this study included a small sample size and an exclusive focus on patients with childhood or adolescent onset of epilepsy. Work of this nature is promising and needs to be replicated across

epilepsy centers and with other tests, in order to rule out the impact of latent variables as described below and to determine how such patterns may differ from patients with adult seizure onset.

There is also growing evidence that different types of learning tasks are mediated by different subregions of the TL. In general, associational learning (e.g., word pairs) has been thought to be related to the hippocampus, but it appears that other aspects of the mesial TL region may actually prove to be more critical (e.g., perirhinal or entorhinal cortices) (Weintrob, Saling, Berkovic, & Reutens, 2007; Weniger, Boucsein, & Irle, 2004). In either case, associational learning tends to be one of the more sensitive tasks to mesial TL dysfunction (Saling, 2009; Squire, 1993). Recall of easier, semantically related word pairs is often mildly impaired in patients with dominant TL dysfunction, while recall of more difficult, unrelated word pairs is often severely compromised. Contextual learning, such as reflected by the commonly used paragraph and story recall tasks, has proven less sensitive to mesial temporal lobe pathology (Rausch & Babb, 1993; Saling et al., 1993). These tasks, along with other measures that lend themselves to being organized semantically (e.g., category-related word list learning), may be more dependent on lateral TL structures. For example, Helmstaedter and colleagues (Helmstaedter, Elger, Hufnagel, Zentner, & Schramm, 1996; Helmstaedter, Grunwald, Lehnertz, Gleissner, & Elger, 1997) demonstrate that selective amygdalohippocampectomies contribute to declines in associational learning (particularly for unrelated information), while standard TL resections (which includes lateral TL as well) also affect list learning and semantically related word pairs. They suggest that lateral TL cortex is related to data acquisition and working memory, while the medial TL is involved in consolidation processes. Saling and colleagues have suggested that the medial TL structures (particularly perirhinal cortex) play a critical role in establishing a relationship between items that are yet to be linked in either personal episodic or semantic memory or which may conflict with preexisting knowledge (Saling, 2009).

TLE patients, particularly those with dominant seizure onset, are also more likely to experience deficits in naming ability (e.g., confrontational naming, naming to description) than healthy controls or patients with extratemporal seizure onset (Mayeux, Brandt, Rosen, & Benson, 1980). Several studies have found that left TLE groups perform worse than right TLE groups on visual confrontational naming tasks (Hermann & Wyler, 1988; Hermann, Wyler, & Somes, 1991; Langfit & Rausch, 1996), although the right TLE groups often perform worse than healthy controls (Langfit & Rausch, 1996). A few studies have found both left and right TLE patients to be equally impaired preoperatively (Hermann, Wyler, Steenman, & Richey, 1988). Patients may be impaired on these tasks for reasons other than seizure focus. For example, those with lower IQ show restricted naming scores which are more likely due to their general level of impairment and subsequent limitations on learning. One recent study provided a regression equation that takes into account such moderator variables in an effort to use a naming task (i.e., Boston Naming Test) to aid in preoperative seizure localization (Busch, Frazier, Haggerty, & Kubu, 2005). This study provides promising results but requires further confirmation and possible refinement. Hamberger and colleagues have introduced a naming-to-description task which appears promising for predicting preoperative lateralization as well (i.e., Columbia Auditory Naming Test) (Hamberger & Seidel, 2003; Hamberger & Tamny, 1999). Finally, patients undergoing dominant TL resection often show significant declines on naming tasks (Davies et al., 1998; Hermann, Davies, Foley, & Bell, 1999), while those undergoing nondominant TL resection do not (Saykin, Stafiniak, Robinson, et al., 1995). This pattern again highlights the seemingly critical involvement of the dominant TL in naming ability.

Evidence exists that the naming deficits of TLE patients may be more extensive than previously recognized. A few studies demonstrate that left (dominant) TLE patients are impaired at naming famous faces (Drane, Ojemann, Aylward, et al., 2008; Glosser, Salvucci, & Chiaravalloti,

2003; Seidenberg, Griffith, Sabsevitz, et al., 2002), and at least two of these studies suggest that these deficits may be worse following ATL resection. Drane et al. (Drane et al., 2008; Drane, Ojemann, Tranel, Ojemann, & Miller, 2004) recently extended these findings to include other visually complex item categories (e.g., famous landmarks, animals) even when performance is completely normal on standard naming measures (e.g., BNT). They have argued that commonly used naming measures lack sensitivity to the specific item categories that appear the most affected by anterior TLE surgery, as such measures employ a restricted range of object type (i.e., mostly man-made objects). Once again, these findings are bolstered by functional imaging paradigms highlighting a critical role for the anterior TLs in naming certain object categories (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Griffith, Richardson, Pyzalski, et al., 2006).

It is also relatively common for presurgical TLE patients to exhibit deficits on verbal fluency tests (i.e., generating items from categories, letter fluency) (Troster et al., 1995). However, deficits in semantic fluency are often present preoperatively in patients with either dominant or nondominant TL seizure onset (Bartha, Benke, Bauer, & Trinka, 2005; Joanette & Goulet, 1986; Martin, Loring, Meador, & Lee, 1990) and can be observed in patients with either dominant or nondominant frontal lobe (FL) seizure onset as well (Drane et al. 2006). As these findings could be affected by the use of AEDs, many of which affect generative fluency and speech production rates (Fritz et al., 2005), it should be noted that other types of lesions in these regions have also been shown to impact semantic fluency in patients without epilepsy (Joanette & Goulet, 1986; Stuss et al., 1998). The complex nature of semantic fluency tasks likely requires the involvement of several neural systems for successful completion. Therefore, the presence of baseline semantic fluency deficits may not be of lateralizing or localizing value when viewed in isolation but may be helpful in this regard if the component parts of this task are examined. For example, one recent study suggests that preoperative patients with FL onset can often be distinguished from those with TL onset using a semantic fluency paradigm that contrasts cued and uncued performance (Drane et al., 2006). This builds upon the idea that semantic fluency requires both an executive component mediated by FL regions (i.e., organization/retrieval problems making it difficult to search one's own semantic memory stores and/or deficits involving initiation of action or self-monitoring) (Sylvester & Shimamura, 2002) and a semantic memory component that is thought to be mediated by the TLs (Martin & Fedio, 1983).

While studies examining postoperative semantic fluency appear to be limited in nature, there is evidence that performance in this domain (e.g., generating types of animals) declines following dominant TL resection (Loring, Meador, & Lee, 1994) and perhaps following nondominant TL resection as well (Martin et al., 1990), although the latter study had only a 1-week postoperative follow-up period. One additional study supports the idea that both left and right TL resections may both affect semantic fluency performance but found that the relative impact of surgery may vary greatly between hemispheres depending upon the category of object (Jokeit, Heger, Ebner, & Markowitsch, 1998).

Performance on letter fluency tasks can be impaired preoperatively due to both FL and TL impairment (Helmstaedter, Kemper, & Elger, 1996; Martin, Sawrie, Edwards, et al., 2000), although performance on these measures typically does not decline following TL surgery. Deficits observed on this task in TL patients may occur due to the disruption of widespread neural networks secondary to epileptiform activity, and some evidence exists that improvement on these measures can be seen if the TL patient becomes completely seizure-free following surgery (Martin et al., 2000). Therefore, as letter fluency performance appears not to decline following TL surgery, this provides further evidence that the anterior TL does not play a major role in performance of this task.

Despite the deficits mentioned in naming ability and generative fluency, presurgical TLE patients do not demonstrate a classic aphasia (unless it is due to a separate neurological injury

or disease, such as a prior stroke). Most TLE patients will not exhibit problems with comprehension, speech fluency, or repetition of words or phrases, nor will they present with positive signs of aphasia in spontaneous speech (e.g., paraphasic errors). Similarly, standard anterior TL resection does not typically lead to declines in these areas (Saykin et al., 1995).

With the exception of interest in visual memory functioning, less work has been focused on the nondominant TL in the context of epilepsy. Most have assumed that the nondominant TL is less critical than the dominant one, and there is likely some truth to this idea. Declines in auditory/verbal memory and naming ability, findings predominantly associated with the dominant TL epilepsy and resective surgery, can be particularly devastating, while many patients seem to be less hampered by visual memory declines. Nevertheless, there is evidence that we may not fully appreciate the functions of the nondominant TL, and the field's tendency to think of visual memory as a unitary construct may be misleading (e.g., creating a visual memory index with several disparate tasks that may eventually prove to rely on different neural substrates). Evidence outside of epilepsy indicates that visual memory may involve several dissociable components (Bird & Burgess, 2008). For example, human "place" cells in the hippocampus are believed to respond to one's position, functioning to activate (recall) broader spatial maps in order to allow for successful localization of position in relation to the environment and objects within it (Byrne, Becker, & Burgess, 2007). In addition, functional neuroimaging studies demonstrate that route learning/way finding, which is rarely assessed clinically, appears to activate both mesial TLs (Treyer, Buck, & Schnider, 2005), and several experimental studies (some examining TLE patients) suggest that performance on these tasks can be compromised by right anterior TL damage (Spiers, Burgess, Maguire, et al., 2001). Finally, object-location tasks also tend to be impaired following right mesial TL dysfunction (Crane & Milner, 2005; Pigott & Milner, 1993), although performance here can be affected by varying task parameters. For example, while right TL patients tend to perform worse on tasks that are three-dimensional, a few studies suggest that left TL patients are more impaired on object-location tasks that are two-dimensional (Kessels, Hendriks, Schouten, Van Asselen, & Postma, 2004).

Recent studies also indicate that nondominant TLE patients often exhibit object recognition deficits. For example, at least four studies demonstrate that postoperative right ATL patients exhibit recognition deficits for famous faces when compared to controls (Drane et al., 2008; Glosser et al., 2003; Seidenberg et al., 2002). There is also evidence that recognition deficits for animals and famous landmarks may occur in patients following nondominant resection as well and that even a sense of "familiarity" may be impaired in these individuals (Drane et al., 2004, 2008). Patients with these deficits have greater difficulty recognizing familiar individuals, which may compromise social functioning.

One perhaps unexpected neurocognitive finding in presurgical TLE patients is evidence that such patients often exhibit deficits in executive functioning tasks thought to be mediated by FL regions (see above paragraph on letter fluency deficits in TLE). This pattern of dysfunction has been attributed to widespread disruption of neural networks by recurrent seizure activity. The "nociferous cortex hypothesis" of Wilder Penfield is sometimes invoked to explain this phenomenon (Penfield & Jasper, 1954). Evidence includes impaired performances observed on neurocognitive measures such as complex problem-solving tasks (e.g., Wisconsin Card Sorting Test) and generative fluency measures (Hermann & Seidenberg, 1995; Kim, Lee, Yoo, Kang, & Lee, 2007; Martin et al., 2000). Similar findings have also recently been reported in children (Rzezak, Fuentes, Guimaraes, et al., 2007). Preliminary work has shown that patients with successful seizure control following TL resection may show significant improvement on these tasks (Hermann, Wyler, & Richey, 1988; Martin et al., 2000), suggesting that these distributed networks are functioning better in the absence of electrophysiological disruption. Similarly, functional neuroimaging studies have demonstrated that TLE patients often show hypometabolism of the FLs that cor-

relates with aspects of executive function performance (Jokeit et al., 1997; Takaya, Hanakawa, Hashikawa, et al., 2006). One additional fMRI study provides evidence that patterns of FL cerebral activation can show "normalization" following successful TL resection (Maccotta, Buckner, Gilliam, & Ojemann, 2007).

Depression is the most common psychiatric comorbidity in epilepsy (Fuller-Thomson & Brennenstuhl, 2009), and preoperative depression has been associated with worse seizure outcome following TL resective surgery (Anhoury, Brown, Krishnamoorthy, & Trimble, 2000). Other psychiatric comorbidities of TLE, most of which have been less well studied than depression, include anxiety disorders, substance abuse, psychosis, and personality disorders (Table 4.1).

Findings in Frontal Lobe Epilepsy (FLE)

Research examining the neurocognitive functioning of presurgical frontal lobe epilepsy (FLE) patients has been less commonly completed. In part, the lack of research in this area is likely due to greater difficulty obtaining adequate sample sizes for such studies, as FLE patients are believed to reflect only 10–20 % of all surgical referrals (Jokeit & Schacher, 2004). It is usually necessary to collaborate across epilepsy centers or to spend many years obtaining large enough sample sizes to achieve adequate statistical power to answer basic questions. Research is also hampered in this area by limitations in our understanding of FL functions and the adequate development of tests and methods to assess them, as well as the same latent variables that plague epilepsy research in general. In addition, there is a great deal of heterogeneity in terms of pathology and seizure localization within FL regions, which contributes to differing neurocognitive profiles. Complex partial seizures in FLE commonly arise from the frontal poles and from the orbital, medial, and dorsolateral FL regions (Williamson, Spencer, Spencer, Novelly, & Mattson, 1985).

While the conclusions drawn in this section should be viewed as more tentative in nature due to the limited number of completed studies, some clear trends appear to be emerging. For example, there is growing evidence that presurgical patients with FLE often exhibit problems with response inhibition (McDonald et al., 2005; Upton & Thompson, 1996), although this problem has not been universally observed (Helmstaedter, Kemper, et al., 1996). One study that compared a sizeable number of FLE and TLE patients found that FLE patients performed significantly worse than the TLE group on a measure of response inhibition (Stroop Color-Word Interference Test) (Upton & Thompson, 1996). In contrast, Helmstaedter, Kemper, et al. (1996) found that their FLE sample performed worse than TLE patients on all Stroop conditions, which suggests their primary limitation may have involved reading or processing speed. McDonald et al. (2005) added a matched control sample to the previous paradigm of comparing FLE and TLE patients, demonstrating that the FLE group was impaired on the Stroop task from the Delis-Kaplan Executive Functioning System (DKEFS) when compared to the control subjects while the TLE group was not. The left FLE group was more impaired than the right FLE group or either TLE group on this portion of the task. There is at least one study suggesting that response inhibition performance may decline with unilateral FLE resections (Helmstaedter, Kemper, et al., 1996).

Performance on motor tasks is often decreased in FLE patients as compared to controls or other samples of epilepsy patients, and there is some evidence that decline occurs on these tasks with some FLE resections. For example, Helmstaedter, Kemper, et al. (1996) demonstrated that a small sample of FLE patients ($n=23$) performed worse than a set of TLE patients on measures of psychomotor speed and motor coordination. Upton and Thompson (1996) compared the performance of presurgical FLE patients to that of TLE patients on a variety of motor tasks, finding that the FLE group performed worse than the TLE group on tasks of motor sequencing and bimanual hand movements (left FLE worse than right FLE). Studies in children with FLE seizure onset have

Table 4.1 Core pre- and postsurgical deficits in temporal lobe epilepsy patients

Type of presurgical deficit	Laterality findings	Change with surgery
Language functions		
Naming (auditory/visual)	Both left and right TLE—frequently exhibit deficits (left > right)	Left TLE—decline Right TLE—no decline
Semantic fluency	Both left and right TLE—frequently exhibit deficits (may vary by type of category)	Left TLE—decline Right TLE—data is sparse/appears decline possible
Letter fluency	Both left and right TLE—often exhibit deficits	Left and right TLE—no decline/may improve with seizure freedom
Action (verb) fluency	Possibly same pattern as letter fluency/data is sparse	Possibly same/data is sparse
Other language functions	Left TLE—usually normal unless patient has dysphasia secondary to an additional neurological cause (e.g., stroke) Right TLE—intact core language functions	Left TLE—no decline unless encroaching on classic language areas Right TLE—no decline
Memory and learning		
Material-specific memory deficits may be observed	Left TLE—often exhibits auditory/verbal memory deficits Right TLE—sometimes (but less consistently) exhibits visual memory deficits	Left TLE—auditory/verbal memory often declines Right TLE—visual memory often declines (depends more on specific tasks than previously recognized)
Task-specific dissociations in performance	Left TLE—impairment on difficult associational and rote learning paradigms more associated with mesial TL dysfunction. Impairment on semantically related tasks more associated with lateral TL dysfunction (e.g., story recall, easy word pairs) Right TLE—often exhibits deficits involving object-location recall (particularly when assessed in three dimensions) and route learning	Declines in functioning can occur that are consistent with the specified preoperative patterns More research is needed to pin down specific structure-function relationships
General memory dysfunction is observed in some TLE patients	Both left and right TLE—sometimes exhibit general or global memory dysfunction at baseline	Decline still seems to reflect the task and material-specific patterns that occur with surgery
Learning and retention patterns may differ by side of seizure onset	Left TLE—often exhibits good initial retention of words, but poor retention over time Right TLE—often exhibits problems with initial learning of visual material but retain most of what is encoded/learned over time	No data has been published examining the differential learning patterns postoperatively
Visuo-perceptual/visual-spatial processing and object recognition		
Visuo-perceptual deficits tend to be infrequent	Right TLE—occasionally has visuo-perceptual deficits	Both left TLE and right TLE—may experience a visual-field cut following surgery Left TLE—no decline on perceptual tasks Right TLE—mild decline on some tasks on occasion
Visual-spatial deficits tend to be infrequent	Right TLE patients—may rarely have visual-spatial deficits (e.g., problems judging spatial features)	Left TLE—no decline Right TLE—very rare decline on some tasks
Category-related object recognition deficits	Left TLE—occasionally sees mild recognition deficits for man-made objects with posterior TL involvement Right TLE—frequently exhibit recognition deficits for famous persons/faces, landmarks, and animals with anterior TL dysfunction	Left TLE—possible decline on recognition of man-made objects with encroachment on left posterior regions Right TLE—frequent decline on recognition of famous persons/faces, landmarks, and animals

(continued)

Table 4.1 (continued)

Type of presurgical deficit	Laterality findings	Change with surgery
General intellectual functioning		
IQ scores	Typically normal in TLE Left TLE will sometimes show greater problems with verbal tasks, and right TLE will sometimes show greater problems with perceptual tasks	May see "material-specific" declines in line with presurgical status
		May see improvements in processing and attention regardless of hemisphere of seizure focus if patient experiences a reduced seizure burden and a reduction in AEDs
Executive control processes		
Complex problem solving, response inhibition, generative fluency, complex attention	Both left and right TLE—often exhibit deficits in one of more of these areas that is assumed to result from the disruption of temporofrontal networks secondary to epileptiform activity	Both left and right TLE—frequently show improved performance in these domains if experiencing seizure freedom

For the purposes of this table, we are assuming normal language lateralization to the left cerebral hemisphere (i.e., left = dominant)
TLE temporal lobe epilepsy, *TL* temporal lobe, *AEDs* antiepileptic drugs

reported greater problems with motor coordination (Hernandez, Sauerwein, Jambaque, et al., 2002) as compared to normal controls or children with other seizure onset.

Performance on complex problem-solving tasks also appears to be impaired in some FLE patients, and this finding has been observed both pre- and postoperatively (Upton & Thompson, 1996). Milner published a classic case study involving patient "K.M.," who demonstrated severe deficits on the WCST following bilateral resection of the anterior FLs for the control of seizures despite maintaining normal IQ. As noted in the section on TLE, however, complex problem-solving deficits can also be seen in patients with TLE, likely due to the spread of seizure activity to FL regions.

Verbal fluency, as noted in the TLE section, is often impaired in presurgical FLE regardless of laterality of seizure onset and includes both semantic and letter fluency. There is also some data indicating that action (verb) fluency is also decreased in FLE patients. Preliminary evidence exists that performance on these tasks can sometimes yield localizing data when explored in ways that examine component skills required for successful completion (Drane et al., 2006).

Design fluency has also been shown to be decreased in FLE patients relative to other epilepsy patients or healthy controls, with some studies suggesting lateralization to the nondominant hemisphere (Jones-Gotman & Milner, 1977) and others not (McDonald, Delis, Norman, Tecoma, & Iragui, 2005). One study reported worse performance for patients with left FLE (McDonald, Delis, Norman, Tecoma, et al., 2005) as compared to right FLE while another demonstrated that FLE patients performed worse than TLE patients regardless of seizure onset laterality (Suchy, Sands, & Chelune, 2003). A fourth study found that patients with FLE produced a similar number of designs as did patients with TLE but made more design errors (Helmstaedter, Kemper, et al., 1996). Discrepancies across studies may in part reflect differences in the design fluency tasks themselves, as these measures differ in regard to the structure they provide, the presence or absence of concomitant task demands (e.g., shifting attention), and the aspect of performance emphasized (e.g., design generation, self-monitoring, shifting).

Some evidence suggests that FLE patients may perform worse than TLE patients on measures of attention, working memory, and psychomotor speed. For example, Helmstaedter, Kemper, et al. (1996) demonstrated that a small sample of FLE patients performed worse than a set of TLE patients on measures of attention and psychomotor speed. In the FLE group, differences were not related to side of seizure focus or

presence of a structural lesion. Upton and Thompson (1996) found that a small group of FLE patients made more errors on a complex visual scanning and tracking measure than did a comparable TLE group.

There are many additional studies with FLE patients demonstrating deficits on a variety of tasks presumed to be sensitive to FL dysfunction, but most of these are isolated findings that have yet to be replicated. Areas of reported dysfunction have included deficient cost estimation (Upton & Thompson, 1996), an elevated rate of questions required to identify objects on the Twenty Questions Test from the DKEFS (Upton & Thompson, 1999), problems with determining temporal order (McAndrews & Milner, 1991), and aspects of social cognition (e.g., humor appreciation, recognition of facial emotion, perception of eye gaze expression) (Farrant, Morris, Russell, et al., 2005). Kemper, Helmstaedter, & Elger (1993) reported that FLE patients performed much worse than TLE patients on a planning task, suggesting that this difference correctly predicted the seizure focus of 80 % of all cases.

Memory performance has not been studied extensively in patients with FL seizure onset, and available results are somewhat mixed. Most studies have either compared performance between FLE and TLE patients with one another or with healthy controls. While some of these studies have failed to demonstrate differences between FLE and controls on memory measures (Delaney, Rosen, Mattson, & Novelly, 1980), others have reported worse functioning for FLE, at least on some types of tasks. FLE patients tend to perform worse on more complex learning paradigms (e.g., list-learning tasks), with their limitations attributed to problems with encoding and/or retrieval.

There have also been some interesting studies suggesting that certain aspects of learning and memory are perhaps more impaired in FLE than in other epilepsy groups. For example, Pigott and Milner (1993) demonstrated that preoperative FLE patients exhibit problems with release from proactive interference (i.e., earlier memories interfere with of learning new information). Milner attributed this deficit to problems with encoding and retrieval mechanisms. McDonald and colleagues (2001) more recently demonstrated this pattern in postoperative FLE patients and provided further evidence that encoding/retrieval deficits may underlie this pattern. In their study, postsurgical TLE patients did not display release from proactive interference, and there was no difference between the TLE and FLE groups in terms of consolidation of stimuli (i.e., they showed similar rates of retention over trials). Milner has also shown that FLE patients have difficulty structuring and segregating events in memory (Milner, 1968b), and her FLE patient samples have also exhibited problems with organization of materials to be learned and have had trouble recalling the temporal order of information (Milner, Petrides, & Smith, 1985). These findings applied to a wide range of stimuli and may be material specific in nature (Milner, Corsi, & Leonard, 1991).

There have been few systematic studies of psychiatric functioning in patients with FLE, although a number of case reports describe wide-ranging interictal behavioral abnormalities. For example, Boone et al. (1988) described a young adolescent girl with FL seizures who experienced reversible behavioral changes including sexual disinhibition, loss of concern for personal hygiene, physical and verbal aggression, and pressured and tangential speech accompanying interictal anterior FL discharges. Patients with anterior cingulate seizure foci have also been reported to develop interictal psychosis, aggression, sociopathic behavior, sexual deviancy, irritability, obsessive-compulsive disorder, and poor impulse control (Devinsky, Morrell, & Vogt, 1995). Additionally, Helmstaedter (2001) has also reported that FLE patients have an elevated rate of behavioral problems compared to other epilepsy patients and controls but noted that these tended to be mild as compared to the findings obtained in other neurological patients with structural FL lesions. Based on the limited studies available, psychiatric conditions such as depression and anxiety appear to be more common in TLE (Gilliam et al., 2004).

In summary, it appears that patients with FLE present with a variety of deficits involving motor functioning, executive control processes, attention,

speed of processing, and aspects of memory performance, as well as some possible behavioral abnormalities. These functions have been minimally explored in FLE patients with few studies using a presurgical/postsurgical decline and most seeming to be underpowered. There have been virtually no attempts to explore functions by FL subregion in any epilepsy study, yet this methodology has proven useful in other areas. Similarly, numerous cognitive functions attributed to the FLs have yet to be explored in FLE patients. Some areas of dysfunction observed in patients with FLE have also been observed in patients with TLE, presumably due to seizure spread across large interconnected neural networks. There also appear to be some distinct patterns between patients with FLE and TLE that may yet be useful for confirming the region of seizure onset (Table 4.2).

Findings in Posterior Cortical Epilepsy (PCE)

Seizures arising from the parietal lobe, the occipital lobe, the occipital border of the temporal lobe, or a combination of these regions are sometimes referred to as posterior cortical epilepsies, as it is difficult to find clear anatomic or pathophysiological differences in these regions (Dalmagro, Bianchin, Velasco, et al., 2005). The occurrence of posterior cortical epilepsies tends to be much rarer, and such conditions have been less well studied (Binder, Lehe, Kral, et al., 2008). Therefore, for the purposes of this chapter, we have decided to consider all of the work related to neurocognitive profiles related to parietal or occipital lobe seizure onset together. Dalmagro and colleagues (2005) reported that just over 5 % of their total referrals for long-term video-EEG monitoring experienced PCE, and of these, approximately half were actually surgical candidates. Overall, this group makes up well under 10 % of the total surgical referrals seen by a standard epilepsy surgical program, making this type of seizure onset even less common than FLE.

Cognitive studies of PCE patients are lacking in general, and there have been no systematic prospective studies of neurocognitive functioning in these patients that include both pre- and postoperative analysis. Studies appearing in the literature tend to involve retrospective analysis of clinical data. For example, one recent study examined retrospective pre- and postsurgical clinical data collected on 28 PCE patients between 1991 and 2000 (Luerding, Boesebeck, & Ebner, 2004). These investigators indicated that mild declines occurred in performance IQ from the WAIS-R regardless of resected hemisphere and also reported declines in some measures of visual-spatial processing. Postsurgical gains were made on some tasks thought to be mediated by the FLs, and there was no decline in WAIS-R verbal IQ. Of note, however, not only was the sample size very small, but this resulted in a pool of subjects with potentially very different lesions (e.g., left temporo-occipital verssu right inferior parietal). Also, only a limited number of subtests from the WAIS-R were available for examination. Overall, while this type of study of neurocognitive function of patients with PCE is sorely needed, such studies cannot definitively answer these questions due to a lack of sufficient power and inadequate coverage of potential domains to be examined. Other retrospective studies of PCE, particularly those involving parietal lobe dysfunction, have reported changes in visual functioning, visual-spatial processing, and visuo-perceptual abilities (Siegel & Williamson, 2000). Sensory changes are sometimes observed when surgical resection extends into the postcentral gyrus, and one study has reported disturbances of body image in a few patients with right inferior parietal corticectomies (Salanova, Andermann, Rasmussen, Olivier, & Quesney, 1995). One very small, retrospective study examining the neurocognitive status of children with occipital lobe (OL) seizure onset suggested that such patients experience an elevated rate of scholastic difficulty, psychiatric disorders (i.e., primarily depression), and cognitive dysfunction involving problems with face processing and making spatial judgments (Chilosi, Brovedani, Moscatelli, Bonanni, & Guerrini, 2006).

A recent study completed in Germany with a small series of OL epilepsy surgical patients

Table 4.2 Core pre- and postsurgical deficits in frontal lobe epilepsy patients

Type of presurgical deficit	Laterality findings	Change with surgery
General intellectual functioning	Typically normal in FLE	Typically no significant change
Language	Typically normal apart from verbal fluency deficits (unless neurologic/functional disruption of classic speech regions, e.g., Broca's area)	Typically no significant change with the exception of verbal fluency performance (see below)
Motor functioning	Left and right FLE—often exhibit motor deficits contralateral to side of seizure focus (e.g., gross motor speed, fine motor speed, and dexterity)	Both left and right FLE—may show a decline in the motor performance of their contralateral limbs (particularly when surgery encroaches on precentral gyrus region)
Response inhibition	Both left and right FLE—often exhibit deficits	Both left and right FLE—may decline depending upon location of FL resection
Complex problem solving	Both left and right FLE—often exhibit deficits	Both left and right FLE—may decline depending upon location of FL resection
Verbal fluency	Both left and right FLE—often exhibit baseline deficits on all types of verbal fluency tasks	Both left and right FLE—may decline on all verbal fluency tasks, although semantic fluency may improve in some cases
Design fluency	Both left and right FLE—often exhibit deficits	Both left and right FLE—may decline
Memory functioning	Both left and right FLE—often exhibit poor learning/encoding and decreased free recall with good recognition memory Both left and right FLE—often exhibit problems with release from proactive interference	Surgery may improve or worsen baseline problems based on location of surgery and postsurgical seizure freedom
Attention	Both left and right FLE—often exhibit deficits in primary and complex attention	Data is lacking. Any change is likely dependent upon seizure status and AED regimen at follow-up assessment
Social cognition	Some patients, regardless of laterality, have shown problems with recognizing humor and faux pas errors, recognition of facial emotion, and perception of eye gaze expression	Data is lacking. Theoretically, it appears that some functions could decline depending upon surgical variables, while seizure freedom and decreased AEDs may contribute to mild gains
Visuo-perceptual, visual-spatial, and constructional praxis	Typically normal on most visuo-perceptual and visual-spatial tasks Often exhibit decreased performance on constructional tasks due to poor organization and planning	Data is lacking. However, no reports of significant declines in these areas exist in the research literature

For the purposes of this table, we are assuming normal language lateralization to the left cerebral hemisphere (i.e., left = dominant)
FLE frontal lobe epilepsy, *AEDs* antiepileptic drugs

prospectively examined visual-field integrity, demonstrating that a significant proportion of these patients experienced visual-field defects postoperatively (i.e., 42 % of OL patients experienced new or increased visual-field defects) (Binder et al., 2008). This study and others have shown that preoperative patients with seizure onset involving the mesial OL are more likely to exhibit baseline visual-field defects (e.g., reports suggest approximately 40–50 %) than those with

Table 4.3 Core pre- and postsurgical deficits in posterior cortical epilepsy patients

Type of presurgical deficit	Laterality findings	Change with surgery
General intellectual functioning	Typically normal in PCE at baseline	Limited research suggests possibly mild declines in PIQ for PCE patients regardless of side of surgery/laterality and mild improvements in VIQ
Language	Depends on seizure focus: Left PLE—may exhibit classic language deficits (e.g., naming, repetition, comprehension) Right PLE and both left and right OLE—unlikely to exhibit language deficits	Typically no significant change with the exception of possible language declines with some left parietal lesions
Visuo-perception, acuity, and visual fields	Both left and right OLE—often exhibit problems with visuo-perception (including face processing/recognition) Left and right OLE—often exhibit baseline visual-field cuts (much more common for medial OL seizure onset) Left and right OLE—might expect baseline deficits in color processing and object localization, as well as positive visual phenomena (yet epilepsy specific research is absent)	Left and right OLE—often exhibit new or increased visual-field cuts Left and right PCE—in general, may exhibit mild or greater visuo-perceptual decrements depending on aspects of surgery (i.e., location and extent)
Visual-spatial processing	Both left and right OLE and right PLE—often exhibit problems with visual-spatial judgments	Both left and right PCE—declines in some aspects of visual-spatial processing (limited research)
Memory	Presumed to be normal	Presumed to remain at baseline apart from possible gains related to improvements in seizure status and reduced AED regimen
Sensory functioning	Both left and right PLE—may exhibit baseline problems with sensory discrimination	Sensory functioning is often worse in patients if surgery encroaches upon postcentral gyrus Disturbance of body image has been reported in patients with inferior parietal resections
Motor	Presumed to be normal	Presumed to be normal

For the purposes of this table, we are assuming normal language lateralization to the left cerebral hemisphere (i.e., left = dominant)
PCE posterior cortical epilepsy, *PLE* parietal lobe epilepsy, *OLE* occipital lobe epilepsy, *AEDs* antiepileptic drugs

lateral OL onset (e.g., ranging from 0 to 18 %) (Binder et al., 2008; Blume, Wiebe, & Tapsell, 2005). While focusing on perceptual rather than cognitive testing per se, this type of pre-/postoperative design is exactly what is needed in this area. At present, we lack definitive profiles for preoperative functioning in the posterior cortical epilepsies and have no prospective postsurgical outcome studies available for this patient group. One would assume, based on available lesion studies in other neurological disorders and functional imaging paradigms, that dysfunction in the OL could cause problems with face recognition, object localization, color processing, or object recognition (Kiper, Zesiger, Maeder, Deonna, & Innocenti, 2002) and that lesions in the parietal region could cause deficits involving visual-spatial processing, object recognition, sensory discrimination, arithmetic skills, and aspects of language functioning (Table 4.3).

Potential Confounds in the Neuropsychological Assessment of the Epilepsy Surgical Patient

In assessing epilepsy surgical patients, a variety of factors can obscure an individual's true neurocognitive profile, including disease- and treatment-related variables, as well as limitations associated with current assessment paradigms and our knowledge of brain-behavior relationships. The clinical neuropsychologist must be aware of these issues in order to take them into consideration when interpreting assessment results. Specific factors with the potential to create "noise" in our assessments include the effect of AEDs on brain functioning, problems with the specific tests being employed, comorbid medical and psychiatric conditions, acute ictal/interictal epileptiform activity, and the acute and long-term impact of seizure activity on brain regions distant from the seizure focus. There is no absolute approach to dealing with these issues, and this leads to a number of decisions regarding when and where to conduct the neuropsychological assessment and the selection of appropriate tests.

Effects of AEDs

Many AEDs can have an appreciable impact upon brain functioning, as they function to dampen the neuronal irritability that constitutes a seizure, yet they also more broadly dampen neuronal excitability in general (Drane & Meador, 2002). This can lead to the emergence of cognitive deficits that are unrelated to the epileptic focus. For example, a TLE patient treated with topiramate may present with limitations in primary attention, verbal fluency, and processing speed that have nothing to do with their underlying seizure focus (Kockelmann, Elger, & Helmstaedter, 2003; Ojemann et al., 2001). Presurgical evaluation in such a patient may fail to confirm the lateralization or localization of the seizure focus and will provide a significant underestimation of the patient's abilities. Knowledge of the effects of AEDs is therefore critical to interpreting neurocognitive results in this patient population, and there may be instances where it is worthwhile to take a patient off of their usual AEDs prior to evaluation.

Problems with Instrument Design

Problems with features of test design and selection can also muddle the interpretation of neurocognitive data. For example, test selection potentially becomes a barrier to discovering accurate brain-behavior relations when we employ measures that require the interaction of multiple cognitive skills controlled by different brain regions without a clear awareness of these relationships. For example, the Family Pictures subtest of the 3rd edition of the Wechsler Memory Scale (Wechsler, 1997) contributes to the Visual Memory Index from this battery, yet there is strong evidence that it loads on a verbal factor (Dulay et al., 2002). This is likely due to the necessity to accurately name the pictured individuals in order to get credit for any aspect of recall on this task. In turn, however, we often see a decline on Family Pictures, as well as the Visual Memory Index to which it contributes, in patients who undergo a dominant (typically left) hemisphere resection (Chapin, Busch, Naugle, & Najm, 2009). If someone were to explore the possibility of material-specific memory deficits in TLE using the Verbal and Visual Memory Indices of the WMS-3, they could easily draw wrong conclusions if they were unaware of this pattern of findings.

Nociferous Cortex Hypothesis

The nociferous cortex or "neural noise" hypothesis suggests that seizure activity can disrupt more expansive neural networks that extend beyond the irritative zone of the seizure (Penfield & Jasper, 1954). As covered earlier, executive control processes thought to be primarily mediated by FL regions (e.g., letter fluency, complex problem solving) can be disrupted in patients

with TL seizure onset (Hermann & Seidenberg, 1995). These apparent deficits frequently resolve with the successful control of the TL seizure activity (Martin et al., 2000), and these alterations in the functioning of the FL cortex can be captured with functional neuroimaging (Jokeit et al., 1997; Maccotta et al., 2007). It is also thought that FL seizures will disrupt limbic and TL regions, although less research is available to confirm such patterns. Overall, the potential for distal effects of epileptiform activity can obviously obscure the central seizure focus.

Effect of Comorbid Conditions

Medical and psychiatric conditions that are often comorbid with epilepsy can also introduce greater noise into a patient's neurocognitive profile. For example, patients with epilepsy experience a higher rate of depression and a slightly elevated rate of psychosis as compared to the general public (Blumer, Montouris, & Hermann, 1995; Manchanda, 2002). Epilepsy patients struggling with mood issues or perhaps even actively psychotic may be less able to actively engage in testing. Similarly, epilepsy sometimes reflects a secondary condition resulting from a more primary medical condition (e.g., brain tumor, stroke, HSV encephalitis) or injury (e.g., traumatic brain injury). The primary disease or injury contributes uniquely to the patient's pattern of dysfunction and can mask any potential lateralizing/localizing neurocognitive findings. For example, patients with focal TL seizure onset resulting from posttraumatic epilepsy may exhibit significant executive function impairment that is related to potentially widespread cerebral dysfunction resulting from the head trauma.

Effect of Ictal and Interictal Discharges

There is growing awareness that acute ictal or interictal epileptiform discharges can alter neurocognitive profiles. While the impact of such epileptiform activity can sometimes accentuate a profile pattern in the case of focal seizure onset, it can also obscure this pattern when there is secondary generalization or non-focal patterns of interictal discharges (Aarts, Binnie, Smit, & Wilkins, 1984; Aldenkamp & Arends, 2004; Binnie, 2003; Kasteleijn-Nolst Trenite & Vermeiren, 2005).

Practice Effects

Neuropsychological assessment in epilepsy requires repeated testing over time, which necessitates consideration of possible practice effects. Some studies have been completed that examine test-retest changes in either epilepsy patients or in healthy controls and that provide *reliable change indices* to allow one to determine if a given change is related to the treatment intervention as opposed to a simple practice effect (Martin, Sawrie, Gilliam, et al., 2002). This can be particularly important when one recognizes that a lack of an expected practice effect may reflect a limitation in a postsurgical patient.

Atypical Language Lateralization

Given that epilepsy is often associated with comorbid neurological disorders/injury, it is not surprising that one observes an elevated rate of atypical language lateralization in this population (i.e., right or bilateral language). Many of these cases appear to represent language reorganization that has occurred in individuals experiencing early-life injuries, although a few studies suggest there is likely a subset of patients with rare but naturally occurring atypical language lateralization (Drane, Ojemann, Ojemann, et al., 2009; Knecht, Jansen, Frank, et al., 2003). The possibility of atypical language lateralization must be borne in mind when analyzing neurocognitive data and making outcome predictions.

In summary, it is recommended that the clinical neuropsychologist makes every effort to be aware of potential latent variables and to control for their presence when possible. In this manner, one may be able to better localize or lateralize a seizure event in a patient that otherwise showed

no focal findings. One may also gain better insight into the patient's genuine performance baseline in the absence of seizure activity. Occasionally, it may also be possible to use these variables to one's advantage such as using ictal or postictal assessment techniques to enhance focal findings.

Decisions About Neuropsychological Assessment in Epilepsy Surgical Patients

Inpatient Versus Outpatient Assessment

There are various pros and cons to either testing presurgical epilepsy patients on the inpatient unit versus in the outpatient clinic, and both practices continued to be employed with regularity by epilepsy surgical programs throughout the world.

Conducting evaluations in the epilepsy monitoring unit (EMU) allows one to be aware of the presence of ictal and interictal epileptiform discharges, as the patient is undergoing continuous video-EEG monitoring. This is probably its largest advantage, as increasing data demonstrates that subclinical and interictal epileptiform activity can have a transient disruptive impact upon neurocognitive functioning (Aldenkamp & Arends, 2004; Kasteleijn-Nolst Trenite & Vermeiren, 2005). It is likely that transient changes in performance sometimes lead to an underestimation of the patient's baseline functioning (see current clinical vignette), which can obscure change over time (e.g., leading one to miss declines in performance subsequent to surgical intervention or other treatment) and contribute to false predictions regarding outcome. For example, if someone appears to have severely impaired verbal memory due to transient epileptiform activity, we might erroneously predict that their risk of decline is small due to their poor baseline. This sort of error potentially gives the patient, the neurosurgeon, and the rest of the treatment team misinformation for making their decisions regarding the risk associated with surgery. On the other hand, having concurrent electrophysiological data allows the neuropsychologist to explore changes in performance in relation to ictal and interictal discharges. Inpatient testing also gives the examiner a greater span of time to conduct tests.

The downside of inpatient assessment involves potentially dealing with acute changes in medications, as the patient's standard AED regimen may be altered or discontinued in order to provoke seizures. Similarly, some EMUs will also employ sleep deprivation as a means to induce seizures more rapidly. Depending upon the practice of the inpatient unit, these issues can often be more effectively managed by agreeing upon a standard start time for neurocognitive testing. In our practice, we initiate the baseline testing at the first full day of monitoring, prior to the patient being sleep deprived and often prior to any changes in AED regimen. This also provides us with electrophysiological data from the day of admit to insure that acute seizure activity has not immediately preceded our assessment.

Ideally, the epilepsy neuropsychology service will have dedicated rooms on the inpatient monitoring unit that preserve the uninterrupted, private environment while allowing the patient to continue with their video-EEG monitoring. If such rooms are not available, bedside testing can also work adequately, if proper steps are taken to educate staff about not interrupting. While dealing with additional staff creates additional work for the examiner, having them available to assist with the patient if a seizure occurs is quite advantageous, particularly with patients that experience seizures on a frequent basis.

The advantages and disadvantages of conducting presurgical evaluations in the outpatient setting are essentially the opposite of those just cited for inpatient assessment. The major disadvantage is that one has no objective knowledge of the immediate electrophysiological functioning of the patient that they are assessing. Epileptiform activity may be occurring during the examination, with direct impact upon the assessment, and neither the examiner nor the patient will be aware of its occurrence. Similarly, the patient may have experienced a seizure within the last 24 h yet lack any recollection of this occurrence. In contrast, the patient is less likely to be sleep deprived, and they are most likely continuing with their standard treatment regimen.

Our group, as well as others, has suggested that the eventual standard for outpatient neuropsychological assessment of epilepsy should include obtaining simultaneous EEG recordings (Patrikelis, Angelakis, & Gatzonis, 2009).

Financial considerations may also play a role in deciding upon assessment venue, as some payors may incentivize one type of assessment over another. Nevertheless, we have often been successful in getting policies adjusted by providing data to explain our preferences in assessment location depending upon the factors involved. This is an area where standardized policies could conceivably be established by interested practice organizations.

Reliable Change Indices Versus Alternate Test Forms

The serial assessment of epilepsy patients undergoing surgery necessitates correction for practice effects. Since the early 1990s, some neuropsychologists have started using advanced methods of measuring change, including the Reliable Change Indices (RCIs) and standard regression-based (SRB) change score norms (Hermann et al., 1996; Sawrie, Chelune, Naugles, & Luders, 1996). Both are methods that attempt to statistically control for test-retest effects and measurement error, allowing the clinician to better evaluate whether change in performance is actually related to a specific treatment intervention. RCI and SRB scores based on the performance of unoperated patients with epilepsy and on healthy control subjects are available for a number of neurocognitive measures (Dikmen, Heaton, Grant, & Temkin, 1999; Heaton et al., 2001; Temkin, Heaton, Grant, & Dikmen, 1999). Examining the performance of the same type of patient allows for the greatest control of other disease-related variables.

Another approach is to use alternative forms of commonly used tests when available. The major problem involved in using alternative test forms relates to the difficulty we have insuring that each alternative version of a test is actually equivalent to the original.

Choice of Neuropsychological Tests

In general, when putting together a battery to assess epilepsy surgical patients, one wants to cover all of the standard neurocognitive domains. However, the relative emphasis to place on a given domain and the choice of specific tests should be guided by the overarching purposes of the neuropsychological evaluation in the epilepsy surgical setting. More specifically, tests should be chosen that are potentially useful for:

(a) *Confirming the epileptic focus*: Knowledge of deficits commonly observed in various epilepsy syndromes preoperatively will aid in the selection of tests that are useful for lateralizing/localizing purposes.
(b) *Demonstrating postoperative change in function*: One should include measures that examine functions known to commonly decline with a particular type of surgery (e.g., verbal memory decline following dominant TL resection), allowing one to assess outcome. Of note, postsurgical change can also be positive, as in the case of someone showing improvement in processing speed and attention secondary to becoming seizure-free and discontinuing their AED regimen.
(c) *Insuring valid interpretation*: Measures chosen in this area assess the impact of latent variables commonly occurring in the epilepsy surgical setting. For example, by using performance validity measures, one determines whether the evaluation has been invalidated by factors such as poor motivation or task engagement on the part of the patient or the possible effect of other disease-related variables (e.g., subclinical or interictal epileptiform discharges).
(d) *Allowing research to be performed*: Measures should be used allowing one to research basic questions about brain-behavior functions and surgical outcome for specific cognitive skills, psychosocial and vocational functioning, emotional/psychiatric processing, seizure freedom, and quality of life.

Table 4.4 lists specific neurocognitive functions proven important to assess for several common types of epilepsy and specific tests that have

Table 4.4 Core neurocognitive functions to be assessed in epilepsy surgical patients and suggested tests

Neurocognitive domains	Within domain areas to emphasize during assessment	Possible tests to consider
Language	– Naming (e.g., visual, auditory/naming to description, category related) – Verbal fluency (semantic, letter, and action) – Screen reading and other core language tasks	– Boston Naming Test, Columbia Auditory Naming Test, Category- Related Naming Tests – Category fluency tasks (e.g., animals, supermarket items), DKEFS Verbal Fluency, Controlled Oral Word Association Test, action fluency – Recognition Reading Subtest of the Wide Range Achievement Test, American Version of the National Adult Reading Test (AMNART), Wechsler Test of Adult Reading, Token Test, sentence repetition
Attention	– Primary attention (auditory and visual) – Complex attention (auditory and visual) – Sustained attention (auditory and visual)	– Digit Span Forward (WAIS), Picture Completion (WAIS) – Digit Span Backwards and Letter-Number Sequencing (WAIS), Trail Making Tests, spatial span – Continuous Performance Test (not used as commonly by most epilepsy centers)
Visual processing	– Visuo-perception – Visual-spatial – Object recognition	– Visual Object and Space Perception (VOSP) Battery, Facial Recognition Test – Judgment of Line Orientation – Famous Faces Test, Category-Related Object Recognition Tests
Constructional praxis	– Graphomotor copying tasks – Assembly tasks	– Copying simple shapes (e.g., Greek cross, Necker cube), Rey Complex Figure Test (Copy) – Block Design (WAIS)

Memory and learning	– Auditory/verbal Learning, memory retention, and recognition
	  – List-learning Tasks
	  – Contextual memory
	  – Associative learning
	– Visual learning, memory retention, and recognition
	– Simple geometric designs
	  – Face recall
	  – Complex visual designs
	– Remote recall
		– Rey Auditory/Verbal Learning Test, California Verbal Learning Test, Verbal Selective Reminding Test
		– Logical Memory Subtest (Wechsler Scales), Reitan Story Memory
		– Verbal Paired Associates (VPA) Subtest (Wechsler Scales; WMS-III VPA appears less helpful than other versions, as it eliminated the easier word pairs)
		– Visual Reproduction (Wechsler Memory Scales: older versions appear to be more useful for lateralization than the 3rd edition)
		– Face Recall/Hospital Facial Recognition Task
		– Rey Complex Figure Test, MCG Complex Figures
		– Information Subtest (WAIS)

Executive control processes	– Complex problem solving – Response inhibition – Complex attention/mental flexibility – Abstract reasoning – Generative fluency tasks (verbal and visual) – Metacognition	– Wisconsin Card Sorting Test, Brixton Spatial Anticipation Task, Iowa Gambling Task – Color-Word Interference (Stroop) Test, Hayling Test, Go/No-Go Tasks – Trail Making Test, Mental Control (WMS) – Similarities Subtest/Matrix Reasoning Subtest (WAIS) – DKEFS Verbal Fluency, DKEFS Design Fluency, 5-Point Design Fluency – Cognitive Estimation Tasks
General intellectual functioning	– Verbal and performance IQ	– Wechsler Adult Intelligence Scale (various editions) – Wechsler ASI

(continued)

Table 4.4 (continued)

Neurocognitive domains	Within domain areas to emphasize during assessment	Possible tests to consider
Academic achievement	– Reading recognition – Reading comprehension – Mathematical skills – Spelling ability	– Wide Range Achievement Test (WRAT)—reading recognition – Gray Oral Reading Test (GORT) – WRAT—arithmetic – WRAT—spelling
Performance validity testing	– Determine task engagement. This can be disrupted due to issues including poor motivation as well as the impact of acute seizures and epileptiform activity	– Word Memory Test – Medical Symptom Validity Test – Victoria Symptom Validity Test – "Embedded" Measures of Task Engagement[a]

WAIS Wechsler Adult Intelligence Scale, *WMS-III* Wechsler Memory Scale (3rd edition), *MCG* Medical College of Georgia

[a]Embedded measures of task engagement refer to attempts to use improbable performances on standard clinical tests in order to recognize possible test invalidity

Table 4.5 Sensory, motor, mood and personality, and quality-of-life variables to be assessed in epilepsy surgical patients and suggested tests

Neurocognitive domains	Within domain areas to emphasize during assessment	Possible tests to consider
Sensory	– Visual, auditory, and tactile acuities	– Snellen eye chart – Extinction to double simultaneous stimulation – Tactile Form Recognition – Reitan-Klove Sensory Examination
Motor	– Handedness – Gross motor speed – Fine motor speed and dexterity – Grip strength – Psychomotor speed	– Edinburgh Handedness Scale – Finger Tapping Test – Grooved Pegboard Test – Hand dynamometer – WAIS subtests (e.g., symbol search, digit symbol)
Mood and personality	– Mood and emotional status – Psychopathology – Personality features – Somatizational/conversion profile	– Minnesota Multiphasic Personality Inventory (2nd edition or restructured form) – Personality Assessment Inventory (PAI) – Brief Self-Report Inventories (e.g., Beck Depression and Anxiety Scales) – Mini Psychiatric Inventory (MINI)
Quality of life	– Adjustment to seizures and treatment (e.g., AEDs, surgical intervention) – Satisfaction with social support and vocational and interpersonal functioning	Quality of Life in Epilepsy (QOLIE) Washington Psychosocial Seizure Inventory (WPSI)

WAIS Wechsler Adult Intelligence Scale, *AEDs* antiepileptic drugs

been used to assess these functions in the context of epilepsy. Table 4.5 presents similar data for motor and sensory functioning, mood, personality, and quality-of-life assessment. Obviously, tests selected for use need to be psychometrically sound (e.g., valid, reliable) and preferably have RCI or SRB scores or alternative forms for repeat assessment. In addition, the following section provides a brief overview of how the findings in each of these neurocognitive domains may be used and integrated in the neuropsychological assessment.

Language

It is essential to assess aspects of naming and verbal fluency given the presurgical baseline deficits in these areas and due to the postsurgical decline in these skills observed following dominant TL

resection (see the presurgical/postsurgical deficits section above and corresponding tables for specifics). Studies suggest sampling a wider array of categories with these tasks and indicate that altering basic task demands can lead to different yet equally important findings (e.g., use of auditory naming-to-description tasks versus standard visual confrontational naming) (Drane et al., 2008; Hamberger & Seidel, 2003). An assessment of reading ability is useful to establish a patient's ability to perform tasks requiring reading, to estimate premorbid function, and to monitor postsurgical changes in this function. Screening other language functions (e.g., auditory comprehension, repetition) is also recommended with epilepsy surgical patients. However, a complete language assessment is typically not required, unless the proposed surgical resection is thought to encroach upon classic language regions (e.g., Wernicke's and Broca's areas), which most do not, or when the epilepsy surgical candidate is experiencing baseline aphasia (e.g., usually the aphasia and seizures are resulting from a common neurological cause in these cases, such as stroke or tumor).

Attention

An assessment of primary attention processing (i.e., with minimal demands placed upon mental manipulation of information) is recommended for a variety of reasons, including the assessment of the effect of AEDs and other medications (which can disrupt this domain) and insuring a patient has the ability to focus on more complex tasks (which can be disturbed in patients not fully recovered from a seizure). More complex aspects of attention should also be assessed that require mental flexibility and alternation/switching between tasks and that place greater demands on working memory capacity. Assessing both auditory and visual aspects of attention is useful, as discrepancies between domains can sometimes be of lateralizing value (Duncan, Mirsky, Lovelace, & Theodore, 2009). Examining sustained attention and response inhibition using a continuous performance paradigm may also be worthwhile but does not appear to be routinely implemented in most clinical evaluations of epilepsy.

Visual Processing and Object Recognition

A thorough assessment should include a screen of visual acuity and gross confrontational evaluation of visual fields to insure that the patient can adequately process visual information (sometimes this information is available from the neurology exam). Additionally, we routinely assess both visuo-perception and visual-spatial processing. We use the former term to denote the ability to perceive visual images (including object recognition) and the latter to refer to the processing of spatial relationships between objects and potentially the viewer. Theoretically, the visual processing stream is divided into an inferior component which mediates visuo-perception/object recognition processing (ventral stream "what" pathway) and a superior stream that is involved in visual-spatial processing (dorsal stream "where" pathway) (Ungerleider & Mishkin, 1982). The ventral stream runs from the occipital lobe to the temporal lobe, while the dorsal stream runs from the occipital lobe to the parietal lobe, and both can be disrupted in a variety of ways by seizures and surgical resection. For example, occipital lobe disturbances can cause a primary loss of vision or disturbance in color processing, parietal lobe disturbances are often associated with deficits in spatial and constructional processing, and inferior TL dysfunction can be associated with object recognition deficits. The Visual Object and Space Perception (VOSP) Battery (Warrington & James, 1991) has four subtests that load on a perceptual factor and four that load on a spatial factor, making it a solid, efficient method of evaluating many of these functions (Rapport, Millis, & Bonello, 1998). Despite a lack of clinical tests, an assessment of object recognition is recommended for epilepsy surgical patients given recent evidence of category-related object recognition deficits in patients with right anterior TL dysfunction (e.g., famous faces, landmarks, animals)

(Drane et al., 2008, 2009; Glosser et al., 2003; Seidenberg et al., 2002). FL dysfunction can also potentially contribute to problems with frontal eye fields and visual tracking (Thurtell, Mohamed, Luders, & Leigh, 2009), as well as the organization/planning that is required for many constructional tasks.

Memory and Learning

Assessment of memory and learning is a core part of the evaluation of epilepsy surgical patients, as the majority of them have seizures arising from TL or FL regions. Patterns of memory dysfunction, as outlined above, can be very helpful for confirming seizure localization to one of these regions and for lateralizing side of seizure onset. In addition, these functions are potentially at risk in such patients and therefore need to be carefully examined.

A minimal assessment of memory in epilepsy should include a variety of test formats (e.g., free recall versus recognition), measures with different learning demands (e.g., associational learning, rote recall, contextual and gist learning), and stimuli tapping different sensory modalities (e.g., auditory/verbal, visual). Including a recognition task format can help to distinguish encoding from retrieval deficits, which can contribute to localization of brain dysfunction (e.g., FL versus TL impairment). Using both auditory/verbal and visual stimuli, one can explore possible material-specific patterns, which can aid in lateralizing the involved cerebral hemisphere. Using tasks that place different demands on forms of learning is recommended due to mounting evidence that performance dissociations frequently occur between learning approaches, which presumably reflects the underlying involvement of different brain regions (Saling, 2009). Ultimately, such data will likely contribute to more specific identification of dysfunctional regions within a hemisphere. While the specific structure-function relationships in this regard remain murky (i.e., which mesial TL structures are associated with which forms of learning?), research is starting to provide preliminary models. In addition, testing different forms of learning can uncover residual functions in a patient upon which one can capitalize in future memory training and target in efforts to improve surgical outcome.

In general, associational learning (e.g., word pairs) has proven to be one of the more sensitive tasks to mesial TL pathology (particularly unrelated word pairs) (Akanuma, Alarcon, Lum, et al., 2003; Hermann et al., 1994; Squire, 1993). Nevertheless, semantically related word pairs may be impacted by lateral TL resection and should be included as well. Having both easy (semantically related) and hard items also provides a better performance floor, which some believe improves our ability to lateralize dysfunction across the cerebral hemispheres. In this regard, the original versions of the Verbal Paired Associates task from the Wechsler Memory Scale have fared better in terms of seizure lateralization than did the version from the 3rd edition of this test, which dropped the easy items. Animal and experimental literature suggests that other forms of associational learning may be beneficial for the assessment of epilepsy as well (e.g., binding sensory/perceptual data with verbal labels).

List-learning tasks have also been shown to be sensitive to left mesial TL dysfunction (Grammaldo, Giampa, Quarato, et al., 2006; Loring, Strauss, Hermann, et al., 2008). As with associational tasks, using lists of words that are more difficult to link semantically places greater demands on mesial TL structures. This is borne out in studies examining the usefulness of various list-learning paradigms, with those allowing for easier categorization (e.g., California Auditory/Verbal Learning Test) appearing less able to lateralize dysfunction (Loring et al., 2008).

Contextual learning, such as reflected by the commonly used paragraph and story recall tasks that are available, has proven less sensitive to mesial temporal lobe pathology (Rausch & Babb, 1993; Saling et al., 1993). However, these measures are affected by lateral TL pathology, and some patients will experience decline on these tasks with a standard TL resection. Inclusion of contextual memory tasks also helps establish whether the patient has any functional memory capacity remaining. Someone performing well

on these tasks seems to retain the capacity to work at many jobs despite declines in other aspects of more complex learning, as they appear to retain the gist of what transpires despite having a difficult time recalling specific details. Such persons can still decline with surgery (particularly resections including lateral cortex), even if associational and rote learning are already severely impaired. Performance on contextual learning tasks has also been associated with drug effects (Salinsky et al., 2005), which can be useful for teasing out the effect of AEDs.

Finally, there are a number of learning paradigms that have yet to be commonly employed in the clinical epilepsy realm that should be explored. These include route learning/wayfinding tasks, visual memory tasks that place greater demands on allocentric memory (i.e., memory that is not based on one's own position in relation to the stimulus of interest), semantic learning, autobiographical memory and learning to criteria paradigms, and complex associational tasks that combine different styles of learning.

Executive Control Processes

Executive control processes refer to complex cognitive activities typically attributed to the FL regions of the brain (e.g., abstract reasoning, self-monitoring, problem solving, response inhibition, mental flexibility, complex attention). These skills coordinate the activity of more general cognitive and perceptual functions mediated by other brain regions (e.g., effectively coordinating motor and perceptual skills while altering performance in response to changing task demands). As mentioned, dysfunction associated with the FLs is often observed in both FL and TL epilepsy patients, with the latter patients presumably experiencing disruption of broader interconnections between brain regions secondary to epileptiform activity (Hermann & Seidenberg, 1995; Penfield & Jasper, 1954). FL dysfunction observed in TL patients will often resolve with successful seizure control (Martin et al., 2000). Given that FL and TL seizure onset represent the bulk of partial epilepsies, the assessment of executive functions frequently plays a role in confirming seizure focus, estimating risk of decline with FL surgery and helping to make predictions about possible areas of post-surgical improvement in TL patients. A thorough evaluation of executive control functions should assess the three major divisions of the FLs (e.g., dorsolateral, orbitofrontal, and mesial frontal). Assessment of executive functions often requires development and use of new tasks, as this is one cognitive area where novelty is particularly important (e.g., problem-solving tasks often become easier once a successful solution has been derived on a given occasion).

General Intellectual Functioning

An assessment of general intellectual functioning, which provides a broad overview of one's overall level of ability, is useful for estimating performance in specific neurocognitive domains and making determinations regarding functional capacity (e.g., ability to live independently, manage finances and medications, capacity to succeed in a vocational or academic environment). General cognitive ability also enters into determining the patient's capacity to make decisions regarding surgery. Performance patterns on IQ testing have not proven to be reliable indicators of lateralized seizure onset. However, they are sometimes helpful for this purpose, particularly when purer indices of verbal and perceptual ability are compared after controlling for problems with attention, processing speed, and motor dysfunction. Finally, general intellectual functioning remains normal in the majority of patients with epilepsy, although lower scores will be observed in a large number of patients, particularly those experiencing an early onset of refractory epilepsy, a long disease duration, comorbid neurological pathology, and a history of multiple episodes of generalized tonic-clonic seizures and status epilepticus (Glosser, Cole, French, Saykin, & Sperling, 1997).

Academic Achievement

An assessment of academic ability can be beneficial for making decisions regarding school functioning, which is particularly important for children and adolescents and adult patients engaged in educational pursuits. A brief screening of academic skills typically assesses word recognition, reading comprehension, spelling, and arithmetic. Presurgical performances in these areas are occasionally helpful in localizing extratemporal seizures. Postsurgical changes in these functions are not very common in FL and TL resections, which again represent the vast majority of surgical patients.

Sensory Functioning

As noted previously, a gross screening of perceptual functioning is essential to establish that patients can adequately perceive test stimuli. This should include checking visual acuity (e.g., Snellen eye chart), testing visual fields to confrontation, and examining basic tactile and auditory sensory functioning. Testing these functions can be incorporated into an evaluation of hemiinattention to visual, auditory, and tactile stimulation (e.g., exploring unilateral as well as bilateral simultaneous stimulation of the sensory modality being tested). Evaluation of apraxia, finger agnosia, astereognosis, right/left orientation, and achromatopsia and a more in-depth examination of tactile form recognition can provide lateralizing/localizing data in some patients. Some research has been completed examining olfactory functioning in TLE patients as well, suggesting that such patients are often deficient at odor naming, discrimination, and recall (usually right TLE worse than left TLE and other epilepsies) (Carroll, Richardson, & Thompson, 1993; Eskenazi, Cain, Novelly, & Mattson, 1983) and that they may experience further decline with surgery. A thorough sensory examination is certainly warranted in cases where posterior cortical epilepsy is suspected and can be useful in all epilepsy surgical patients even if they have recently undergone a neurological exam.

Motor Functioning

Evaluation of grip strength and manual dexterity of both upper extremities is recommended. The Finger Tapping Test provides a measure of gross motor speed while a task like the grooved pegboard evaluates fine motor dexterity and speed. These functions are sometimes diminished in patients with FL dysfunction (Helmstaedter, Kemper, et al., 1996) and may decrease in patients undergoing resections that encroach upon the precentral gyrus of the FL (motor strip) (Helmstaedter et al., 1998). A careful assessment of handedness is also needed, as this can inform predictions regarding language lateralization. Research suggests that "footedness" may add additional predictive value as well (Drane, 2006). A quick way to assess both in lieu of a standardized rating scale can be to ask about which hand the patient uses to write and which foot they would prefer to use to kick a ball through a goalpost in American football.

Mood, Personality, and Psychiatric Inventories

Measures are needed to examine current mood and emotional issues, to examine lifetime prevalence of psychiatric disorders, and to rule out psychogenic nonepileptic spells (PNES). Measures of mood are useful for monitoring levels of distress, tracking change over time, and picking up on critical issues in need of intervention (e.g., active suicidal ideation). Epilepsy patients exhibit higher rates of psychiatric disturbance than does the general population, with commonly occurring comorbid conditions including depression, anxiety disorders, and substance abuse (Manchanda, 2002). In the surgical context, it is important to recognize and effectively deal with any psychiatric issues prior to undergoing surgery and to recognize the development of any postsurgical problems in this regard. Of note, however, measures of mood do not typically allow for making psychiatric diagnoses and do not provide any information with regard to lifetime prevalence rates. Kanner and colleagues

have demonstrated that knowledge of psychiatric syndrome and personal and familial psychiatric history can be of benefit in predicting adverse responses to AEDs (Kanner, 2009; Kanner, Wuu, Faught, et al., 2003) and in determining the optimal treatment regimen for patients with such comorbid conditions (Kanner & Barry, 2003). Therefore, structured psychiatric inventories are helpful for both clinical and research purposes if time permits for their use.

PNES occurs in a subset of epilepsy patients, although base rates of comorbid occurrence of this condition tend to be overestimated in most studies. Research using the most rigorous diagnostic criteria suggests that approximately 5–10 % of patients with epilepsy will also experience PNES events (Martin, Burneo, Prasad, et al., 2003). There are also a handful of studies suggesting that some patients undergoing surgery will develop these events and that these events were not apparent prior to their surgery. We have found that there may be risk factors for developing PNES following surgery.

Quality of Life

Measures have been developed to examine patient satisfaction with various aspects of life functioning, and these measures have frequently been adopted as end points in outcome studies. Quality-of-life measures attempt to evaluate the noxious impact of seizures and their treatment (e.g., side effects of AEDs) on self-ratings of cognitive functioning, mood, and satisfaction with social support, vocational/academic performance, and other aspects of daily functioning. One criticism with quality-of-life measures has been that they sometimes share too much overlap with measures of mood and psychopathology.

Clinical Interview and Medical Record Review

There are key pieces of supporting information that need to be gathered through clinical interview and record review that set the context for the neuropsychological data and make it possible to predict outcome related to surgery. Such information includes age of seizure onset, duration of epilepsy, occurrence of febrile seizures, number of AEDs being taken, and developmental history. One also needs to know about general medical and psychiatric history, a history of head trauma, and a detailed history of the patient's seizures (e.g., types of spells, frequency of each seizure type, occurrence of secondary generalization, episodes of status epilepticus). Knowledge of AED regimen is also required to take their impact on cognitive into account. There will often be available neuroimaging data (e.g., MRI, SPECT, PET) and EEG findings available for review, as well as information regarding language laterality (e.g., fMRI data, Wada results). Video-EEG results will frequently provide information regarding seizure focus and can be informative regarding interictal discharges (discharges occurring between seizures). Results of the MRI of the brain will often identify structural abnormalities if present. In particular, the presence of mesial temporal sclerosis has proven useful in predicting neuropsychological outcome.

Throughout the entire interview and assessment, one should take note of signs of seizure occurrence, including brief pauses in performance or alterations in response style. When subtle changes appear to be observed, it can be useful to ask the patient if they have experienced a loss of time or if they recall what they were thinking about, and orientation can be rechecked as well.

Common Test Batteries

Given the difficulty involved in amassing adequate data to answer many research questions, there has been a recent push by the National Institutes of Health to create "common data elements" for many neurological diseases including epilepsy. A committee was tasked with creating a core set of neurocognitive tests for use in epilepsy during 2009 and these suggestions were published during 2011 (Loring et al., 2011). As with other common data element projects, the

resulting battery is intended to serve as a minimum collection of tests, taking no more than 1 h to administer. This provides epilepsy researchers with a common core of data available for future studies pooling information across centers. It also provides epilepsy researchers who do not traditionally include cognitive elements with some very basic guidelines for collecting such data when appropriate.

Since the 1980s, a loose collaboration of neuropsychology labs from several major epilepsy centers in the USA has existed as the Bozeman consortium. This group has used this model of sharing data to publish a number of papers that the member sites could not have completed on their own (Hermann, Perrine, Chelune, et al., 1999; Lee, Westerveld, Blackburn, Park, & Loring, 2005; Wilde et al., 2003). Their data-sharing initiative should serve as a model for future collaborations, which can be particularly useful for studying events with low-frequency base rates, such as the occurrence of FL and posterior cortical epilepsies. Such collaborations also lead to new projects as interactions contribute to cross-fertilization of ideas.

Predicting Outcome in Epilepsy Surgery

Neuropsychological assessment can be useful in the prediction of neurocognitive outcome, postsurgical emotional and psychiatric status, and even seizure freedom. There are some general rules of thumb that have developed related to outcome prediction (see Table 4.6), and there are also a limited number of available prediction formulas. However, most of the available formulas relate to specific tests only and often have been produced exclusively for TLE patients.

Table 4.6 Factors predictive of outcome in temporal lobe epilepsy patients undergoing surgery

Factors associated with a favorable neurocognitive outcome	Factors associated with a poor neurocognitive outcome
Presence of mesial temporal sclerosis on MRI	Normal brain imaging
Younger age of patient at time of surgery	Older age of patient at time of surgery
Early age of seizure onset (<15 years at onset)	Adult onset of seizures
Surgery performed on nondominant cerebral hemisphere	Surgery performed on language dominant cerebral hemisphere
Wada memory performance intact for cerebral hemisphere contralateral to seizure focus	Wada memory performance impaired for cerebral hemisphere contralateral to seizure focus
Impaired neurocognitive ability	Intact neurocognitive ability (more to lose)

Functional Reserve and Functional Adequacy Hypotheses in TLE Surgery

The *functional reserve hypothesis* was based primarily on studies documenting severe amnestic disorders of patients with bilateral mesial TL dysfunction resulting from disease or resection (Scoville & Milner, 1957). Research with the Wada procedure contributed additional support to this model, as it has become clear that patient's performing poorly on memory tasks during testing of the contralateral (i.e., remaining) TL structures are at increased risk for significant postsurgical memory decline (Chelune, 1995). While the structural integrity of the contralateral hippocampal structures appear to be important for avoiding global amnesia, having a functionally adequate hippocampus has not prevented material-specific memory loss with unilateral TL resection (such changes are common).

The *functional adequacy* model has support from growing evidence that the adequacy of the ipsilateral hippocampus (i.e., structure on side to be resected) better predicts material-specific postsurgical memory declines. This model predicts that TLE patients with intact memory function are likely to experience more pronounced decline in memory performance than those for whom memory is already impaired. This is a common finding from years of memory research in TLE surgery, and the functional adequacy model also accounts for the observation that patients with high presurgical memory function-

ing are at greater risk for significant decline in this area than those with low average or impaired presurgical memory performance.

Pertinent Information to Relay to the Referring Physician or Epilepsy Monitoring Unit Team

In preparing a written report of the neuropsychological assessment of an epilepsy patient, it is typically important to comment on whether the findings suggest lateralized or localized dysfunction and to relate these findings to the other available test results (e.g., MRI, video-EEG results). One should also convey a thorough baseline of performance in terms of both neurocognitive ability and emotional status and attempt to assess the risks and benefits of potential treatment options (e.g., surgery, changes in AED regimen). One should recognize when it is possible that brain reorganization appears likely (e.g., naming and verbal memory deficits are observed in a patient with right TL seizure onset and normal visual memory) or when it is possible that ongoing seizures are likely disrupting distal brain regions (e.g., executive dysfunction in TL patients with no other findings of FL abnormality) and work these hypotheses into the final summary of results. Recommendations should be provided for interventions that may be required prior to surgery, such as completion of a Wada or fMRI study or a referral for psychotherapy in someone with untreated psychiatric issues or a high risk of developing PNES events. Recommendations for follow-up testing and referral for cognitive rehabilitation should be made as appropriate as well.

Clinical Vignette

The following brief case study is intended to highlight several of the principles from the current chapter, including a description of the process of examining the neurocognitive results for lateralizing or localizing patterns for use in confirming seizure focus, integrating other medical findings, considering the impact of latent variables upon neurocognitive performance (e.g., subclinical epileptiform activity), and prediction of outcome.

Background

Mr. Jones is a 42-year-old, right-handed, married, Caucasian male who was referred for neuropsychological assessment while undergoing video-EEG monitoring as part of a presurgical evaluation for possible epilepsy surgery. The patient has a reported history of measles encephalitis at the age of 5 and later developed complex partial seizures at the age of 14. The patient's seizures are characterized by unresponsiveness and lip smacking, but there is no evidence of motor involvement, loss of bowel or bladder control, or tongue biting. The patient believes that he experiences clusters of spells every 1–3 months. Medical records suggest that he has experienced rare secondary generalization of seizures, all in the context of medical noncompliance or subtherapeutic AED levels. Mr. Jones has no history of birth injury, developmental delay, febrile seizures, or head trauma. He denied any personal or familial history of psychiatric disturbance. Current medications included sodium valproate (1,250 mg TID), gabapentin (600 mg TID), and mephobarbital (200 mg BID). The patient completed high school and junior college and has been employed as a technician for the telephone company for the past 15 years. He and his wife have been married for more than 20 years and have two children together.

Results of Other Relevant Medical Procedures

MRI of the brain revealed the presence of left mesial temporal sclerosis and mild, diffuse volume loss. Video-EEG results were unavailable at the time of our evaluation. However, we would later learn that the patient was experiencing frequent left anterior TL spikes throughout the monitoring, as well as several subclinical events during our clinical interview and testing.

Neuropsychological Findings

Mr. Jones' neuropsychological test scores appear in Table 4.7, including his initial presurgical evaluation completed during inpatient video-EEG monitoring and a brief follow-up that was completed when he came back to undergo the Wada procedure. As will become clear, his initial testing appeared to be impacted by subclinical epileptiform activity, which actually contributed to our ability to confirm the seizure focus, yet also transiently disrupted his performance resulting in an underestimation of his actual baseline abilities. We first suspected that his performance was affected by some latent variable when he produced a genuine impairment profile on a performance validity test, as well as severely impaired memory scores on multiple measures of complex auditory/verbal learning and memory. This pattern suggested that Mr. Jones was either severely amnestic/demented (which was not consistent with his presentation, which included a good recent work history) or that some unknown factor was creating noise in his profile. When we met as a group to discuss the surgical cases for the week, it was discovered that the patient had experienced subclinical epileptiform discharges involving the left TL almost continuously throughout our evaluation. Neither the patient nor his examiners had suspected that his performance was altered. However, by completing additional testing when the patient returned approximately 6 weeks later to undergo the Wada procedure, the patient exhibited average performances in these domains, presumably when not experiencing such activity. AED regimen was unchanged at follow-up assessment. This confirmed our suspicions that the patient's inpatient performance was likely disrupted secondary to epileptiform activity and also afforded us the opportunity to better document his baseline ability. As the test sessions were very close together, we decided to use alternate forms of measures or similar tests thought to tap the same neurocognitive domains of interest. Of note, an underestimation of a patient's baseline performance can affect the neurosurgeon's approach to their case, as they could assume that an impaired memory performance means that there is nothing to lose secondary to surgery. Likewise, an underestimation of baseline performance could also lead to erroneous conclusions in outcome studies or research using neurocognitive scores as an end point (e.g., we might falsely determine that there was no decline or even an improvement following surgery, when instead the patient may have actually gotten worse).

As can be seen from examining his initial assessment results in Table 4.7, Mr. Jones exhibited a pattern of performance that suggested left frontotemporal lobe dysfunction, including severely impaired performances on most tasks of auditory/verbal learning and memory and visual confrontational naming ability despite average to high-average visual memory performance. Mr. Jones also exhibited mild deficits involving aspects of executive functioning, including problems with generative fluency, response inhibition, and mental flexibility. Of note, however, as performance on semantic fluency (impaired) was much worse than letter fluency (low average), this pattern could again suggest primarily TL dysfunction. It is also important to recognize that despite the acute epileptiform activity, the patient still exhibited many scores that were average or better on tasks involving visual memory, general intellectual functioning, remaining executive skills, and most aspects of language processing. Overall, this pattern was suggestive of dominant (presumably left) TL dysfunction, with possible disruption of FL regions as well. The latter finding could be conceptualized as perhaps reflecting dysfunction of the broader temporofrontal lobe networks secondary to ongoing seizures, a finding that we have noted is often observed in TLE patients (see earlier coverage of the nociferous cortex hypothesis).

An examination of Mr. Jones' follow-up testing from approximately 6 weeks later when he returned for the Wada procedure demonstrated that the initial findings during video-EEG monitoring were suboptimal for him. We felt confident that these results reflected the transient impact of epileptiform activity that was not present on the day of the Wada. While the same performance pattern was present, the patient's baseline ability was clearly far better than our initial assessment

Table 4.7 Select results of neurocognitive testing during video-EEG monitoring and 1 month later at time of Wada procedure

Tests administered	Results during video-EEG stay	Results on day of Wada
General IQ	WAIS-III FSIQ = 99, VIQ = 104, PIQ = 91	WASI FSIQ = 108, VIQ = 110, PIQ = 102
Performance validity testing	Failed 3/3 effort measures from the Word Memory Test (oral version) but produced a genuine impairment profile	Passed all performance validity tests, including the Medical Symptom Validity Test and the Word Memory Test (oral version)
Boston Naming Test	Raw = 39/60, impaired	Raw = 48/60, mildly impaired
Semantic fluency (animals)	Raw = 9, <1st percentile	Raw = 14, 4th percentile
Letter fluency (COWA)	Raw = 18, 2nd percentile	Raw = 24, 4th percentile
Screen of auditory comprehension and repetition	Normal	Normal
Complex list learning	Rey Auditory/Verbal Learning Test Trial 1 = 4/15, 6th percentile Trial 5 = 6/15, 1st percentile Trial 5 total = 27/75, 1st percentile Immediate = 0/15, <1st percentile Delayed = 2/15, 1st percentile Recognition = 3/15, <1st percentile	Verbal Selective Reminding Test (Form 1) LTS = 108, 44th percentile CLTR = 74, 23rd percentile Delayed = 11/12, 51st percentile Recognition = 12/12 normal
WMS-III Logical Memory Immediate recall	Raw = 41, 50th percentile	N/A
Delayed recall	Raw = 17, 25th percentile	
Verbal Paired Associates	WMS-III	WMS-I
Immediate	Raw = 2, 1st percentile	Raw = 16, 21st percentile
Delayed	Raw = 0, 1st percentile	Raw = 9, 12th percentile
Face recall	WMS-III faces	N/A
Immediate	Raw = 34, 25th percentile	
Delayed	Raw = 40, 75th percentile	
Recall of designs	WMS-III Visual Reproduction	N/A
Immediate Delayed	Raw = 76, 16th percentile Raw = 77, 75th percentile	
Recognition	Raw = 44, 50th percentile	
Trail Making Test	Part A = 29 s, 23rd percentile Part B = 129 s, 1st percentile	Part A = 26 s, 37th percentile Part B = 68 s, 30th percentile
Finger Tapping Test Dominant hand	Raw = 49, 21st percentile	Raw = 54, 50th percentile
Nondominant hand	Raw = 46, 30th percentile	Raw = 48, 45th percentile
Grip strength Dominant hand	Raw = 45, 18th percentile	Raw = 45, 18th percentile
Nondominant hand	Raw = 43, 18th percentile	Raw = 43, 18th percentile
Category test	13 errors, normal	N/A

IQ intellectual quotient, *WAIS-III* Wechsler Adult Intelligence Scale (3rd edition), *FSIQ* full-scale IQ, *VIQ* verbal IQ, *PIQ* performance IQ, *WASI* Wechsler Abbreviated Scale of Intelligence, *COWA* Controlled Oral Word Association Test, *LTS* long-term storage, *CLTR* continuous long-term retrieval, *WMS-III* Wechsler Memory Scale (3rd edition), *WMS-I* Wechsler Memory Scale

had suggested. This latter performance was also more in keeping with the patient's reported daily functioning. As can be seen from examining Table 4.7, the patient continued to exhibit mild deficits in auditory/verbal learning and naming ability during the second evaluation, yet these results were much better than the severely impaired performances initially observed during monitoring. It is interesting to note the dissociation between the contextual memory test and the

list-learning and associative-learning tasks, as the former did not appear to be affected by the subclinical epileptiform activity. This finding highlights the dissociation that occurs between tests of memory and is supportive of the position that the latter tasks are more dependent on mesial TL structures. The patient also exhibited mild gains on some of the attentional measures and overall IQ, although it is difficult to disentangle practice effects and differences between measures for these smaller changes.

Mr. Jones did not exhibit any significant emotional distress during clinical interview or on formal measures of mood, although he did report some mild anxiety and concern over the effect of ongoing seizures and what he viewed as transient disruptions in his ability to function at work and at home. He did not have any risk factors for developing PNES events and did not exhibit somatizational tendencies on formal personality assessment.

Mr. Jones' Wada results demonstrated left hemispheric language lateralization and demonstrated that his right cerebral hemisphere was independently capable of encoding novel information. Therefore, he was scheduled for surgical resection. Based on the constellation of findings from neurocognitive performance and the other available data, we predicted that he would be at risk for further auditory/verbal memory decline with surgery. Primarily, this is because he had grossly intact baseline naming and verbal memory functioning (i.e., something to lose), and the resection was to be performed on his dominant cerebral hemisphere. Seizure onset was during his teen years, although there was really no indication of any brain reorganization based on available preoperative data. For example, he was exhibiting baseline deficits in naming and verbal memory (i.e., the areas that we were examining for evidence of a possible reorganization), and these deficits were enhanced by experiencing epileptiform activity involving the left TL (i.e., suggesting that they are still mediated by this region). The one factor arguing against a decline with surgery, and which we mentioned could possibly mediate the effects of surgery, was the presence of MTS. The patient decided to have surgery and was counseled regarding the potential risks of decline that he might face. These risks have to be balanced against the impact of ongoing seizures, which obviously contribute to transient disruptions of functioning and for some individuals likely contribute to more permanent changes in brain functioning over time. The patient will ultimately be scheduled for a 1-year postsurgical follow-up with our service, at which time we will repeat most of the initial battery of tests.

Direction of Future Practice and Research

Clinical neuropsychology in the epilepsy surgical setting already holds a solid position as a means of confirming the epileptic seizure focus, establishing a baseline level of functioning for the patient, and providing natural end points for outcome studies and other research. The ongoing effort to improve our ability to localize and lateralize functions should continue in the future, with an emphasis on developing improved techniques for assessing the extratemporal epilepsies. This will include further establishing the validity and usefulness of current measures for testing FL subregions and posterior cortical epilepsies, as well as developing new tests and paradigms. The assessment of FL function in particular will likely benefit from efforts to examine broader test patterns (e.g., teasing out the relative contribution of non-frontal lobe functions to executive control processes). Establishing collaborative efforts across centers (such as the NIH Common Data Elements Initiative) will also be critical for obtaining adequate sample sizes to explore many pertinent questions with these less common epilepsy syndromes. Another area of needed growth in the neuropsychology of epilepsy involves developing and implementing better methods of assessing functional capacity and monitoring a wider array of outcome variables (e.g., vocational success, avoidance of disability, marital statistics). Although not emphasized in the current chapter due to coverage elsewhere in this book, the need for neuropsychologists to be actively

involved in broader assessment paradigms such as cortical stimulation mapping, Wada evaluations, and development of fMRI paradigms for language lateralization and other purposes is greatly encouraged. The future also holds a place for combining neuropsychological data with many of the emerging technologies, such as structural volumetric analysis, diffusion imaging, magnetoencephalography, dense array EEG, and virtual reality paradigms for the purposes of better understanding brain functioning and developing new means for assessing presurgical function and preventing postsurgical decline.

References

Aarts, J. H., Binnie, C. D., Smit, A. M., & Wilkins, A. J. (1984). Selective cognitive impairment during focal and generalized epileptiform EEG activity. *Brain, 107*, 239–308.

Akanuma, N., Alarcon, G., Lum, F., Kissani, N., Koutroumanidis, M., Adachi, N. et al. (2003). Lateralizing value of neuropsychological protocols for presurgical assessment of temporal lobe epilepsy. *Epilepsia, 44*, 408–418.

Aldenkamp, A. P., & Arends, J. (2004). The relative influence of epileptic EEG discharges, short nonconvulsive seizures, and type of epilepsy on cognitive function. *Epilepsia, 45*, 54–63.

Anhoury, S., Brown, R. J., Krishnamoorthy, E. S., & Trimble, M. R. (2000). Psychiatric outcome after temporal lobectomy: A predictive study. *Epilepsia, 41*, 1608–1615.

Barr, W. B., Chelune, G. J., Hermann, B. P., Loring, D. W., Perrine, K., Strauss, E., et al. (1997). The use of figural reproduction tests as measures of nonverbal memory in epilepsy surgery candidates. *Journal of the International Neuropsychological Society, 3*, 435–443.

Bartha, L., Benke, T., Bauer, G., & Trinka, E. (2005). Interictal language functions in temporal lobe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*, 808–814.

Binder, D. K., Lehe, M. V., Kral, T., Bien, C. G., Urbach, H., Schramm, J., et al. (2008). Surgical treatment of occipital lobe epilepsy. *Journal of Neurosurgery, 109*, 57–69.

Binnie, C. D. (2003). Cognitive impairment during epileptiform discharges: Is it ever justifiable to treat the EEG? *The Lancet. Neurology, 2*, 725–730.

Bird, C. M., & Burgess, N. (2008). The hippocampus and memory: Insights from spatial processing. *Nature Reviews. Neuroscience, 9*, 182–194.

Blakemore, C. B., & Falconer, M. A. (1967). Long-term effects of anterior temporal lobectomy on certain cognitive functions. *Journal of Neurology, Neurosurgery, and Psychiatry, 30*, 364–367.

Blume, W. T., Wiebe, S., & Tapsell, L. M. (2005). Occipital epilepsy: Lateral versus mesial. *Brain, 128*, 1209–1225.

Blumer, D., Montouris, G., & Hermann, B. (1995). Psychiatric morbidity in seizure patients on a neurodiagnostic monitoring unit. *The Journal of Neuropsychiatry and Clinical Neurosciences, 7*, 445–456.

Boone, K. B., Miller, B. L., Rosenberg, L., Durazo, A., McIntyre, H., & Weil, M. (1988). Neuropsychological and behavioral abnormalities in an adolescent with frontal lobe seizures. *Neurology, 38*, 583–586.

Busch, R. M., Frazier, T. W., Haggerty, K. A., & Kubu, C. S. (2005). Utility of the Boston Naming Test in predicting ultimate side of surgery in patients with medically intractable temporal lobe epilepsy. *Epilepsia, 46*, 1773–1779.

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: A neural model of spatial memory and imagery. *Psychological Review, 114*, 340–375.

Carroll, B., Richardson, J. T., & Thompson, P. (1993). Olfactory information processing and temporal lobe epilepsy. *Brain and Cognition, 22*, 230–243.

Chapin, J. S., Busch, R. M., Naugle, R. I., & Najm, I. M. (2009). The Family Pictures subtest of the WMS-III: Relationship to verbal and visual memory following temporal lobectomy for intractable epilepsy. *Journal of Clinical and Experimental Neuropsychology, 31*(4), 498–504.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology, 10*, 413–432.

Cheung, M. C., Chan, A. S., Chan, Y. L., Lam, J. M., & Lam, W. (2006). Effects of illness duration on memory processing of patients with temporal lobe epilepsy. *Epilepsia, 47*, 1320–1328.

Chilosi, A. M., Brovedani, P., Moscatelli, M., Bonanni, P., & Guerrini, R. (2006). Neuropsychological findings in idiopathic occipital lobe epilepsies. *Epilepsia, 47*, 76–78.

Crane, J., & Milner, B. (2005). What went where? Impaired object location learning in patients with right hippocampal lesions. *Hippocampus, 15*, 216–231.

Dalmagro, C. L., Bianchin, M. M., Velasco, T. R., Alexandre, V., Jr., Walz, R., Terra-Bustamante, V. C., et al. (2005). Clinical features of patients with posterior cortical epilepsies and predictors of surgical outcome. *Epilepsia, 46*, 1442–1449.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. (1996). A neural basis for lexical retrieval. *Nature, 380*, 499–505.

Davies, K. G., Bell, B. D., Bush, A., Hermann, B. P., Dohan, F. C. J., & Jaap, A. S. (1998). Naming decline after left anterior temporal lobectomy correlates with pathological status of resected hippocampus. *Epilepsia, 39*, 407–419.

Delaney, R. C., Rosen, A. J., Mattson, R. H., & Novelly, R. A. (1980). Memory function in focal epilepsy: A comparison of non-surgical, unilateral temporal lobe and frontal lobe samples. *Cortex, 16*, 103–117.

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contribution of anterior cingulate cortex to behaviour. *Brain, 118*, 279–306.

Dikmen, S. S., Heaton, R. K., Grant, I., & Temkin, N. R. (1999). Test–retest reliability and practice effects of Expanded Halstead–Reitan Neuropsychological Test Battery. *Journal of the International Neuropsychological Society, 5*, 346–356.

Drane, D. L. (2006). The intracarotid amobarbital procedure (Wada test) should nearly always be performed in temporal lobectomy candidates. In J. W. Miller & D. L. Silbergeld (Eds.), *Epilepsy surgery: Principles and controversy*. New York, NY: Taylor & Francis.

Drane, D. L., Lee, G. P., Cech, H., Huthwaite, J. S., Ojemann, G. A., Ojemann, J. G., et al. (2006). Structured cueing on a semantic fluency task differentiates patients with temporal versus frontal lobe seizure onset. *Epilepsy and Behavior, 9*, 339–344.

Drane, D. L., & Meador, K. J. (Eds.). (2002). *Cognitive toxicity of antiepileptic drugs*. Boston, MA: Butterworth-Heinemann.

Drane, D., Ojemann, G., Aylward, E., et al. Ojemann, J. G., Johnson, L. C., Silbergeld, D. L., et al. (2008). Category-specific naming and recognition deficits in temporal lobe epilepsy. *Neuropsychologia, 46*, 1242–1255.

Drane, D. L., Ojemann, G. A., Ojemann, J. G., Aylward, E., Silbergeld, D. L., Miller, J. W., et al. (2009). Category-specific recognition and naming deficits following resection of a right anterior temporal lobe tumor in a patient with atypical language lateralization. *Cortex, 450*, 630–640.

Drane, D. L., Ojemann, G. A., Tranel, D., Ojemann, J. G., & Miller, J. W. (2004). Category-specific naming and recognition deficits in patients with temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 10*, 202.

Dulay, M. F., Schefft, B. K., Testa, S. M., Fargo, J. D., Privitera, M., & Yeh, H. S. (2002). What does the Family Picture subtest of the Wechsler Memory Scale-III Measure? Insight gained from patients evaluated for epilepsy surgery. *The Clinical Neuropsychologist, 16*, 452–462.

Duncan, C. C., Mirsky, A. F., Lovelace, C. T., & Theodore, W. H. (2009). Assessment of the attention impairment in absence epilepsy: Comparison of visual and auditory P300. *International Journal of Psychophysiology, 73*, 118–122.

Eskenazi, B., Cain, W. S., Novelly, R. A., & Mattson, R. (1983). Odor perception in temporal lobe epilepsy patients with and without temporal lobectomy. *Neuropsychologia, 24*, 553–562.

Farrant, A., Morris, R. G., Russell, T., Elwes, R., Akanuma, N., Alarcon, G., et al. (2005). Social cognition in frontal lobe epilepsy. *Epilepsy and Behavior, 7*, 506–516.

Fritz, N., Glogau, S., Hoffmann, J., Rademacher, M., Elger, C. E., & Helmstaedter, C. (2005). Efficacy and cognitive side effects of tiagabine and topiramate in patients with epilepsy. *Epilepsy & Behavior, 6*, 373–381.

Fuller-Thomson, E., & Brennenstuhl, S. (2009). The association between depression and epilepsy in a nationally representative sample. *Epilepsia, 50*, 1051–1058.

Gilliam, F. G., Santos, J., Vahle, V., Carter, J., Brown, K., & Hecimovic, H. (2004). Depression in epilepsy: Ignoring clinical expression of neural network dysfunction? *Epilepsia, 45*(Suppl. 2), 28–33.

Glosser, G., Cole, L. C., French, J. A., Saykin, A. J., & Sperling, M. R. (1997). Predictors of intellectual performance in adults with intractable temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 3*, 252–259.

Glosser, G., Salvucci, A. E., & Chiaravalloti, N. D. (2003). Naming and recognizing famous faces in temporal lobe epilepsy. *Neurology, 61*, 81–86.

Golby, A. J., Poldrack, R. A., Brewer, J. B., Spencer, D., Desmond, J. E., Aron, A. P., et al. (2001). Material-specific lateralization in the mesial temporal lobe and prefrontal cortex during memory encoding. *Brain, 124*, 1841–1854.

Grammaldo, L. G., Giampa, T., Quarato, P. P., Picardi, A., Mascia, A., Sparano, A., et al. (2006). Lateralizing value of memory tests in drug-resistant temporal lobe epilepsy. *European Journal of Neurology, 13*, 371–376.

Griffith, H. R., Richardson, E., Pyzalski, R. W., Bell, B., Dow, C., Hermann, B. P., et al. (2006). Memory for famous faces and the temporal pole: Functional imaging findings in temporal lobe epilepsy. *Epilepsy and Behavior, 9*, 173–180.

Hamberger, M. J., & Seidel, W. T. (2003). Auditory and visual naming tests: Normative and patient data for accuracy, response time, and tip-of-the-tongue. *Journal of the International Neuropsychological Society, 9*, 479–489.

Hamberger, M. J., & Tamny, T. R. (1999). Auditory naming and temporal lobe epilepsy. *Epilepsy Research, 35*, 229–243.

Heaton, R. K., Temkin, N., Dikmen, S., Avitable, N., Taylor, M. J., Marcotte, T. D., et al. (2001). Detecting change: A comparison of three neuropsychological methods, using normal and clinical samples. *Archives of Clinical Neuropsychology, 16*, 75–91.

Helmstaedter, C. (2001). Behavioral aspects of frontal lobe epilepsy. *Epilepsy and Behavior, 2*, 384–395.

Helmstaedter, C., Elger, C. E., Hufnagel, A., Zentner, J., & Schramm, J. (1996). Different effects of anterior temporal lobectomy, selective amygdalohippocampectomy, and temporal cortical lesionectomy, and temporal cortical lesionectomy on verbal learning, memory, and recognition. *Journal of Epilepsy, 9*, 35–45.

Helmstaedter, C., Gleissner, U., Zentner, J., & Elger, C. E. (1998). Neuropsychological consequences of epilepsy surgery in frontal lobe epilepsy. *Neuropsychologia, 36*, 681–689.

Helmstaedter, C., Grunwald, T., Lehnertz, K., Gleissner, U., & Elger, C. E. (1997). Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: Evidence

from temporal lobe epilepsy. *Brain and Cognition, 35*, 110–131.

Helmstaedter, C., Kemper, B., & Elger, C. E. (1996). Neuropsychological aspects of frontal lobe epilepsy. *Neuropsychologia, 34*, 399–406.

Hermann, B., Davies, K., Foley, K., & Bell, B. (1999). Visual confrontation naming outcome after standard left anterior temporal lobectomy with sparing versus resection of the superior temporal gyrus: A randomized prospective clinical trial. *Epilepsia, 40*, 1070–1076.

Hermann, B. P., Perrine, K., Chelune, G. J., et al. (1999). Visual confrontation naming following left anterior temporal lobectomy: A comparison of surgical approaches. *Neuropsychology, 13*, 3–9.

Hermann, B., & Seidenberg, M. (1995). Executive system dysfunction in temporal lobe epilepsy: Effects of nociferous cortex versus hippocampal pathology. *Journal of Clinical and Experimental Neuropsychology, 17*, 809–819.

Hermann, B., Seidenberg, M., Lee, E. J., Chan, F., & Rutecki, P. (2007). Cognitive phenotypes in temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 13*, 12–20.

Hermann, B. P., Seidenberg, M., Schoenfeld, J., Peterson, J., Leveroni, C., & Wyler, A. R. (1996). Empirical techniques for determining the reliability, magnitude, and pattern of neuropsychological change after epilepsy surgery. *Epilepsia, 37*, 942–950.

Hermann, B. P., & Wyler, A. R. (1988). Effects of anterior temporal lobectomy on language function: A controlled study. *Annals of Neurology, 23*, 585–588.

Hermann, B. P., Wyler, A. R., Somes, G., Dohan, F. C., Berry, A. D., & Clement, L. (1994). Declarative memory following anterior temporal lobectomy in humans. *Behavioral Neuroscience, 108*, 3–10.

Hermann, B. P., Wyler, A. R., Steenman, H., & Richey, E. T. (1988). The interrelationship between language function and verbal learning/memory performance in patients with complex partial seizures. *Cortex, 24*, 245–253.

Hermann, B. P., Wyler, A. R., & Richey, E. T. (1988). Wisconsin Card Sorting Test performance in patients with complex partial seizures of temporal-lobe origin. *Journal of Clinical and Experimental Neuropsychology, 10*, 467–476.

Hermann, B. P., Wyler, A. R., & Somes, G. (1991). Language function following anterior temporal lobectomy: Frequency and correlates. *Neurosurgery, 35*, 52–57.

Hernandez, M. T., Sauerwein, H. C., Jambaque, I., De Guise, E., Lussier, F., Lortie, A., et al. (2002). Deficits in executive function and motor coordination in children with frontal lobe epilepsy. *Neuropsychologia, 40*, 384–400.

Holmes, M. D., Miles, A. N., Dodrill, C. B., Ojemann, G. A., & Wilensky, A. J. (2003). Identifying potential surgical candidates in patients with evidence of bitemporal epilepsy. *Epilepsia, 44*, 1075–1079.

Joanette, Y., & Goulet, P. (1986). Criterion-specific reduction of verbal fluency in right brain-damaged right-handers. *Neuropsychologia, 24*, 875–879.

Jokeit, H., Heger, R., Ebner, A., & Markowitsch, H. J. (1998). Hemispheric asymmetries in category-specific word retrieval. *NeuroReport, 9*, 2371–2373.

Jokeit, H., & Schacher, M. (2004). Neuropsychological aspects of type of epilepsy and etiological factors in adults. *Epilepsy & Behavior, 5*, 14–20.

Jokeit, H., Seitz, R. J., Markowitsch, H. J., Neumann, N., Witte, O. W., & Ebner, A. (1997). Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain, 120*, 2283–2294.

Jones-Gotman, M. (1986). Right hippocampal excision impairs learning and recall of a list of abstract designs. *Neuropsychologia, 24*, 659–670.

Jones-Gotman, M., & Milner, B. (1977). Design fluency: The invention of nonsense drawings after focal cortical lesions. *Neuropsychologia, 15*, 653–674.

Jones-Gotman, M., Zatorre, R. J., Olivier, A., Andermann, F., Cendes, F., & Staunton, H. (1997). Learning and retention of words and designs following excision from medial or lateral temporal-lobe structures. *Neuropsychologia, 35*, 963–973.

Kanner, A. M. (2009). Can antiepileptic drugs unmask a susceptibility to psychiatric disorders? *Nature Clinical Practice. Neurology, 5*, 132–133.

Kanner, A. M., & Barry, J. J. (2003). The impact of mood disorders in neurological diseases: Should neurologists be concerned? *Epilepsy & Behavior, 4*, 3–13.

Kanner, A. M., Wuu, J., Faught, E., Tatum, W. O., 4th, Fix, A., French, J. A., et al. (2003). A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy and Behavior, 4*, 548–552.

Kasteleijn-Nolst Trenite, D. G., & Vermeiren, R. (2005). The impact of subclinical epileptiform discharges on complex tasks and cognition: Relevance for aircrew and air traffic controllers. *Epilepsy and Behavior, 6*, 31–34.

Kemper, B., Helmstaedter, C., & Elger, C. E. (1993). Neuropsychological assessment in patients with frontal lobe epilepsy. *Epilepsia, 34*, 170.

Kennepohl, S., Sziklas, V., Garver, K. E., Wagner, D. D., & Jones-Gotman, M. (2007). Memory and the medial temporal lobe: Hemispheric specialization reconsidered. *NeuroImage, 36*, 969–978.

Kessels, R. P. C., Hendriks, M. P. H., Schouten, J., Van Asselen, M., & Postma, A. (2004). Spatial memory deficits in patients after unilateral selective amygdalohippocampectomy. *Journal of the International Neuropsychological Society, 10*, 907–912.

Kim, C. H., Lee, S. A., Yoo, H. J., Kang, J. K., & Lee, J. K. (2007). Executive performance on the Wisconsin Card Sorting Test in mesial temporal lobe epilepsy. *European Neurology, 57*, 39–46.

Kiper, D. C., Zesiger, P., Maeder, P., Deonna, T., & Innocenti, G. M. (2002). Vision after early-onset lesions of the occipital cortex: I. Neuropsychological and psychophysiological studies. *Neural Plasticity, 9*, 1–25.

Knecht, S., Jansen, A., Frank, A., van Randenborgh, J., Sommer, J., Kanowski, M., et al. (2003). How atypical

is atypical language dominance? *NeuroImage, 18*, 917–927.

Kockelmann, E., Elger, C. E., & Helmstaedter, C. (2003). Significant improvement in frontal lobe associated neuropsychological functions after withdrawal of topiramate in epilepsy patients. *Epilepsy Research, 54*, 171–178.

Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Hauser, A. W., Mathern, G., et al. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia, 51*(6), 1069–1077.

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *New England Journal of Medicine, 342*, 314–319.

Langfit, J. T., & Rausch, R. (1996). Word-finding deficits persist after left anterotemporal lobectomy. *Archives of Neurology, 53*, 72–76.

Lee, G. P., Westerveld, M., Blackburn, L. B., Park, Y. D., & Loring, D. W. (2005). Prediction of verbal memory decline after epilepsy surgery in children: Effectiveness of Wada memory asymmetries. *Epilepsia, 46*, 97–103.

Lineweaver, T. T., Morris, H. H., Naugle, R. I., Najm, I. M., Diehl, B., & Bingaman, W. (2006). Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. *Epilepsia, 47*, 1895–1903.

Loring, D. W., Lee, G. P., Martin, R. C., & Meador, K. J. (1988). Material-specific learning in patients with partial complex seizures of temporal lobe origin: Convergent validation of memory constructs. *Journal of Epilepsy, 1*, 53–59.

Loring, D. W., Lowenstein, D. H., Barbaro, N. M., Fureman, B. E., Odenkirchen, J., Jacob, M. P. et al. (2011). Common data elements in epilepsy research: Development and implementation of the NINDS epilepsy CDE project. *Epilepsia, 52*, 1186–1191.

Loring, D. W., Meador, K. J., & Lee, G. P. (1994). Effects of temporal lobectomy on generative fluency and other language functions. *Archives of Clinical Neuropsychology, 9*, 229–238.

Loring, D. W., Strauss, E., Hermann, B. P., Barr, W. B., Perrine, K., Trenerry, M. R., et al. (2008). Differential neuropsychological test sensitivity to left temporal lobe epilepsy. *Journal of the International Neuropsychological Society, 14*, 394–400.

Luerding, R., Boesebeck, F., & Ebner, A. (2004). Cognitive changes after epilepsy surgery in the posterior cortex. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*, 583–587.

Maccotta, L., Buckner, R. L., Gilliam, F. G., & Ojemann, J. G. (2007). Changing frontal contributions to memory before and after medial temporal lobectomy. *Cerebral Cortex, 17*, 443–456.

Manchanda, R. (2002). Psychiatric disorders in epilepsy: Clinical aspects. *Epilepsy and Behavior, 3*, 39–45.

Majdan, A., Sziklas, V., & Jones-Gotman, M. (1996). Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology, 18*, 416–430.

Martin, R., Burneo, J. G., Prasad, A., Powell, T., Faught, E., Knowlton, R., et al. (2003). Frequency of epilepsy in patients with psychogenic nonepileptic seizures monitored by video-EEG. *Neurology, 61*, 1791–1792.

Martin, A., & Fedio, P. (1983). Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. *Brain and Language, 19*, 124–141.

Martin, R. C., Loring, D. W., Meador, K. J., & Lee, G. P. (1990). The effects of lateralized temporal lobe dysfunction on formal and semantic word fluency. *Neuropsychologia, 28*, 823–829.

Martin, R. C., Sawrie, S. M., Edwards, R., Roth, D. L., Faught, E., Kuzniecky, R. I., et al. (2000). Investigation of executive function change following anterior temporal lobectomy: Selective normalization of verbal fluency. *Neuropsychology, 14*, 501–508.

Martin, R., Sawrie, S., Gilliam, F., Mackey, M., Faught, E., Knowlton, R., et al. (2002). Determining reliable cognitive change after epilepsy surgery: Development of reliable change indices and standardized regression-based change norms for the WMS-III and WAIS-III. *Epilepsia, 43*, 1551–1558.

Mayeux, R., Brandt, J., Rosen, J., & Benson, D. F. (1980). Interictal memory and language impairment in temporal lobe epilepsy. *Neurology, 30*, 120–125.

McAndrews, M. P., & Milner, B. (1991). The frontal cortex and memory for temporal order. *Neuropsychologia, 29*, 849–859.

McDonald, C. R., Bauer, R. M., Grande, L., Gilmore, R., & Roper, S. (2001). The role of the frontal lobes in memory: Evidence from unilateral frontal resections for relief of intractable epilepsy. *Archives of Clinical Neuropsychology, 16*, 571–585.

McDonald, C. R., Delis, D. C., Norman, M. A., Tecoma, E. S., & Iragui, V. J. (2005). Discriminating patients with frontal-lobe epilepsy and temporal-lobe epilepsy: Utility of a multilevel design fluency test. *Neuropsychology, 19*, 806–813.

McDonald, C. R., Delis, D. C., Norman, M. A., Wetter, S. R., Tecoma, E. S., & Iragui, V. J. (2005). Response inhibition and set shifting in patients with frontal lobe epilepsy or temporal lobe epilepsy. *Epilepsy and Behavior, 7*, 438–446.

Milner, B. (1958). Psychological deficits produced by temporal lobe excision. In H. C. Solomon, S. Cobb, & W. Penfield (Eds.), *The brain and human behavior: Proceedings of the Association for Research in Nervous and Mental Disease*. Baltimore, MD: The Williams and Wilkins Company.

Milner, B. (1968a). Visual recognition and recall after right temporal-lobe excision in man. *Neuropsychologia, 6*, 191–209.

Milner, B. (1968b). Effects of different brain lesions on card sorting. *Archives of Neurology, 9*, 90–100.

Milner, B., Corsi, P., & Leonard, G. (1991). Frontal-lobe contribution to recency judgments. *Neuropsychologia, 29*, 601–618.

Milner, B., Petrides, M., & Smith, M. L. (1985). Frontal lobes and the temporal organization of memory. *Human Neurobiology, 4*, 137–142.

Ojemann, L. M., Ojemann, G. A., Dodrill, C. B., Crawford, C. A., Holmes, M. D., & Dudley, D. L. (2001). Language disturbances as side effects of topiramate and zonisamide therapy. *Epilepsy and Behavior, 2*, 579–584.

Patrikelis, P., Angelakis, E., & Gatzonis, S. (2009). Neurocognitive and behavioral functioning in frontal lobe epilepsy: A review. *Epilepsy and Behavior, 14*, 19–26.

Penfield, W., & Jasper, H. H. (1954). *Epilepsy and the functional anatomy of the human brain*. Boston, MA: Little, Brown.

Pigott, S., & Milner, B. (1993). Memory for different aspects of complex visual scenes after unilateral temporal- or frontal-lobe resection. *Neuropsychologia, 31*, 1–15.

Pillon, B., Bazin, B., Deweer, B., Ehrlé, N., Baulac, M., & Dubois, B. (1999). Specificity of memory deficits after right or left temporal lobectomy. *Cortex, 35*, 561–571.

Powell, H. W., Koepp, M. J., Symms, M. R., Boulby, P. A., Salek-Haddadi, A., Thompson, P. J., et al. (2005). Material-specific lateralization of memory encoding in the medial temporal lobe: Blocked versus event-related design. *NeuroImage, 27*, 231–239.

Rapport, L. J., Millis, S. R., & Bonello, P. J. (1998). Validation of the Warrington theory of visual processing and the Visual Object and Space Perception Battery. *Journal of Clinical and Experimental Neuropsychology, 20*, 211–220.

Rausch, R., & Babb, T. L. (1993). Hippocampal neuron loss and memory scores before and after temporal lobe surgery for epilepsy. *Archives of Neurology, 50*, 812–817.

Rzezak, P., Fuentes, D., Guimaraes, C. A., Thome-Souza, S., Kuczynski, E., Li, L. M., et al. (2007). Frontal lobe dysfunction in children with temporal lobe epilepsy. *Pediatric Neurology, 37*, 176–185.

Salanova, V., Andermann, F., Rasmussen, T., Olivier, A., & Quesney, L. F. (1995). Parietal lobe epilepsy: Clinical manifestations and outcome in 82 patients treated surgical between 1929 and 1988. *Brain, 118*, 607–627.

Saling, M. M. (2009). Verbal memory in temporal lobe epilepsy: Beyond material specificity. *Brain, 132*, 570–582.

Saling, M. M., Berkovic, S. F., O'Shea, M. F., Kalnins, R., Darby, D., & Bladin, P. (1993). Lateralization of verbal memory and unilateral hippocampal sclerosis: Evidence of task-specific effects. *Journal of Clinical and Experimental Neuropsychology, 15*, 608–618.

Salinsky, M. C., Storzbach, D., Spencer, D. C., Oken, B. S., Landry, T., & Dodrill, C. B. (2005). Effects of topiramate and gabapentin on cognitive abilities in healthy volunteers. *Neurology, 64*, 792–798.

Sawrie, S. M., Chelune, G. J., Naugles, R. I., & Luders, H. O. (1996). Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. *Journal of the International Neuropsychological Society, 2*, 556–564.

Saykin, A. J., Stafiniak, P., Robinson, L. J., Flannery, K. A., Gur, R. C., O'Connor, M. J., et al. (1995). Language before and after temporal lobectomy: Specificity of acute changes and relation to early risk factors. *Epilepsia, 33*, 1071–1077.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *The Journal of Neuropsychiatry and Clinical Neurosciences, 12*, 103–113.

Seidenberg, M., Griffith, R., Sabsevitz, D., Moran, M., Haltiner, A., Bell, B., et al. (2002). Recognition and identification of famous faces in patients with unilateral temporal lobe epilepsy. *Neuropsychologia, 40*, 446–456.

Siegel, A. M., & Williamson, P. D. (2000). Parietal lobe epilepsy. *Advances in Neurology, 84*, 189–199.

Spiers, H. J., Burgess, N., Maguire, E. A., Baxendale, S. A., Hartley, T., Thompson, P. J., et al. (2001). Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. *Brain, 124*, 2476–2489.

Squire, L. R. (1993). The organization of declarative and nondeclarative memory. In T. Ono, L. R. Squire, M. E. Raichle, M. Fukuda, & D. I. Perret (Eds.), *Brain mechanisms of perception and memory: From neuron to behaviour*. New York, N:Y: Oxford University Press.

Stuss, D. T., Alexander, M. P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., et al. (1998). The effects of focal anterior and posterior brain lesions on verbal fluency. *Journal of the International Neuropsychological Society, 4*, 265–278.

Suchy, Y., Sands, K., & Chelune, G. J. (2003). Verbal and nonverbal fluency performance before and after seizure surgery. *Journal of Clinical and Experimental Neuropsychology, 25*, 190–200.

Sylvester, C.-Y. C., & Shimamura, A. P. (2002). Evidence for intact semantic representations in patients with frontal lobe lesions. *Neuropsychology, 16*, 197–207.

Takaya, S., Hanakawa, T., Hashikawa, K., Ikeda, A., Sawamoto, N., Nagamine, T., et al. (2006). Prefrontal hypofunction in patients with mesial temporal lobe epilepsy. *Neurology, 67*, 1674–1676.

Temkin, N. R., Heaton, R. K., Grant, I., & Dikmen, S. S. (1999). Detecting significant change in neuropsychological test performance: A comparison of four models. *Journal of the International Neuropsychological Society, 5*, 357–369.

Thurtell, M. J., Mohamed, A., Luders, H. O., & Leigh, R. J. (2009). Evidence for three-dimensional cortical control of gaze from epileptic patients. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*, 683–685.

Treyer, V., Buck, A., & Schnider, A. (2005). Processing content or location: Distinct brain activation in a memory task. *Hippocampus, 15*, 684–689.

Troster, A. I., Warmflash, V., Osorio, I., Paolo, A. M., Alexander, L. J., & Barr, W. B. (1995). The roles of semantic networks and search efficiency in verbal

fluency performance in intractable temporal lobe epilepsy. *Epilepsy Research, 21*, 19–26.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

Upton, D., & Thompson, P. J. (1996). General neuropsychological characteristics of frontal lobe epilepsy. *Epilepsy Research, 23*, 169–177.

Upton, D., & Thompson, P. J. (1999). Twenty questions task and frontal lobe dysfunction. *Archives of Clinical Neuropsychology, 14*, 203–216.

Vannest, J., Szaflarski, J. P., Privitera, M. D., Schefft, B. K., & Holland, S. K. (2008). Medial temporal fMRI activation reflects memory lateralization and memory performance in patients with epilepsy. *Epilepsy and Behavior, 12*, 410–418.

Warrington, E. K., & James, M. (1991). *Visual Object and Space Perception Battery*. Edmunds, UK: Thames Valley Company.

Weber, B., Fliessbach, K., Lange, N., Kugler, F., & Elger, C. E. (2007). Material-specific memory processing is related to language dominance. *NeuroImage, 37*, 611–617.

Wechsler, D. (1997). *Wechsler memory scale—3rd edition* (3rd ed.). San Antonio, TX: The Psychological Corporation.

Weintrob, D. L., Saling, M. M., Berkovic, S. F., & Reutens, D. C. (2007). Impaired verbal associative learning after resection of left perirhinal cortex. *Brain, 130*, 1423–1431.

Weniger, G., Boucsein, K., & Irle, E. (2004). Impaired associative memory in temporal lobe epilepsy subjects after lesions of hippocampus, parahippocampal gyrus, and amygdala. *Hippocampus, 14*, 785–796.

Wiebe, S., Blume, W. T., Girvin, J. P., & Eliasziw, M. (2001). Effectiveness and efficiency of surgery for temporal lobe epilepsy group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *New England Journal of Medicine, 345*, 311–318.

Wilde, N. J., Strauss, E., Chelune, G. J., Hermann, B. P., Hunter, M., Loring, D. W., et al. (2003). Confirmatory factor analysis of the WMS-III in patients with temporal lobe epilepsy. *Psychological Assessment, 15*, 56–63.

Williamson, P. D. (1987). Intensive monitoring of complex partial seizures: Diagnosis and subclassification. *Advances in Neurology, 46*, 69–84.

Williamson, P., Spencer, D. D., Spencer, S. S., Novelly, R. A., & Mattson, R. H. (1985). Complex partial seizures of frontal lobe origin. *Annals of Neurology, 18*, 497–504.

The Wada Test: Current Perspectives and Applications

5

David W. Loring and Kimford J. Meador

The Wada test has been an integral part of the preoperative evaluation for epilepsy surgery since the 1950s. Originally designed to establish cerebral language laterality, it was subsequently modified by including a memory component to estimate postoperative risk to recent memory function following unilateral temporal lobe resection. This chapter will briefly review the use of Wada testing, discuss the various approaches used to transiently anesthetize brain regions prior to cognitive assessment, and conclude with the specific methods developed at the Medical College of Georgia (MCG). The Wada test is not only employed to predict postoperative risks of language and memory deficits but is also a marker of temporal lobe dysfunction and as such should be sensitive to seizure-onset laterality in patients with temporal lobe epilepsy. Wada test results should always be interpreted within the context of other clinical and diagnostic test findings. The lessons learned from pitfalls in Wada testing should be carefully considered in the development and application of other techniques to assess focal cerebral function/dysfunction.

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Historical Background

The Wada test was conceived by Juhn Wada in post World War II Japan as a technique to limit bilateral seizure effects of ECT in acute schizophrenic psychosis and manic-depressive illness (Wada, 1997). Wada reasoned that by "anesthetization through a carotid route to prevent seizure bilateralization," the cognitive side effects associated with bilateral ECT would be minimized. Before Wada was able to implement this approach with patients undergoing bilateral ECT, he was faced with a patient with repeated episodes of partial status epilepticus and occasional generalization following a penetrating missile injury. Chloral hydrate, the standard treatment of status epilepticus at that time, failed to break the partial status. Consequently, Wada chose to administer the amobarbital, which he had procured for ECT use, in an attempt to arrest the status, and unilateral carotid amobarbital injection to this patient was successful in stopping the status.

The Wada procedure as a technique to establish cerebral language representation in epilepsy surgery candidates was introduced to the Montreal Neurological Institute (MNI) in 1956 when Dr. Wada was at the MNI on fellowship. Since epilepsy was known to potentially alter

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cerebral language dominance, the approach of introducing transient hemispheric anesthesia became routine when any possibility of atypical language existed, and Wada testing became the gold standard for determining language laterality.

The memory component of the Wada was introduced several years later after several cases of severe memory decline were observed following unilateral temporal lobectomy (Penfield & Milner, 1958). The memory declines in these patients were thought to be the results of significant bilateral disease that went unrecognized during the presurgical evaluation. In these patients with significant temporal lobe disease contralateral to surgery, there was insufficient residual temporal lobe function following surgery to sustain new memory formation. At this time in the late 1950s, the state of the art in diagnostic imaging was the pneumoencephalogram. In addition, the standard clinical EEG consisted of only eight channels, and video/EEG monitoring was years away. Thus, the number of tools to identify significant temporal lobe impairment contralateral to the proposed surgery was limited. By introducing items to be remembered during the period of hemispheric anesthesia, Milner reasoned that the effects of surgical resection on memory could be modeled and risk for significant postsurgical decline estimated (Milner, Branch, & Rasmussen, 1962).

The initial and still the most common anesthetic agent used in Wada testing is amobarbital, although shortages and limitations of availability worldwide have led to other medications being employed. Although initially introduced using a direct carotid stick, the medication is routinely delivered via a femoral catheter through the aortic arch and into the carotid artery. Most centers administer drug by hand rather than machine injection, and the anterior two-thirds of each hemisphere is transiently anesthetized while the patient is presented with multiple language and other cognitive tasks.

The Wada test is more accurately characterized as a procedure rather than a test, since no standardized protocol exists across epilepsy centers. There are multiple procedural variations including medication dose, language and memory stimuli, scoring criteria, as well as the anesthetic agent used. Because of the variability in testing protocols, it has been difficult to establish a representative evidence base for Wada testing overall, with some centers reporting robust findings, while other centers have failed to find clinically relevant results. Further, a major methodological limitation has been the confound that Wada results are often used to establish surgical candidacy. Consequently, the predictor and outcome variables are not completely independent. Finally, some centers perform Wada testing only on selected patients, precluding a consecutive series of patients from being reported, thus introducing methodological bias into the results.

Language

In most patients, the identification of cerebral language dominance is straightforward, since most individuals have left cerebral language dominance. In these cases, there is disruption of multiple aspects of language following left hemisphere injection, such as speech arrest, loss of comprehension, naming deficits, and during recovery, paraphasic errors. In contrast, there is no change in language abilities following right hemisphere injection. However, as is the case with memory testing, the reliability and validity of Wada language testing, particularly in the case of atypical language representation, depends in part on which language tasks are used and the criteria that are employed for inferring language representation based upon patient response.

As the number of epilepsy surgery centers began to expand in the mid-1980s, concern emerged over the large discrepancy in reported prevalence of bilateral language representation. Specifically, some epilepsy centers observed bilateral language as often as 60 % of patients being studied, whereas other centers reported bilateral language rarely or in some cases never (Snyder, Novelly, & Harris, 1990).

The observed discrepancy in rates of bilateral language exceeded what could easily be attributed to patient population differences given the relative homogeneity of most epilepsy surgical samples

with similar syndrome classification. Instead, this disparity reflected center differences in the classification criteria used to infer bilateral language since uniform standards do not exist to guide interpretation. High rates of bilateral language were reported in centers using speech cessation to infer language representation. Subsequent investigations of Wada language criteria compared to fMRI activation patterns, however, revealed that speech cessation was unrelated to language activation using fMRI (Benbadis et al., 1998). Speech arrest following nondominant hemisphere injection may result from acute drug effects associated with a bolus of amobarbital and, thus, lead to inflated estimates of bilaterality.

We consider the presence of positive paraphasic errors to be a much stronger sign of linguistic impairment related to language representation than negative responses, such as speech arrest or failure to respond to task requests. However, the absence of response to multiple linguistic tasks (e.g., comprehension, naming) helps provide greater confidence of linguistic impairment compared to an isolated failure on a single task such as expressive speech cessation. Paraphasic errors are less likely to be observed following short-acting agents such as methohexital given the rapid return to baseline levels of function.

Wada Language Validity

There are three primary approaches to validate Wada language testing. The first is not truly statistical in nature and involves the degree to which language representation inferred by Wada testing is confirmed in patients undergoing electrical stimulation language mapping. There are multiple reports indicating a strong correlation in patients with left hemisphere language findings (Ojemann, 1980; Wyllie et al., 1990), but this relationship is more convincing for patients with atypical language representation in the right hemisphere given the very high base rates of left hemisphere language. Although infrequent, patients with right hemisphere or bilateral language in whom stimulation mapping can be performed during right-sided surgery have exhibited the expected relationships (Jabbour, Hempel, Gates, Zhang, & Risse, 2005; Loring et al., 1990a).

The second approach to validate the use of Wada language results is to examine the degree to which Wada language results predict postoperative change in naming ability. Although the robust relationship between naming decline and left/language resection vs. right/nonlanguage resection has been adequately described (Glosser & Donofrio, 2001; Ruff et al., 2007), surprisingly, there appears to be only a single report in the literate directly addressing the issue of Wada laterality scores and language outcomes. In a series of 24 patients undergoing left anterior temporal lobectomy, the Wada language asymmetry score reflecting the interhemispheric difference language performance following left and right hemisphere injections was significantly related to the magnitude of postoperative decline on the Boston naming test (Sabsevitz et al., 2003). However, in these patients, an even stronger predictor of postoperative naming decline was language asymmetry scores using fMRI.

The final approach to validating the Wada language component has used noninvasive approaches such as fMRI and MEG. Although the majority of these studies have relied on Wada results as the gold standard of language and as the independent variable, the strong relationship between Wada language results and these noninvasive measures provides support that language testing during hemispheric anesthesia reliably establishes cerebral language representation (Arora et al., 2009; Binder et al., 1996; Doss, Zhang, Risse, & Dickens, 2009; Gaillard et al., 2002; Papanicolaou et al., 2004; Suarez et al., 2009; Woermann et al., 2003). Despite overall agreement across studies in the 90 % range, the reasons for the discrepancies between approaches continue to be explored and debated. In general, the greatest disagreements occur in patients considered to have bilateral language representation by one approach and unilateral language by another, with complete disagreements of results being rare (Gaillard et al., 2004).

Memory

Wada memory testing is used primarily to evaluate risk for postoperative memory decline, although Wada memory interhemispheric difference score may also be used to verify seizure-onset laterality. When the hemisphere ipsilateral to a medial temporal lobe seizure focus is anesthetized, the *functional reserve* capacity of the contralateral temporal lobe to sustain memory function in isolation is assessed (Chelune, 1995). This score provides an estimate of the ability of the contralateral temporal lobe to sustain recent memory function when the temporal lobe with the seizure focus is resected. Functional reserve assessment was the original goal of Wada memory testing in order to avoid significant postoperative amnesia following unilateral temporal lobe resection (Milner et al., 1962).

In the early 1990s, improved MRI imaging techniques (Jack et al., 1992) created greater interest examining the degree of sclerosis in the temporal lobe to be resected. Since there are varying degrees of residual function in the diseased/ipsilateral temporal lobe, the *functional adequacy* of the temporal lobe associated with seizure onset is assessed by the injection contralateral to seizure onset. Thus, ipsilateral and contralateral injections contribute differently to memory function in the preoperative patient with temporal lobe epilepsy and are used to predict different aspects of postoperative memory outcomes.

Because Wada protocols are not standardized, it is difficult to estimate to what degree method variance contributes to some of the reported variability in memory outcome prediction. For example, protocol differences in memory stimuli will lead to different results about the utility of Wada testing as part of a comprehensive epilepsy surgery evaluation (Testa, Ward, Crone, & Brandt, 2008). We have shown that factors such as stimulus type (pictures vs. real objects) (Loring et al., 1997), timing of stimulus presentation (Loring, Meador, et al., 1994), mixed stimuli (Lee, Park, Westerveld, Hempel, & Loring, 2002), and amobarbital dose (Loring, Meador, & Lee, 1992) affect Wada memory correlations with seizure-onset laterality. Although the goal of Wada memory testing is to forecast postoperative memory decline, demonstrating the sensitivity of Wada memory results to lateralized temporal lobe impairments provides a surrogate to the goal of postoperative seizure outcome prediction. Thus, in the absence of a strong relationship between Wada memory asymmetry findings and seizure-onset laterality, it should not be surprising to conclude that the Wada test is a poor predictor of memory outcome. The potential confound of aphasia on verbal memory stimuli is well recognized (Kirsch et al., 2005), but many Wada protocols include words as memory items. Thus, generalizations of specific Wada memory findings to other Wada memory protocols must necessarily be made cautiously (Meador & Loring, 2005).

Even within our own center, we have reported different "utility" of the Wada test based upon different methodologies employed at the time. For example, we observed that successful postoperative memory outcomes could be observed following Wada memory failure (Loring, Lee, et al., 1990); our Wada protocol at that time employed relatively large total doses of amobarbital with some patient demonstrating greater sedation which was induced by multiple incremental amobarbital injections. However, after we demonstrated an adverse dose effect on Wada memory results, we established a protocol with real objects and lower dosing, and we observed a case of postoperative amnesia in which Wada memory results appeared to predict that outcome (Loring, Hermann, et al., 1994).

Establishing the validity of Wada memory testing presents multiple challenges. Prior to the mid-1980s, when there were few techniques other than the Wada test to identify patients at risk for postoperative memory decline, a major problem with establishing validity was the confounding of the independent and dependent variables associated with using Wada memory results to establish surgical candidacy. Thus, patients thought to be at risk for significant postoperative memory decline were excluded from surgery, and the ability of Wada memory testing to predict postoperative amnesia could not be established.

However, as other methods to predict postoperative memory change such as MRI or PET started to emerge as additional approaches to forecast cognitive outcomes, patients with questionable Wada memory results could more often proceed to surgery than when Wada was only a technique to predict cognitive change. Thus, the existence of some "false-positive" error rate could be established.

Wada validity has relied on a number of indirect approaches, the most common being seizure-onset laterality as a surrogate measure of hippocampal function. On the group level, patients with unilateral temporal lobe epilepsy should perform relatively high levels when the hemisphere ipsilateral to seizure onset is injected since the relatively diseased and nonfunctioning temporal lobe is being anesthetized and thus should create little additional memory impairment. In contrast, when the hemisphere contralateral to seizure onset is injected, there should be poor memory due to bilateral temporal lobe dysfunction due to effects of the seizure focus on one side and the disruptive effects of the pharmacologic inactivation on the other side.

Interhemispheric Wada memory asymmetry (WMA) scores have often been considered lateralizing based solely on the direction of WMA (Cohen-Gadol, Westerveld, Alvarez-Carilles, & Spencer, 2004; Lee, Westerveld, Blackburn, Park, & Loring, 2005; Sabsevitz, Swanson, Morris, Mueller, & Seidenberg, 2001), although other reports have required a larger discrepancy to be considered lateralizing (Perrine et al., 1995; Sperling et al., 1994) or have determined WMAs based on the pattern of Wada memory failure between both hemispheres (Alpherts, Vermeulen, & van Veelen, 2000). Using a single cut point for Wada asymmetry classification discards potentially relevant information from interval measurement scaling by using cut points to create a dichotomous outcome. Multiple-level likelihood ratios (LRs) avoid artificial classification dichotomies by examining classification rates across a range of scores (Grimes & Schulz, 2005; Hosmer & Lemeshaw, 2000; Strauss, Richardson, Glasziou, & Haynes, 2005).

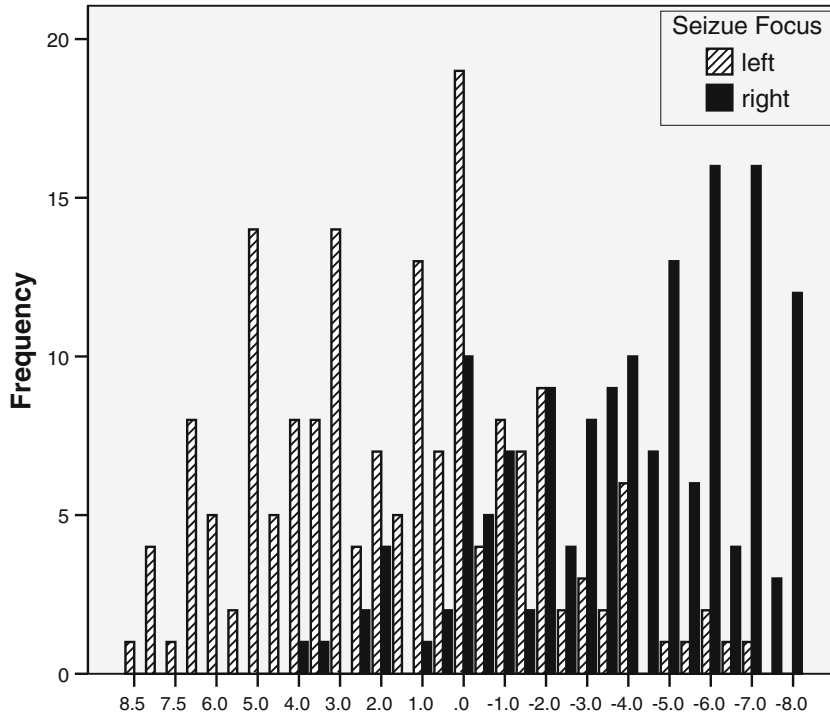

Fig. 5.1 Histogram of WMA in MCG patient series of TL patients by seizure-onset laterality. (From Loring et al., 2009)

Table 5.1 Multiple-level likelihood ratios (LRs) for different magnitudes of WMAs using the MCG Wada protocol

	Left TL ($N=172$)	Right TL ($N=152$)	
WMAs	Freq (column %)	Freq (column %)	LRs
>4.0	40 (23.3)	0 (0.0)	Infinitively large
2.5 to 4.0	34 (19.8)	4 (2.6)	7.6
0.5 to 2.0	32 (18.6)	7 (4.6)	4.0
−1.5 to −0.0	38 (22.1)	24 (15.7)	1.4
−3.5 to −2.0	16 (9.3)	30 (19.7)	0.47
−5.5 to −4.0	8 (4.7)	36 (23.7)	0.20
−7.5 to −6.0	4 (2.3)	39 (25.7)	0.089
−8.0	0 (0.0)	12 (7.9)	Zero

From Loring et al., 2009

WMA Wada memory asymmetries, *TL* temporal lobe

The use of different cut points is illustrated in a recent report from our MCG patient series (Loring, Bowden, Lee, & Meador, 2009). As illustrated in Fig. 5.1, the magnitude of WMA in this group of temporal lobe epilepsy (TLE) patients who went to surgery varies as a function of seizure-onset laterality, although there is also considerable overlap. For patients with left TLE, the average memory score following left hemisphere injection was 4.2/8 (SD = 2.5) and following right injection = 2.7/8 (SD = 2.8), with a WMA = 1.6 (SD = 3.4). For patients with right TLE, the average memory score following left hemisphere injection was 1.7/8 (SD = 2.2) and following right injection = 5.6/8 (SD = 2.2), with an average WMA = −3.9 (SD = 2.8). Although the left and right WMA are in the correct direction, it is clear from examining the language of the WMA for each group that that disruptive effects of language impairment following left hemisphere injection appear to affect the asymmetry score by approximately 2 points.

Classifying patients using multiple-level LRs, we observed that 40 left TLE patients (23.3 %) obtained asymmetry scores greater than +4, whereas no right TLE patients obtained asymmetry scores in this range (see Table 5.1). At the other extreme, no left TL patients obtained a difference score of −8 or less, although 12 right TLE patients (7.9 %) obtained a difference score of −8. Thus, the left TL LR is infinitely large for WMAs greater than +4 and infinitely small for WMAs = −8. In contrast to traditional sensitivity and specificity classification using logistic regression, or dichotomous LRs, the multiple-level LRs indicate greater diagnostic sensitivity for larger WMA magnitudes.

In addition to memory outcome studies, numerous reports indicate a relationship between Wada memory scores and hippocampal volume or cell counts (Baxendale et al., 1997; Cohen-Gadol et al., 2004; Davies, Hermann, & Foley, 1996; Loring et al., 1993; Sass et al., 1991). Both hippocampal volumes and Wada memory asymmetries are related to postoperative verbal memory decline (Cohen-Gadol et al., 2004; Lee et al., 2005; Loring et al., 1995; Perrine et al., 1995; Sabsevitz et al., 2001; Sperling et al., 1994; Stroup et al., 2003).

Although intact baseline verbal memory function and Wada memory performance following injection contralateral to the seizure focus both make independent contributions to verbal memory outcome prediction beyond laterality of resection and presence of lesions other than medial temporal sclerosis (MTS), baseline delayed verbal memory predicted post-op outcome at a higher level of statistical significance compared to Wada memory (Stroup et al., 2003). However, this report employed real objects for only 75 % of the memory stimuli, and individual Wada scores for each group following left and right hemisphere injections are not presented.

In a separate report, Wada memory scores were superior to baseline neuropsychological test findings in predicting verbal memory change following left temporal lobectomy, although the magnitude of this improvement was sufficiently small that the authors did not feel that significant "added benefit" was obtained to justify subjecting all patients to Wada testing (Baxendale, Thompson, Harkness, & Duncan, 2007). However, we note that the Wada protocol employed contained four verbal (naming to description) and four visual memory stimuli (real

objects); further, four of the eight stimuli were presented again during active drug effect with four foils, and postdrug recognition memory testing was performed with the other four targets and four additional foils. Thus, their memory scores combined performance during active drug and following return to baseline, employed a target to foil ratio of 1:1, and used both verbal and nonverbal stimuli. Across this patient series, the left minus right injection WMA for left temporal lobectomy (TL) patients was −0.15 (SD = 1.2), whereas the WMA for right TL patients was −1.8 (SD = 1.5), indicating little sensitivity to seizure-onset laterality. The average score for left TL patients following left hemisphere injection was 7.1/8 and following right hemisphere injection was 7.2/8 or declines from a nondrug state of only 10–11 %. This compares to declines in left TL patients of 48 % (left hemisphere injection) and 66 % (right hemisphere injection) compared to nondrug expectations in the MCG patient series (Loring et al., 2009).

The same concern exists for a different report stating that Wada memory added nothing to postoperative outcome prediction over baseline neuropsychological testing and MRI in patients undergoing left anterior temporal lobectomy (ATL) (Elshorst et al., 2009). Their primary Wada memory protocol consists of 18 items (4 objects, 5 written words, 1 number, 1 color, 1 command, 3 pictures, 1 phase, and 2 definitions). Unlike the Baxendale results above, the authors report a clear effect of medication with an average recognition score of 62 % following the left (ipsilateral) injection but only 39 % following right (contralateral) hemisphere injection in this series of left ATL patients. However, almost 25 % of their sample had atypical cerebral language representation (right or bilateral), and it is unclear what the effects of language impairment may have had in this sample given the prominent linguistic content of their memory stimuli. A better test of predicting outcome may have been to study patients with typical left hemisphere language dominance, as well as reporting bilateral Wada memory scores in those undergoing right ATL.

Comparing performances across procedures indicates nonequivalence of protocols and different sensitivity to lateralized temporal lobe dysfunction. The failure of Wada memory testing to satisfactorily predict postoperative outcome may simply reflect protocol-specific limitations rather than suggesting that all Wada protocols fall short in this regard. In general, those centers that strongly advocate against the utility of the Wada test have protocols that may be less robust (e.g., Kirsch et al., 2005). If a Wada protocol has not been empirically validated by any of the approaches described above (e.g., sensitivity to seizure-onset laterality across left and right TLE patients), then the likelihood of clinical outcome prediction may indeed be poor since the protocol itself may be inadequate to demonstrate unilateral temporal lobe dysfunction.

In a comparison of fMRI and Wada memory with other predictors of verbal memory outcome following ATL, baseline memory and age of seizure onset together accounted for roughly 50 % of the variance in memory outcome, and fMRI explained an additional 10 % of this variance (Binder et al., 2008). Neither Wada memory asymmetry nor Wada language asymmetry added additional predictive power beyond these noninvasive measures. The Wada protocol employed at the Medical College of Wisconsin (MCW) is based upon the MCG protocol and employs real objects. However, even here there are potentially important procedural differences, with the presumed side of seizure onset at MCW always injected first, whereas the order of injection for the MCG protocol randomized across patients. Thus, there is the potential for diminished WMA scores in the Binder series if there is any residual drug effect from the initial (ipsilateral) injection when performing the second (contralateral) study.

WMA scores that are inconsistent with the side of seizure onset appear to indicate a risk for predicting postoperative verbal memory change (Baxendale et al., 2007; Sabsevitz et al., 2001). This relationship would be expected since WMA scores are a combination of functional reserve and functional adequacy. In addition, Wada memory

testing suggests that verbal memory Wada results (right hemisphere injection) are moderately correlated with baseline neuropsychological verbal memory results (Vingerhoets, Miatton, Vonck, Seurinck, & Boon, 2006). One limitation of the Wada test, at least currently in the US healthcare system, is that the number of patients seen in follow-up is low. In fact, follow-up rates are increasingly low due to insurance coverage limitations in which follow-up assessments are not covered, except in the instances of significant postoperative change. Current levels of evidence required by the journal *Neurology* require a loss to follow-up rate of 20 % or less in order to infer a Class I level (Gross & Johnston, 2009).

Alternative Medications

The availability of amobarbital became sporadic beginning in the late 1990s. In addition, amobarbital is no longer manufactured by Lilly but is produced by Raxbury, which does not distribute the drug outside the USA. This had two direct effects on Wada testing. First, alternative anesthetic agents including methohexital, propofol, and etomidate were explored as agents to create hemispheric anesthesia for traditional Wada language and memory testing. The second effect, however, was to focus attention on issues regarding whether Wada testing should be the standard of care in the evaluation of all epilepsy surgery candidates.

Although formal surveying has not been done, the second most common anesthetic after amobarbital is likely methohexital (Brevital). Methohexital was introduced for Wada testing at the University of Florida due to its relatively short duration of action that would facilitate both hemispheres being studied on the same day because left and right amobarbital Wada injections were performed on different days at many surgical centers (Gilmore, Heilman, Schmidt, Fennell, & Quisling, 1992). The largest study using methohexital is from the University of Michigan (Buchtel, Passaro, Selwa, Deveikis, & Gomez-Hassan, 2002), and this drug has also been more recently adopted by the Cleveland Clinic (Lineweaver et al., 2006). In contrast to amobarbital administration, methohexital is typically given in divided doses of 3 mg followed shortly by 2 mg, although the reasons for this rather than a single mg injection are not clear and whether this approach is superior in any way to a single 5 mg injection has not been established. Single doses of 6–8 mg have been used without any apparent difficulty (Marla Hamberger, personal communication, December 5, 2009). In general, language and memory results using methohexital appear to be equivalent to those obtained using amobarbital. However, there appears to be increased seizure risk since methohexital is associated with a decreased seizure threshold (Loddenkemper, Moddel, Schuele, Wyllie, & Morris, 2007).

Propofol is a nonbarbiturate anesthesia with a very short duration of action and has been successfully used as a substitute for amobarbital. Dosing of 20 mg of propofol produces results comparable to 120 mg of amobarbital as reflected by the time to verbal and nonverbal responses (Mikati et al., 2009). However, due to its short duration of action, a number of patients require incremental injections to maintain the desired level of motor weakness. Approximately one-third of patients had an adverse event following propofol injection, with 12 % of all patients having increased muscle tone with twitching, rhythmic movements, or tonic posturing. Patients older than 55 or receiving a total injection dose greater than 20 mg were more likely to have significant adverse events, which in turn carries a risk of incompletion or inaccuracy of the Wada test.

Another nonbarbiturate anesthetic alternative to amobarbital is etomidate, which has rapid onset and short duration of action. Several approaches to etomidate administration have been successfully employed. At the MNI, a bolus of 2 mg etomidate that is administered followed by infusion insures a uniform period of anesthesia (Jones-Gotman et al., 2005). The bolus is followed by an infusion (0.003–0.004 mg/kg/min) at a rate of 6 mL/h. The use of a constant infusion allows direct control of the period of hemispheric anesthesia, insuring that all testing and memory item presentation is presented during maximum anesthesia rather than during recovery from anes-

thesia in which the medication effects are not fully known and may not be equivalent between hemispheres.

Comment

The difficulty in obtaining amobarbital has had the benefit of making centers ask the question of whether Wada testing can be or should be performed in all patients and to evaluate to what degree Wada testing should continue to be performed in preoperative epilepsy surgery evaluation. Advances in functional and structural imaging have provided predictors of memory outcome, thereby decreasing the sole reliance on Wada memory results in this context. However, there continues to be confusion about the role of the Wada test since so many procedural variations exist. Further, difficulty also exists given the variability in neuropsychological memory outcome measures and what the definitions of "significant change" are employed. Ultimately, these pieces of information are necessary to inform epilepsy programs which patient should be considered for Wada testing since the cost/benefit ratio will vary based upon clinical semiology, patient characteristics, and Wada protocol employed.

Miscellaneous

The potency of anesthetic effects of amobarbital is reduced by carbonic anhydrase inhibitor medications such as topiramate or zonisamide (Bookheimer, Schrader, Rausch, Sankar, & Engel, 2005; Burns et al., 2009; Kipervasser et al., 2004). Thus, amobarbital dose adjustments may be required, or testing patients off their carbonic anhydrase medications may be preferred.

Medical College of Georgia (MCG) Wada Protocol: Clinical Core

The total duration of amobarbital anesthetic effect depends both on the initial drug dose, whether additional incremental injections are administered (to produce a flaccid contralateral hemiplegia), and individual patient differences in drug responsivity. However, behavioral recovery tends to be rapid, rarely lasting more than 10 min. In our experience, comprehension of complex two-stage commands involving inverted syntax is typically the last language-related ability to recover, and repetition is the next most sensitive language measure to mild residual medication effects. Typically, the last motor deficits to resolve include pronator drift, decreased motor speed, or asterixis contralateral to the side of injection. Return of language and motor functions to baseline levels is necessary prior to assessing memory.

Patients undergoing Wada testing have a pretest baseline evaluation that serves two purposes. The first is to familiarize the patient with the specific techniques that will be administered during the test. The second is to establish a baseline level of function, which is particularly useful for language tasks since they may be affected by schooling, clinical history, as well as having idiosyncratic regional dialects. With few exceptions, patients will obtain perfect scores of 8/8 for memory testing using our recognition approach. The order of injection between the presumed ipsilateral and contralateral sides is alternated across patients in order to ensure that there is not a systematic confound associated with injection order. For example, to the extent that there are residual amobarbital effects lasting beyond the typical testing window, always beginning the ipsilateral injection may tend to decrease WMA magnitude. Both hemispheres are typically tested on the same day, with a minimum of 30 min separating the two hemispheric studies. Patients are forewarned that they may experience arm weakness or difficulty talking, although memory for either impairment is often poor. Patients are also told that the medication makes some people feel a little bit drunk or sleepy. This is included to reduce anxiety and to create an expectancy to help the patient interpret subjective drug-induced effects. After beginning to tell patients about potential subjective drug effects, we have decreased the number of "confused" or mildly agitated responses to nearly zero.

General

Patients begin counting repeatedly from 1 to 20 with their hands held up, their palms turned upward, and fingers spread. An injection of 100 mg amobarbital is administered by hand over a 4–5 s interval via a percutaneous transfemoral catheter. Following demonstration of hemiplegia and evaluation of eye-gaze deviation, the patient is requested to execute a simple midline command (e.g., "stick out your tongue"). We do not require a complete flaccid hemiplegia in order to proceed with cognitive testing and do not base our timing of stimulus presentation according to EEG-based information. If there is only minimal change in muscle tone, an incremental injection of 25 mg may be used. However, we try to avoid more than one additional dose increment since it has been our experience that multiple injections increase the likelihood of patient obtundation compared to an identical total dose delivered with a single bolus. Complete lack of motor deficit suggests misplacement of the catheter.

Following evaluation of simple comprehension for midline commands and eye gaze, eight common objects are presented for 4–8 s each in the visual field midline and ipsilateral to the injection, and the object names are repeated twice to the patient. On average, this occurs beginning approximately 30–45 s following injection. Examples of Wada memory items include a combination of ordinary household items (e.g., fork, mousetrap), small toys (e.g., doll, plastic shark), and plastic food (e.g., hotdog, pizza). At times, due to patient confusion, inattention, or nonresponsiveness, the patient's eyes are held open. Language, discussed below, is assessed in detail following presentation of memory items. We also impose a minimum of 10 min between drug administration and memory assessment. Recognition memory of material presented during the procedure is tested after amobarbital effects have worn off as demonstrated by return baseline language performance on all tasks described below, return of 5/5 strength, and absence of pronator drift, tactile extinction, asterixis, and bradykinesia.

Language

Language assessment contains five common language domains (viz., counting disruption, comprehension, naming, repetition, and reading). Although we have developed a formalized approach to calculate a language laterality ratio [(left score minus right score)/(left score plus right score), (L − R)/(L + R)], this laterality ratio is used for research purposes and is not routinely reported clinically (Loring et al., 1990b).

Expressive Language/Counting

At the outset of the Wada test, patients begin counting from 1 to 20 repeatedly. The expressive language score (0–4) is based upon disruption of counting (4 = normal, slowed, or brief pause <~20 s; 3 = counting perseveration with normal sequencing; 2 = sequencing errors; 1 = single number or word perseveration; 0 = arrest >~20 s). Based upon the findings that a brief language pause following drug administration does not correspond to laterality scores obtained from fMRI (Benbadis et al., 1998), we require at least a 20 s speech arrest to insure that counting interruption is not due to acute generalized medication effects. If speech arrest occurs, patients are immediately asked to begin counting again starting with "1, 2, 3, …" since the overlearned portion of the initial counting sequence will be less likely disrupted from generalized medication effects.

Comprehension

Simple comprehension is assessed after the assessment of eye-gaze deviation, by requesting the patient to execute a simple midline command (e.g., "stick out your tongue"). The ability to execute simple midline commands is one of the first comprehension tasks that patients with aphasia are able to execute and is included at this point in the assessment to help evaluate an early possible dissociation between receptive and expressive

language. Following object memory stimulus presentation, comprehension is systematically assessed with a modified token test. The token test consists of four geometric shapes of different colors, which are presented vertically to the subject's ipsilateral visual field. They are presented vertically to minimize the effects of visual field or visual attentional deficits associated with unilateral injection.

Comprehension is rated based upon the level of syntactic complexity in the command that is correctly executed: 1. "point to the blue circle after the red square"; 2. "point to the red circle and then point to the blue square"; and 3. "point to the red square." A score of 3 is awarded for completion of a complex two-stage command with inverted syntax, a score of 2 reflects successful simple two-stage command, 1 is scored for one-stage command, and 0 if the subject cannot perform any commands.

A screen and metric approach to assessment is used, although significant discretion is afforded to the examiner. For a typical language-dominant patient, in which complete speech arrest is obtained, subjects are presented with the most simple one-step command in order to test the current status of receptive language systems. If the patient is able to successfully perform the task, then the syntax complexity is incrementally made more difficult. In contrast, with a nondominant hemisphere injection, the patient is typically presented initially with the most difficult of the available tasks.

Confrontation Naming

Two line drawings of common objects (i.e., watch and jacket) are presented and the subject is asked to name the objects and parts of the objects (e.g., watchband, collar). Performance is qualitatively scored on a 0–3 point scale. Both items are presented for both left and right hemisphere injections.

Repetition

Following object naming, the patient repeats phrases (e.g., "No if's, and's, or but's") and repetition is graded on a 0–3 rating scale. If unable to provide any response, the patient is asked to repeat "Mary had a little lamb."

Reading

Patients are asked to read either "The car backed over the curb" or "The rabbit hopped down the lane." Performance is qualitatively rated on a 0–3 point scale.

General Language Considerations

When language impairments are present, language stimuli are presented throughout the recovery phase to monitor drug effects, and the time of complete language recovery is noted. The same or alternative stimuli as those employed during the initial assessment are used with the exception of repetition. Repetition is a very sensitive measure of mild language impairment, and additional repetition items such as "Methodist-Episcopal" and sentences from the Boston Diagnostic Aphasia Examination are used to monitor recovery (e.g., "The spy fled to Greece"). Positive paraphasic responses are considered the single strongest evidence of language representation in the hemisphere being studied.

Memory

A minimum of 10 min following amobarbital injection is required prior to memory assessment. Although free recall of object memory stimuli is obtained, clinical interpretation of Wada memory performance is based solely on object recognition.

Ipsilateral Performance

Each of the eight objects is presented randomly interspersed with 16 foils, and forced choice recognition is obtained. One-half the number of false-positive responses is subtracted from the number of objects correctly recognized to correct

for possible response bias and guessing. Thus, the expected score in the absence of true recognition is 0.

Laterality Scores

Since Wada memory scores are used to assist in seizure-onset lateralization by demonstrating lateralized dysfunction, the order of injection is randomized across subjects and memory results are interpreted in a blind fashion. To assess lateralized asymmetries, interhemispheric Wada memory difference scores (i.e., [left injection] – [right injection]) derived from corrected memory performances are computed; positive scores suggest left temporal lobe dysfunction and negative scores suggest right temporal lobe impairment.

The eight target objects are interspersed with 16 distractor items. Each item is presented to the patient, and they are asked to indicate whether or not they saw each item previously. Occasionally a patient will indicate that they saw an item but that it was not in the current stimulus set. They are then asked if they had seen it anytime during the Wada procedure, and they are given credit even if they believe that they had seen the item during a previous stimulus set. To correct for guessing, we subtract one-half the number of false-positive recognitions from the total number of targets correctly recognized. Thus, any random response set in the absence of any true memory signal will lead to an expected value of zero. However, it is unusual that there are more than one to two false-positive errors, and we have always obtained similar group findings when we analyzed our data with raw or corrected memory scores.

General Memory Considerations

Fixed pass/fail criteria are not employed for memory performance following injection ipsilateral to the seizure onset. However, we generally require a score of at least 2/8 following the injection ipsilateral to the seizure focus in order to not repeat the Wada memory assessment and are more comfortable with scores of at least 3/8 correct. Wada memory asymmetries (WMA) of at least two are interpreted as evidence of lateralized impairment, although greater asymmetries are interpreted with more confidence and provide more diagnostically useful information (Loring et al., 2009). In addition, allowances may be made for the presence of aphasia, which tend to dampen the overall group performance following left hemisphere injection by approximately one point. When asymmetries in the "wrong" direction are observed, they are cause for particular concern, and the procedure may be repeated bilaterally using a 75 mg dose beginning on the side ipsilateral to the presumed seizure onset.

Conclusions

The preoperative evaluation for epilepsy surgery involves not only localization of the epileptic focus but also localization of cerebral dysfunction. Wada test results are not considered absolute and are always considered in the context of other clinical factors, such as consistency of seizure onset; presence of a structural lesion, such as tumor or hippocampal atrophy on MRI; and other functional measures (e.g., fMRI, PET). We suggest that as part of studies describing Wada clinical utility or lack thereof, the sensitivity of the specific Wada protocol to seizure-onset laterality as a surrogate marker of temporal lobe dysfunction should also be reported. In the future, use of the Wada test is likely to decline as less invasive procedures to localize cerebral dysfunction are employed. The lessons learned from Wada testing should be considered to avoid repeating past mistakes.

References

Alpherts, W. C. J., Vermeulen, J., & van Veelen, C. W. M. (2000). The Wada test: Prediction of focus lateralization by asymmetric and symmetric recall. *Epilepsy Research, 39*(3), 239–249.

Arora, J., Pugh, K., Westerveld, M., Spencer, S., Spencer, D. D., & Todd Constable, R. (2009). Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. *Epilepsia, 50*(10), 2225–2241.

Baxendale, S., Thompson, P., Harkness, W., & Duncan, J. (2007). The role of the intracarotid amobarbital procedure in predicting verbal memory decline after temporal lobe resection. *Epilepsia, 48*(3), 546–552.

Baxendale, S. A., Van Paesschen, W., Thompson, P. J., Duncan, J. S., Shorvon, S. D., & Connelly, A. (1997). The relation between quantitative MRI measures of hippocampal structure and the intracarotid amobarbital test. *Epilepsia, 38*(9), 998–1007.

Benbadis, S. R., Binder, J. R., Swanson, S. J., Fischer, M., Hammeke, T. A., Morris, G. L., et al. (1998). Is speech arrest during Wada testing a valid method for determining hemispheric representation of language? *Brain and Language, 65*(3), 441–446.

Binder, J. R., Sabsevitz, D. S., Swanson, S. J., Hammeke, T. A., Raghavan, M., & Mueller, W. M. (2008). Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. *Epilepsia, 49*(8), 1377–1394.

Binder, J. R., Swanson, S. J., Hammeke, T. A., Morris, G. L., Mueller, W. M., Fischer, M., et al. (1996). Determination of language dominance using functional MRI: A comparison with the Wada test. *Neurology, 46*(4), 978–984.

Bookheimer, S., Schrader, L. M., Rausch, R., Sankar, R., & Engel, J. (2005). Reduced anesthetization during the intracarotid amobarbital (Wada) test in patients taking carbonic anhydrase-inhibiting medications. *Epilepsia, 46*(2), 236–243.

Buchtel, H. A., Passaro, E. A., Selwa, L. M., Deveikis, J., & Gomez-Hassan, D. (2002). Sodium methohexital (Brevital) as an anesthetic in the Wada test. *Epilepsia, 43*(9), 1056–1061.

Burns, T. G., Lee, G. P., McCormick, M. L., Pettoni, A. N., Flamini, J. R., & Cohen, M. (2009). Carbonic anhydrase-inhibiting medications and the intracarotid amobarbital procedure in children. *Epilepsy & Behavior, 15*(2), 240–244.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology, 10*, 413–432.

Cohen-Gadol, A. A., Westerveld, M., Alvarez-Carilles, J., & Spencer, D. D. (2004). Intracarotid Amytal memory test and hippocampal magnetic resonance imaging volumetry: Validity of the Wada test as an indicator of hippocampal integrity among candidates for epilepsy surgery. *Journal of Neurosurgery, 101*(6), 926–931.

Davies, K. G., Hermann, B. P., & Foley, K. T. (1996). Relation between intracarotid amobarbital memory asymmetry scores and hippocampal sclerosis in patients undergoing anterior temporal lobe resections. *Epilepsia, 37*(6), 522–525.

Doss, R. C., Zhang, W., Risse, G. L., & Dickens, D. L. (2009). Lateralizing language with magnetic source imaging: Validation based on the Wada test. *Epilepsia, 50*(10), 2242–2248.

Elshorst, N., Pohlmann-Eden, B., Horstmann, S., Schulz, R., Woermann, F., & McAndrews, M. P. (2009). Postoperative memory prediction in left temporal lobe epilepsy: The Wada test is of no added value to preoperative neuropsychological assessment and MRI. *Epilepsy & Behavior, 16*(2), 335–340.

Gaillard, W. D., Balsamo, L., Xu, B., Grandin, C. B., Braniecki, S. H., Papero, P. H., et al. (2002). Language dominance in partial epilepsy patients identified with an fMRI reading task. *Neurology, 59*(2), 256–265.

Gaillard, W. D., Balsamo, L., Xu, B., McKinney, C., Papero, P. H., Weinstein, S., et al. (2004). fMRI language task panel improves determination of language dominance. *Neurology, 63*(8), 1403–1408.

Gilmore, R. L., Heilman, K. M., Schmidt, R. P., Fennell, E. M., & Quisling, R. (1992). Anosognosia during Wada testing. *Neurology, 42*(4), 925–927.

Glosser, G., & Donofrio, N. (2001). Differences between nouns and verbs after anterior temporal lobectomy. *Neuropsychology, 15*, 39–47.

Grimes, D. A., & Schulz, K. F. (2005). Refining clinical diagnosis with likelihood ratios. *The Lancet, 365*(9469), 1500–1505.

Gross, R. A., & Johnston, K. C. (2009). Levels of evidence: Taking neurology(R) to the next level. *Neurology, 72*(1), 8–10.

Hosmer, D. W., & Lemeshaw, S. (2000). *Applied logistic regression* (2nd ed.). New York, NY: John Wiley & Sons.

Jabbour, R. A., Hempel, A., Gates, J. R., Zhang, W., & Risse, G. L. (2005). Right hemisphere language mapping in patients with bilateral language. *Epilepsy & Behavior, 6*(4), 587–592.

Jack, C. R., Jr., Sharbrough, F. W., Cascino, G. D., Hirschorn, K. A., O'Brien, P. C., & Marsh, W. R. (1992). Magnetic resonance image-based hippocampal volumetry: Correlation with outcome after temporal lobectomy. *Annals of Neurology, 31*(2), 138–146.

Jones-Gotman, M., Sziklas, V., Djordjevic, J., Dubeau, F., Gotman, J., Angle, M., et al. (2005). Etomidate speech and memory test (eSAM): A new drug and improved intracarotid procedure. *Neurology, 65*(11), 1723–1729.

Kipervasser, S., Andelman, F., Kramer, U., Nagar, S., Fried, I., & Neufeld, M. Y. (2004). Effects of topiramate on memory performance on the intracarotid amobarbital (Wada) test. *Epilepsy & Behavior, 5*(2), 197–203.

Kirsch, H. E., Walker, J. A., Winstanley, F. S., Hendrickson, R., Wong, S. T., Barbaro, N. M., et al. (2005). Limitations of Wada memory asymmetry as a predictor of outcomes after temporal lobectomy. *Neurology, 65*(5), 676–680.

Lee, G. P., Park, Y. D., Westerveld, M., Hempel, A., & Loring, D. W. (2002). Effect of Wada methodology in predicting lateralized memory impairment in pediatric epilepsy surgery candidates. *Epilepsy & Behavior, 3*(5), 439–447.

Lee, G. P., Westerveld, M., Blackburn, L. B., Park, Y. D., & Loring, D. W. (2005). Prediction of verbal memory decline after epilepsy surgery in children: Effectiveness

of Wada memory asymmetries. *Epilepsia, 46*(1), 97–103.

Lineweaver, T. T., Morris, H. H., Naugle, R. I., Najm, I. M., Diehl, B., & Bingaman, W. (2006). Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. *Epilepsia, 47*(11), 1895–1903.

Loddenkemper, T., Moddel, G., Schuele, S. U., Wyllie, E., & Morris, H. H., III. (2007). Seizures during intracarotid methohexital and amobarbital testing. *Epilepsy & Behavior, 10*(1), 49–54.

Loring, D. W., Bowden, S. C., Lee, G. P., & Meador, K. J. (2009). Diagnostic utility of Wada Memory Asymmetries: Sensitivity, specificity, and likelihood ratio characterization. *Neuropsychology, 23*(6), 687–693.

Loring, D. W., Hermann, B. P., Meador, K. J., Lee, G. P., Gallagher, B. B., King, D. W., et al. (1994). Amnesia after unilateral temporal lobectomy: A case report. *Epilepsia, 35*(4), 757–763.

Loring, D. W., Hermann, B. P., Perrine, K., Plenger, P. M., Lee, G. P., & Meador, K. J. (1997). Effect of Wada memory stimulus type in discriminating lateralized temporal lobe impairment. *Epilepsia, 38*(2), 219–224.

Loring, D. W., Lee, G. P., Meador, K. J., Flanigin, H. F., Smith, J. R., Figueroa, R. E., et al. (1990). The intracarotid amobarbital procedure as a predictor of memory failure following unilateral temporal lobectomy. *Neurology, 40*(4), 605–610.

Loring, D. W., Meador, K. J., Lee, G. P., Flanigin, H. F., King, D. W., & Smith, J. R. (1990a). Crossed aphasia in a patient with complex partial seizures: Evidence from intracarotid amobarbital testing, functional cortical mapping, and neuropsychological assessment. *Journal of Clinical and Experimental Neuropsychology, 12*(2), 340–354.

Loring, D. W., Meador, K. J., Lee, G. P., King, D. W., Gallagher, B. B., Murro, A. M., et al. (1994). Stimulus timing effects on Wada memory testing. *Archives of Neurology, 51*(8), 806–810.

Loring, D. W., Meador, K. J., Lee, G. P., King, D. W., Nichols, M. E., Park, Y. D., et al. (1995). Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. *Neurology, 45*(7), 1329–1333.

Loring, D. W., Meador, K. J., Lee, G. P., Murro, A. M., Smith, J. R., Flanigin, H. F., et al. (1990b). Cerebral language lateralization: Evidence from intracarotid amobarbital testing. *Neuropsychologia, 28*(8), 831–838.

Loring, D. W., Meador, K. J., & Lee, G. P. (1992). Amobarbital dose effects on Wada memory testing. *Journal of Epilepsy, 5*, 171–174.

Loring, D. W., Murro, A. M., Meador, K. J., Lee, G. P., Gratton, C. A., Nichols, M. E., et al. (1993). Wada memory testing and hippocampal volume measurements in the evaluation for temporal lobectomy. *Neurology, 43*(9), 1789–1793.

Meador, K. J., & Loring, D. W. (2005). The Wada test for language and memory lateralization. *Neurology, 65*(5), 659.

Mikati, M. A., Naasan, G., Tarabay, H., El Yamen, S., Baydoun, A., & Comair, Y. G. (2009). Intracarotid propofol testing: A comparative study with amobarbital. *Epilepsy & Behavior, 14*(3), 503–507.

Milner, B., Branch, C., & Rasmussen, T. (1962). Study of short-term memory after intracarotid injection of sodium Amytal. *Transactions of the American Neurological Association, 87*, 224–226.

Ojemann, G. A. (1980). Brain mechanisms for language: Observations during neurosurgery. In J. S. Lockard & A. A. Ward (Eds.), *Epilepsy: A window to brain mechanisms*. New York, NY: Raven.

Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., et al. (2004). Magnetocephalography: A noninvasive alternative to the Wada procedure. *Journal of Neurosurgery, 100*(5), 867–876.

Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *Archives of Neurology and Psychiatry, 79*, 475–497.

Perrine, K., Westerveld, M., Sass, K. J., Devinsky, O., Dogali, M., Spencer, D. D., et al. (1995). Wada memory disparities predict seizure laterality and postoperative seizure control. *Epilepsia, 36*(9), 851–856.

Ruff, I. M., Swanson, S. J., Hammeke, T. A., Sabsevitz, D., Mueller, W. M., & Morris, G. L. (2007). Predictors of naming decline after dominant temporal lobectomy: Age at onset of epilepsy and age of word acquisition. *Epilepsy & Behavior, 10*(2), 272–277.

Sabsevitz, D. S., Swanson, S. J., Hammeke, T. A., Spanaki, M. V., Possing, E. T., Morris, G. L., III, et al. (2003). Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology, 60*(11), 1788–1792.

Sabsevitz, D. S., Swanson, S. J., Morris, G. L., Mueller, W. M., & Seidenberg, M. (2001). Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. *Epilepsia, 42*(11), 1408–1415.

Sass, K. J., Lencz, T., Westerveld, M., Novelly, R. A., Spencer, D. D., & Kim, J. H. (1991). The neural substrate of memory impairment demonstrated by the intracarotid amobarbital procedure. *Archives of Neurology, 48*(1), 48–52.

Snyder, P. J., Novelly, R. A., & Harris, L. J. (1990). Mixed speech dominance in the Intracarotid Sodium Amytal Procedure: Validity and criteria issues. *Journal of Clinical and Experimental Neuropsychology, 12*(5), 629–643.

Sperling, M. R., Saykin, A. J., Glosser, G., Moran, M., French, J. A., Brooks, M., et al. (1994). Predictors of outcome after anterior temporal lobectomy: The intracarotid amobarbital test. *Neurology, 44*(12), 2325–2330.

Strauss, S. E., Richardson, W. S., Glasziou, P., & Haynes, R. B. (2005). *Evidence-based medicine: How to practice and teach EBAM* (3rd ed.). Edinburgh: Elsevier Churchill-Livingstone.

Stroup, E., Langfitt, J., Berg, M., McDermott, M., Pilcher, W., & Como, P. (2003). Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology, 60*(8), 1266–1273.

Suarez, R. O., Whalen, S., Nelson, A. P., Tie, Y., Meadows, M. E., Radmanesh, A., et al. (2009). Threshold-independent functional MRI determination of language dominance: A validation study against clinical gold standards. *Epilepsy & Behavior, 16*(2), 288–297.

Testa, S. M., Ward, J., Crone, N. E., & Brandt, J. (2008). Stimulus type affects Wada memory performance. *Epilepsy & Behavior, 13*(3), 458–462.

Vingerhoets, G., Miatton, M., Vonck, K., Seurinck, R., & Boon, P. (2006). Memory performance during the intracarotid amobarbital procedure and neuropsychological assessment in medial temporal lobe epilepsy: The limits of material specificity. *Epilepsy & Behavior, 8*(2), 422–428.

Wada, J. A. (1997). Youthful season revisited. *Brain and Cognition, 33*, 7–13.

Woermann, F. G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., et al. (2003). Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology, 61*(5), 699–701.

Wyllie, E., Luders, H., Murphy, D., Morris, H., III, Dinner, D., Lesser, R., et al. (1990). Intracarotid amobarbital (Wada) test for language dominance: Correlation with results of cortical stimulation. *Epilepsia, 31*(2), 156–161.

Electrocortical Mapping of Language

6

Chris Morrison and Chad E. Carlson

Cortical mapping, whether intraoperative or at the patient's bedside, involves direct stimulation of the brain in order to determine the functionality of the underlying cortex with regard to specific sensory, motor, or cognitive processes. Cortical mapping procedures provide neurosurgeons with functional data which can be correlated with the anatomical landmarks underlying the implanted electrodes. This procedure is particularly useful when working with patients at risk for atypical cortical representation of function. While the anatomy of primary cortical regions may seem relatively fixed, primary sensory and motor areas may be atypically distributed in a brain that has malformations and/or disease from an early age (Farrell, Burbank, Lettich, & Ojemann, 2007). Relative to primary sensory and motor regions, language areas can be even less definitively localized and may be atypically distributed in the brain of an individual with epileptogenic foci or other form of pathology such as focal lesions or malformations of cortical development (Burchiel, Clark, & Ojemann, 1989; Devinsky et al., 2000; Ojemann, Ojemann, Lettich, & Berger, 1989). Identification of neuroanatomical landmarks and regions of eloquent cortex via mapping procedures can impact the extent of surgical resection. For example, if regions of eloquent cortex are identified near to or overlapping with the planned resection zone, then a more restricted resection may be made in an effort to reduce postoperative language deficits. Conversely, demonstrating the absence of eloquent language cortex near the planned surgery may allow for a more aggressive resection.

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History of Cortical Mapping

Mapping procedures have been used in standard clinical practice for over 70 years. Early reports of this technique describe intraoperative mapping of motor and somatosensory regions (Foerster, 1936). The work of Penfield and Ojemann, among others (see, e.g., Ojemann, 1979; Penfield & Roberts, 1959), greatly expanded knowledge and use of cortical mapping and demonstrated how the procedure could be used to identify not just motor and sensory cortex but more cognitively based (e.g., language functions) cortical regions. Language mapping as a technique has been used in patients with epilepsy and those with focal lesions in a language zone and no epilepsy.

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In the early years, mapping procedures were conducted intraoperatively under local anesthesia and could last several hours (Luders et al., 1988), which could be quite arduous for patients. In the late 1970s and early 1980s, chronic implantation of intracranial electrodes became increasingly prevalent. Intracranial EEG monitoring over a sustained period of time (i.e., days to weeks) to capture seizures allowed for improved lateralization and localization of the ictal onset zone(s) as more detailed recordings from larger contiguous brain areas could be obtained (Lueders et al., 1982). Chronically implanted electrodes also facilitated extra-operative mapping of cortical functions that could be performed at the patient's bedside (Lesser, Hahn, Lueders, Rothner, & Erenberg, 1981). Moving the mapping procedure from the operating room to the bedside provided significant advantages for both the clinician and the patient. Intraoperative mapping can increase the overall duration of the procedure, thereby increasing the duration of immobility and exposure to general anesthesia. In addition, most patients tolerate mapping better in the less intimidating setting of the bedside, compared with an awake craniotomy; improved tolerability often translates to improved cooperation and thereby improved quality of the data obtained. Although it is not always possible, bedside mapping can eliminate the need for an awake craniotomy in many patients.

Indications for Language Mapping

Ultimately, the need for cortical mapping will be assessed by the surgical team and is based on the location of the planned resection and the potential for overlap of that region with eloquent cortex. If the surgeon feels that the resection can be performed with no significant risk to eloquent cortex, mapping will not be necessary. As is true with many aspects of cortical mapping, a fair amount of variability will be seen between centers and between surgeons. That is, verification of hemispheric language dominance with invasive (i.e., intracarotid amobarbital procedure [IAP] or Wada test) or noninvasive (e.g., functional MRI [fMRI] or magnetoencephalography, MEG) procedures may increase or decrease the likelihood of mapping. Specifically, if hemispheric language dominance is found to be contralateral to the planned resection, mapping can be avoided; if it is ipsilateral, mapping may be necessary. The localization information obtained from the procedures listed above may help to make this decision.

Absent these data, mapping is generally indicated in a left-hemispheric resection of frontal or temporal regions in a right-handed person. Clinicians may also consider language mapping in a right-hemispheric procedure when the patient is left-handed and/or there is a family history of left-handedness as the potential for partial or complete language representation in the right hemisphere is much higher than in right-handed individuals (Rassmussen & Milner, 1977). A left-hemispheric developmental abnormality or lesion (i.e., a lesion that was present prior to or around the development of language) may also result in mixed or right dominant cortical organization of language (Rassmussen & Milner, 1977). A preoperative IAP in these circumstances is recommended as it may minimize or eliminate the need for a mapping procedure. Finally, mapping of select language functions is recommended when a mixed language dominance pattern is seen during the IAP. In this setting, focused mapping of a subset of language abilities may be necessary. For example, if during an IAP receptive language is localized contralaterally and expressive language (or, e.g., just naming) is localized ipsilateral to the surgical side, then just those latter abilities may need to be mapped.

Bedside Mapping

As with the IAP, language mapping with direct cortical stimulation has never been standardized in the way that neuropsychological tests are. As a result, there is substantial variability in the stimulation techniques (and equipment), testing stimuli, and the clinicians involved with the mapping procedure across surgical centers. Given

this variability, a definitive set of "rules for mapping" cannot be delineated, particularly given the fact that the variability is in large part due to limited, if any, published data or protocols. As a result, the discussion below will provide the reader with examples of methodology and a case example for demonstration of how the procedure is performed at our and other regional centers. We will try to identify points of variation that may be seen and what potential advantages or disadvantages these may convey to the examiner and the patient.

Before the Mapping Procedure

Cortical mapping at the patient's bedside is predicated on the presence of intracranial electrodes which can be isolated and stimulated directly with a cortical stimulator. These electrodes are placed via a craniotomy and/or burr hole performed by the neurosurgeon. Several companies currently manufacture electrodes, and each company has a variety of electrode arrays. These arrays can range from two contact strips up to 64 contact grids and beyond. In general, the electrodes are small discs of either stainless steel or platinum. The surgeon places these electrodes subdurally, directly on the surface of the pia. Depth electrodes are thin electrodes that are placed, as the name implies, directly into the cortex and underlying white matter. These are often utilized to sample mesial structures (e.g., cingulate cortex or hippocampus) which are not accessible with subdurally placed strips or grids. In some cases, technical issues such as dural adhesions will limit or prohibit subdural placement of the electrode arrays. In these situations, surgeons will either forego placement of electrodes in that region, utilize depth electrodes, or place the electrodes epidurally. Stimulation of electrodes placed epidurally will produce significant pain and as such should be avoided. Once all electrodes are implanted, the wires will be tunneled and the surgeon will close the craniotomy site. The head is wrapped securely and the connections from the intracranially placed electrodes are visible outside the head wrap. Subsequently, the EEG technician will connect the intracranial electrodes to the EEG amplifier system. The cables that connect the electrodes to the amplifier vary based upon the vendor, and the exact process will depend on the equipment. Similarly, different video-EEG system vendors will have variations in the process by which the computer software recognizes the electrodes and how many electrodes can be simultaneously recorded; most systems can record at least 128 channels simultaneously. Once this process is completed, the patient will be monitored to capture interictal and ictal data as needed.

As is the case with any evaluation of neurocognitive functions, there are numerous factors which can affect the mapping procedure. Among the most important is the impact of the patient's antiepileptic drug (AED) regimen or lack thereof. If a patient was just re-initiated on full-dosage AEDs (e.g., after being off AEDs for several days) an hour before mapping, significantly poorer performance on cognitive tasks may be seen due to medication side effects such as sedation or nausea. As a result, an effort should be made to limit AED administration (particularly of sedating AEDs) immediately prior to mapping; if AEDs need to be loaded intravenously or orally prior to mapping, it is best to allow for at least an hour or more for the patient to return to baseline following the loading doses.

Although the approach to AED adjustments can vary from physician to physician, in general, video-EEG monitoring focuses on capturing the beginning of the seizure on EEG (i.e., capturing and characterizing the ictal onset zone) to determine the region(s) to be resected. In order to record seizures, AED dosages may be decreased or discontinued. Once an adequate number of seizures have been captured to determine the ictal onset zone and the resection plan, AEDs are restarted. At our center, mapping is typically done after adequate ictal data are available and AEDs are restarted; some centers choose to perform functional mapping prior to the initial AED reduction or in multiple sessions throughout the recording period. The advantage to mapping after the ictal data are collected is that the surgical

resection is largely planned, and thus mapping can be targeted to the area(s) in question; if mapping is done prior to capturing ictal data, a broader mapping effort is often required to prepare for different potential ictal onset zones. The disadvantage to mapping after all the ictal data are collected is that it often leads to very limited windows of time in which to perform the mapping. This limited time window is of greatest importance in patients who have technically difficult mapping procedures (i.e., frequent afterdischarges or seizures) in which obtaining adequate data prior to the resection becomes difficult or impossible.

Afterdischarges (ADs) are, as their name implies, epileptiform discharges that occur in response to direct stimulation of the cortex; these can range from a single discharge that spontaneously resolves to a train of discharges which evolve into a clinical seizure. As with AEDs, ADs and/or stimulation-induced seizures can impact the baseline cognitive performance of the patient. The need to stimulate regions of the cortex with increased baseline excitability (i.e., the area of ictal onset or tissue overlying lesions) necessitates both appropriate prophylaxis with AEDs prior to stimulation and vigilance on the part of the team to monitor for epileptiform activity. At our center, mapping is done with an EEG system at the bedside so that ADs can be identified and, when necessary, disrupted. For electrode sites with extremely frequent ADs, testing may not be possible as the effects of stimulation versus the effects of the ADs may be difficult or impossible to separate. At our center, if either clinical seizures or very frequent ADs are seen, additional AEDs are given to facilitate reliable testing. If clinical seizures are triggered at a site, typically an effort is made to avoid further stimulation at that location; in general, testing is performed at sites with ADs that do not disrupt performance of the task. At our center, with frequent ADs, "baseline" task performance is reassessed while ADs are active. If ADs disrupt performance of the task, the response to stimulation at that electrode pair cannot be fully evaluated if ADs persist as ADs may involve additional cortical regions beyond the stimulated pair.

Baseline Language Testing: Once the patient is on the AED regimen deemed appropriate for mapping by the epilepsy team, baseline testing should be performed. Baseline language testing serves as a "dress rehearsal" for the patient and for the team independent of the potential confounding influence of ADs, seizures, and cortical stimulation. It allows patients to become familiar with the procedure and helps them to be more relaxed and comfortable with the process. Given the frequency with which these individuals have had prior experience with neuropsychological testing (which often includes 5–6 h of challenging testing), they may come to the procedure with concerns and anxieties about their ability to meet the challenges of the tasks in this situation. A second and equally important reason for performing the pre-mapping baseline testing relates to the need to establish the patient's post-implant level of performance as this may not be the same as that obtained during the presurgical neuropsychological evaluation. Finally, thorough baseline testing using all of the planned stimuli also allows the team to gauge the patient's current performance level throughout the entire procedure; many patients will develop significant fatigue as the mapping progresses, and baseline performance may worsen significantly. Ultimately, the more clearly delineated baseline performance is, the easier it will to detect a deviation from this level of functioning to identify "hits" for language disruption.

Patient Education: We have found that thoroughly educating the patient in what to expect and how they contribute to the mapping process (beyond responding to stimulus cues and instructions) is very effective in reducing anxiety and adverse reactions that can lead to reduced cooperation and degradations of responses. For example, the triggering of a seizure can be distressing to patients and is a risk of the procedure that must be discussed prior to stimulation to minimize any distress this may cause. Stimulation-induced motor responses, if unexpected, can be also distressing to patients. Similarly, the possibility of ipsilateral facial involvement or dural spread (resulting in physical discomfort) should be addressed prior to

stimulation. Once the procedure has been thoroughly explained, the patient is adequately protected from potential seizures with AEDs, and a baseline level of performance has been established, it is time to begin the actual cortical stimulation.

Stimulating the Brain

Although some variations will be present for the exact stimulation parameters, cortical stimulation is predicated on delivering short trains of high-frequency electrical stimulation to focal regions of the cortex. At our center, we stimulate with 50 Hz trains. High-frequency stimulation temporarily disrupts functioning in local populations of neurons, thereby creating a "functional" lesion while the stimulation is applied. When stimulation is removed, neuronal functioning returns to normal. It is this property that is utilized to identify eloquent cortex. For example, when a threshold level of stimulation is applied to a region involved in language output while the patient is producing continuous speech (e.g., reciting a phrase or poem), speech arrest may be observed. In this manner "critical areas" (i.e., areas that, when disrupted, will disrupt function) for language functioning can be identified.

Pain and discomfort are a concern for patients prior to beginning the mapping procedure. Because the brain has no nociceptive receptors, stimulation of the cortex is not painful. When the grid is in close proximity to the seventh cranial nerve and there is sufficient current spread, the patient may experience ipsilateral sensation/pain or face motor contraction. These phenomena will generally be noticeable at low current levels. Unlike the cortex, the dura mater and vascular structures do have nociceptors, and stimulation that reaches these structures can produce discomfort or overt pain depending on the location, structure(s) involved, and intensity of stimulation. Dural spread is most frequent near the edges of a grid or on smaller strips (e.g., single row of four electrodes). For these reasons, the stimulation amperage should be started at very low levels (e.g., 1–5 mA) and gradually increased over brief 2–3 s stimulation durations until the target amperage is reached (at least 12 mA, preferably 15 mA) (Lesser et al., 1987). While stimulation at lower levels may elicit a motor response or sensory experience, stimulation below 11 mA in our experience may not be sufficient to reliably disrupt language functions. To efficiently utilize the "titration" phase of stimulation, which allows for assessment of AD thresholds and minimizes the likelihood of significant pain, we ask the patient to count out loud so that speech or motor disruptions at low levels of stimulation can be identified. Once the safety and tolerability of stimulation at the target current is established, stimulation during the language tasks is typically executed for 3 s (multiple short durations of stimulation during expressive prose) to 7 s (during comprehension items).

Stimulation is performed with an electrode pair; adjacent electrodes are selected and isolated for stimulation either directly (e.g., by removing them from the recording system and placing them in the stimulator) or electronically (e.g., via a selection interface and hardware systems for isolating electrodes provided by some EEG manufacturers). For "screening," testing is typically done at electrodes 1–2, and then at 3–4, and then 5–6, and so forth. Testing electrodes two at a time can expedite the process of identifying language silent brain regions. If further spatial accuracy is necessary, an electrode pair that is associated with language disruption can be "split" to determine if one or both of the electrodes overlay eloquent cortex. In the example above testing could then be done at 1–2, and then 2–3, and then 3–4. In addition, testing of an electrode of interest with an electrode that is vertically related (e.g., in a typical 8×8 contact grid, 1–9) can allow even greater spatial information. Additional spatial information may also be possible with the use of smaller electrode arrays (e.g., with smaller electrode diameters and ½ centimeter or smaller interelectrode distances). The team must be aware of the technical limitations of their cortical stimulator system and the testing it has undergone; many systems have not had safety testing for these newer small electrode arrays.

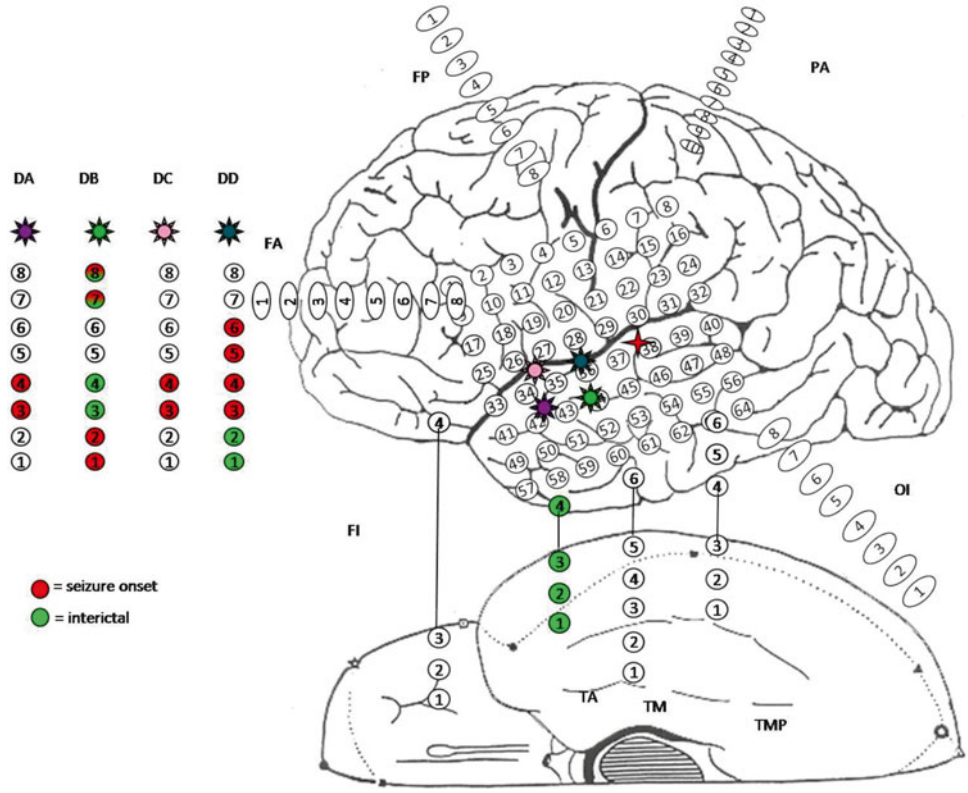

Fig. 6.1 Schematic representation of the electrode implantation. Depth electrodes are designated on the schematic with a *color-coded star* to illustrate their relative placement anatomically. Colored electrodes represent the ictal onset zone (*red*) or additional regions of cortical hyperexcitability (*green*)

When considering a strategy for moving through the grid of electrodes, if there is a neocortical (as opposed to hippocampal) ictal onset zone, it is generally prudent to start the mapping process at electrodes that are distal from those determined to overly ictal foci and then proceed through the grid in a systematic fashion (see case example below). The approach for moving through the grid will also be guided by known functional neuroanatomy. For example, when the grid is placed over frontotemporal regions in an individual with temporal lobe seizure onset, language mapping the posterior superior portion of the grid, which may overly post-central gyrus, may not be necessary. In this setting, starting inferiorly and working up until motor and/or somatosensory responses occur with stimulation (indicating that the electrodes are now superior to the sylvian fissure) is the most expeditious approach and minimizes fatigue for the patient.

When performing the mapping procedure, it is helpful to work from some type of graphic representation. Some integrated electrode switching systems will have a schematic representation built directly into the switching software. Prior to utilizing this integrated system, we utilized a schematic representation of the implanted electrodes across the hemisphere with color designations of the ictal and interictal findings during monitoring (see Fig. 6.1). This schematic reflects the surgeon's approximation of where the grid is located; it is not intended to represent an exact scale representation of the electrode locations. For more precise anatomical representations, post-implant neuroimaging (e.g., CT or MRI

scans), with or without intraoperative photos, can be reviewed and even reconstructed to provide very detailed and accurate images of the electrode localizations in relation to cerebral structures. Even when working from precise figural representations of the electrodes on the brain, a thorough mapping procedure, which identifies not only language but also at least one motor/sensory response, is necessary to produce a more exact interpretation of the electrode localizations in relation to specific landmarks of eloquent cortex (e.g., primary motor or somatosensory areas). Identifying the location of these landmarks is not necessarily as straightforward as might be expected as patients with long-standing cerebral abnormalities may have developed atypical organization of functions. This makes identification of key anatomical landmarks particularly important when efforts are being made to reduce postoperative functional deficits.

Language Testing

General Principles

There are many types of language tasks utilized in mapping procedures. Before discussing specific tasks, some general principles of the language mapping procedure are presented. In terms of item selection, regardless of the modality being tested, the stimulus items need to be chosen such that the patient can respond quickly and without any hesitation. For each patient, several items may need to be screened, and difficult stimuli for that patient should be eliminated. Therefore, for every modality assessed during the procedure, clinicians will need a somewhat large pool of items as each patient may not find them all equally easy. Typically a set of eight to ten items for each modality is utilized in pseudorandom rotation during the procedure. Practice effects are not an issue when eloquent language cortex is temporarily rendered nonfunctional via electrical stimulation; therefore, it is not problematic to use the same set of stimuli repeatedly throughout the procedure.

It is important to avoid exclusively using yes/no questions, to limit the potentially misleading effects of patient guessing. It is not uncommon for patients to try to be overly compliant with this "test." They are, with good reason, highly invested in the process and often try their best to "answer correctly" to, from their perspective, facilitate the process. As a result, they may try to guess at answers to "get it right and be a good patient." Even if yes/no response formats are avoided, a patient may try to "guess" the appropriate response from the pool of eight to ten possibilities that they have become very familiar with over the course of the procedure. This can be avoided by counseling the patient in advance that they should not guess as this will only confound the results.

Timing of item presentation and response must be precisely coordinated. Specifically, items and responses must be provided during the stimulation epoch. For example, the clinician should not begin providing an auditory comprehension item prior to stimulation onset, and the response must be given before stimulation is discontinued for the site to be considered "cleared" for that language function. If the patient responds after discontinuation of the stimulation or not at all, then, provided other causes for response failure are ruled out (e.g., ADs or motor responses), the site is considered a "hit" for that function. Thus, the clinician who is controlling the stimulation and the clinician who is performing the behavioral testing need to be working together to ensure a reliable and accurate mapping result.

The necessary inter-trial interval will vary from patient to patient. While Devinsky, Perrine, Llinas, Luciano, and Dogali (1993) recommend 20 s between trials, some patients will be able to proceed at a faster pace without any decrease in their language quality or response reliability. However, patients with particularly irritable cortex resulting in frequent ADs (and perhaps seizures), those who are particularly fatiguable, individuals who are lower functioning cognitively, or those who are evidencing a great many "hits" during the mapping process may require longer inter-trial intervals to avoid overtaxing their

ability to respond. This balance between expeditious completion of testing and avoiding difficulties from repeated, frequent stimulation requires ongoing assessment of both the clinical performance and electrographic responses.

The criteria for a pass (an area of cortex is "cleared," i.e., it does not subserve that language function) or fail (i.e., a "hit") vary across surgical centers. We utilize and recommend a procedure wherein any missed items clearly reflect pathognomonic performance (i.e., a "hit") as all items utilized were answered correctly with 100 % accuracy at baseline testing. If the patient reliably misses a second item of the same type (e.g., two pictures are not named during separate stimulation trials), then that site is considered to be eloquent for that function. It is recommended that at least two trials of each task at an electrode pair are answered correctly to "clear" a cortical site. This serves to clarify the reliability of the response. If stimulation is applied adjacent to a language zone, then testing may result in intermittent correct and incorrect responses. Such a phenomenon might be classified as a partial hit and indicate that the underlying brain region may subserve language functioning but that a postoperative language deficit might not occur if it were removed.

If the patient appeared to lose focus or the results were unclear from the initial stimulus trials, additional items can be administered. Prior to continuing with stimulation testing, baseline testing (i.e., testing without stimulation) should be performed again. Thereafter, presentation trials should proceed with intermittent stimulation during some of the item trials to look for disruption of a correct response pattern. We will often utilize this intermittent stimulation paradigm in a blinded fashion wherein the neuropsychologist is not informed at the time of presentation as to whether stimulation is being performed. This allows for a more objective assessment of performance and its relationship (or lack thereof) to stimulation.

An alternate method for establishing pass/fail criteria uses a specified percentage above the baseline error rate as a criterion (Ojemann, 1983b). However, this method assumes that the patient's error rate remains constant throughout the procedure (which we have found is not always the case) and necessitates numerous trials to establish the percentage. Another method involves clearing a site after establishing that a high proportion of stimulation trials are responded to accurately at a given site (Hamberger, Goodman, Perrine, & Tamny, 2001); however, again this necessitates numerous trials for each function at each electrode pair tested. This approach will prolong the procedure and fatigue the patient.

There may be several points during the mapping where an item is "failed." At these times, it is important to ascertain that the item is truly failed and not spoiled by other factors. In addition, important clinical information can be gleaned through secondary assessment following the "failed" stimulation trial. If, for example, on a repetition, naming, or comprehension item, a response is not provided during stimulation, after discontinuing stimulation ask the patient to repeat the item or name the object that was presented. It is often enlightening if the patient can then comply with repeating the phrase/question or naming the stimulus item (i.e., naming the pictured object that may still be in visual working memory) that was presented during stimulation, as this helps to validate the language "hit."

When mapping in the frontal lobe near primary or secondary motor areas, it must be determined that an incorrect or distorted response is not due to motor phenomena rather than language disruption. Speech may sound dysarthric or the patient may report that they "felt something" in their mouth or throat area during stimulation. This can reflect motor contractions as a result of stimulation of the mouth/face area of the motor strip. Have the patient produce sustained nonlinguistic speech sounds that utilize different levels of the speech apparatus (e.g., "kakakakaka" or "lalalalala") while delivering intermittent stimulation for durations of 1–2 s each. If production of these sounds is disrupted with stimulation, then a motor, rather than a language, area has been identified. When stimulating electrodes that are directly overlying the motor strip or are somewhat more anterior and superior,

more obvious motor phenomena are evident (e.g., contralateral facial contraction, forced tongue deviation or retraction). If it is suspected that tongue motor involvement is disrupting the language response, have the patient extend their tongue and look for forced tongue retraction/deviation during stimulation. Occasionally there are very subtle motor effects (due to current spread) which can be "talked through." That is, the patient may be able to tolerate the motor phenomenon and try to produce the language response despite the stimulation effects on oral motor functioning. It is important to try this when possible as there can be interdigitation between motor and language areas (Lesser, Gordon, & Uematsu, 1994). Attempting language testing at these "soft" motor sites may help to exonerate language cortex in a planned resection zone.

With auditory comprehension, it is important to be mindful of how a patient's interpretation of their experience can shape their responses. It is not uncommon for patients to report that they did not "hear" the stimulus item that was presented (e.g., during an auditory naming or sentence completion item). In this circumstance, first determine if in fact there is a primary perceptual problem. Often the bandaging around the head can cover the ear and reduce auditory acuity. However, when there is a comprehension deficit due to stimulation, it may be reported by the patient as a "hearing" problem as this may be how the patient interprets their inability to understand the command or sentence.

There can be reasons for item failure that are independent of the language and motor effects of stimulation. Afterdischarges can disrupt cognitive functioning (Lesser et al., 1987). Therefore, when language disruption is noted during stimulation, it is critical that the EEG be monitored to determine whether the impaired response occurred in the context of ADs or whether the EEG immediately post stimulation was "clean." If there were ADs, then the trial must be repeated until it is determined that the patient can/cannot complete the task in the absence of epileptiform activity. Finally, the cumulative effects of ADs, small seizures, and/or fatigue can progressively decrease the patient's ability to reliably respond correctly. In this situation, try taking a 10–15 min break. Depending on the health, endurance, and tolerance of the patient, as well as how irritable (hyperexcitable) the cortex within the region of stimulation is, the mapping procedure may need to be discontinued and resumed on another day to achieve maximum reliability and quality of responses. To the greatest extent possible, include this potential need for additional hours (or days) in the pre-resection surgery planning.

Language Testing: Specific Tasks

Expressive Speech

Stimulation during continuous speech has been shown to be a sensitive method for identifying language eloquent cortex (Lesser et al., 1987). However, selection of the stimulus material is important. The content of the speech monologue must not contain prosody (such as having the patient sing a song) as this may engage language centers in the contralateral hemisphere. Counting should also not be used for this purpose as knowledge of numbers can be so overlearned that the patient may be able to produce accurate responses even when stimulation of that site would ordinarily disrupt other more complex types of verbal output (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2000). Instead, a monologue that is syntactically more complex but is well known to the patient and can be repeatedly produced accurately should be used. For individuals who are born and educated in the United States we often use the Pledge of Allegiance for this purpose. Other types of monologues that can be used include prayers, poems, or lines from a play that are very well known to the patient. These types of passages are selected because they are rote for the patient but not resilient to disruption caused by stimulation, such as can be the case with reciting numbers. If no well-known fixed monologue can be identified for a particular patient, then, as a last resort, the patient can be instructed to speak on a topic of their choice. This latter choice is somewhat risky

as it is more difficult for the examiners to identify errors and paraphasias since the words and sentences are not provided in a predetermined and fixed manner. As an alternative, patients can be asked to recite the months of the year or days of the week in a continuous and repeating manner. We tend to use this type of task with lower functioning individuals.

Visual confrontation naming has been used as one of the "gold standards" for identifying language eloquent cortex during mapping since the time the procedure was developed. This type of task has been one of the most sensitive in identifying language eloquent cortex (Ojemann, 1983a). Contrary to the clinical neuropsychology setting where tasks with graduating difficulty are often used (e.g., the Boston Naming Test), in the mapping setting, pictures of items that are easily, rapidly, and consistently named by the individual should be used. As indicated, the clinician should have a large selection of picture stimuli available and then determine at baseline a patient-specific set of approximately ten items that the patient can respond to easily at the time of mapping. We have found the stimuli published by Snodgrass and Vanderwart (1980) to be extremely useful for this purpose.

Although visual naming has been the most common format for assessing word retrieval in the context of brain mapping, Hamberger and others (Hamberger et al., 2001; Lesser et al., 1987) have demonstrated that auditory naming (also known as descriptive or responsive naming) tasks can yield important and unique information. Specifically, it has been established that auditory and visual confrontation naming can be co-localized; however, in many instances these functions can also be distributed across distinct sites in the brain. It could be argued that auditory naming (i.e., retrieving a specific word while you are formulating what you want to say) can be considered more ecologically valid than visual naming, or at least as critical as naming an object in one's visual field. Thus, it is an important language function to assess during the mapping procedure. Examples of auditory naming items include "what is the thing that unlocks a door" or "what do we tell time with?" At our center, we use the stimuli developed by the Columbia group for this purpose (Hamberger & Tamny, 1999).

In terms of verbal generative fluency, traditional verbal fluency tasks (i.e., continuous productions for words belonging to a specific category, such as those that start with a specific letter) are not widely used in mapping procedures. They can be problematic for the same reason that, for example, continuous extemporaneous speech can be. Specifically, if the patient naturally hesitates in their speech or in their thought process during completion of the task, it could be confused as a "hit," rather a natural pause. Ojemann and colleagues have used a somewhat related single-word generation task (Ojemann, Ojemann, & Lettich, 2002). Borrowing from the functional imaging literature, they employed a verb generation task. In this task, patients are shown a picture of a concrete noun and asked to generate a verb appropriate to the picture stimulus. Consistent with the robust findings from functional imaging studies, Ojemann et al. (2002) were able show both overlapping and disparate verb generation sites relative to those showing disruption of object naming in the frontal and temporoparietal cortices.

Select types of aphasia can be differentiated based on whether repetition functions are intact or not. Repetition tasks assess the integrity of connections between phonological input and output. Tasks that can be included in a mapping procedure may involve presenting a word or short phrase and having the patient repeat it during a stimulation trial. It is important to keep in mind that the phrase/sentence length should not be too long as this will prolong the stimulation duration unnecessarily, perhaps leading to ADs or seizures.

Comprehension

Assessment of comprehension is a critical part of the language mapping process, particularly when stimulating in the posterior regions of the temporal lobe or the temporal-parietal juncture. There are a range of methods for assessing

auditory comprehension, such as token tasks, asking the patient to follow simple commands (e.g., point to your nose, point to the door), or having the patient provide the final word in a sentence stem. An example of the latter type of task includes "The bicycle had a flat ____." It should be noted, however, that the sentence stem task also has a naming component and therefore is likely assessing multiple language functions simultaneously. Nevertheless, we have often seen dissociations between auditory and visual naming performances and the ability to respond accurately to sentence stems. Once again, the commands and sentence stems should not be overly long as the item and response must be provided during a single stimulation trial.

Reading

Having the patient read single phonologically regular words or passages has been found to be a sensitive task during language mapping for detecting areas specific to this function (Devinsky et al., 1993; Lesser, Lueders, Dinner, Hahn, & Cohen, 1984). This procedure can be executed by having the patient attempt to read single words on a card during stimulation. Another method for executing this task is to have the patient read from a book or magazine of their choosing while the clinician periodically introduces stimulation. A method for assessing reading comprehension involves having the patient read sentences and complete the missing last word (Devinsky et al., 1993). However, it is important to note that this function actually requires two separate stages of written language processing, the ability to read and the ability to comprehend, which are separable language processes. If the patient passes these latter types of items, then that area of underlying cortex is cleared for both reading ability and reading comprehension. However, if the patient "fails" these written sentence completion items, then a separate reading task (without a comprehension component) can be administered to determine if the skills are dissociated at that site.

Writing

Although writing can be assessed during a mapping procedure (Lesser et al., 1984), this type of task can be difficult due to the time constraints of completing an item during a stimulation trial. Single words may be produced to command or with presentation of a stimulus item (e.g., picture). However, this type of task requires multiple stages of language processing which are not separable using this method. Some success with identifying independent cortex eloquent for writing when using a writing-to-dictation paradigm has been seen (Lubrano, Roux, & Demonet, 2004).

Mapping in Special Populations

The procedures described thus far apply to the routine monolingual adult patient. Naturally the clinician will encounter situations where the standard procedures require modification. When working with bilingual or multilingual individuals, additional decisions must be made regarding which language(s) to map. In those individuals who function in two or more languages in their daily life, it is important to map all the languages that the patient relies on for either work or interacting with family and friends. Mapping each language relevant to the patient's adaptive functioning is critical as the dominant and secondary languages can be co-localized in some brain regions and differentially distributed in others (Lucas, Mckhann, & Ojemann, 2004). In situations where the patient is multilingual but they do not rely on their secondary language(s) for work or home interactions, we have not mapped the additional language. Finally, we do not typically map a secondary language in which the patient is not fluent.

Pediatric patients can prove to be a special challenge and, as might be expected, working with children requires some adjustment to the procedure. For example, the stimulation parameters might need to be adjusted. Such modifications can include lengthening stimulation

durations (Lesser et al., 1994) to give a longer time for responses. Depending on the age of the child, cooperation can be an issue. To assess comprehension, for example, several of the child's toys can be lined up in an array, and commands such as pick up/touch/point to a certain toy can be given during stimulation. The child may also be asked a series of question to which he/she is very familiar with the answer (e.g., "What color is Barney?"). With regard to expressive speech, identifying and/or encouraging a child to repeatedly generate prose could prove difficult or impossible in some cases. At these times, having the child say a nursery rhyme or perhaps just generating speech via telling a story may be the only options. For example, one could ask the child to tell the story of Red Riding Hood and periodically deliver stimulation during the child's discourse to observe if there is speech disruption. When attempting a mapping procedure in a young patient, it should be kept in mind that language mapping results in children under the ages of 10–12 have been found to be less reliable; the exact etiology for this finding remains unclear (Schevon et al., 2007).

Case Example

There are many options for tasks and procedures (outlined above) when mapping eloquent language cortex. The following is a description of a typical mapping procedure as executed at our center. The patient is a 54-year-old right-handed high-school educated woman with a 22-year history of treatment-resistant focal epilepsy. Seizure semiology and video/EEG monitoring indicated a left temporal seizure focus for some of her recorded events; some semiologically similar events were surface negative on scalp video/EEG. An MRI of the brain showed mild increased T2 signal in the left temporal lobe cortex, amygdale, and hippocampal formation. The patient underwent an IAP which revealed left hemisphere dominance for language. Memory functioning was similar and relatively preserved bilaterally (left = 9/12; right = 8/12) by the standards used at our center. Neuropsychological testing found average general intellectual functioning (WAIS-III GAI = 93) with comparable verbal and performance abilities. Verbal abstract reasoning, self-monitoring, and rapid behavioral flexibility were subtle areas of weakness. The patient's approach to the testing process reflected difficulty with staying focused on tasks that she perceived as overwhelming. At other times, she tended to sacrifice speed for accuracy, which adversely affected some scores. New learning deficits were observed when she was presented with large amounts of material at once. Long-term retention and retrieval of newly learned information were often more preserved when information was presented in a piecemeal fashion, over multiple learning trials, and/or in dual modalities. This pattern of scores, with somewhat worse performance on verbal memory tasks, was interpreted as suggesting relative left frontotemporal dysfunction.

The patient underwent implantation of a left frontotemporal grid and depth electrodes. On the schematic representation shown in Fig. 6.1, the ictal onset zone for her typical clinical seizure is shown in red, and regions of cortical hyperexcitability beyond the ictal onset zone (i.e., additional regions demonstrating epileptiform sharp waves and/or spikes) are shown in green. Seizures were recorded from the left anterior temporal lobe arising on the distal and, to a lesser extent, proximal contacts of the depth electrodes.

In preparation for the mapping procedure, a post-implant baseline was established. The patient is a monolingual English speaker who was easily able to recite The Pledge of Allegiance with only two practice trials. A set of ten pictures, eight auditory naming stimuli, and eight sentence completion items that she could answer easily were identified from the Hamberger and Seidel (2003) stimuli. As is typical of our protocol, mapping began with the anterior inferior electrode pair, and we proceeded posteriorly across the rows. Figure 6.2 shows a schematic representation of the functional mapping results. Multiple sites with disruption of language function were identified including regions with impairment of spontaneous speech, visual naming, auditory naming, and comprehension.

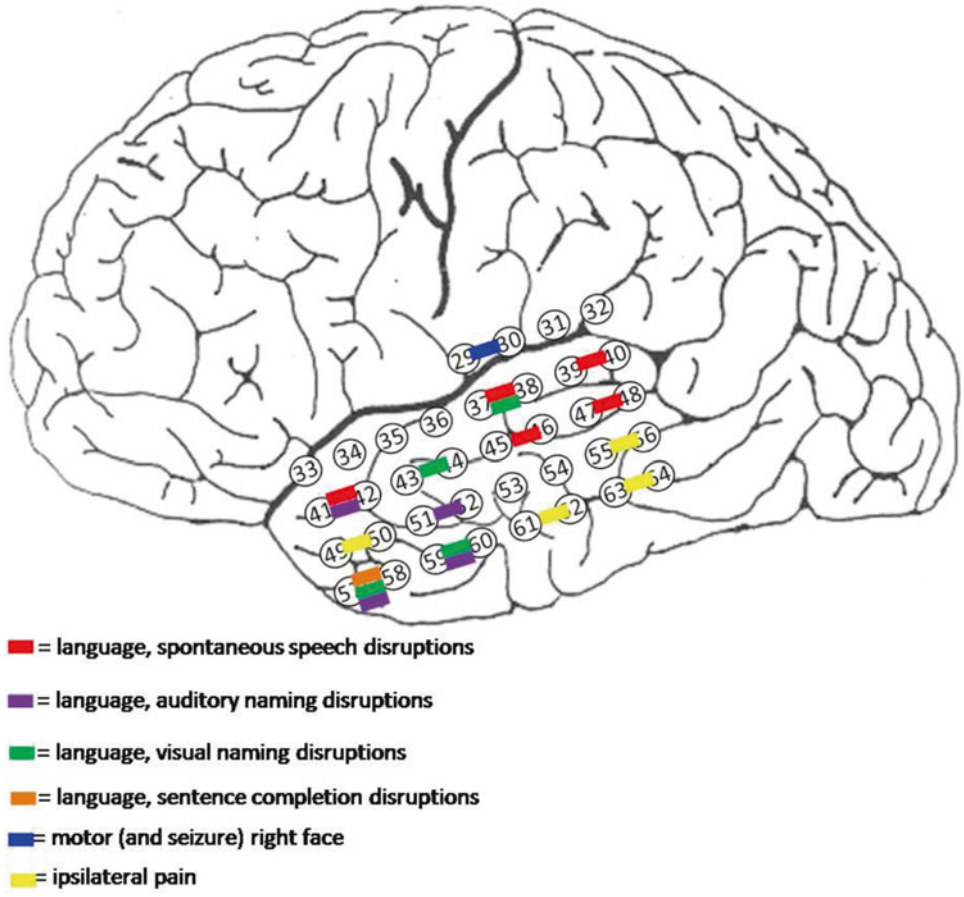

Fig. 6.2 Schematic representation of cortical mapping results. Each response elicited is designated by the color. Sites for which multiple findings were obtained are designated with *bars* representing each individual finding

As is typical of our testing protocol, a motor response (tongue) was identified; this serves as confirmation of electrode locations superior to the Sylvian fissure. In this patient, resection was planned for the anterior and mesial and left temporal lobe; as a result, no mapping beyond the identified motor responses was required.

While some clinicians may choose to conduct the mapping procedure alone (i.e., a single person operates the stimulator, performs all the behavioral testing, observes verbal and nonverbal responses from the patient, monitors the EEG, records all the necessary information, and changes the electrodes), we have found that a multidisciplinary approach with a team that includes neurologists/epileptologists and neuropsychologists improves both the accuracy of the test results (with multiple observers for correlating behavior and EEG findings) and efficiency (with the epileptologist primarily responsible for setting up and executing individual stimulation trials and correlating EEG activity and the neuropsychologist responsible for assessing baseline performance and presenting test stimuli). In addition, the overlapping, but unique skill sets and knowledge domains of the two specializations have improved assessment of responses and problem solving in cases with unique responses or potential technical concerns; continued testing is performed until a consensus is reached for each electrode pair.

Intraoperative Mapping

When placement of a subdural grid to record seizure activity is not necessary, there is no opportunity for a bedside mapping procedure. On these occasions, such as when a patient is undergoing brain tumor resection, the clinician will be performing the mapping procedure intraoperatively with the surgical team. Intraoperative language mapping may also be required if bedside mapping identified language cortex within the planned resection zone. In this circumstance, the surgeon may want to more carefully map the language regions identified at bedside. This process serves to verify the bedside language findings. It is possible, due to such factors as shifting of the grid during surgery, that the identified language cortex does not exactly correlate with the language map schematic that was developed from the bedside procedure. Thus, in an effort to reduce the potential for a postoperative language deficit, intraoperative mapping may result in modifications to the planned surgery.

When performing an intraoperative procedure, the mapping team is generally called into the procedure after the craniotomy is performed and the patient is waking from general anesthesia. This may be a slow process for some patients. Once the patient is sufficiently awake, reestablishing a baseline will be necessary. For all but the highest functioning and stalwart patients, a simplification of the language stimuli is likely to be necessary. For example, often patients are too fatigued or are in too much discomfort to focus on The Pledge of Allegiance, therefore, repeated recitation of the months of the year and days of the week is often used. While we attempt to include both visual and auditory confrontation naming, there are times when we may omit auditory naming due to the need to expedite the procedure in the intraoperative setting. The selection of visual over auditory naming is made based on the former identified as the "gold standard"; however, there has been some evolution in thinking on this point (Hamberger, 2007). The procedure in the operating room is somewhat more complicated than that of the bedside mapping as there is now a third person to coordinate with in terms of presenting items and noting responses during stimulation. The neurosurgeon will be holding the probe directly on the brain while the neurologist engages and disengages stimulation. The third member of the team (often a neuropsychologist) will present stimuli (auditory or visual) and observe responses while coordinating with the neurologist to ensure that stimuli and responses are given during stimulation.

The intraoperative environment can present barriers to the patient's ability to cooperate. Not infrequently patients complain that their throat hurts or their mouth/lips are too dry to talk. In these circumstances it is helpful to moisten their lips with a wet gauze or to let them suck on a wet gauze. Nausea, pain, and lethargy can all limit a patient's ability to focus on the language testing. The anesthesiologist can often provide medication to alleviate these symptoms. Due to the sterile draping around the craniotomy site, part of the patient's visual field may be obstructed, thus reducing their ability to perceive visually presented stimuli. Sometimes it is possible to work with the surgical team to make adjustments that will reduce this problem; often the neuropsychologist needs to reposition to make him/herself and the stimuli visible to the patient. Some patients become upset, anxious, or fearful during the awake portion of the surgical procedure. Understandably, this is quite a unique experience that some individuals find rather disconcerting. These symptoms can interfere with or completely derail the mapping procedure due to the patient's inability to remain calm enough to comply with the task demands. We have found that counseling the patient presurgically and even presurgical baseline testing itself helps reduce their anxieties and prepare them for the procedure to come. Finally, as with the bedside procedure, lethargy can decrease the quality of the patient's responses; however, in the intraoperative setting the threshold for fatigue is generally much sooner than when testing at the bedside. In this circumstance brief breaks might be necessary, and the team will want to be mindful not to "overtest." If the patient's ability to respond

degrades, the difficulty of the task might need to be lowered. For example, if the patient was reciting the Pledge of Allegiance, switching to months of the year might be helpful.

Occasionally surgeons may guide the extent of the resection based on ongoing feedback about the patient's language functioning. Thus it might be necessary to engage the patient in an ongoing dialogue during the resection to assess quality of speech output and comprehension. At these times, we typically engage the patient in "small talk," asking them questions about themselves, as autobiographical information and/or areas of personal interest are generally easy for people to have a discourse on. During this time the neuropsychologist is listening to the quality of the speech output (e.g., if paraphasias or increased word-finding difficulty occurs) and the patient's ability to respond appropriately to questions or commands (which may herald a developing comprehension deficit) and notifying the surgeon of any changes from the intraoperative baseline. Frequent breaks are key in this process as the patient will generally become more fatigued and less able to focus and respond as the procedure goes on.

Summary

In the overview above we have provided a brief history of electrocortical language mapping in the context of a planned surgical resection, as well as a summary of many of the specific language tasks used for this process. In addition, we highlight a number of potential pit falls, complications, and logistical challenges that can occur during this procedure. Finally, using a case example, we illustrate how we perform a language mapping procedure at our center. While there is certainly variance in how this procedure is performed across surgical centers, we provided specific pros and cons for many of the standard techniques that are widely used. What we have found most useful in performing these procedures is an integrated multidisciplinary approach that takes advantage of the skill set and specialized knowledge that neurologists, neurosurgeons, and neuropsychologists bring to the table.

References

Bookheimer, S. Y., Zeffiro, T. A., Blaxton, T. A., Gaillard, W. D., & Theodore, W. H. (2000). Activation of language cortex with automatic speech tasks. *Neurology, 55*, 1157.

Burchiel, K., Clark, H., & Ojemann, G. A. (1989). Use of stimulation mapping and corticography in the excision of arteriovenous malformations in sensorimotor and language-related neocortex. *Neurosurgery, 24*(3), 323–327.

Devinsky, O., Perrine, K., Hirsch, J., McMullen, W., Pacia, S., & Doyle, W. (2000). Relation of cortical language distribution and cognitive function in surgical epilepsy patients. *Epilepsia, 41*, 400–404.

Devinsky, O., Perrine, K., Llinas, R., Luciano, D., & Dogali, M. (1993). Anterior temporal language areas in patients with early onset of temporal lobe epilepsy. *Annals of Neurology, 34*, 727–732.

Farrell, D., Burbank, N., Lettich, E., & Ojemann, G. A. (2007). Individual variation in human motor-sensory (rolandic) cortex. *Journal of Clinical Neurophysiology, 24*(3), 286–293.

Foerster, O. (1936). The motor cortex in man in the light of Hughling Jackson's doctrines. *Brain, 59*, 135–159.

Hamberger, M. J. (2007). Cortical language mapping in epilepsy: A critical review. *Neuropsychology Review, 17*, 477–489.

Hamberger, M. J., Goodman, R. R., Perrine, K., & Tamny, T. (2001). Anatomic dissociation of auditory and visual naming in the lateral temporal cortex. *Neurology, 56*, 56–61.

Hamberger, M. J., & Seidel, W. T. (2003). Auditory and visual naming tests: Normative and patient data for accuracy, response time, and tip-of-the-tongue. *Journal of the International Neuropsychological Society, 9*, 479–489.

Hamberger, M., & Tamny, T. (1999). Auditory naming and temporal lobe epilepsy. *Epilepsy Research, 35*, 229–243.

Lesser, R., Gordon, B., & Uematsu, S. (1994). Electrical stimulation and language. *Journal of Clinical Neurophysiology, 11*, 191–204.

Lesser, R. P., Hahn, J., Luеders, H., Rothner, A., & Erenberg, G. (1981). The use of chronic subdural electrodes for cortical mapping of speech. *Epilepsia, 22*, 240.

Lesser, R., Luders, H. O., Klem, G., Dinner, D. S., Morris, H. H., Hahn, J. F., et al. (1987). Extraoperative cortical functional localization in patients with epilepsy. *Journal of Clinical Neurophysiology, 4*, 27–53.

Lesser, R. P., Lueders, H., Dinner, D., Hahn, J., & Cohen, D. (1984). The location of speech and writing functions in the frontal language area. *Brain, 107*, 275–291.

Lubrano, V., Roux, F., & Demonet, J. (2004). Writing-specific sites in frontal areas: A cortical stimulation study. *Journal of Neurosurgery, 101*, 787–798.

Lucas, T., II, Mckhann, G., II, & Ojemann, G. A. (2004). Functional separation of languages in the bilingual

brain: A comparison of electrical stimulation language mapping in 25 bilingual and 117 monolingual control patients. *Journal of Neurosurgery, 101*, 449–457.

Luders, H., Lesser, R. P., Dinner, D. S., Morris, H., Wyllie, E., & Godoy, J. (1988). Localization of cortical function: New information from extraoperative monitoring of patients with epilepsy. *Epilepsia, 29*, S56–S65.

Lueders, H., Hahn, J., Lesser, R. P., Dinner, D. S., Rothner, D., & Erenberg, G. (1982). Localization of epileptogenic spike foci: Comparative study of closely spaced scalp electrodes, nasopharyngeal, sphenoidal, subdural, and depth electrodes. In H. Akimoti, H. Kazamatsuri, M. Seino, & A. Ward (Eds.), *Advances in epileptology. XIII Epilepsy International Symposium* (pp. 185–189). New York, NY: Raven.

Ojemann, G. A. (1979). Individual variability in cortical localization of language. *Journal of Neurosurgery, 50*, 164–169.

Ojemann, G. A. (1983a). Brain organization for language from the perspective of electrical stimulation mapping. *Behavioral and Brain Sciences, 6*, 190–206.

Ojemann, G. A. (1983b). Electrical stimulation and the neurobiology of language. *The Behavioral and Brain Sciences, 2*, 221–230.

Ojemann, G. A., Ojemann, J., Lettich, E., & Berger, M. (1989). Cortical language localization in the left, dominant hemisphere. *Journal of Neurosurgery, 71*, 316–326.

Ojemann, J., Ojemann, G. A., & Lettich, E. (2002). Cortical stimulation mapping of language cortex by using a verb generation task: Effects of learning and comparison to mapping based on object naming. *Journal of Neurosurgery, 97*, 33–38.

Penfield, W., & Roberts, L. (1959). *Speech and brain-mechanisms*. Princeton, NJ: Princeton University Press.

Rassmussen, T., & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences, 299*, 355–369.

Schevon, C., Carlson, C., Zaroff, C., Weiner, H., Doyle, W., Miles, D., et al. (2007). Pediatric language mapping: Sensitivity of neurostimulation and Wada testing in epilepsy surgery. *Epilepsia, 48*, 539–545.

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology, 6*, 174–215.

Structural and Quantitative MRI in Epilepsy

7

Karen Blackmon and Thomas Thesen

Introduction

Magnetic resonance imaging (MRI) is a critical component of the basic clinical assessment of epilepsy. Detection of abnormalities on MRI is essential to establishing an initial diagnosis (idiopathic, cryptogenic, or symptomatic) and determining options for treatment. MRI studies are especially critical in focal epilepsy, as resective surgery of an epileptogenic lesion has the potential to render many patients seizure-free (Engel, 1996; Wiebe, Blume, Girvin, & Eliasziw, 2001). Improvements in high-resolution MRI and quantitative post-processing methods now permit detection of structural abnormalities in patients that are not otherwise visually apparent. This is especially important as an MRI-identified lesion is associated both with poorer response to medications (Cardoso et al., 2006; Spooner, Berkovic, Mitchell, Wrennall, & Harvey, 2006) and with a greater likelihood of seizure freedom following resective surgery (Berkovic et al., 1995; Jeha et al., 2007).

Accurate and sensitive presurgical identification of abnormal tissue allows for more targeted placement of intracranial EEG electrodes, potentially more complete resection of abnormal tissue, and improved surgical outcome (Sisodiya et al., 1997). The most reliable predictor of seizure freedom after surgery for cortical malformations is the extent to which the lesion is resected with incomplete resection decreasing the chance of seizure freedom from 77 to 20 % (Lerner et al., 2009). Therefore, imaging methods that increase sensitivity and accuracy in delineating the presence and extent of lesions are a valuable addition to preoperative evaluations. An MRI study is also important in determining the extent of healthy tissue, which can inform predictions of postsurgical functional status.

The following chapter will review MRI methods and applications that are commonly used in comprehensive epilepsy centers, with a particular emphasis on the role of structural MRI in presurgical evaluations. Although there is evidence to suggest that there may be structural abnormalities associated with idiopathic generalized epilepsy (Betting et al., 2006; Woermann, Sisodiya, Free, & Duncan, 1998), research in this area is limited with generally nonspecific findings and no current clinical application. Therefore, the focus of this chapter will be limited to structural MRI methods used to detect abnormalities in localization-related epilepsy. Additionally, a special mention will be made of the integration of quantitative MRI with neuropsychological assessment methods in focal epilepsy syndromes, although this is a very new and exciting research area that has yet to be fully realized in most clinical settings.

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Table 7.1 Basic clinical MRI sequences for visualizing brain structure and pathology

Images	Description	Advantages
T1-weighted images	CSF is black Gray matter is dark White matter is bright	Good visualization of brain morphology Used to initially define brain anatomy
T2-weighted images	CSF is white Gray matter is bright White matter is dark	Pathological areas stand out as brighter (increased signal)
Fluid-attenuated inversion recovery images (FLAIR)	CSF is black Gray matter is bright White matter is dark	Pathological areas stand out as brighter (increased signal) Focal cortical lesions are easier to identify; however, there is increased artifactual signal in mesial temporal regions

This table describes MRI sequences that are typically acquired as part of the standard epilepsy diagnostic workup

The Epilepsy Protocol

In a typical comprehensive epilepsy evaluation, structural MRI images are presented as T1-weighted images, T2-weighted images, and T2 fluid-attenuated inversion recovery (FLAIR), with advantages associated with each (see Table 7.1). It is essential that a dedicated center-specific "epilepsy" MRI protocol be developed through a collaborative process involving both radiologists and epileptologists. Careful consideration must be given to disease-specific factors (Jackson & Kuzniecky, 2008). The importance of an epilepsy-dedicated protocol was demonstrated in a prospective study of 123 consecutive patients undergoing epilepsy surgery evaluations (Von Oertzen et al., 2002). Sensitivity of "nonexpert" review of standard MRI reports for focal lesions was 39 %; of "expert" review of standard MRI, 50 %; and of epilepsy-dedicated MRI, 91 %. Dedicated MRI showed focal lesions in 85 % of patients with "non-lesional" standard MRI. In particular, hippocampal sclerosis was missed in 86 % of cases. Neuropathological diagnoses were predicted correctly (with histopathological confirmation) in 89 % of dedicated MRI reports compared to only 22 % of "nonexpert" standard MRI reports.

The most important factor in optimizing an MRI protocol for epilepsy is clear visualization of mesial temporal structures. This requires thinner slices, with voxel volumes of 1 mm^4 being the current norm at 3T, which improves spatial resolution but also increases scan time and noise. Images must be obtained with appropriate alignment around the "hippocampal axis" rather than the "machine axis" so that the whole of the hippocampus can be visualized in a single slice with minimal partial volume effects. Coronal images should transect the hippocampus at right angles, and axial images should follow the long axis of the hippocampus. Good spatial resolution and signal-to-noise ratio are essential components of a dedicated epilepsy MRI protocol. The most commonly used sequence is magnetization-prepared 180° radio-frequency pulses and rapid gradient echo (MPRAGE). One-to-two mm coronal MPRAGE slices (which provide T1 contrast) are typically used to evaluate the temporal lobe, whereas axial slices are obtained if extratemporal epilepsy is suspected. When focal cortical dysplasias are suspected, a T1-weighted sequence optimized for gray-white matter contrast is important, as abnormal imaging features include increased cortical thickness and blurring of the gray-white matter boundary. For a detailed list of recommended high-contrast T1 sequences for various scanner types, see http://www.loni.ucla.edu/ADNI/Research/Cores/.

What Can Be Identified on MRI with the Visual Eye in Epilepsy?

Detection of hippocampal sclerosis (HS) is an important goal of a basic MRI screening study, as this pathology is the most prevalent of the focal abnormalities in partial epilepsy. Features of HS include altered signal in the hippocampus, hippocampal asymmetries, and loss of internal hippocampal architecture (Jackson & Kuzniecky, 2008). Using T2 optimized sequences, high-intensity signal associated with sclerosis can be detected in the hippocampal gray matter. Abnormal signal can best be seen on FLAIR images; however, artifactual errors are common

in the mesial temporal regions. Therefore, expert interpretation and confirmation with T2 sequences are recommended. Hippocampal atrophy is often subtle and only visually apparent with well-aligned images free of partial volume effects. Furthermore, unilateral atrophy must be differentiated from normal variations in right and left hippocampal asymmetries (Mingrino et al., n.d.; Walhovd et al., 2009). Finally, morphometric variations in internal hippocampal architecture can be best seen on heavily T1-weighted sequences, such as an inversion recovery sequence. Although experts who are trained in mesial temporal anatomy can make such differentiations, quantitative methods are becoming more influential in detecting hippocampal shape abnormalities and atrophy.

Malformations of cortical development (MCDs), particularly focal cortical dysplasia (FCD), are increasingly recognized as the most common etiology in pediatric epilepsy and the second most common etiology in adults with medically intractable seizures (Lerner et al., 2009). Advances in MR imaging have allowed for improved visual detection and diagnosis of FCD and other cortical malformations in patients with epilepsy (Barkovich, Kuzniecky, & Dobyns, 2001). Common features of FCD include abnormal gyral and sulcal pattern, thickening of the cortical gray matter, blurring of the gray-white matter junction, abnormal neural and glia-derived cell types, and high signal on T2 or FLAIR sequences (Barkovich et al., 2001; Palmini et al., 2004; Widdess-Walsh, Diehl, & Najm, 2006). In a sample of 102 individuals with MCDs (84 % of whom had epilepsy), abnormally small hippocampi were found in 30 %, along with abnormal hippocampal rotation and shape and abnormally large hippocampi in individuals with lissencephaly and subcortical laminar heterotopia (Montenegro et al., 2006).

Initial MRI screening is also important in the detection of tumors, vascular abnormalities, and traumatic and developmental lesions that are apparent to the visual eye. In the case of more subtle lesions such as small areas of sclerotic tissue or cortical dysplasia, more intensive MRI studies should be considered, such as 3D volumetric acquisition sequences, T2 relaxometry, magnetic resonance spectroscopy, and quantitative methods.

Quantitative MRI

Advantages over Visual Analysis

Automated MRI brain image analysis techniques, such as voxel-based morphometry (VBM) (Ashburner & Friston, 2000), offer advantages over subjective techniques (e.g., visual inspection) and have been employed to detect subtle anatomical anomalies in individual neurological patients compared to healthy controls (Bernasconi et al., 2004; Mehta, Grabowski, Trivedi, & Damasio, 2003; Wilke, Kassubek, Ziyeh, Schulze-Bonhage, & Huppertz, 2003). Morphometric analysis of structural MRI has become a widely used and established approach to study normal brain development and neurological diseases. T1-weighted images are primarily used to study gray matter properties, whereas diffusion tensor imaging (DTI) is employed in the investigation of white matter features.

Whereas most conventional clinical MRI review is performed by visual inspection of images slice by slice, quantitative MRI involves 3D image acquisition and systematic quantification of brain morphology, typically across the entire brain. Brain structures may be traced manually for volumetric estimation; however, as this is very labor-intensive, it is not feasible in a clinical setting and therefore largely constrained to research studies. The availability of increased computing power and advancements in signal processing in medical imaging has enabled automatic quantification of brain structures with minimal user intervention and, crucially, within reasonable time frames. Importantly, quantitative MRI has the potential to detect subtle abnormalities in an individual patient by comparing metrics derived from a single scan to large normal control data sets.

Different Methodologies and Software for Quantitative MRI Analyses

Voxel-Based Morphometry

Voxel-based morphometry is the most widely used method for automatic quantification of brain structure and whole-brain structure-symptom analyses (Wright et al., 1995). A detailed review of VBM methods is provided by Ashburner and Friston (Ashburner & Friston, 2000). VBM first aligns brains into a common stereotactic space by morphing each individual brain to a standard template. The most often used template is an average of 152 brains provided by the Montreal Neurological Institute (i.e., MNI152). Averaging brains to a standard template allows matching of anatomical structures across individuals and comparisons of findings, for example, from reported *x*–*y*–*z* coordinates of areas of significant differences found in other studies (Ashburner & Friston, 1999). The next step segments tissue into white and gray matter based on image intensities from T1-weighted images. This requires an MRI image with high gray-white matter contrast. The gray matter partitions obtained from the segmentation are compared statistically on a voxel-by-voxel basis. The result is a statistical parametric map across the whole brain that identifies and localizes areas of significant differences in gray matter concentration/density between groups or between a group and a single patient.

The main advantage of VBM is that it represents a comprehensive assessment of anatomical differences throughout the brain and therefore does not require any a priori clinically defined anatomical region nor is it biased to any well-defined structures. Some VBM tools, such as SPM, have a very useful batch scripting tool that, once set up by an expert, allows quick and easy analysis and visualization of VBM results by nonexperts. The main disadvantage of VBM is that there is potential for misalignment of cortical structures during registration procedures. Cortical variability in folding patterns complicates registration from native space to standard space, increasing the probability of misclassifying gray and white matter tissue, even after nonlinear warping procedures have been applied. This may reduce the sensitivity to detect group differences in cortical regions (Ashburner & Friston, 1999). Likewise, VBM's smoothing step neglects the increased variability in anatomical relationships across a folded surface (Singh et al., 2006).

Applications of VBM in Epilepsy

VBM investigations have identified widespread cortical and subcortical abnormalities associated with temporal lobe epilepsy that are not apparent upon visual inspection. In addition to hippocampal atrophy (Bernasconi et al., 2003; Salmenperä, Kälviäinen, Partanen, & Pitkänen, 2001), structural abnormalities are found in the entorhinal cortex (Bonilha et al., 2007), fornix (Kuzniecky et al., 1999), parahippocampal gyrus (Bernasconi et al., 2003), amygdala (Bernasconi et al., 2003; Salmenperä et al., 2001), basal ganglia (Dreifuss et al., 2001), thalamus (DeCarli et al., 1998), lateral temporal lobe (Jutila et al., 2001; J. W. Lee et al., 1998; Moran, Lemieux, Kitchen, Fish, & Shorvon, 2001), and cerebellum (Sandok, O'Brien, Jack, & So, 2000). As summarized in a comprehensive review of VBM group studies comparing patients with TLE to healthy controls (Keller & Roberts, 2008), hippocampal atrophy ipsilateral to the seizure focus and bilateral thalamic atrophy are common findings; however, several neocortical abnormalities can also be observed. Such findings are consistent with the diverse cognitive deficits demonstrated in TLE outside of memory impairment (Hermann, Lin, Jones, & Seidenberg, 2009). However, widespread neocortical atrophy associated with seizure burden must be differentiated from the presence of dual pathology, as the presence of extratemporal structural abnormalities is associated with a reduction in the likelihood of seizure freedom following a mesial temporal resection (Sisodiya et al., 1997).

VBM methods have also been applied to the characterization of focal cortical abnormalities in individuals with visually apparent malformations of cortical development. In one study, VBM identified gray matter abnormalities in 79 % of

visually identified FCDs, as well as abnormalities extending beyond the known lesion (Colliot et al., 2006). In another investigation, 9 out of 11 patients showed significant gray matter concentration excess that was correspondent to the visually detected FCD (Leonardo Bonilha et al., 2006). VBM methods have also reliably identified regions of increased T2 signal that correspond to visually identified MCDs in 18 out of 20 patients (Rugg-Gunn, Boulby, Symms, Barker, & Duncan, 2005). Importantly, all of these studies identified additional gray matter abnormalities that were not apparent to the visual eye. However, the epileptogenic potential of such putatively occult lesions was not demonstrated, and the detection of so-called "MRI-negative" lesions remains an active area of research.

Surface-Based Morphometry

More recent developments in brain morphometry include surface-based methods for registration and group comparison of cortical structures. The fundamental difference from volume-based approaches, such as VBM, is that computations are not performed on voxels within a 3D volume but involve the more elaborate geometric construction of inner and outer cortical boundaries or surfaces (Fischl & Dale, 2000; Miller, Massie, Ratnanather, Botteron, & Csernansky, 2000). The point of measurement in volume-based approaches is the voxel; when dealing with surfaces, it is the vertex. This allows for more precise matching of cortical structures to a standard spherical template by directly aligning corresponding sulcal and gyral patterns (Fischl, Sereno, & Dale, 1999). Surfaces also offer advantages in visualization as they can be inflated to show abnormalities hidden in sulci. A common measure obtained from surface-based methods is cortical thickness, derived from measuring the distance between corresponding points on the white and pial surfaces across the whole brain (see Fig. 7.1). For example, FreeSurfer (http://surfer.nmr.mgh.harvard.edu) is a popular comprehensive toolbox that performs automatic subcortical segmentation and surface reconstruction, as well as measures several volume and surface-based morphological MRI features.

Applications of Surface-Based Methods in Epilepsy

Consistent with VBM studies, surface-based methods have identified widespread neocortical abnormalities associated with mesial temporal lobe epilepsy (MTLE), particularly cortical thinning of the frontal and lateral temporal regions (Lin et al., 2007; McDonald et al., 2008b). Greater asymmetries in cortical thickness have been observed in the medial temporal cortex of MTLE patients relative to controls, with more abnormalities in the regions ipsilateral to the seizure focus (Bernhardt et al., 2008; Lin et al., 2007; McDonald et al., 2008b). Ipsilateral abnormalities are also apparent in frontal regions (Bernhardt et al., 2008). However, both cortical thinning and reduction in cortical complexity are found in bilateral extratemporal regions, even in the case of unilateral seizure foci (Lin et al., 2007). Interestingly, differential patterns of neocortical thinning are observed in TLE with MTS (TLE-MTS) and TLE without MTS (TLE-no), with more thinning in the inferior medial and posterior temporal regions in TLE-MTS and more thinning in lateral temporal and opercular regions in TLE-no (Mueller et al., 2009). This suggests that surface features can help to distinguish whether differential epileptogenic networks might be involved in TLE with and without MTS. An exciting area for further research would be to determine whether there is a relationship between these differential patterns of cortical thinning and different patterns of performance on neuropsychological tests (e.g., greater memory deficits associated with MTS and greater word-finding difficulties associated with MTS-no).

Studies on the relationship between surface-based measures of neocortical abnormalities and cognitive dysfunction in TLE are only beginning to emerge. A relationship between cortical thinning and general cognitive phenotypical patterns has been recently demonstrated. Increasing abnormalities in temporal and extratemporal

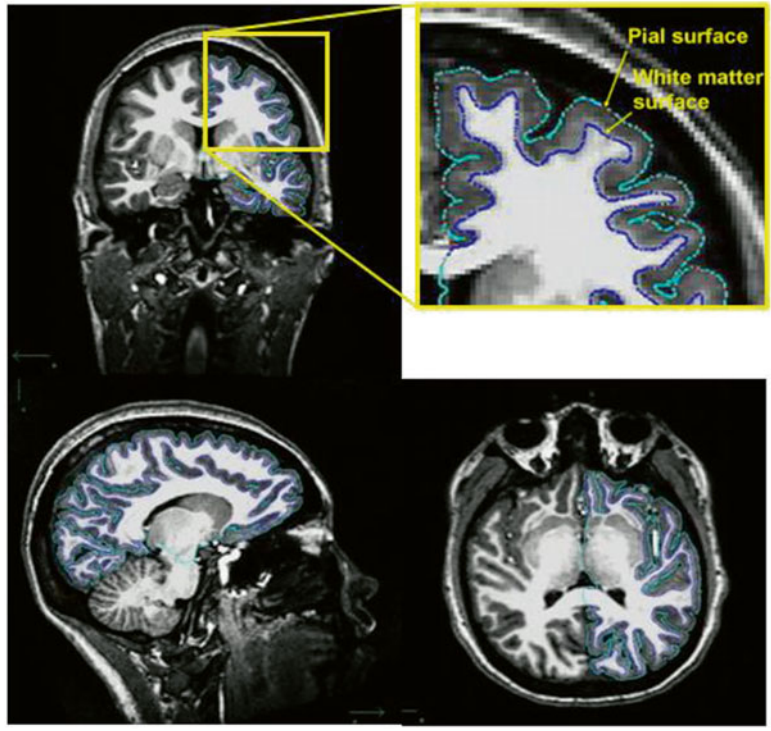

Fig. 7.1 T1-weighted 3D anatomical MRI scan with imaging sequence optimized for gray-white matter contrast. Automated tracing of white matter (*green*) and pial (*blue*) surfaces

cortical thickness were found to distinguish between different cognitive phenotypes (minimally impaired; memory impaired; memory, executive function, and speed impaired) in a stepwise fashion, with the most cognitively impaired group demonstrating the most significant cortical thinning (Dabbs, Jones, Seidenberg, & Hermann, 2009).

Also consistent with VBM studies, surface-based methods can be used to detect cortical abnormalities associated with MCDs. Surface-based methods have identified that areas of focal cortical dysplasia can be preferentially located at the bottom of abnormally deep sulci (Besson, Andermann, Dubeau, & Bernasconi, 2008), a finding which may be used to direct the search for developmental abnormalities, particularly when MRI features are only mildly abnormal or absent. Uniquely, surface-based methods can characterize subtle surface features, such as cortical thickening, blurred gray-white matter boundary, and hyperintense T1 signal (Besson, Bernasconi, Colliot, Evans, & Bernasconi, 2008). These characteristic features, particularly in combination, can be used to detect subtle abnormalities that escape visual detection. Figure 7.2 shows an example of a 38-year-old female patient who had suffered from epilepsy all her life. Several past MRIs showed no sign of a focal lesion until she was referred to our epilepsy center, and a small T2-FLAIR abnormality was discovered in her right mesial frontal lobe. Quantitative comparison revealed significant thickening and blurring in the same region, imaging features consistent with focal cortical dysplasia. The epileptogenic character of the region was subsequently confirmed by intracranial electrophysiology, as well as pathology and outcome after resection.

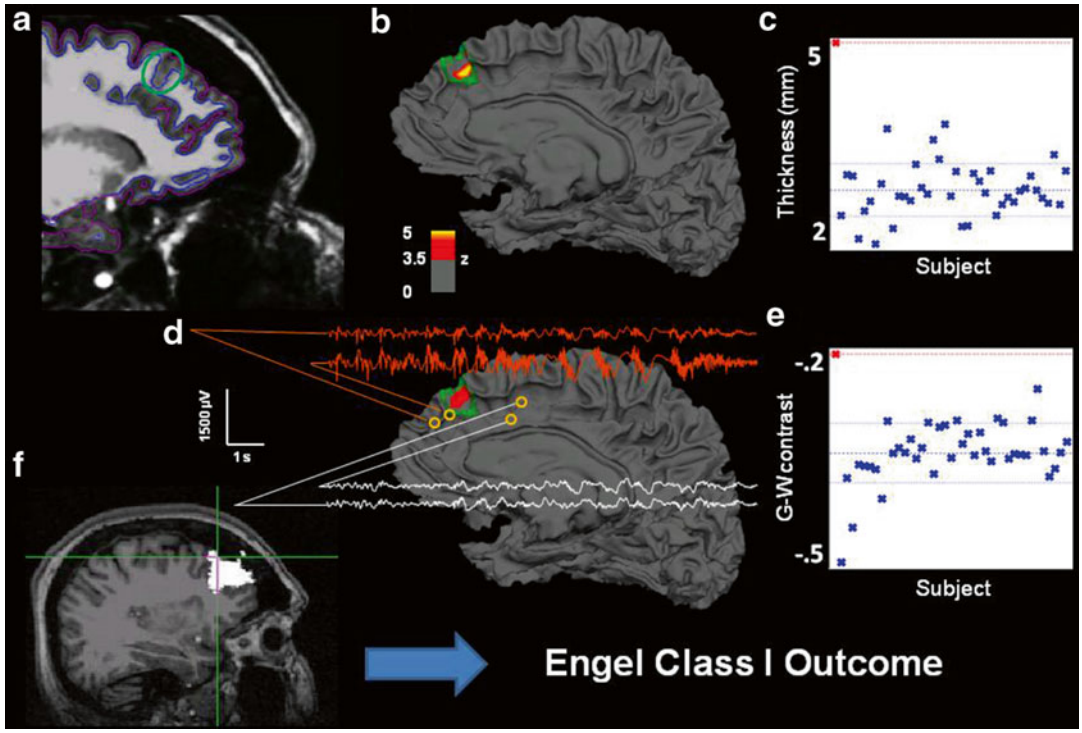

Fig. 7.2 Multimodal results for Patient 4. (**a**) Sagittal T1 with pial and white matter surface tracings used for calculating cortical thickness and G-W contrast. *Green circle* marks area of visually identified focal cortical dysplasia. (**b**) Patient's reconstructed white matter surface with area of significant cortical thickening marked in *red/yellow* ($z>3.5$, cluster corrected) within the expert-delineated lesion margin (*green tracing*). (**c**) Mean cortical thickness of the true positive cluster for patient (*red cross*, *top left*) and all normal control subjects in *blue*. (**d**) Same as **b**, but for gray-white matter contrast. The significant cluster shows an area of significant blurring of the gray-white matter junction. EEG traces from intracranial electrodes near the dysplastic area showing focal interictal and ictal discharges (*orange*), compared to slightly more distant electrode locations (*white*), showing a co-localization of detected lesion and pathological electrophysiology. (**e**) Mean gray-white matter contrast for the single patient and all control subjects. More positive values denote increased gray-white boundary blurring. (**f**) Resected area after surgery (in *white*). *Cross hair* marks area of maximum thickness increase within the detected lesion. This patient is seizure-free 1 year after surgery

Subcortical Segmentation

Surface-based coordinate systems are appropriate for registration of cortical structures; however, different methods are necessary for alignment and intersubject averaging of white matter and subcortical gray matter structures. Automated segmentation tools for obtaining subcortical volumetric information involve shape and image intensity characteristics. Widely used software packages that perform automatic segmentation and volume calculations for various subcortical structures (such as hippocampus, amygdala, thalamus, caudate, etc.) include Harvard's FreeSurfer and Oxford's FIRST. Both programs require a good-quality, high-resolution T1-weigthed MPRAGE scan as input and function with only minimal manual intervention.

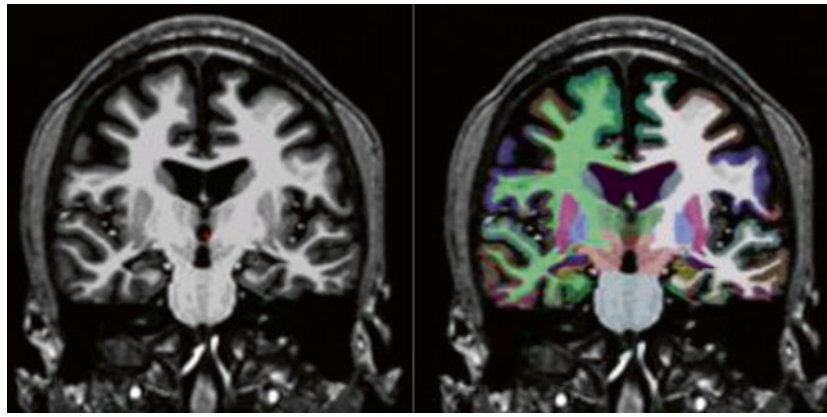

Fig. 7.3 Subcortical segmentation of a patient with bilateral HC atrophy. MRI volumetry revealed: left HC volume = 1,731 mm^3, right HC = 1,790 mm^3, left HC volume = −5.61, and right HC volume = −7.74. SDs below age-matched control volumes

Applications of Automatic Segmentation in Epilepsy

Automatic subcortical segmentation methods have had as high as a 74 % accuracy rate in the lateralization of epilepsy through hippocampal volumetric comparisons, compared to 78 % with manual segmentation methods (Akhondi-Asl, Jafari-Khouzani, Elisevich, & Soltanian-Zadeh, 2010). Reductions in hippocampal volumes ipsilateral to seizure focus in MTLE have been identified, along with bilateral reductions in thalamic and cerebellar gray matter volumes (McDonald et al., 2008a). Some companies, like San Diego-based CorTechs, Inc., offer FDA-approved user-friendly processing and visualization of quantitative MRI morphometry with automatic report generation, which are reimbursable by insurance companies. An example where quantitative analysis offered increased accuracy compared to visual inspection alone is shown by a patient evaluated at our center for presurgical evaluation and who had undergone a full epilepsy MRI protocol. The clinical MRI report indicated right hippocampal atrophy. However, when a subcortical segmentation was performed and the patient's hippocampal volumes were compared to 40 normal controls, it was evident that both hippocampi were severely atrophied, with more atrophy seen in the right hemisphere (Fig. 7.3).

Diffusion Tensor Imaging

DTI allows the measurement of fiber tracts in the brain by calculating water diffusion. Water molecules diffuse more easily along structures and thus showing larger anisotropy on diffusion scans where white matter tracts are present. The most widely used index in DTI, fractional anisotropy (FA), is expressed in values between 0 and 1, with higher anisotropy occurring in white matter and the corpus callosum and lower values in cerebrospinal fluid and gray matter. FA is often used in studies as a measure of white matter integrity. Tractography is more limited in the vicinity of mesiotemporal and neocortical regions, where fibers are of smaller diameter, have more branching, and are more likely to cross, increasing the difficulty of determining directionality. Methods are being developed to correct for this by improved partial volume corrections and calculation of secondary fiber directions.

Applications of DTI in Epilepsy

A general decrease in white matter volume in chronic TLE has been well documented; however, DTI allows for the investigation of specific fiber tract integrity. Bilateral symmetrical reduction in

fractional anisotropy (FA) is observed in the fornix and cingulum of patients with TLE (Concha, Beaulieu, & Gross, 2005), as well as frontotemporal white matter tracts (arcuate fasciculus and uncinate fasciculus) (Lin, Riley, Juranek, & Cramer, 2008; Matsumoto et al., 2008; Rodrigo et al., 2007), temporal-occipital connections (inferior longitudinal fasciculus), frontal-occipital connections (inferior frontal-occipital fasciculus) (Ahmadi et al., 2009), and the corpus callosum (Arfanakis et al., 2002; Concha, Beaulieu, Collins, & Gross, 2009). Patients with left TLE have greater, more diffuse changes in FA values across multiple fiber tracts, whereas patients with right TLE showed changes that are primarily ipsilateral to the side of seizure onset (Ahmadi et al., 2009).

Consistent with cortical abnormalities found in TLE, whole-brain voxelwise analysis of DTI data has revealed extensive bilateral white matter diffusion abnormalities in the frontal and temporal lobes, with more involvement in the hemisphere ipsilateral to seizure onset (Shon et al., 2010; Thivard et al., 2005). In TLE patients with left- and right-sided resective surgery, widespread tract degradation was observed in the uncinate fasciculus, the fronto-occipital fasciculus, the superior longitudinal fasciculus, the corpus callosum, and the corticospinal tract (Schoene-Bake et al., 2009). Furthermore, tract degradation has been shown to be associated with memory and language impairments in TLE patients (McDonald et al., 2008), suggesting that DTI can provide important information for predicting cognitive status in individuals with epilepsy (Table 7.2).

Conclusions/Future Possibilities

Visual inspection of MRI images obtained through a dedicated epilepsy protocol has become a standard component of the comprehensive epilepsy workup. Quantitative MRI methods provide a valuable tool in the assessment of structural abnormalities associated with epilepsy; however, the systematic implementation of such methods in the basic clinical assessment of epilepsy has yet to be realized in many comprehensive centers. Reasons for this lag between research findings and clinical implementation include the need for labor-intensive, expert-dependent manual tracings and operator-dependent interpretation of results, both of which are impractical in most clinical settings (Brewer, 2009). Recent quantitative tools have solved these problems with full automation of registration, segmentation, and comparison procedures, which provide output that is relatively quick to generate and clinically interpretable.

Quantitative MRI methods also have the promising potential of being able to incorporate neuropsychological data directly into an analysis. Appreciation of structural and behavioral correlates can be done simultaneously and empirically. Such information could prove to be invaluable in the lateralization and localization of focal epilepsy, as well as in characterizing the extent of structural and functional damage associated with seizure activity.

The general trend toward standardization of neuroimaging data in making group or individual comparisons is intuitive for most neuropsychologists. Difficulties in accurate registration of brain structures to a standard template are not unlike the dilemma neuropsychologists face in choosing normative groups that are demographically similar to their individual patient. Similarly, quantitative neuroimaging methods might benefit from implementation of standard neuropsychological practices such as limiting the normative group to a more constrained age range or education bracket. Identification of abnormalities must be sensitive and specific, a goal that is shared by neuroimagers and neuropsychologists. Whether this goal can be more precisely realized through direct combination of neuroimaging and neuropsychological methods will be exciting to see in the near future.

Table 7.2 Software packages for structural MRI analysis

Method	Software package	Web site	
VBM			
	SPM	http://www.fil.ion.ucl.ac.uk/spm/	Free
	FSLVBM	http://www.fmrib.ox.ac.uk/fsl/fslvbm	Free
	Jena VBM	http://dbm.neuro.uni-jena.de/vbm/	Free
Segmentation			
	NVM	http://neuromorphometrics.org:8080/nvm/	Free
	FSL FIRST	http://www.fmrib.ox.ac.uk/fsl/first/index.html	Free
	BrainVISA	http://brainvisa.info/	Free
	BioImage Suite	http://bioimagesuite.org/	Free
	Caret	http://brainvis.wustl.edu/wiki/index.php/Caret:About	Free
	ITK-SNAP	http://www.itksnap.org/pmwiki/pmwiki.php	Free
	FreeSurfer	http://surfer.nmr.mgh.harvard.edu/	Free
	LONI Brain Parser	http://loni.ucla.edu/Software/BrainParser	
	NeuroQuant	http://www.cortechs.net/products/neuroquant.php	Commercial
Surface based			
	FreeSurfer	http://surfer.nmr.mgh.harvard.edu/	Free
	Caret	http://brainvis.wustl.edu/wiki/index.php/Caret:About	Free
	BrainVISA	http://brainvisa.info/	Free
	LONI BrainSuite	http://loni.ucla.edu/Software/BrainSuite	
DTI			
	DSI Studio	http://dsi-studio.labsolver.org/	Free
	FSL FTD	http://www.fmrib.ox.ac.uk/fsl/fdt/index.html	Free
	BrainMagix	http://www.imagilys.com/brainmagix-neuroimaging-fmri-software/	Commercial
	BioImage Suite	http://bioimagesuite.org/	Free
	Camino	http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php	
Manual tracing	LONI MultiTracer	http://loni.ucla.edu/Software/MultiTracer	
Visualization			
	3D Slicer	www.slicer.org	Free
	BrainVoyager	http://www.brainvoyager.com/	Commercial
	MRIcro	http://www.cabiatl.com/mricro/mricro/index.html	Free
	FSLView	http://www.fmrib.ox.ac.uk/fsl/fslview/index.html	Free
	Mango	http://ric.uthscsa.edu/mango/	
	DICOMWorks	http://dicom.online.fr/	Free

This is by no means intended as an exhaustive list of all available neuroimaging tools but does list the most popular software toolboxes used in clinical and basic research. Further information on software packages for neuroimaging is available at the NIH Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) http://www.nitrc.org/

References

Ahmadi, M. E., Hagler, D. J., McDonald, C. R., Tecoma, E. S., Iragui, V. J., Dale, A. M., et al. (2009). Side matters: Diffusion tensor imaging tractography in left and right temporal lobe epilepsy. *AJNR. American Journal of Neuroradiology, 30*(9), 1740–1747. doi:10.3174/ajnr.A1650.

Akhondi-Asl, A., Jafari-Khouzani, K., Elisevich, K., & Soltanian-Zadeh, H. (2010). Hippocampal volumetry for lateralization of temporal lobe epilepsy: Automated versus manual methods. *NeuroImage*. doi:10.1016/j.neuroimage.2010.03.066.

Arfanakis, K., Hermann, B. P., Rogers, B. P., Carew, J. D., Seidenberg, M., & Meyerand, M. E. (2002). Diffusion tensor MRI in temporal lobe epilepsy. *Magnetic Resonance Imaging, 20*(7), 511–519.

Ashburner, J., & Friston, K. J. (1999). Nonlinear spatial normalization using basis functions. *Human Brain Mapping, 7*(4), 254–266.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage, 11*(6 Pt 1), 805–821. doi:10.1006/nimg.2000.0582.

Barkovich, A. J., Kuzniecky, R. I., & Dobyns, W. B. (2001). Radiologic classification of malformations of cortical development. *Current Opinion in Neurology, 14*(2), 145–149.

Berkovic, S. F., McIntosh, A. M., Kalnins, R. M., Jackson, G. D., Fabinyi, G. C., Brazenor, G. A., et al. (1995). Preoperative MRI predicts outcome of temporal lobectomy: An actuarial analysis. *Neurology, 45*(7), 1358–1363.

Bernasconi, N., Bernasconi, A., Caramanos, Z., Antel, S. B., Andermann, F., & Arnold, D. L. (2003). Mesial temporal damage in temporal lobe epilepsy: A volumetric MRI study of the hippocampus, amygdala and parahippocampal region. *Brain, 126*(Pt 2), 462–469.

Bernasconi, N., Duchesne, S., Janke, A., Lerch, J., Collins, D. L., & Bernasconi, A. (2004). Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. *NeuroImage, 23*(2), 717–723. doi:10.1016/j.neuroimage.2004.06.015.

Bernhardt, B. C., Worsley, K. J., Besson, P., Concha, L., Lerch, J. P., Evans, A. C., et al. (2008). Mapping limbic network organization in temporal lobe epilepsy using morphometric correlations: Insights on the relation between mesiotemporal connectivity and cortical atrophy. *NeuroImage, 42*(2), 515–524. doi:10.1016/j.neuroimage.2008.04.261.

Besson, P., Andermann, F., Dubeau, F., & Bernasconi, A. (2008). Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus. *Brain, 131*(Pt 12), 3246–3255. doi:10.1093/brain/awn224.

Besson, P., Bernasconi, N., Colliot, O., Evans, A., & Bernasconi, A. (2008). Surface-based texture and morphological analysis detects subtle cortical dysplasia. *Medical Image Computing and Computer-Assisted Intervention, 11*(Pt 1), 645–652.

Betting, L. E., Mory, S. B., Lopes-Cendes, I., Li, L. M., Guerreiro, M. M., Guerreiro, C., et al. (2006). MRI reveals structural abnormalities in patients with idiopathic generalized epilepsy. *Neurology, 67*(5), 848–852. doi:10.1212/01.wnl.0000233886.55203.bd.

Bonilha, L., Montenegro, M. A., Rorden, C., Castellano, G., Guerreiro, M. M., Cendes, F., et al. (2006). Voxel-based morphometry reveals excess gray matter concentration in patients with focal cortical dysplasia. *Epilepsia, 47*(5),908–915.doi:10.1111/j.1528-1167.2006.00548.x.

Bonilha, L., Rorden, C., Halford, J. J., Eckert, M., Appenzeller, S., Cendes, F., et al. (2007). Asymmetrical extra-hippocampal grey matter loss related to hippocampal atrophy in patients with medial temporal lobe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*(3), 286–294. doi:10.1136/jnnp.2006.103994.

Brewer, J. B. (2009). Fully-automated volumetric MRI with normative ranges: Translation to clinical practice. *Behavioural Neurology, 21*(1), 21–28. doi:10.3233/BEN-2009-0226.

Cardoso, T. A. M., Coan, A. C., Kobayashi, E., Guerreiro, C. A. M., Li, L. M., & Cendes, F. (2006). Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal. *Neurology, 67*(1), 134–136. doi:10.1212/01.wnl.0000223350.08394.06.

Colliot, O., Mansi, T., Bernasconi, N., Naessens, V., Klironomos, D., & Bernasconi, A. (2006). Segmentation of focal cortical dysplasia lesions on MRI using level set evolution. *NeuroImage, 32*(4), 1621–1630. doi:10.1016/j.neuroimage.2006.04.225.

Concha, L., Beaulieu, C., Collins, D. L., & Gross, D. W. (2009). White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 80*(3), 312–319. doi:10.1136/jnnp.2007.139287.

Concha, L., Beaulieu, C., & Gross, D. W. (2005). Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Annals of Neurology, 57*(2), 188–196. doi:10.1002/ana.20334.

Dabbs, K., Jones, J., Seidenberg, M., & Hermann, B. (2009). Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. *Epilepsy & Behavior, 15*(4), 445–451. doi:10.1016/j.yebeh.2009.05.012.

DeCarli, C., Hatta, J., Fazilat, S., Fazilat, S., Gaillard, W. D., & Theodore, W. H. (1998). Extratemporal atrophy in patients with complex partial seizures of left temporal origin. *Annals of Neurology, 43*(1), 41–45. doi:10.1002/ana.410430110.

Dreifuss, S., Vingerhoets, F. J., Lazeyras, F., Andino, S. G., Spinelli, L., Delavelle, J., et al. (2001). Volumetric measurements of subcortical nuclei in patients with temporal lobe epilepsy. *Neurology, 57*(9), 1636–1641.

Engel, J. (1996). Surgery for seizures. *The New England Journal of Medicine, 334*(10), 647–652.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America, 97*(20), 11050–11055. doi:10.1073/pnas.200033797.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage, 9*(2), 195–207. doi:10.1006/nimg.1998.0396.

Hermann, B. P., Lin, J. J., Jones, J. E., & Seidenberg, M. (2009). The emerging architecture of neuropsychological impairment in epilepsy. *Neurologic Clinics, 27*(4), 881–907. doi:10.1016/j.ncl.2009.08.001.

Jackson, G., & Kuzniecky, R. I. (2008). Structural neuroimaging. In J. Engel, T. A. Pedley, J. Aicardi, et al. (Eds.), *Epilepsy: A comprehensive textbook* (2nd ed., pp. 917–944). Philadelphia, PA: Lippincott Williams & Wilkins.

Jeha, L. E., Najm, I., Bingaman, W., Dinner, D., Widdess-Walsh, P., & Lüders, H. (2007). Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain, 130*(Pt 2), 574–584. doi:10.1093/brain/awl364.

Jutila, L., Ylinen, A., Partanen, K., Alafuzoff, I., Mervaala, E., Partanen, J., et al. (2001). MR volumetry of the entorhinal, perirhinal, and temporopolar cortices in drug-refractory temporal lobe epilepsy. *AJNR. American Journal of Neuroradiology, 22*(8), 1490–1501.

Keller, S. S., & Roberts, N. (2008). Voxel-based morphometry of temporal lobe epilepsy: An introduction and review of the literature. *Epilepsia, 49*(5), 741–757. doi:10.1111/j.1528-1167.2007.01485.x.

Kuzniecky, R., Bilir, E., Gilliam, F., Faught, E., Martin, R., & Hugg, J. (1999). Quantitative MRI in temporal lobe epilepsy: Evidence for fornix atrophy. *Neurology, 53*(3), 496–501.

Lee, J. W., Andermann, F., Dubeau, F., Bernasconi, A., MacDonald, D., Evans, A., et al. (1998). Morphometric analysis of the temporal lobe in temporal lobe epilepsy. *Epilepsia, 39*(7), 727–736.

Lerner, J. T., Salamon, N., Hauptman, J. S., Velasco, T. R., Hemb, M., Wu, J. Y., et al. (2009). Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience. *Epilepsia, 50*(6), 1310–1335. doi:10.1111/j.1528-1167.2008.01998.x.

Lin, J. J., Riley, J. D., Juranek, J., & Cramer, S. C. (2008). Vulnerability of the frontal-temporal connections in temporal lobe epilepsy. *Epilepsy Research, 82*(2–3), 162–170. doi:10.1016/j.eplepsyres.2008.07.020.

Lin, J. J., Salamon, N., Lee, A. D., Dutton, R. A., Geaga, J. A., Hayashi, K. M., et al. (2007). Reduced neocortical thickness and complexity mapped in mesial temporal lobe epilepsy with hippocampal sclerosis. *Cerebral Cortex, 17*(9), 2007–2018. doi:10.1093/cercor/bhl109.

Matsumoto, R., Okada, T., Mikuni, N., Mitsueda-Ono, T., Taki, J., Sawamoto, N., et al. (2008). Hemispheric asymmetry of the arcuate fasciculus: A preliminary diffusion tensor tractography study in patients with unilateral language dominance defined by Wada test. *Journal of Neurology, 255*(11), 1703–1711. doi:10.1007/s00415-008-0005-9.

McDonald, C. R., Ahmadi, M. E., Hagler, D. J., Tecoma, E. S., Iragui, V. J., Gharapetian, L., et al. (2008). Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. *Neurology, 71*(23), 1869–1876. doi:10.1212/01.wnl.0000327824.05348.3b.

McDonald, C. R., Hagler, D. J., Ahmadi, M. E., Tecoma, E., Iragui, V., Dale, A. M., et al. (2008a). Subcortical and cerebellar atrophy in mesial temporal lobe epilepsy revealed by automatic segmentation. *Epilepsy Research, 79*(2–3), 130–138. doi:10.1016/j.eplepsyres.2008.01.006.

McDonald, C. R., Hagler, D. J., Jr., Ahmadi, M. E., Tecoma, E., Iragui, V., Gharapetian, L., et al. (2008b). Regional neocortical thinning in mesial temporal lobe epilepsy. *Epilepsia, 49*(5), 794–803. doi:10.1111/j.1528-1167.2008.01539.x.

Mehta, S., Grabowski, T. J., Trivedi, Y., & Damasio, H. (2003). Evaluation of voxel-based morphometry for focal lesion detection in individuals. *NeuroImage, 20*(3), 1438–1454.

Miller, M. I., Massie, A. B., Ratnanather, J. T., Botteron, K. N., & Csernansky, J. G. (2000). Bayesian construction of geometrically based cortical thickness metrics. *NeuroImage, 12*(6), 676–687. doi:10.1006/nimg.2000.0666.

Mingrino, J., Blackmon, K., Halgren, E., Devinsky, O., Carlson, C., Dubois, J., et al. (n.d.). Morphometric variations in cortical gray matter, white matter, and subcortical volumes across the early to middle adult lifespan. *Submitted to Epilepsy Research and Treatment*.

Montenegro, M. A., Kinay, D., Cendes, F., Bernasconi, A., Bernasconi, N., Coan, A. C., et al. (2006). Patterns of hippocampal abnormalities in malformations of cortical development. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*(3), 367–371. doi:10.1136/jnnp.2005.070417.

Moran, N. F., Lemieux, L., Kitchen, N. D., Fish, D. R., & Shorvon, S. D. (2001). Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis. *Brain, 124*(Pt 1), 167–175.

Mueller, S. G., Laxer, K. D., Barakos, J., Cheong, I., Garcia, P., & Weiner, M. W. (2009). Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. *NeuroImage, 46*(2), 353–359. doi:10.1016/j.neuroimage.2009.02.020.

Palmini, A., Najm, I., Avanzini, G., Babb, T., Guerrini, R., Foldvary-Schaefer, N., et al. (2004). Terminology and classification of the cortical dysplasias. *Neurology, 62*(6 Suppl 3), S2–S8.

Rodrigo, S., Oppenheim, C., Chassoux, F., Golestani, N., Cointepas, Y., Poupon, C., et al. (2007). Uncinate fasciculus fiber tracking in mesial temporal lobe epilepsy. Initial findings. *European Radiology, 17*(7), 1663–1668. doi:10.1007/s00330-006-0558-x.

Rugg-Gunn, F. J., Boulby, P. A., Symms, M. R., Barker, G. J., & Duncan, J. S. (2005). Whole-brain T2 mapping demonstrates occult abnormalities in focal epilepsy. *Neurology, 64*(2), 318–325. doi:10.1212/01.WNL.0000149642.93493.F4.

Salmenperä, T., Kälviäinen, R., Partanen, K., & Pitkänen, A. (2001). Hippocampal and amygdaloid damage in partial epilepsy: A cross-sectional MRI study of 241 patients. *Epilepsy Research, 46*(1), 69–82.

Sandok, E. K., O'Brien, T. J., Jack, C. R., & So, E. L. (2000). Significance of cerebellar atrophy in intractable temporal lobe epilepsy: A quantitative MRI study. *Epilepsia, 41*(10), 1315–1320.

Schoene-Bake, J., Faber, J., Trautner, P., Kaaden, S., Tittgemeyer, M., Elger, C. E., et al. (2009). Widespread affections of large fiber tracts in postoperative temporal lobe epilepsy. *NeuroImage, 46*(3), 569–576. doi:10.1016/j.neuroimage.2009.03.013.

Shon, Y., Kim, Y., Koo, B., Lee, J., Kim, H. J., Kim, W. J., et al. (2010). Group-specific regional white matter abnormality revealed in diffusion tensor imaging of medial temporal lobe epilepsy without hippocampal

sclerosis. *Epilepsia, 51*(4), 529–535. doi:10.1111/j.1528-1167.2009.02327.x.

Singh, V., Chertkow, H., Lerch, J. P., Evans, A. C., Dorr, A. E., & Kabani, N. J. (2006). Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain, 129*(Pt 11), 2885–2893. doi:10.1093/brain/awl256.

Sisodiya, S. M., Moran, N., Free, S. L., Kitchen, N. D., Stevens, J. M., Harkness, W. F., et al. (1997). Correlation of widespread preoperative magnetic resonance imaging changes with unsuccessful surgery for hippocampal sclerosis. *Annals of Neurology, 41*(4), 490–496. doi:10.1002/ana.410410412.

Spooner, C. G., Berkovic, S. F., Mitchell, L. A., Wrennall, J. A., & Harvey, A. S. (2006). New-onset temporal lobe epilepsy in children: Lesion on MRI predicts poor seizure outcome. *Neurology, 67*(12), 2147–2153. doi:10.1212/01.wnl.0000248189.93630.4f.

Thivard, L., Lehéricy, S., Krainik, A., Adam, C., Dormont, D., Chiras, J., et al. (2005). Diffusion tensor imaging in medial temporal lobe epilepsy with hippocampal sclerosis. *NeuroImage, 28*(3), 682–690. doi:10.1016/j.neuroimage.2005.06.045.

Von Oertzen, J., Urbach, H., Jungbluth, S., Kurthen, M., Reuber, M., Fernández, G., et al. (2002). Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 73*(6), 643–647.

Walhovd, K. B., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., et al. (2009). Consistent neuroanatomical age-related volume differences across multiple samples. *Neurobiology of Aging*. doi:10.1016/j.neurobiolaging.2009.05.013.

Widdess-Walsh, P., Diehl, B., & Najm, I. (2006). Neuroimaging of focal cortical dysplasia. *Journal of Neuroimaging, 16*(3), 185–196. doi:10.1111/j.1552-6569.2006.00025.x.

Wiebe, S., Blume, W. T., Girvin, J. P., & Eliasziw, M. (2001). A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England Journal of Medicine, 345*(5), 311–318.

Wilke, M., Kassubek, J., Ziyeh, S., Schulze-Bonhage, A., & Huppertz, H. J. (2003). Automated detection of gray matter malformations using optimized voxel-based morphometry: A systematic approach. *NeuroImage, 20*(1), 330–343.

Woermann, F., Sisodiya, S., Free, S., & Duncan, J. (1998). Quantitative MRI in patients with idiopathic generalized epilepsy. Evidence of widespread cerebral structural changes. *Brain, 121*(9), 1661–1667. doi:10.1093/brain/121.9.1661.

Wright, I. C., McGuire, P. K., Poline, J. B., Travere, J. M., Murray, R. M., Frith, C. D., et al. (1995). A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *NeuroImage, 2*(4), 244–252. doi:10.1006/nimg.1995.1032.

Functional MRI in the Presurgical Epilepsy Evaluation

8

Sara J. Swanson, Jeffrey R. Binder, Manoj Raghavan, and Matthew Euler

Introduction

In the past two decades, functional neuroimaging techniques have revolutionized our understanding of normal brain functioning (Binder, Desai, et al., 2009; D'Esposito, 2000) and contributed to the evaluation and treatment of patients with neurological disorders (Bookheimer, 2007; Detre, 2006; Freilich & Gaillard, 2010). Understanding how and when to use functional localization methods such as fMRI in combination with or as an alternative to more traditional mapping methods such as the intracarotid amobarbital (Wada) test is critical for the clinical treatment of epilepsy surgery candidates. FMRI detects task-correlated or event-related changes in blood flow associated with underlying neuronal activity and is now considered a noninvasive alternative to Wada testing for language (Binder, 2011). Provides information not only about lateralization of higher cognitive functions but also localization and outcome prediction allowing epileptologists, neurosurgeons, and patients to make informed decisions prior to undertaking resective surgery.

While neuropsychologists historically used cognitive test data to aid in lateralization and localization of dysfunction relative to a focal seizure disorder (Jones-Gotman, 1991), sophisticated anatomical and electrographic methods are typically relied upon for surgical decision making. For example, EEG and MRI, when combined, are of high lateralization value (93 %) with neuropsychological testing adding little additional variance (2 %) (Akanuma, Alarcon, et al., 2003; Moser, Bauer, et al., 2000; Swanson, 2006). However, preoperative neuropsychological test data provide essential information for making predictions about risks for language and memory morbidity after anterior temporal lobe (ATL) resection. The best outcome predictions are made by combining preoperative cognitive data, fMRI language laterality indexes (LIs), side of seizure focus, hippocampal status, and age at onset of seizures (Baxendale & Thompson, 2010; Binder, Gross, et al., 2010; Binder, Sabsevitz, et al., 2008; Bonelli, Powell, et al., 2010; Powell, Richardson, et al., 2008; Richardson, Strange, et al., 2006; Sabsevitz, Swanson, et al., 2003). Therefore, neuropsychologists will benefit from understanding how to combine functional imaging, history, and cognitive variables when working with epilepsy surgery candidates.

The present chapter aims to provide clinicians with a practical understanding of how to conduct

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fMRI with epilepsy surgery candidates. Technical and clinical information necessary for conducting fMRI are discussed including how to select the necessary equipment, data analysis software packages, and cognitive task combinations as well as how to detect valid task-correlated activity, compute language lateralization indexes (LIs), and use regression formulas for predicting language and memory outcomes following ATL surgery.

fMRI

Biophysical Basis of fMRI

Most fMRI scanning is based on detection of local changes in oxygen concentration resulting from changes in neural activity, known as blood oxygen level-dependent (BOLD) imaging (Ogawa, Lee, et al., 1990). Though the phenomena underlying the BOLD signal are quite complex, the main processes can be briefly summarized. Localized increases in neural activity produce a chemical signal that leads to localized increases in blood flow to the activated region, a process called neurovascular coupling. The increase in blood flow is relatively slow and delayed compared to the change in neural activity, beginning within a second or so but reaching a peak only 4–5 s after the neural event. This delayed change in blood flow is called the hemodynamic response function and is important to keep in mind for understanding data analysis and certain timing issues in data acquisition and task design. The localized increase in blood flow floods the activated region with highly oxygenated blood in the form of oxygenated hemoglobin molecules, resulting in a net increase in the ratio of oxygenated to deoxygenated hemoglobin.

"BOLD signal" refers to the fact that the brightness, or signal level, of a voxel (volume element) in an fMRI image increases as a function of the oxyhemoglobin/deoxyhemoglobin ratio in that voxel. To understand why this is, consider that a voxel in a brain image contains numerous small blood vessels, each of which carry hemoglobin molecules. A hemoglobin molecule in the deoxygenated state is paramagnetic, i.e., it functions as a microscopic magnet and alters the homogeneity (uniformity of strength) of the scanner's magnetic field, while oxygenated hemoglobin is magnetically inert and has no effect on the underlying magnetic field. Microscopic variations in the magnetic field strength within a voxel (resulting from deoxyhemoglobin molecules) cause the protons within the voxel to spin (or *precess*) at slightly different frequencies, because the spin frequency is directly related to field strength. Protons within a voxel spinning at different frequencies will over time become out of phase with each other ("intravoxel spin dephasing"). Because the signal measured by an MRI scanner is stronger when more protons are spinning in phase with each other, the MRI signal from a given voxel will be higher when the hemoglobin molecules in the voxel are oxygenated (highly uniform field) and lower when the hemoglobin is deoxygenated (less uniform field). This dependency of the MRI signal on homogeneity of the magnetic field within a voxel is referred to as the T2* ("T2 star") effect.

Although BOLD is the most popular form of fMRI, other techniques are also used. The most common alternative is to measure local changes in blood flow more directly, an approach known generally as perfusion imaging. Perfusion imaging can be based on tracking an injected bolus of gadolinium (Belliveau, Kennedy, et al., 1991), but a more common approach is to "label" protons with a magnetic pulse as they enter the cranium and track their movement into higher image slices, a technique known as arterial spin labeling (Alsop & Detre, 1998). One advantage of perfusion imaging is that it provides a more direct measure of blood flow than BOLD imaging, which can be useful in certain situations. As discussed below, BOLD imaging is susceptible to image degradation resulting from nonuniformity of the magnetic field, which is not the case with perfusion imaging. On the other hand, BOLD methods generally provide a higher signal-to-noise ratio (SNR) and better temporal resolution than perfusion techniques.

Image Acquisition Hardware

fMRI depends on rapid image acquisition in order to track hemodynamic responses occurring throughout the brain. BOLD fMRI uses specialized pulse sequences designed to be sensitive to intra-voxel spin dephasing, known as T2*-weighted sequences. Echoplanar imaging (EPI) is a pulse sequence capable of very fast acquisition of T2*-weighted images and is the most common sequence used for BOLD fMRI. Related T2* methods such as spiral imaging are also used (Noll, Stenger, et al., 1999). All of these methods require very rapid alterations of the magnetic field to create a spatial grid for pulse excitation and signal localization (i.e., spatial encoding), necessitating high-performance gradient coils. MRI scanners continue to improve in terms of the speed (slew rate) and amplitude of these gradient devices, which are the main factors determining the number of voxels that can be encoded in a given amount of time and thus the spatial and temporal resolution that can be achieved.

The signal measured in MRI is based on energy given off by protons after excitation with a brief (radiofrequency range, or RF) magnetic pulse. This signal is detected by coils called RF receive coils, which are positioned as close to the head as possible to maximize sensitivity, typically in a cylindrical, cage-like structure surrounding the head. Most current scanners employ multichannel RF coil arrays with 8–32 receive coils providing input to separate channels on the scanner. This arrangement improves SNR by summation of signals across channels and makes possible a newer technique called parallel imaging. Parallel imaging takes advantage of the spatial arrangement of receivers in a multichannel array coil to reduce the number of gradient changes needed for spatial encoding. This translates into faster image acquisition, though with some reduction of SNR.

Pulse Sequence Parameters

An understanding of some imaging parameters can be helpful in choosing an optimal fMRI protocol. Repetition time, or TR, is the time required for one cycle of the pulse sequence, and with EPI sequences this is usually equivalent to the time required to collect one image volume. Typical values are 2 or 3 s. The term TR is also often used loosely to refer to the image volume collected in each cycle of the pulse sequence. Echo time, TE, is the time between the excitation pulse and registration of the signal by the RF receive coils. Typical values are 40–50 ms when scanning at 1.5 T and 25–35 ms at 3 T. Voxel dimensions are determined by the slice thickness, the rectangular dimensions of each slice (called the field of view, or FOV), and the in-plane matrix, which is simply the number of voxels within the x, y spatial grid of the slice. The in-plane voxel dimensions are obtained simply by dividing the FOV by the matrix dimensions. For example, a FOV of 208 mm × 240 mm and matrix of 64 × 64 produces voxels with in-plane size 3.2 mm × 3.75 mm. A FOV of 192 mm × 192 mm, matrix of 96 × 96, and slice thickness of 2.5 mm would yield perfectly cubic (or *isotropic*) voxels measuring 2.5 mm in each direction.

A significant problem with T2* imaging, particularly EPI, is extreme loss of signal ("signal dropout") near air-tissue and air-bone interfaces in the head, such as the frontal and temporal sinuses (Ojemann, Akbudak, et al., 1997). These interfaces produce macroscopic gradients in the magnetic field that often extend several centimeters into the brain tissue, causing severe intravoxel spin dephasing in the affected areas. This dephasing, of course, is the same phenomenon that underlies the BOLD signal but operates over a larger spatial scale. As a result, the same T2*-weighted images that are optimally sensitive to microscopic gradients from deoxyhemoglobin molecules always contain areas of severe signal loss from macroscopic gradients. The main brain regions affected are the ventromedial frontal lobes, anteromedial temporal lobes (often including the amygdala), and the middle portion of the ventrolateral temporal lobes (inferior temporal and fusiform gyri). Figure 8.1 shows consistent regions of signal loss.

Imaging parameters can be adjusted to reduce the severity of signal dropout (Merboldt,

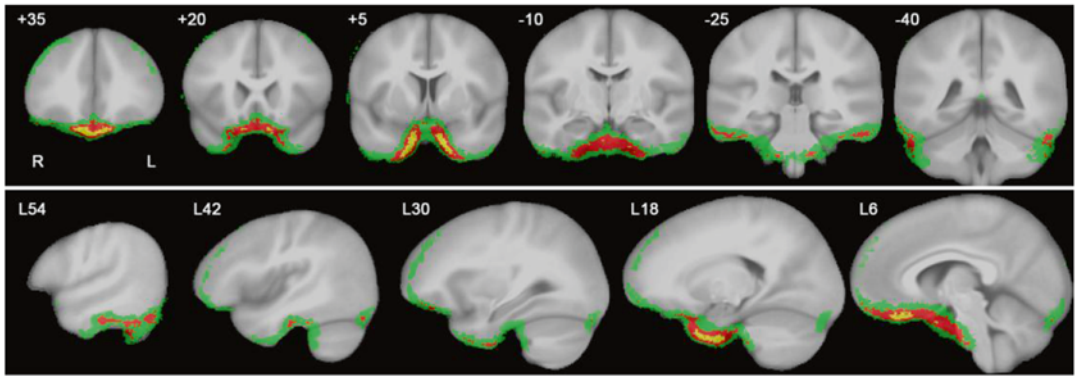

Fig. 8.1 Probabilistic map of areas showing severe signal loss in a typical fMRI study using echoplanar imaging. The study was done at 3 T using TE = 25 ms and voxel size = 2.5-mm isotropic. Signal-to-fluctuation noise ratio (SFNR) maps were calculated for each of 34 healthy control subjects and thresholded to identify voxels with SFNR values below 20. The overlap of these low SFNR regions across subjects after normalization to stereotaxic space is shown. *Green* indicates overlap in at least 25 % of the sample, *red* overlap in at least 50 %, and *yellow* overlap in at least 75 %

Finterbusch, et al., 2000; Morawetz, Holz, et al., 2008). The shorter the TE, the less time is available for spins to become out of phase within a voxel, thus the smaller is the effect of an intravoxel gradient. Unfortunately, shortening the TE will also reduce the size of the BOLD effect, for the same reason. Use of smaller voxels can be helpful, since differences in field strength across a gradient spanning the voxel will be smaller, producing less dephasing. Decreasing the voxel size also improves spatial resolution, but this strategy is limited by the fact that smaller voxels contain fewer protons, thus signal levels will be smaller in regions not affected by macroscopic gradients. Reducing the voxel size also means that more voxels are needed to cover the entire brain, which requires more time (i.e., a longer TR), resulting in lower temporal resolution. Fortunately, these limitations are becoming less important with the advent of parallel imaging and continued improvements in gradient speed.

Geometric Distortion and Motion Artifacts

EPI images typically show varying degrees of geometric distortion or "warping" of the image due to underlying field inhomogeneity and other factors, and these effects tend to increase with field strength and matrix size. The result of this warping is a spatial mismatch between some regions of the EPI image and the high-resolution structural images that are usually obtained as an anatomical reference. A common method for reducing geometric distortion is to acquire special images during the scan that are used later to construct maps of the underlying magnetic field (Jezzard & Balaban, 1995). The phase information in these maps can then be used to "unwarp" the EPI data off-line, using, for example, the FUGUE program available in FSL (www.fmrib.ox.ac.uk/fsl/fugue/).

Artifacts due to head motion should be reduced as much as possible during image acquisition using three techniques. First, the patient should be made as comfortable as possible with cushions for support and blankets if needed for warmth. Second, freedom of head movement with the head array coil should be reduced with comfortable pads at the temples and perhaps tape across the forehead. In our experience, highly restrictive devices such as bite bars and rigid molded head pillows can induce anxiety and discomfort and are usually counterproductive, though some centers use these routinely. Finally, the patient should be encouraged before each scan to relax the body, especially the shoulders

and neck, and should receive verbal feedback on the degree of movement that occurred in the previous scan, if this information is available from an online analysis tool.

Noise due to head motion can be reduced during post-processing using 3-dimensional image registration. A variety of tools are available for this purpose, such as the "3dvolreg" (rigid-body alignment) or "3dAllineate" (nonlinear warping) routines in AFNI (www.afni.nimh.nih.gov/pub/dist/doc/program_help/3dvolreg.html). In addition to registering the successive images in an fMRI time series to each other, these programs produce a text file containing the estimated movement that occurred at each time point, relative to the base image, in terms of three translation and three rotation parameters. These movement vectors can be used later as noise covariates when modeling the observed time series, an approach that in our experience improves the sensitivity and specificity of the activation maps (Johnstone, Ores Walsh, et al., 2006; Morgan, Dawant, et al., 2007).

Stimulus and Task Apparatus

A variety of MRI-compatible stimulus presentation and response recording devices are available for fMRI. Visual stimuli are typically presented with a video projector and a screen placed at the foot of the patient or via goggles containing miniature LCD displays. A variety of headphones are available for audio. The least expensive of these operate by air conduction of sound through a length of plastic tubing, which is inserted into the subject's ear canal at one end and attached at the other end to a small speaker at some distance from the magnet. These devices generally include either an ear plug or an external muff for passive attenuation of the scanner noise. The main limitation of this approach is the severe loss of high-frequency sounds during air conduction through the tube, which can only be partly corrected by boosting these frequencies at the source and which results in a somewhat muffled sound with speech stimuli. Much higher-quality audio is available using MRI-compatible electrostatic speakers, which are available in a small in-ear format (http://www.stax.co.jp/index-E.html). These devices do not yet provide any passive attenuation and so must be used with an over-the-ear muff.

Manual responses can be recorded with button or key-press boxes, joysticks, and other devices. Several technologies are available for operation within a strong magnetic field, and all work well. Vocal responses can also be recorded during scanning. The best device for this purpose is an adaptive noise-canceling microphone designed specifically for MRI use (http://www.optoacoustics.com/medical/fomri-iii). In our experience this device is easy to use and provides good quality recordings even during continuous EPI image acquisition.

A number of software products are available for controlling stimulus presentation and logging input from response devices (Table 8.1). These vary in cost, ease of use, reliability, capabilities, and availability of technical support, and all have relative strengths and drawbacks.

General Principles of Task Design and Timing

A great variety of tasks and timing schemes have been used successfully in fMRI studies. Some aspects of task selection for language and verbal memory paradigms are discussed in a later section. In designing paradigms for functional mapping in individuals, it is critical to bear in mind that fMRI measurements contain significant amounts of "noise" and that signal averaging is necessary to produce stable maps (Desmond & Glover, 2002; Huettel & McCarthy, 2001). Many clinicians overemphasize the need to keep scanning sessions short because of concerns over patient fatigue or (more likely) scanning costs. Radiology practitioners are often accustomed to running structural MRI protocols that last no more 30 min, whereas a high-quality fMRI study generally requires much more time, particularly if several activation protocols are attempted in the same session. In our experience, almost all adolescent and adult neurology patients easily

Table 8.1 Software for fMRI stimulus presentation and response timing

Name and vendor/source	Free	OS	Ease	Satisfaction
E-Prime (Psychology Software Tools)	No	Win	Good	High
DMDX (http://www.u.arizona.edu/~kforster/dmdx/dmdx.htm)	Yes	Win	Fair	High
Presentation (http://www.neuro-bs.com)	No	Win	Low	Fair
Psyscope X (http://psy.ck.sissa.it)	Yes	Mac	Good	High
Psyscope Classic (http://psyscope.psy.cmu.edu)	Yes	Mac Classic	Good	Low
ERTS (www.erts.edu)	No	MS-DOS	Good	Low
SuperLab (www.superlab.com)	No	Mac, Win	Good	Low
Matlab (www.mathworks.com)	No	All	Low	Fair

tolerate an hour in the scanner, and most have no problem with a 90-min session. As a general rule of thumb, we advise a *minimum* of 5 min of total scanning (summed across blocks or trial events) for *each* condition of an fMRI contrast. For a simple design contrasting two conditions, this means a minimum of 10 min of scanning, whereas a complex, factorial, or parametric design might require much more. We emphasize this aspect of protocol design because it is undeniable that increasing the sample size (i.e., number of data points) significantly improves power, sensitivity, and reliability in fMRI studies, and underpowered results are a waste of effort and resources that can only lead to substandard clinical care.

The term "block design" refers to the grouping of trials in a particular condition into blocks. The blocks can all be of equal length or vary randomly in length. In general, blocks should not be longer than about 30 s, as the noise in fMRI is dominated by low frequencies, which can reduce SNR if the frequency of the block alternation becomes too low (Aguirre & D'Esposito, 1999). The main use of block designs is for contrasts between "task sets," for example, a semantic decision task and a phonological decision task. In such cases, the stimuli used in the contrasting conditions are often matched on a number of variables, and the focus is on the top-down effects of altering attention to different aspects of the stimuli or retrieving different kinds of information associated with the stimuli. In such experiments the stimuli are blocked to reduce the amount of task switching needed and to allow the subject to settle fully into each task state.

"Event related" or "single trial" refers to a design in which trials are not blocked by condition. This approach is more appropriate when a single task set is maintained throughout a scan, and the focus is on bottom-up effects of particular stimulus characteristics. Some well-known examples include passive listening to speech vs. reversed speech, naming animal vs. tool object pictures, lexical decision on words vs. pseudowords, recognition testing on novel vs. previously encoded words, grammaticality judgments on active vs. passive sentences, etc. Event-related designs minimize top-down attention, arousal, and "cognitive strategy" differences between conditions because the random intermixing of stimuli from different conditions makes it impossible for the subject to anticipate the type of stimulus coming next. Differences in attention and arousal can be important confounds in block design studies and also lead to differences between conditions in the degree of "mind wandering" that occurs. It is frequently said that event-related designs are less sensitive than block designs because blocking elicits a larger change in the BOLD signal. One should keep in mind, however, that some of this larger change in BOLD signal could be due to nonspecific attention and arousal differences associated with blocking rather than to the effects of interest.

Event-related designs also allow trials to be sorted or modeled according to performance measures such as accuracy or reaction time. These parameters can be entered into the analysis model to identify the neural correlates of, for example, a correct vs. incorrect response, a

remembered vs. forgotten word, or a long vs. short RT. A final advantage of event-related designs is in experiments that use an overt vocal response, such as naming or reading tasks. Vocal responses produce significant movement artifact in the BOLD signal time course. However, because the hemodynamic response to a single trial occurs later than the artifact from a spoken response, the trial-by-trial modeling of the hemodynamic response in event-related designs can distinguish these two sources of signal change.

The analysis of event-related fMRI data assumes a linear summation of hemodynamic responses from adjacent trials. This assumption appears to be reasonable as long as trials are not too closely spaced (Buckner & Braver, 1999). The spacing of trials depends to some degree on the hypothesized timing of neural events. For a low-level perceptual stimulus such as a flash of light or brief tone, the neural events of interest might be over within a few hundred ms, and trials can be separated by as little as 1 s or so. With more complex stimuli and tasks, such as naming a picture, the neural events might last well over 1 s, and trials should be separated by a longer interval. As a general rule of thumb, space the trials by at least twice the average RT on the task. Varying or "jittering" the interstimulus interval on a pseudorandom schedule is also helpful for statistical separation of adjacent hemodynamic responses during the analysis. Several freely available tools exist for designing statistically optimal stimulus and ISI sequences for event-related fMRI, such as Optseq (http://surfer.nmr.mgh.harvard.edu/optseq/) and the RSFgen tool in AFNI.

A final type of design involves "sparse" or "clustered" acquisition of images (Hall, Haggard, et al., 1999). Image volumes in fMRI are collected initially as a sequence of adjacent 2-dimensional slices, which are later combined to construct image volumes for each TR. By default, most fMRI sequences distribute the collection of the 2-D slices evenly throughout each TR. The rapid gradient switching necessary for spatial encoding in fMRI creates a loud acoustic noise burst during each 2-D acquisition. In some settings it is desirable to create periods of silence during scanning, such as in difficult auditory perceptual tasks or when high-quality vocal recordings are needed. Clustered acquisition refers to grouping the acquisition of the 2-D slices comprising each volume as closely in time as possible (typically 2 s or less) and separating these volume acquisitions by a silent period. The silent period can be relatively brief, though the 4–5-s delay to the peak of the hemodynamic response should be kept in mind to optimize image acquisition at the peak of the response rather than the trough. A longer silent period can be used to minimize contamination of the fMRI data by neural responses to the scanner noise, which is especially useful for mapping early auditory cortex (Humphries, Liebenthal, et al., 2010).

Some Principles of Data Analysis

The general approach to analysis of fMRI data is to model the effects, over time, of one or more experimental variables (or conditions) on each voxel's BOLD signal, typically with a multivariable general linear regression model. A beta coefficient and statistical parameter are returned for each variable in the model at each voxel location, resulting in a 3-D array of values known as a statistical parametric map. The beta coefficient is a response amplitude index that reflects the amount of change in the BOLD signal, relative to baseline, that can be attributed to the corresponding experimental condition. Planned contrasts can be conducted comparing the size of the response between conditions. A uniform threshold is typically applied across all voxels to depict the areas of "significant" activation.

Thresholding of activation maps is a complex and contentious issue, particularly for clinical applications. The purpose of thresholding is to highlight regions of strong or reliable activation. A traditional alpha threshold of $p < 0.05$ is often adopted, though because statistical tests are typically performed on thousands of voxels, a correction for multiple comparisons is necessary to avoid an unacceptable level of false-positive results. Bonferroni correction and similar methods are overly conservative, and a standard

Bonferroni correction for, say, 10,000 voxels (a typical number for the whole brain) would require a p threshold of 0.000005. A common alternative method is to combine a more lenient voxel p threshold, say $p<0.001$, with a cluster size threshold (Forman, Cohen, et al., 1995). That is, after thresholding at $p<0.001$, clusters of surviving voxels are eliminated if they do not exceed a minimum size. The rationale for this approach is that false-positive voxels are unlikely by chance to form large contiguous clusters. Methods are available in most software packages for determining the probability of a cluster surviving any given combination of voxel-wise p threshold and cluster size threshold, using either random field theory (e.g., SPM) or randomization testing (AFNI).

There are potential problems with standard thresholding approaches in clinical contexts. Thresholds are inevitably arbitrary, and it is not at all clear what threshold is optimal for valid separation of "clinically meaningful" from "clinically unimportant" activation. For presurgical mapping, we advocate use of relatively lenient thresholds to avoid false-negative results, with clear color coding of the values to indicate relative levels of significance. Another problem arises from the nature of statistical measurements. Standard statistical values such as z or t scores depend both on the amplitude of a signal and on measurement noise. Measurement noise arises from many sources, including head movement, respiratory and cardiac aliasing, and hardware fluctuations, and the level of noise can vary considerably between subjects and even across scans in the same subject. This variation results in large variations in the overall distribution of observed statistical values and thus the proportion of voxels that survive thresholding. In our experience, it is not uncommon to see over a tenfold difference between subjects in the number of voxels that survive standard thresholding. As discussed above, measurement noise is suppressed by repeated averaging, but there are practical limits to this. For presurgical mapping, it may be that the amplitude of the response (e.g., beta coefficient or percent signal change) is more relevant than its statistical significance. Response amplitude also appears to be less variable from session to session than significance values and is far less dependent on sample size (Voyvodic, 2006). At the moment, much more research is needed to define optimal methods for thresholding in presurgical mapping applications.

For most clinical applications, the focus is on activations in individual subjects. It is common in research studies, however, to construct "average" group maps by combining beta coefficients (or other similar measures of response amplitude) across subjects after spatial normalization. Spatial normalization refers to fitting each subject's image data to a common spatial template, which can be done using several methods. The simplest approach is a multiparameter linear fitting of the volume to a template brain. Other volumetric methods use nonlinear deformation algorithms, which can dramatically improve the precision of matching to a template (Klein, Andersson, et al., 2009). Other approaches project the volumetric data onto a 2-dimensional surface model of the subject's cortex and use nonlinear warping methods to align the subject's surface to a template surface (Fischl, Sereno, et al., 1999). None of these methods can perfectly align brain structures from different subjects, however, nor are the relative locations of functional areas expected to be exactly the same across subjects. Therefore it is necessary in the creation of group maps to spatially smooth individual activation maps to maximize the spatial summation of activation. Smoothing is typically performed using a 3-D Gaussian kernel. The degree of smoothing is typically in the range of 3–8 mm full width at half maximum, with smaller values appropriate when higher spatial resolution is desired.

Several free, well-supported software packages are available for fMRI data analysis. SPM (http://www.fil.ion.ucl.ac.uk/spm/) is the most widely used and is popular because of its ease of use and broad range of capabilities, including a full range of preprocessing and statistical tools, several methods for volumetric spatial normalization, advanced connectivity modeling tools, and extensions for EEG and MEG data. SPM requires MATLAB software to be installed for

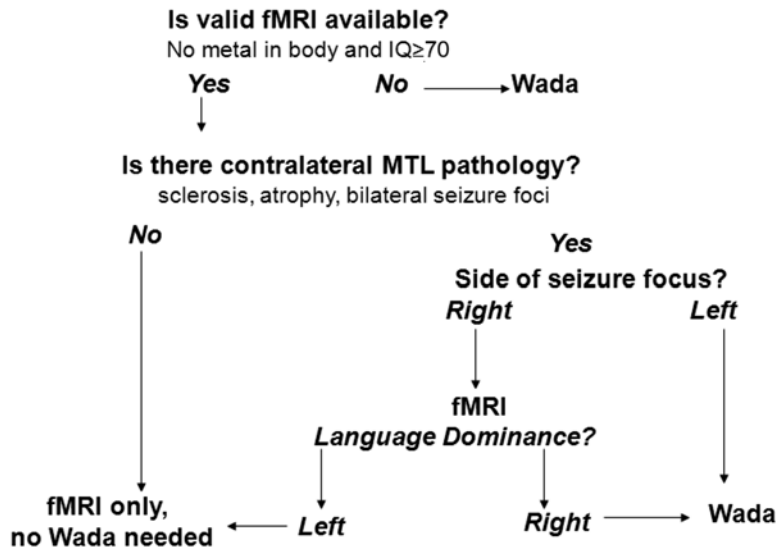

Fig. 8.2 Algorithm for determining when to conduct fMRI or Wada testing

full functionality (http://www.mathworks.com/products/matlab/index.html). AFNI (http://afni.nimh.nih.gov/afni) is also widely used and powerful, with a full range of preprocessing, parametric and nonparametric statistical tools, and a range of normalization options. AFNI emphasizes flexibility with its open architecture, multiple line-command subprograms, and support for plug-ins. AFNI also provides support for surface-based analysis through its SUMA module. AFNI requires no additional software. FSL (http://www.fmrib.ox.ac.uk/fsl/) is a suite of modules that cover a range of standard fMRI analysis steps and also includes advanced tools for segmentation of structural MRI volumes, image unwarping and normalization, and analysis of diffusion tensor imaging data. SPM, AFNI, and FSL all run on multiple operating system platforms, and all use the common NIFTI image format, allowing flexible combinations of modules and subprograms from different packages to be used on the same data.

Patient Selection

The first step in conducting clinical functional neuroimaging is determining who should have fMRI and Wada or more than one mapping method prior to surgery. Figure 8.2 provides an algorithm for making this decision. This algorithm is based on the empirical data supporting three contentions: (1) fMRI is suitable for mapping language (Binder, 2011), (2) fMRI predicts both language and memory outcome after ATL more accurately than Wada (Binder, Sabsevitz, et al., 2008; Sabsevitz et al., 2003), and (3) there is no empirical data showing that fMRI can predict or prevent amnesia. In situations where there is a risk for developing an amnestic syndrome (e.g., evidence of temporal lobe pathology contralateral to the side of seizure focus), a Wada alone or in addition to an fMRI is recommended.

Using this algorithm, if a patient has an implanted metal device or cognitive dysfunction that precludes fMRI task compliance, the patient should be referred for Wada testing. If the patient has evidence of pathology contralateral to a left-sided seizure focus such as hippocampal sclerosis, contralateral epileptiform activity, temporal lesion, or atrophy (thereby increasing risk for amnesia after left ATL), a Wada should be conducted. If there is evidence of pathology contralateral to a right-sided seizure focus, an fMRI can be conducted. However, if the fMRI shows right language dominance in a patient with a right seizure focus and contralateral (left) pathology, a Wada should be conducted as well.

Participation in cognitive fMRI studies typically requires a higher level of cognitive functioning and sustained attention than does participation in Wada testing. Individuals with intellectual functioning below full-scale IQ of 70, slow processing speed, or severe inattention likely will have difficulty performing most tasks developed for fMRI. Task instructions can be modified, and rate of administration of stimuli can be slowed to be suitable for children down to the age of 10 and adults with cognitive impairment. For example, with a semantic decision task, patients are asked to press a button for animal names that are both found in the United States and used by humans (Binder, Swanson, et al., 1996). The semantic decision task instructions can be simplified to just one decision, "animals that are used by humans." For children the instructions may be modified to "animals that have four legs" or "animals with fur." Individuals with verbal intellectual abilities below full-scale IQ of 70 typically will not have the semantic knowledge or attentional capacity to perform above chance on semantic decision tasks. Those with severely impaired processing speed or working memory cannot keep pace with the rate of presentation of stimuli or lose track of the number of targets presented. When performance falls below chance, the validity of the activation patterns should be questioned. In such instances, these patients may be better served by Wada testing if a suitable task is not available. Testing the patient on the task outside of the scanner prior to scheduling an fMRI will allow the examiner to avoid the expense of wasted scanner time.

Subject factors other than level of cognitive functioning that affect the quality of the imaging data include head motion, age, body habitus (morbid obesity, head size, cranial vault abnormalities, neck length), motivational state, adoption of idiosyncratic task strategies, and task performance (Hammeke, Bellgowan, et al., 2000; Weber, Wellmer, et al., 2006). For patients with implanted metal devices, it is necessary to have the vendor and part/serial number of the medical device from the physician. Information on device safety for 1.5- and 3-T scanners can be obtained from www.MRIsafety.com or from the local MRI safety committee. Patients with vagal nerve stimulators can undergo anatomical imaging if the device is turned off, but VNS has not been approved for fMRI pulse sequences at either 1.5 or 3 T.

Clinical Use of fMRI by Neuropsychologists: CPT Codes

The fundamental difference between functional and anatomical imaging is the application of cognitive tasks during the imaging procedure. The proper execution of fMRI requires a multidisciplinary team including those knowledgeable in neuropsychology, radiology, biophysics, statistics, and neuroanatomy. The cognitive tasks conducted during fMRI require expertise in the development of psychological tests by behavioral neurologists or neuropsychologists to optimally probe cognitive systems of interest, and for the development of control or contrast tasks that eliminate unwanted or nonessential activation. Neuropsychologists with training in functional neuroanatomy and psychometric principles are ideally suited for developing tasks and conducting fMRI since the ability to produce valid maps of higher cognitive functions requires an understanding of the function of interest as well as the nonessential cognitive processing subcomponents that may be activated by the task. Neuropsychologists conducting fMRI bill medical insurance (since in the case of epilepsy surgery candidates the diagnosis of epilepsy is medical) using CPT code 96020. This code covers testing of language, memory, cognition, motor skills, and other neurological functions in association with fMRI. The code descriptor from CPT 2009 for 96020 specifies "neurofunctional testing selection and administration during noninvasive imaging functional brain mapping, with test administered entirely by a physician or *psychologist*, with review of test results and report."

An official position statement was published by the Division of Clinical Neuropsychology (Division 40 of the American Psychological Association) on the role of neuropsychologists in the clinical use of fMRI (2004). In addition, the

recommended training for neuropsychologists engaged in functional neuroimaging has been described (Bobholz, Rao, et al., 2007). A physician, often a radiologist or behavioral neurologist, bills 70555, and the neuropsychologist bills 96020 for (1) administering tests of higher cognitive functioning such as memory, attention, language, and executive functioning, (2) instructing and practicing with the patient prior to the scanning, (3) adapting the tests as necessary based on the patient's behavioral performance, (4) monitoring behavioral response performance during the scanning, (5) collaborating with physicians on test findings, and (6) generating a clinical report.

fMRI Tasks

The validity of fMRI maps critically depends on the activation protocol since poorly designed probe or contrast tasks can lead to both false-positive and false-negative mapping errors. A variety of stimuli have been used to induce language processing. These include auditory nonspeech (e.g., pure tones), auditory phonemes (speech sounds, pseudowords), visual nonletter (false font), visual nonpronounceable letter strings (FKJVB), visual pseudowords with orthographic and phonological features of real words (e.g., SNADE), visual and auditory words and sentences, and visual objects. Tasks may require phonetic decision (detecting rhymes or syllables), orthographic decision (letter identification, case matching), and semantic decision (requiring decisions based on stimulus meaning). Sentence reading and story listening may require no decision but automatically elicit complex semantic processing. The various language tasks place different demands with respect to semantic search and lexical retrieval (e.g., naming, word generation). Different combinations of task contrasts will result in different patterns of activation based on the subtraction analysis. See Binder (2009) for a complete review of the regions in which robust activations are typically observed in association with various task contrasts for language mapping (Binder, 2009).

Tasks used during fMRI can be classified as passive or active, overt or covert (Binder, Swanson, et al., 2008). The ideal task is active and 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 processes unrelated to the cognitive function of interest. Word generation tasks (e.g., generating a verb or series of verbs in response to a noun or generating words in response to phonemic or categorical semantic cues) are commonly used for language mapping. While word generation is considered an active task, it is typically conducted covertly leading to uncertainty about task compliance and often is contrasted with rest. Another drawback of silent word generation tasks is that activation has been observed predominantly in frontal areas (Benson, FitzGerald, et al., 1999), and concordance between fMRI and Wada has been found in frontal but not temporal regions of interest (Lehericy, Cohen, et al., 2000), making it unlikely that this data could ever be used for tailoring temporal resections.

While there are no universally agreed upon tasks for language and memory mapping, some common methodological pitfalls can be avoided. These pitfalls are (1) using rest, visual fixation, or a non-perceptually matched contrast task during language and memory activation paradigms, (2) failing to incorporate behavior monitoring, and (3) attempting to image memory without considering that episodic memory encoding occurs continuously.

When attempting to image higher cognitive functions such as language and memory, it is not possible to find a task that activates the function of interest and no extraneous or more elementary functions in the process. The contrast between the component functions subsumed by the tasks should be theoretically selected to isolate the cognitive function of interest. For the purpose of concisely describing "how to" conduct fMRI in epilepsy surgery patients, the present chapter will focus on a well-documented semantic decision task that has been shown to be reliable (Binder, Hammeke, et al., 2001), concordant with the

Table 8.2 Functional components of two language activation tasks

Semantic monitoring task		
Functional components	Tone discrimination	Semantic decision
Semantic processing		+
Phonetic processing		+
Attention, working memory	+	+
Auditory processing	+	+
Motor response	+	+

Wada test (Binder, Swanson, et al., 1996), accurate in representing language lateralization across a continuum from left to right dominance (Springer, Binder, et al., 1999), and predictive of language (Sabsevitz, et al., 2003) and verbal memory outcome after left ATL resection (Binder, Sabsevitz, et al., 2008).

Table 8.2 shows the theoretical underpinning for the probe and contrast conditions used in the semantic decision task (Binder, Frost, et al., 1997; Démonet, Chollet, et al., 1992). In this paradigm, the probe task involves pressing a button in response to animal names that are both "found in the United States" and "used by humans." This is contrasted in a block design with a tone decision task. Subjects hear a brief series of tones of varying pitch and are instructed to press a button in response to tone trains containing two high tones. The semantic and tone decision tasks were matched for stimulus intensity and duration, trial duration, and frequency of targets. The contrast task is nonlinguistic and controls for auditory, motor, executive, and working memory functions that are not specific to language. E-Prime scripts (Psychology Software Tools, www.pstnet.com) for teaching and running the tasks in the scanner are available from the authors on request.

Rest or visual fixation does not provide an optimal baseline condition for language or memory studies (Stark & Squire, 2001) and is known to be an active state characterized by unconstrained conceptual processing or spontaneous neural activity during which self-initiated linguistic and semantic processes occur (Binder, Frost, et al., 1999; McKiernan, D'Angelo, et al., 2006; McKiernan, Kaufman, et al., 2003). In fact, recent studies capitalize on resting state coherence, the activation and connectivity between neurons that occur at rest as a measure of the default mode network with both fMRI and MEG (de Pasquale, Della Penna, et al., 2010; Fox & Raichle, 2007; Liu, Fukunaga, et al., 2010; Smith, Fox, et al., 2009). These widely distributed resting state networks closely resemble those evoked by cognitive tasks. To further emphasize this point, a recent study compared maps obtained using the semantic decision-tone decision (perceptual control) task contrast to activation maps obtained with a semantic decision/rest contrast (Binder, Swanson, et al., 2008). Figure 8.3 shows that there were fewer areas of activation seen when language is contrasted with rest than when language is contrasted with a perceptual control task, presumably because language that occurs automatically during rest has been subtracted out. This reduces the sensitivity of the language protocol such that critical language areas can be missed.

Figure 8.4 shows the overlap (in green) of areas activated in the language/perceptual control and language/rest contrasts and the areas removed in a typical ATL resection for epilepsy (red). There is very little language activation within the typical resection volume when rest is used as a contrast task. Activation observed in the left angular gyrus, posterior cingulate gyrus, left medial frontal lobe, and left medial temporal lobe during semantic decision contrasted with tone decision disappeared when semantic decision was contrasted with rest. If maps derived using rest as a control task are used for surgical planning, a poor cognitive outcome could result.

An alternative language task is an auditory responsive naming task that requires a spoken response. Clustered acquisition techniques (scanning immediately after each spoken response) can be used to allow patients to speak in the scanner so that imaging of language production systems can be conducted. Such tasks should be contrasted with a control task that also includes an oral motor response if the aim is to image expressive language rather than the oral motor apparatus. Normative data has been published for

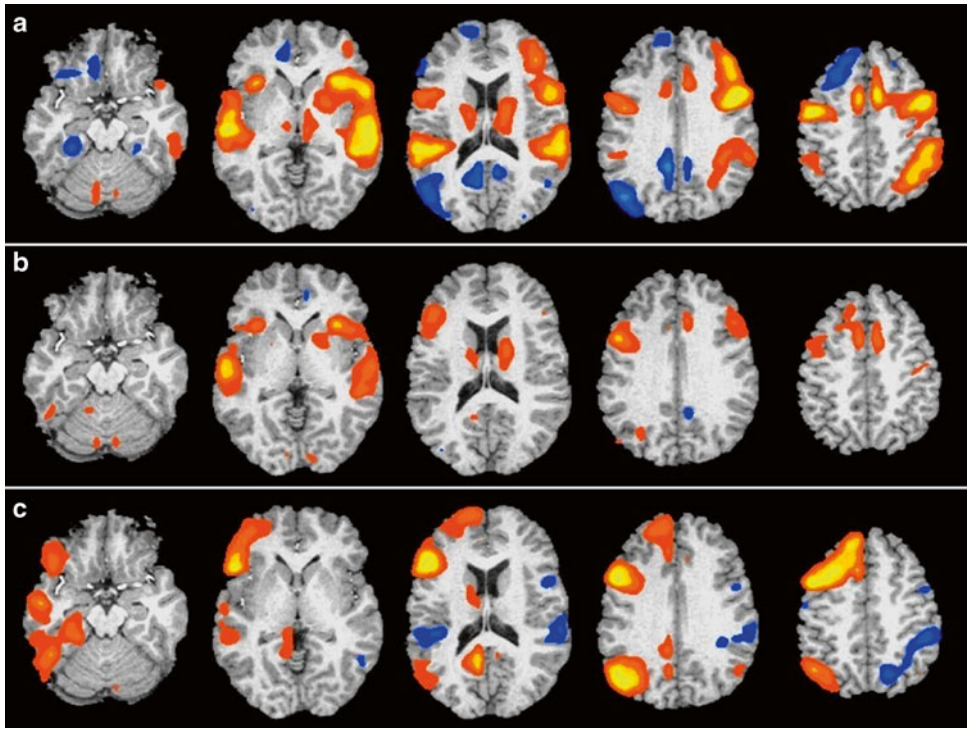

Fig. 8.3 Activation patterns from 30 health participants obtained for contrasts between (**a**) tone decision versus rest, (**b**) semantic decision versus rest, and (**c**) semantic decision versus tone decision. The maps show group activations thresholded at whole-brain corrected $p<0.05$. The left side of the brain is on the reader's *left*. In (**a**) tone monitoring was contrasted with "rest" and shows regions in *blue* that are more active during the resting state ("default network") than during this nonlinguistic task. These include angular gyrus, posterior cingulate gyrus, medial and ventral frontal lobe, and ventral temporal lobe. In (**b**) semantic decision is contrasted with "rest." Note that the default network regions in (**a**) show relatively little activation, indicating equivalent BOLD signals during the semantic decision task and the resting state. In (**c**) semantic decision is contrasted with tone monitoring. Strong left-lateralized activation is observed throughout the default network, inferior frontal lobe, and temporal lobe

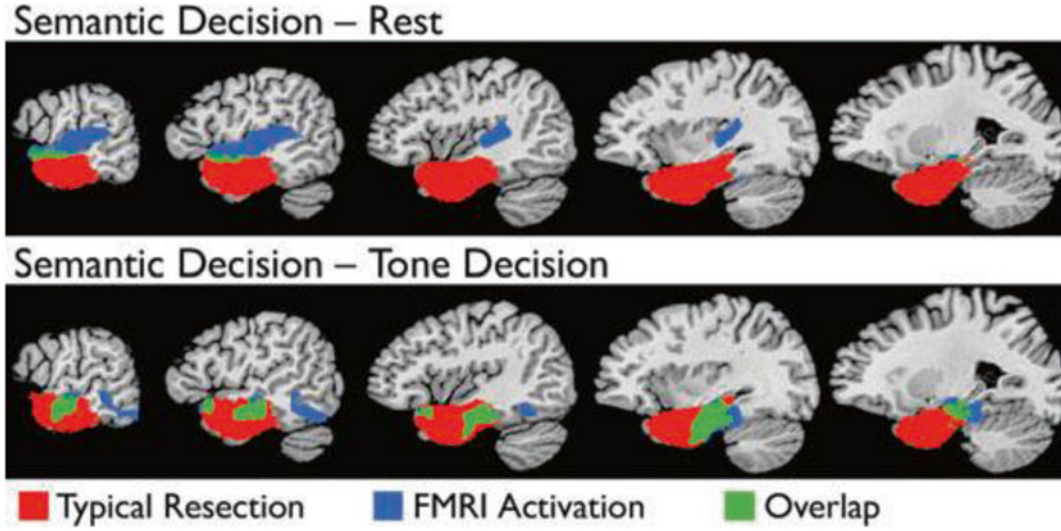

Fig. 8.4 Amount of activation within (*green*) and outside (*blue*) the typical resection volume (*red*) when semantic decision is contrasted with rest (*top panel*) and a perceptual control task (*bottom panel*)

this auditory responsive naming or definition naming task (Hammeke, Kortenkamp, et al., 2005). In this task, subjects are provided with an auditory cue such as "jewelry for the finger" or "first president of the United States" which elicits a verbal response of a common or proper, living, or nonliving noun. The contrast task involves the presentation of brief sequences of noise filtered for high band frequencies matching the same spectrum of human speech. A rising pitch was added to some stimuli (the targets). Patients are asked to say aloud the number of target stimuli. While this task requires a spoken response, the definition naming task activates cerebral regions associated with both language production and "receptive" language semantic system because it requires comprehension of the semantic cue.

The LI from the definition naming task significantly correlates with the Wada language score and the LI from semantic decision (Larson, Hammeke, et al., 2004). One advantage of the definition naming task is that it produces greater activation of the anterior temporal lobes, proportionally greater on the left side. The finding of greater anterior temporal activation associated with naming to an auditory cue is consistent with previous extra-operative grid mapping studies showing a greater number of anterior temporal "hits" with auditory compared to visual naming stimuli (Hamberger, McClelland, et al., 2007).

Finally, some investigators have advocated use of multiple language tasks or a task panel to improve concordance with the Wada (Gaillard, Balsamo, et al., 2004). When using a combination of language tasks, one can examine areas of activation overlap across tasks which reduces the likelihood of false-positive activated voxels.

Behavioral Monitoring

Behavioral monitoring during mapping of higher cognitive functions helps ensure task compliance and allows one to compare accuracy (difficulty) between the probe and contrast task. However, a high rate of response accuracy does not seem to be critical for obtaining valid fMRI data. In an fMRI language study of 195 epilepsy patients with vastly different performance levels on a semantic decision task (Weber et al., 2006), there was no significant difference in the LIs for the group with the best performance compared to patients with the worst performance. It was concluded that the fMRI language LIs were independent of task performance though behavioral monitoring is necessary to ensure task compliance and that the patients are performing above chance levels.

Episodic Memory

Attempts to conduct fMRI of memory are fraught with methodological issues since episodic memory is always "on" making selection of contrast states difficult. Investigators have compared encoding of stimuli to recognition of stimuli without considering that during the recognition trial, the foils are being encoded along with the second exposure to the previously viewed targets. In this case, the contrast task has subtracted out a good deal of the function of interest. An event-related memory task that compares stimuli that are later recalled or recognized outside the scanner to targets that were not later recognized is one method for avoiding this problem.

Another method for avoiding the confound of being unable to "turn off" episodic memory is to contrast stimuli that are highly encodable (e.g., complex scenes) with stimuli that are poorly recalled (e.g., randomly retiled images of the scenes) (Binder, Bellgowan, et al., 2005). However, since verbal memory decline occurs with much greater frequency after left ATL (Baxendale & Thompson, 2005; Baxendale, Thompson, et al., 2006; Bell, Lin, et al., 2011; Chelune, 1995; Dulay, Levin, et al., 2009; Leunen, Caroff, et al., 2009; Martin, Sawrie, et al., 1998; Naugle, Chelune, et al., 1993; Sabsevitz, Swanson, et al., 2001) than nonverbal memory decline occurs after right ATL (Dulay et al., 2009; Leunen et al., 2009), the optimal memory task for presurgical epilepsy patients is one that results in maximal activation in the left hippocampus or left temporal lobe. Nonverbal tasks like Roland's Hometown Walking Task (Roland, Eriksson, et al., 1987) and scene encoding tasks (Avila, Barros-Loscertales, et al., 2006; Bellgowan, Binder, et al., 1998; Szaflarski,

Holland, et al., 2004; Vannest, Szaflarski, et al., 2008) are more likely to produce bilateral hippocampal activation, correlate with Wada memory scores (Jokeit, Okujava, et al., 2001; Rabin, Narayan, et al., 2004), and are associated with side of seizure focus (Bellgowan et al., 1998; Jokeit et al., 2001). However, tasks that produce bihippocampal activation are less useful for predicting verbal memory decline than semantic tasks with verbally encodable information. In fact, preoperative language lateralization was correlated with postoperative verbal memory decline (Binder, Swanson, et al., 2010; Labudda, Mertens, et al., 2010), while hippocampal activation during a scene encoding task which tends to produce bilateral hippocampal activation was not related to verbal memory outcome (Binder, Swanson, et al., 2010). However, activation asymmetries during scene encoding related to side of seizure focus and Wada memory asymmetry scores (Binder, Swanson, et al., 2010).

Thus, risk for verbal memory decline is related to lateralization of semantic material-specific networks, and it appears that hippocampal adequacy (degree to which there is functional tissue ipsilateral to the seizure focus) is more important than functional reserve (capacity of the hippocampus contralateral to the seizure focus to subserve memory). This thinking is in line with studies and reviews showing that the degree of ipsilateral hippocampal sclerosis is a strong predictor of verbal memory outcome after left ATL (Chelune, 1995; Hermann, Wyler, et al., 1992, 1994a, 1994b; Seidenberg, Hermann, et al., 1996; Trenerry, Jack, et al., 1993) and a better predictor than the functional reserve of the contralateral hippocampus. Also consistent with the functional adequacy model, verbal memory decline was predicted by fMRI activation in the dominant but not the nondominant hippocampus (Powell et al., 2008). In this study, pictures, faces, and words were presented visually during scanning. Images later recognized were examined in an event-related analysis. Using this paradigm, greater ipsilateral activation in response to words was associated with greater verbal memory decline after dominant ATL.

In conclusion, verbal semantic or verbal encoding tasks that maximize dominant temporal lobe activation seem to be most useful for predicting verbal memory decline after left ATL. Nonverbal memory rarely declines and tasks that produce bilateral activation are better suited for determining side of seizure focus. Both structural and functional imaging studies support the notion that obtaining information about functional adequacy of the hippocampus ipsilateral to the resection is most predictive of the type of memory morbidity associated with left ATL.

Clinical Applications of fMRI in Epilepsy Surgery Candidates

Introduction

There are a variety of clinical applications for fMRI in epilepsy surgery candidates (Bookheimer, 1996; Detre, 2004; Powell & Duncan, 2005). These include localization of motor and sensory areas (Bookheimer, 1996), lateralization and localization of language (for reviews see Bookheimer, 2007; Swanson, Sabsevitz, et al., 2007), determination of hemispheric representation of memory functions (Binder, Swanson, et al., 2010; Detre, Maccotta, et al., 1998; Golby, Poldrack, et al., 2002; Koylu, Trinka, et al., 2006; Powell, Koepp, et al., 2004; Powell, Richardson, et al., 2007; Szaflarski et al., 2004; Vannest et al., 2008), predicting side of seizure focus (Bellgowan et al., 1998; Jokeit et al., 2001), and predicting outcome after temporal lobectomy with regard to seizures (Killgore, Glosser, et al., 1999), language (Sabsevitz et al., 2003), and memory (Binder, Sabsevitz, et al., 2008; Labudda et al., 2010; Powell et al., 2008; Rabin et al., 2004; Richardson, Strange, et al., 2004). The present chapter focuses on the primary clinical role for fMRI in the presurgical work-up which is language and memory mapping for the purpose of predicting cognitive outcome.

Steps for Conducting Clinical fMRI

Since preoperative language and memory abilities along with age at seizure onset are predictors of postoperative cognitive decline (Baxendale et al., 2006; Binder, Sabsevitz, et al., 2008;

Chelune, Naugle, et al., 1991; Hermann et al., 1994a, 1994b; Sabsevitz et al., 2003), data from neuropsychological testing is necessary to incorporate into fMRI regression formulas for cognitive outcome prediction. Preoperative neuropsychological testing is recommended for all epilepsy surgery candidates (Jones-Gotman, Smith, et al., 2010) given the risk for cognitive morbidity in object naming and verbal memory that occurs with left ATL. The National Institute of Neurological Disorders and Stroke Epilepsy Standards and Common Data Elements recommendations for neuropsychological test selection can be viewed online at: http://www.commondataelements.ninds.nih.gov/Doc/EPI/AssessmentsAndExaminations/Recommended Neuro-psychology Instruments Adult.doc. Declines in object naming occur in 25–60 % of patients who undergo left ATL (Bell, Davies, et al., 2000; Davies, Bell, et al., 1998; Hermann, Perrine, et al., 1999; Langfitt & Rausch, 1996; Sabsevitz et al., 2003; Stafiniak, Saykin, et al., 1990). Similarly significant verbal memory decline has been reported in 30–60 % of patients who undergo left ATL (Baxendale et al., 2006; Binder, Sabsevitz, et al., 2008; Lineweaver, Morris, et al., 2006; Naugle et al., 1993; Sabsevitz et al., 2001; Stroup, Langfitt, et al., 2003).

The battery of tests administered to epilepsy surgery candidates should include an auditory or visual object naming test such as the Boston Naming Test (Kaplan, Goodglass, et al., 2001) available at Psychological Assessment Resources (PAR) and measures of verbal memory. While story memory tasks are recommended for their face validity since much new learning is contextual, verbal list learning tasks are most sensitive to decline after left ATL. A list learning task such as the Rey AVLT (Schmidt, 1996), Buschke Selective Reminding Test (SRT) (Buschke, 1973; Buschke & Fuld, 1974), or California Verbal Learning Test (CVLT) (Delis, Kramer, et al., 2000) is recommended. The currently published regression equation (Binder, Sabsevitz, et al., 2008) for predicting memory outcome using fMRI is based on the SRT, but the Rey AVLT (Schmidt, 1996) is recommended in the Common Data Elements for its ease of administration and scoring as well as cost. The SRT and Rey AVLT are available without cost. It is expected that an outcome prediction formula for the Rey AVLT will be developed in the near future. For the present, the SRT can be administered prior to surgery if precise verbal memory outcome predictions are desired.

All of the primary aims for presurgical language and memory mapping including predicting cognitive morbidity can be accomplished with the semantic decision task. Thus, for the purpose of a description of "how to" conduct fMRI, we will describe the procedure using semantic decision for fMRI and using the Boston Naming Test and Selective Reminding Test for pre- and postoperative testing.

The algorithm outlined in Fig. 8.2 is applied to determine if the patient is suitable for undergoing fMRI. Patients are requested to arrive at the scanner 1 h prior to their imaging session to complete the Edinburgh Handedness Questionnaire (Oldfield, 1971) and safety screening questionnaires and undergo pre-scan training on the cognitive tasks. The patient is fitted with headphones, padding is placed in the head coil to reduce head movement, the button box is positioned for use with the nondominant hand, and the patient is provided with a squeeze ball which activates an alarm system to use in case of emergency. Imaging can be conducted on a 1.5- or 3-T scanner. High-resolution, T1-weighted anatomical reference images of the entire brain are acquired using a spoiled-gradient-echo sequence. Whole-brain functional imaging using a T2*-weighted gradient-echo and echoplanar sequence has the following parameters at 1.5 T: TE = 40 ms, TR = 3,000 ms, field of view = 240 mm, pixel matrix = 4 × 64, 19 sagittal slices, and voxel size = 3.75 × 3.75 × 7 mm. Imaging parameters for 3 T are TE = 25 ms, TR = 3000 ms, field of view = 224, pixel matrix = 64 × 64, 34 axial slices, and voxel size = 3.5 mm^3.

The sound system is checked to ensure that the patient can hear the stimuli over the scanner noise following the acquisition of the anatomical imaging. Real-time data is displayed showing head movement in multiple vectors within the scanner which can be used to provide feedback to

the patient. Prior to beginning the semantic task, the patient is briefly re-instructed on how to conduct the task and to remain motionless with eyes closed. Two runs are acquired using a block design with alternation between probe (semantic decision) and contrast (tone decision) tasks. Both tasks are active and both require a behavioral response.

Images are processed and statistical analyses are conducted using AFNI (http://afni.nimh.nih.gov/afni) for individual subjects by first aligning the images to reduce movement artifact. Multiple regression is used to detect task-related MR signal changes. This method compares the time series of MRI signal values in each image voxel with an idealized hemodynamic response to the task alternation. The idealized response is modeled by convolving a gamma function with a time series of impulses representing each task trial. The regression model includes six movement vectors to reduce the effects of head movement on the estimation of the task response.

Language lateralization is measured for five regions of interest: frontal, temporal, lateral angular, and whole hemisphere (minus the cerebellum). Significantly activated voxels (uncorrected $p<0.001$) are counted for each ROI on the left and right. Laterality indexes (LIs) represent the relative activation for each ROI based on the differences between number of activated voxels in the left and right hemisphere where the LI for each ROI $=(L-R)/(L+R)$ (Binder, Frost, et al., 1996; Binder, Sabsevitz, et al., 2008; Sabsevitz et al., 2003; Springer et al., 1999). LIs range from +1 (completely left hemisphere dominant) to −1 (completely right hemisphere dominant).

Predicting Cognitive Outcome with Laterality Indexes

Using the temporal ROI laterality index, the formula shown in Table 8.3 is used to determine predicted BNT decline from pre- to post-left ATL. BNT outcome is predicted by preoperative raw score on BNT and the fMRI LI for the temporal lobe. Age at seizure onset, while typically a significant predictor of decline, did not predict variance in outcome above that predicted by the temporal lobe ROI and preoperative BNT score. Using a >2 standard deviation decline from the largest decline in the R-ATL group to define poor outcome, the fMRI temporal lobe LI showed 100 % sensitivity and 73 % specificity for a positive predictive value of 81 % for predicting poor outcome with the LI threshold set at 0.25 (Sabsevitz et al., 2003).

Table 8.3 Regression formulas for predicting naming and verbal memory outcome with fMRI

Predicted score	= Constant − β (preop score) − β (age at seizure onset) − β (fMRI LI)
BNT change	= 13. 64 − 0.3334 (preop BNT) − 10.528 (fMRI temporal LI)
LTS change	= 22.92 − 0.621 (preop LTS) − 0.304 (age at onset) − 12.57 (fMRI lateral LI)
CLTR change	= 17.67 − 0.704 (preop CLTR) − 0.280 (age at onset) − 12.1 (fMRI lateral LI)
Delayed recall	= 3.76 − 0.688 (pre-delayed recall) − 0.093 (age at onset) − 2.14 (fMRI lateral LI)

BNT Boston Naming Test, *LTS* long-term storage, *CLTR* consistent long-term retrieval

Three memory scores derived from the SRT can be predicted using the fMRI lateral ROI LI. These include (1) long-term storage (LTS) which is any word that is recalled on two consecutive trials, (2) consistent long-term retrieval (CLTR) which is an index of the ability to consistently retrieve the word (words recalled on every subsequent trial), and (3) delayed recall which is the number of words freely recalled after a 30-min delay. The prediction formulas are presented in Table 8.3. Using these regression equations, preoperative score and age at onset of seizures accounted for 37, 49, and 54 % of the variance in outcome on LTS, CLTR, and delayed recall, respectively. The fMRI lateral LI added significantly to outcome prediction raising the amount of variance predicted to 48 % for LTS, 59 % for CLTR, and 61 % for delayed recall. The addition of Wada language LI or Wada memory asymmetry scores did not predict significant additional variance beyond fMRI (Binder, Sabsevitz, et al., 2008).

In conclusion, greater lateralization toward the left hemisphere and higher preoperative scores predict more significant decline in object

naming and verbal memory after left ATL. In addition, earlier age at seizure onset predicts less memory decline. Using regression equations, predicted outcome scores can be obtained which are useful for counseling patients about potential cognitive morbidity. Measures of hippocampal sclerosis or volume eventually will need to be incorporated into regression equations since studies show that structural status of the hippocampus is a strong predictor of verbal memory outcome (Baxendale, van Paesschen, et al., 1998; Chelune, 1995; Hermann et al., 1992, 1994a, 1994b; Seidenberg et al., 1996; Trenerry et al., 1993; Wendel, Trenerry, et al., 2001),

Tailoring Resections

It is not clear whether activation maps from language protocols can be used to precisely guide the resection boundaries since it has not been demonstrated that resection of activated voxels is correlated with language decline. There are no published empirical studies that indicate that the fMRI maps can be used to tailor surgical resections for epilepsy patients. To obtain more robust anterior temporal activation within the surgical zone, a semantically complex story listening task can be contrasted with a semantically shallow serial addition task (Binder, Gross, et al., 2010). The story task requires attentive listening to Aesop's fables vignettes with controlled word rate, speaking style, and prosodic features. Following the presentation of the vignette, the participant is given a forced two-choice alternative about the main theme of the story, with a required button press (left button for the first choice, right button for the second choice). This task combination produces bilateral activation in lateral and medial temporal lobes due to the semantic and conceptual processing demands of the task. This task provides more information about the activation in the surgical region of interest which can be used in combination with the lateralization data from the semantic decision task. However, outcome data is needed before these maps can be used to tailor resections.

EEG/fMRI

In addition to using fMRI for mapping higher cognitive functions, BOLD signal changes associated with interictal epileptiform spikes can be used for localizing epileptic foci (Al-Asmi, Benar, et al., 2003; Archer, Briellmann, et al., 2003; Baudewig, Bittermann, et al., 2001; Benar, Aghakhani, et al., 2003; Jager, Werhahn, et al., 2002; Krakow, Woermann, et al., 1999; Lazeyras, Blanke, et al., 2000; Patel, Blum, et al., 1999; Symms, Allen, et al., 1999; Vulliemoz, Lemieux, et al., 2010; Warach, Ives, et al., 1996). Continuously recording EEG during scanning allows detection of interictal epileptiform discharges which can be used to trigger echoplanar image acquisitions at a fixed time interval after the spike. This allows for the imaging of hemodynamic correlates of EEG events. Multislice data is typically acquired by having an epileptologist manually trigger the scanner within 3–5 s of spike detection. The data acquired within several seconds of triggering is within the window for the hemodynamic response following spikes (Benar, Gross, et al., 2002).

Functional MRI activation associated with interictal spikes correlates with other methods for localizing spike generators including intracranial EEG recordings (Al-Asmi et al., 2003; Bagshaw, Aghakhani, et al., 2004; Detre, Sirven, et al., 1995) and EEG dipole modeling (Lemieux, Krakow, et al., 2001; Seeck, Michel, et al., 2001). One study examined seizure outcome after surgical resection in ten patients who underwent EEG-triggered fMRI (Thornton, Laufs, et al., 2010). Seven of the ten patients were seizure free after surgery, and, of these, six of seven had the areas of maximal BOLD signal change that was "concordant" with the resection. In the three who were not seizure free, EEG-correlated BOLD signal lay outside the resection.

Technical issues and methodological limitations associated with conducting EEG spike-triggered fMRI include differences between the duration of the hemodynamic response when compared to the time course for neuronal events (limited temporal resolution), signal dropout in the temporal lobes (Bagshaw et al., 2004), dependence on identification

of spikes using scalp EEG, requirement that patients have frequent well-defined interictal spikes, and uncertainty about whether the spikes are an indication of the "irritative zone" versus the "epileptogenic zone."

Resting State or Neuronal Connectivity Studies

Historically fMRI has been used to image brain activation in response to a stimulus or correlated with a cognitive task. There has been an explosion of studies examining the "default network" or connectivity between populations of neurons determined by spontaneous fluctuations in brain activity by studying the brain at rest (Fox & Raichle, 2007). While beyond the scope of this chapter, studies of connectivity in diseased brains or patients with epilepsy hold great promise for determining the functional viability of the tissue around epileptogenic foci (Bettus, Bartolomei, et al., 2010).

fMRI Sample Report

See Fig. 8.5 for a sample report with tables (behavioral data, LIs, predicted change scores) of an fMRI clinical report on a patient being considered for left ATL. See Fig. 8.6 for the activation maps associated LIs and predicted decline scores described in the sample report.

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Language Functional Magnetic Resonance Imaging
Cognitive Testing

NAME: Patient X	DATE OF BIRTH: x/xx/1987
FMLH#: 00000000	DATE OF EVALUATION: xx/xx/2010

Mr. X is a 23 year old mixed (primarily left) handed young man who underwent language functional magnetic resonance imaging on referral from his epileptologist, Dr. Y, MD, to determine hemispheric lateralization and localization of language functions and for the purpose of predicting potential language and memory outcome following a left hemisphere surgery. Seizures of unknown etiology began at age 19. Seizure semiology is characterized by a feeling of dizziness, racing heart, and diaphoresis that lasts about 30 seconds and is associated with altered but not complete loss of awareness. Video EEG monitoring showed subtle left temporal slowing during his complex partial seizures. Brain MRI was normal. Neuropsychological testing showed average intelligence and subtle dominant hemisphere dysfunction due to relative weaknesses in verbal contextual memory and confrontation naming.

Imaging Parameters:
MRI studies were conducted on a 3.0 Tesla GE Signa scanner.

Fig. 8.5 fMRI sample report

FMRI Language Activation Tasks:

Semantic Decision-Tone Decision:
In the Semantic Decision task, the patient heard spoken English nouns designating animals (e.g., "sheep") and responded according to specified semantic criteria. Target words were animals that are both "found in the United States" and "used by humans." The patient heard trains of three to seven 500 Hz or 750 Hz tones in the tone decision (control) task. The patient was instructed to press a button for any train containing two high-pitched (750 Hz) tones. The two tasks were matched for stimulus intensity, average stimulus duration, average trial duration, and frequency of positive targets. The semantic decision - tone decision contrast highlights activation in speech perception, phonological word-form, semantic memory, and lexical-semantic retrieval systems, as well as language-specific working memory components.

FMRI data analysis:

FMRI LIs were calculated using the formula ($[V_L - V_R] / [V_L + V_R]$) X 100, where V_L and V_R are activation volumes for the homologous left and right ROIs. This approach yields fMRI LIs ranging between +100 (strong left hemisphere dominance) and -100 (strong right hemisphere dominance).

Behavioral Response Data for Semantic Decision and Tone Decision:

	Semantic Decision	Tone Decision
#trials	107	144
%correct	**89.7**	**98.6**
#correct	96	142
#hits	34	52
#misses	5	2
#FAs	6	0
#CRs	62	90
RT.all	1612.8	2468.2
RT.hits	1466.2	2468.2

For comparison purposes, the mean and standard deviation on the SD task for individuals without epilepsy is 90.7 (sd 6.2) and for patients with epilepsy is 81.2 (sd 10.9). The mean and standard deviation on the TD task for individuals without epilepsy is 97.0 (sd 3.9) and for patients with epilepsy is 90.4 (sd 11.9).

The patient's behavioral performance of 90% correct for Semantic Decision and 99% correct for Tone Decision is considered above average for epilepsy patients and adequate for interpretation of the data.

Fig. 8.5 (continued)

Language Lateralization Results:

SD-TD

Region of Interest	*Voxel Count Left*	*Voxel Count Right*	*LI*
Whole Hem	90631	36645	**42.2**
Lateral	45402	15377	**49.4**
Frontal	43823	19147	**39.2**
Temporal	12061	5411	**38.1**
Angular	11706	1038	**83.7**

Prediction of Memory and Language Outcome:

Test	**Pre-op Raw Score**	**Predicted Raw Score Decline**	**Predicted % Decline**
New Learning (LTS)	56	24	42%
Consistent Recall (CLTR)	32	16	50%
Delayed Recall	10	6	60%
Boston Naming Test	44	5	11%

Based on these formulas, it is predicted that Mr. X will experience a decline of 5 points or 11% on the Boston Naming Test (pre-operative score is 44/60) if he undergoes a left ATL. His verbal memory is predicted to decline between 42 to 60% after left ATL.

Summary: Results of fMRI language testing indicate that the patient is left hemisphere dominant for language based on the Semantic Decision task with strong left lateralization in the angular gyrus ROI.

Mr. X's predicted decline in object naming is considered relatively mild. Less decline is predicted for naming than for memory because his naming score is already in the impaired range. Predicted decline for verbal memory is considered significant. Factors contributing his risk for memory morbidity include his later age at onset of seizures, left hemisphere language dominance and his average pre-operative memory scores. In addition, the absence of MTS on MRI also is predictive of risk for memory decline following left ATL.

Fig. 8.5 (continued)

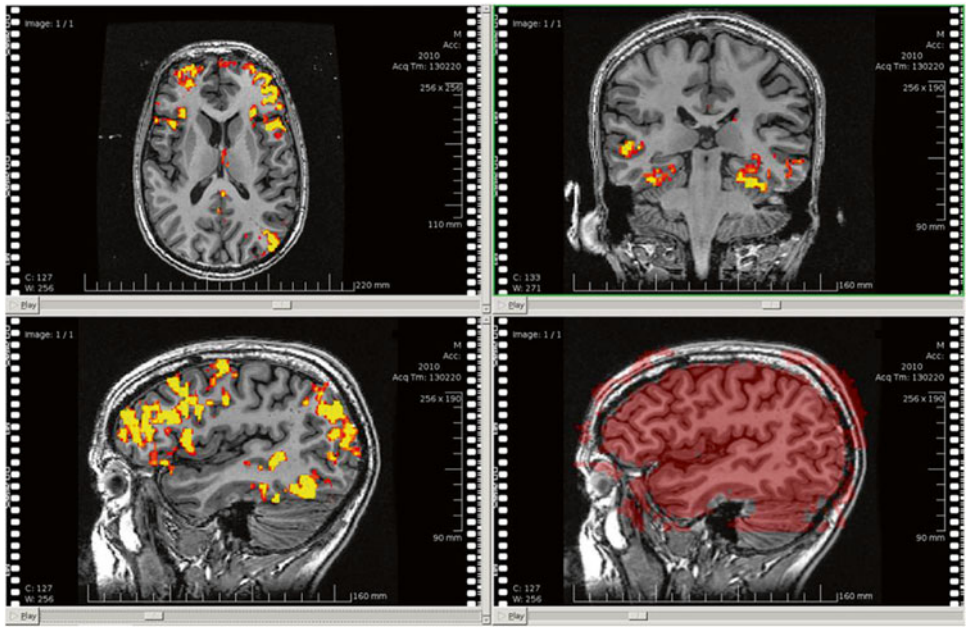

Fig. 8.6 Language maps for the case described in the sample report. The data are displayed in axial, coronal, and sagittal sections using a DICOM image viewer that allows the user to step through each volume in 1-mm increments using a slider. The image at lower right is a signal-to-fluctuation noise ratio (SFNR) map thresholded to show in *red* areas with acceptable SFNR (>20). This map allows clinicians to better judge the quality of the data, especially in typical regions of signal dropout

Conclusions

Functional MRI for language mapping has become a vital part of the work-up for epilepsy surgery candidates and can be used as a replacement for more invasive mapping methods such as Wada testing. Language lateralization indexes can be examined for various brain regions of interest. These LIs, when combined with knowledge of the side of seizure focus, age at onset of the seizures or initial precipitating event, and most importantly, preoperative neuropsychological test scores, contribute significantly to predicting cognitive morbidity in patients undergoing left anterior temporal lobectomy. Moreover, while fMRI memory protocols have not been refined, data shows that fMRI language lateralization scores predict cognitive morbidity not only for language (object naming) but also for memory (verbal list learning) better than functional MRI data obtained from hippocampi. fMRI data and outcome predictions can be used to inform professionals as they select surgical candidates and to counsel patients about potential cognitive risks prior to surgical intervention. In the future, it is anticipated that refinement in functional imaging with fMRI, MEG (as discussed in the following chapter), and resting state functional connectivity studies will produce maps for individual patients that can precisely guide surgical interventions.

References

Aguirre, G. K., & D'Esposito, M. (1999). Experimental design for brain fMRI. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 369–380). Berlin: Springer-Verlag.

Akanuma, N., Alarcon, G., et al. (2003). Lateralising value of neuropsychological protocols for presurgical assessment of temporal lobe epilepsy. *Epilepsia, 44*(3), 408–418 [Erratum appears in *Epilepsia*, 2003, 44(7), 990].

Al-Asmi, A., Benar, C. G., et al. (2003). fMRI activation in continuous and spike-triggered EEG-fMRI studies of epileptic spikes. *Epilepsia, 44*(10), 1328–1339.

Alsop, D. C., & Detre, J. A. (1998). Multisection cerebral blood flow MR imaging with continuous arterial spin labeling. *Radiology, 208*, 410–416.

American Psychological Association. (2004). Official position of the division of clinical neuropsychology (APA division 40) on the role of neuropsychologists in clinical use of fMRI: approved by the Division 40 Executive Committee July 28, 2004. *Clinical Neuropsychologist, 18*(3), 349–351.

Archer, J. S., Briellmann, R. S., et al. (2003). Spike-triggered fMRI in reading epilepsy: Involvement of left frontal cortex working memory area. *Neurology, 60*(3), 415–421.

Avila, C., Barros-Loscertales, A., et al. (2006). Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR. American Journal of Neuroradiology, 27*(3), 498–503.

Bagshaw, A. P., Aghakhani, Y., et al. (2004). EEG-fMRI of focal epileptic spikes: analysis with multiple haemodynamic functions and comparison with gadolinium-enhanced MR angiograms. *Human Brain Mapping, 22*(3), 179–192.

Baudewig, J., Bittermann, H. J., et al. (2001). Simultaneous EEG and functional MRI of epileptic activity: A case report. *Clinical Neurophysiology, 112*(7), 1196–1200.

Baxendale, S., & Thompson, P. (2005). Defining meaningful postoperative change in epilepsy surgery patients: Measuring the unmeasurable? *Epilepsy and Behavior, 6*(2), 207–211.

Baxendale, S., & Thompson, P. (2010). Beyond localization: The role of traditional neuropsychological tests in an age of imaging. *Epilepsia, 51*(11), 2225–2230.

Baxendale, S., Thompson, P., et al. (2006). Predicting memory decline following epilepsy surgery: A multivariate approach. *Epilepsia, 47*(11), 1887–1894.

Baxendale, S. A., van Paesschen, W., et al. (1998). The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia, 39*(2), 158–166.

Bell, B. D., Davies, K. G., et al. (2000). Confrontation naming after anterior temporal lobectomy is related to age of acquisition of the object names. *Neuropsychologia, 38*(1), 83–92.

Bell, B., Lin, J. J., et al. (2011). The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nature Reviews Neuroscience, 7*(3), 154–164.

Bellgowan, P. S., Binder, J. R., et al. (1998). Side of seizure focus predicts left medial temporal lobe activation during verbal encoding. *Neurology, 51*(2), 479–484.

Belliveau, J. W., Kennedy, D. N., et al. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. *Science, 254*, 716–719.

Benar, C., Aghakhani, Y., et al. (2003). Quality of EEG in simultaneous EEG-fMRI for epilepsy. *Clinical Neurophysiology, 114*(3), 569–580.

Benar, C. G., Gross, D. W., et al. (2002). The BOLD response to interictal epileptiform discharges. *NeuroImage, 17*(3), 1182–1192.

Benson, R. R., FitzGerald, D. B., et al. (1999). Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology, 52*(4), 798–809.

Bettus, G., Bartolomei, F., et al. (2010). Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 81*(10), 1147–1154.

Binder, J. R. (Ed.). (2009). *fMRI of language systems. fMRI techniques and protocols, neuromethods*. New York, NY: Humana.

Binder, J. R. (2011). Functional MRI is a valid noninvasive alternative to Wada testing. *Epilepsy and Behavior, 20*(2), 214–222.

Binder, J. R., Bellgowan, P. S. F., et al. (2005). A comparison of two FMRI protocols for eliciting hippocampal activation. *Epilepsia, 46*(7), 1061–1070.

Binder, J. R., Desai, R. H., et al. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex, 19*(12), 2767–2796.

Binder, J. R., Frost, J. A., et al. (1996). Function of the left planum temporale in auditory and linguistic processing. *Brain, 119*(Pt 4), 1239–1247.

Binder, J. R., Frost, J. A., et al. (1997). Human brain language areas identified by functional MRI. *Journal of Neuroscience, 17*(1), 353–362.

Binder, J. R., Frost, J. A., et al. (1999). Conceptual processing during the conscious resting state. A functional MRI study. *Journal of Cognitive Neuroscience, 11*(1), 80–95.

Binder, J. R., Gross, W. L., et al. (2010). Mapping anterior temporal lobe language areas with fMRI: A multicenter normative study. *NeuroImage, 54*(2), 1465–1475.

Binder, J. R., Hammeke, T. A., et al. (2001). Reliability and validity of language dominance assessment with functional MRI. *Neurology, 56*(Suppl A), 158.

Binder, J. R., Sabsevitz, D. S., et al. (2008). Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. *Epilepsia, 49*(8), 1377–1394.

Binder, J. R., Swanson, S. J., et al. (1996). Determination of language dominance using functional MRI: A comparison with the Wada test. *Neurology, 46*(4), 978–984.

Binder, J. R., Swanson, S. J., et al. (2008). A comparison of five fMRI protocols for mapping speech comprehension systems. *Epilepsia, 49*(12), 1980–1997.

Binder, J. R., Swanson, S. J., et al. (2010). A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: Language lateralization versus hippocampal activation asymmetry. *Epilepsia, 51*(4), 618–626.

Bobholz, J. A., Rao, S. M., et al. (2007). Clinical use of functional magnetic resonance imaging: reflections on the new CPT codes. *Neuropsychology Review, 17*(2), 189–191.

Bonelli, S. B., Powell, R. H. W., et al. (2010). Imaging memory in temporal lobe epilepsy: Predicting the effects of temporal lobe resection. *Brain, 133*(Pt 4), 1186–1199.

Bookheimer, S. Y. (1996). Functional MRI applications in clinical epilepsy. *NeuroImage, 4*(3 Pt 3), S139–S146.

Bookheimer, S. (2007). Pre-surgical language mapping with functional magnetic resonance imaging. *Neuropsychology Review, 17*(2), 145–155.

Buckner, R. L., & Braver, T. S. (1999). Event-related functional MRI. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 441–452). Berlin: Springer.

Buschke, H. (1973). Selective reminding for analysis of memory and learning. *Journal of Verbal Learning and Verbal Behavior, 12*, 543–550.

Buschke, H., & Fuld, P. A. (1974). Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology, 24*(11), 1019–1025.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology, 10*(5), 413–432.

Chelune, G. J., Naugle, R. I., et al. (1991). Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. *Neurology, 41*(3), 399–404.

Davies, K. G., Bell, B. D., et al. (1998). Prediction of verbal memory loss in individuals after anterior temporal lobectomy. *Epilepsia, 39*(8), 820–828.

de Pasquale, F., Della Penna, S., et al. (2010). Temporal dynamics of spontaneous MEG activity in brain networks. *Proceedings of the National Academy of Sciences of the United States of America, 107*(13), 6040–6045.

Delis, D. C., Kramer, J. H., et al. (2000). *California Verbal Learning Test – Second edition. Adult version*. San Antonio, TX: The Psychological Corporation.

Démonet, J.-F., Chollet, F., et al. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain, 115*, 1753–1768.

Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: Statistical power analyses. *Journal of Neuroscience Methods, 118*, 115–128.

D'Esposito, M. (2000). Functional neuroimaging of cognition. *Seminars in Neurology, 20*(4), 487–498.

Detre, J. A. (2004). fMRI: Applications in epilepsy. *Epilepsia, 45*(Suppl 4), 26–31.

Detre, J. A. (2006). Clinical applicability of functional MRI. *Journal of Magnetic Resonance Imaging, 23*(6), 808–815.

Detre, J. A., Maccotta, L., et al. (1998). Functional MRI lateralization of memory in temporal lobe epilepsy. *Neurology, 50*(4), 926–932.

Detre, J. A., Sirven, J. I., et al. (1995). Localization of subclinical ictal activity by functional magnetic resonance imaging: Correlation with invasive monitoring. *Annals of Neurology, 38*(4), 618–624.

Dulay, M. F., Levin, H. S., et al. (2009). Changes in individual and group spatial and verbal learning characteristics after anterior temporal lobectomy. *Epilepsia, 50*(6), 1385–1395.

Fischl, B., Sereno, M. I., et al. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping, 8*, 272–284.

Forman, S. D., Cohen, J. D., et al. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine, 33*(5), 636–647.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*(9), 700–711.

Freilich, E. R., & Gaillard, W. D. (2010). Utility of functional MRI in pediatric neurology. *Current Neurology and Neuroscience Reports, 10*(1), 40–46.

Gaillard, W. D., Balsamo, L., et al. (2004). fMRI language task panel improves determination of language dominance. *Neurology, 63*(8), 1403–1408.

Golby, A. J., Poldrack, R. A., et al. (2002). Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. *Epilepsia, 43*(8), 855–863.

Hall, D. A., Haggard, M. P., et al. (1999). Sparse temporal sampling in auditory fMRI. *Human Brain Mapping, 7*, 213–223.

Hamberger, M. J., McClelland, S., 3rd, et al. (2007). Distribution of auditory and visual naming sites in nonlesional temporal lobe epilepsy patients and patients with space-occupying temporal lobe lesions. *Epilepsia, 48*(3), 531–538.

Hammeke, T. A., Bellgowan, P. S., et al. (2000). fMRI: Methodology–cognitive function mapping. *Advances in Neurology, 83*, 221–233.

Hammeke, T. A., Kortenkamp, S. J., et al. (2005). Normative data on 372 stimuli for descriptive naming. *Epilepsy Research, 66*(1–3), 45–57.

Hermann, B. P., Perrine, K., et al. (1999). Visual confrontation naming following left anterior temporal lobectomy: A comparison of surgical approaches. *Neuropsychology, 13*(1), 3–9.

Hermann, B. P., Wyler, A. R., et al. (1992). Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. *Neurosurgery, 31*(4), 652–656. discussion 656–657.

Hermann, B. P., Wyler, A. R., et al. (1994a). Dysnomia after left anterior temporal lobectomy without functional mapping: Frequency and correlates. *Neurosurgery, 35*(1), 52–56. discussion 56–57.

Hermann, B. P., Wyler, A. R., et al. (1994b). Declarative memory following anterior temporal lobectomy in humans. *Behavioral Neuroscience, 108*(1), 3–10.

Huettel, S. A., & McCarthy, G. (2001). The effects of single-trial averaging upon the spatial extent of fMRI activation. *Neuroreport, 12*, 2411–2416.

Humphries, C., Liebenthal, E., et al. (2010). Tonotopic organization in human auditory cortex. *NeuroImage, 50*(3), 1202–1211.

Jager, L., Werhahn, K. J., et al. (2002). Focal epileptiform activity in the brain: Detection with spike-related functional MR imaging–preliminary results. *Radiology, 223*(3), 860–869.

Jezzard, P., & Balaban, R. S. (1995). Correction for geometric distortion in echo planar images from B0-field variations. *Magnetic Resonance in Medicine, 34*, 65–73.

Johnstone, T., Ores Walsh, K. S., et al. (2006). Motion correction and the use of motion covariates in multiple-subject fMRI analysis. *Human Brain Mapping, 27*(10), 779–788.

Jokeit, H., Okujava, M., et al. (2001). Memory fMRI lateralizes temporal lobe epilepsy. *Neurology, 57*(10), 1786–1793.

Jones-Gotman, M. (1991). Localization of lesions by neuropsychological testing. *Epilepsia, 32*(Suppl 5), S41–S52.

Jones-Gotman, M., Smith, M. L., et al. (2010). The contribution of neuropsychology to diagnostic assessment in epilepsy. *Epilepsy and Behavior, 18*(1–2), 3–12.

Kaplan, E., Goodglass, H., et al. (2001). *The Boston Naming Test* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Killgore, W. D., Glosser, G., et al. (1999). Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control. *Seizure, 8*(8), 450–455.

Klein, A., Andersson, J., et al. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *NeuroImage, 46*(3), 786–802.

Koylu, B., Trinka, E., et al. (2006). Neural correlates of verbal semantic memory in patients with temporal lobe epilepsy. *Epilepsy Research, 72*(2–3), 178–191.

Krakow, K., Woermann, F. G., et al. (1999). EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures. *Brain, 122*(Pt 9), 1679–1688.

Labudda, K., Mertens, M., et al. (2010). Presurgical language fMRI activation correlates with postsurgical verbal memory decline in left-sided temporal lobe epilepsy. *Epilepsy Research, 92*(2–3), 258–261.

Langfitt, J. T., & Rausch, R. (1996). Word-finding deficits persist after left anterotemporal lobectomy. *Archives of Neurology, 53*(1), 72–76.

Larson, E. R., Hammeke, T. A., et al. (2004). Comparison of receptive and expressive language fMRI activation and Wada language lateralization. *Epilepsia, 45*, 175.

Lazeyras, F., Blanke, O., et al. (2000). EEG-triggered functional MRI in patients with pharmacoresistant epilepsy. *Journal of Magnetic Resonance Imaging, 12*(1), 177–185.

Lehericy, S., Cohen, L., et al. (2000). Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology, 54*(8), 1625–1633.

Lemieux, L., Krakow, K., et al. (2001). Comparison of spike-triggered functional MRI BOLD activation and EEG dipole model localization. *NeuroImage, 14*(5), 1097–1104.

Leunen, D., Caroff, X., et al. (2009). Verbal and spatial learning after temporal lobe excisions in children: An adaptation of the Grober and Buschke procedure. *Epilepsy and Behavior, 16*(3), 534–538.

Lineweaver, T. T., Morris, H. H., et al. (2006). Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. *Epilepsia, 47*(11), 1895–1903.

Liu, Z., Fukunaga, M., et al. (2010). Large-scale spontaneous fluctuations and correlations in brain electrical activity observed with magnetoencephalography. *NeuroImage, 51*(1), 102–111.

Martin, R. C., Sawrie, S. M., et al. (1998). Individual memory change after anterior temporal lobectomy: A base rate analysis using regression-based outcome methodology. *Epilepsia, 39*(10), 1075–1082.

McKiernan, K. A., D'Angelo, B. R., et al. (2006). Interrupting the "stream of consciousness": An fMRI investigation. *NeuroImage, 29*(4), 1185–1191.

McKiernan, K. A., Kaufman, J. N., et al. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience, 15*(3), 394–408.

Merboldt, K. D., Finterbusch, J., et al. (2000). Reducing inhomogeneity artifacts in functional MRI of human brain activation: Thin sections vs. gradient compensation. *Journal of Magnetic Resonance, 145*, 184–191.

Morawetz, C., Holz, P., et al. (2008). Improved functional mapping of the human amygdala using a standard functional magnetic resonance imaging sequence with simple modifications. *Magnetic Resonance Imaging, 26*, 45–53.

Morgan, V. L., Dawant, B. M., et al. (2007). Comparison of fMRI statistical software packages and strategies for analysis of images containing random and stimulus-correlated motion. *Computerized Medical Imaging and Graphics, 31*(6), 436–446.

Moser, D. J., Bauer, R. M., et al. (2000). Electroencephalographic, volumetric, and neuropsychological indicators of seizure focus lateralization in temporal lobe epilepsy. *Archives of Neurology, 57*(5), 707–712.

Naugle, R. I., Chelune, G. J., et al. (1993). Detection of changes in material-specific memory following temporal lobectomy using the Wechsler Memory Scale-Revised. *Archives of Clinical Neuropsychology, 8*(5), 381–395.

Noll, D. C., Stenger, V. A., et al. (1999). Spiral scanning in fMRI. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 149–160). Berlin: Springer.

Ogawa, S., Lee, T. M., et al. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America, 87*, 9868–9872.

Ojemann, J. G., Akbudak, E., et al. (1997). Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *NeuroImage, 6*, 156–167.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Patel, M. R., Blum, A., et al. (1999). Echo-planar functional MR imaging of epilepsy with concurrent EEG monitoring. *AJNR. American Journal of Neuroradiology, 20*(10), 1916–1919.

Powell, H. W. R., & Duncan, J. S. (2005). Functional magnetic resonance imaging for assessment of

language and memory in clinical practice. *Current Opinion in Neurology, 18*(2), 161–166.

Powell, H. W. R., Koepp, M. J., et al. (2004). The application of functional MRI of memory in temporal lobe epilepsy: A clinical review. *Epilepsia, 45*(7), 855–863.

Powell, H. W. R., Richardson, M. P., et al. (2007). Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. *Epilepsia, 48*(8), 1512–1525.

Powell, H. W. R., Richardson, M. P., et al. (2008). Preoperative fMRI predicts memory decline following anterior temporal lobe resection. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(6), 686–693.

Rabin, M. L., Narayan, V. M., et al. (2004). Functional MRI predicts post-surgical memory following temporal lobectomy. *Brain, 127*(Pt 10), 2286–2298.

Richardson, M. P., Strange, B. A., et al. (2004). Preoperative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain, 127*(Pt 11), 2419–2426.

Richardson, M. P., Strange, B. A., et al. (2006). Memory fMRI in left hippocampal sclerosis: Optimizing the approach to predicting postsurgical memory. *Neurology, 66*(5), 699–705.

Roland, P. E., Eriksson, L., et al. (1987). Does mental navigation along memorized routes activate the hippocampus, precuneus, and insula. *Journal of Neuroscience, 7*, 2373–2389.

Sabsevitz, D. S., Swanson, S. J., et al. (2001). Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. *Epilepsia, 42*(11), 1408–1415.

Sabsevitz, D. S., Swanson, S. J., et al. (2003). Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery. *Neurology, 60*(11), 1788–1792.

Schmidt, M. (1996). *Rey Auditory and Verbal Learning Test: A handbook*. Los Angeles, CA: Western Psychological Services.

Seeck, M., Michel, C. M., et al. (2001). EEG mapping and functional MRI in presurgical epilepsy evaluation. *Revue Neurologique (Paris), 157*(8–9 Pt 1), 747–751.

Seidenberg, M., Hermann, B. P., et al. (1996). Hippocampal sclerosis and verbal encoding ability following anterior temporal lobectomy. *Neuropsychologia, 34*(7), 699–708.

Smith, S. M., Fox, P. T., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America, 106*(31), 13040–13045.

Springer, J. A., Binder, J. R., et al. (1999). Language dominance in neurologically normal and epilepsy subjects: A functional MRI study.[see comment]. *Brain, 122* (Pt 11), 2033–2046.

Stafiniak, P., Saykin, A. J., et al. (1990). Acute naming deficits following dominant temporal lobectomy: Prediction by age at 1st risk for seizures. *Neurology, 40*(10), 1509–1512.

Stark, C. E., & Squire, L. R. (2001). When zero is not zero: The problem of ambiguous baseline conditions in fMRI. *Proceedings of the National Academy of Sciences of the United States of America, 98*(22), 12760–12766.

Stroup, E., Langfitt, J., et al. (2003). Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology, 60*(8), 1266–1273.

Swanson, S. J. (2006). Neuropsychological testing is of limited value for predicting the epileptogenic zone. In J. M. D. Silbergeld (Ed.), *Controversies in epilepsy surgery* (pp. 215–220). New York, NY: Marcel Dekker Inc.

Swanson, S. J., Sabsevitz, D. S., et al. (2007). Functional magnetic resonance imaging of language in epilepsy. *Neuropsychology Review, 17*(4), 491–504.

Symms, M. R., Allen, P. J., et al. (1999). Reproducible localization of interictal epileptiform discharges using EEG-triggered fMRI. *Physics in Medicine and Biology, 44*(7), N161–N168.

Szaflarski, J. P., Holland, S. K., et al. (2004). High-resolution functional MRI at 3T in healthy and epilepsy subjects: Hippocampal activation with picture encoding task. *Epilepsy and Behavior, 5*(2), 244–252.

Thornton, R., Laufs, H., et al. (2010). EEG correlated functional MRI and postoperative outcome in focal epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 81*(8), 922–927.

Trenerry, M. R., Jack, C. R., Jr., et al. (1993). MRI hippocampal volumes and memory function before and after temporal lobectomy. *Neurology, 43*(9), 1800–1805.

Vannest, J., Szaflarski, J. P., et al. (2008). Medial temporal fMRI activation reflects memory lateralization and memory performance in patients with epilepsy. *Epilepsy and Behavior, 12*(3), 410–418.

Voyvodic, J. T. (2006). Activation mapping as a percentage of local excitation: fMRI stability within scans, between scans and across field strengths. *Magnetic Resonance Imaging, 24*, 1249–1261.

Vulliemoz, S., Lemieux, L., et al. (2010). The combination of EEG source imaging and EEG-correlated functional MRI to map epileptic networks. *Epilepsia, 51*(4), 491–505.

Warach, S., Ives, J. R., et al. (1996). EEG-triggered echo-planar functional MRI in epilepsy. *Neurology, 47*(1), 89–93.

Weber, B., Wellmer, J., et al. (2006). Presurgical language fMRI in patients with drug-resistant epilepsy: Effects of task performance. *Epilepsia, 47*(5), 880–886.

Wendel, J. D., Trenerry, M. R., et al. (2001). The relationship between quantitative T2 relaxometry and memory in nonlesional temporal lobe epilepsy. *Epilepsia, 42*(7), 863–868.

MEG in the Presurgical Epilepsy Evaluation

9

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Magnetoencephalography involves noninvasively measuring the magnetic fields generated by brain activity. These fields result from the rapid electrochemical activity of neural cell assemblies and can be measured essentially in real time. MEG thus provides a direct measure of neural activity with excellent temporal resolution. When combined with detailed spatial information obtained from structural (and even functional) MRI, MEG enables the creation of spatiotemporal cortical activation maps with millisecond temporal resolution and sub-centimeter spatial resolution (Kaufmann & Lu, 2003). Thus, it is a powerful tool to help understand various aspects of both healthy cognition and neuropathology in the context of presurgical evaluation for medically intractable epilepsy. Below, we review the critical conceptual and practical details of MEG data collection and analysis, and the emerging literature on its role in localization of language and memory functions in presurgical epilepsy evaluations.

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Physiological Basis of MEG signals

As understood from basic cellular neurophysiology, the depolarization or hyperpolarization of a neural membrane due to synaptic activity results in the flow of charged ions into or out of the cell. These ion flows and resulting electrical potential changes constitute excitatory or inhibitory postsynaptic potentials (E/IPSPs), respectively. Due to the longitudinal structure of pyramidal cells (possessing basal dendrites near the soma and apical dendrites at the distal end), changes in the transmembrane potential at either end of the cell result in the creation of an ionic current source-sink dynamic across its length and of a complementary magnetic field around the resulting intracellular current. When a population of similarly oriented cells is synchronously activated due to E/IPSPs, the resulting net electric current generates a very small magnetic field, which nonetheless is of sufficient strength to be detected extracranially.

Thus, the magnetic fields measured in MEG principally result from ionic current flows created by synchronous E/IPSPs within populations of pyramidal cells (Baillet, Mosher, & Leahy, 2001; Kaufmann & Lu, 2003). Due to several favorable aspects of their anatomical organization,

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pyramidal cell assemblies within neocortical layers II/III and V in particular generate magnetic fields of sufficient strength (approximately $10fT = 10e^{-15}$ T) to be detectable outside of the head (Baillet, 2010). These cell aggregates are generally understood to form the basic generators of most MEG signals. Theoretically, fields of this magnitude may correspond to populations of approximately 50,000 synchronously active pyramidal cells, within cortical areas of about 1 mm^2 or larger, and current flows arising perpendicularly to the cortical surface (Lopes da Silva, 2010; Murakami & Okada, 2006).

In addition to understanding the mechanism by which neural ionic currents result in detectable extracranial magnetic fields, there are two additional considerations pertinent to understanding the basis of MEG signals. MEG source imaging was originally thought to be relatively less sensitive to fields emanating from gyral crests and deeper sources, than to those generated by sources located within sulcal walls (Vrba & Robinson, 2001). Fortunately, advances in the modeling of the physics of electromagnetic fields in head tissues permit state-of-the-art whole-head MEG systems to detect the majority of cortical signals (Hillebrand & Barnes, 2002). Moreover, detection of various subcortical and cerebellar sources is increasingly being reported under suitable experimental conditions (e.g., Attal, et al., 2009; Martin, et al., 2006; Riggs, et al., 2009). It should also be noted that the contribution of action potentials to MEG signals are assumed to be negligible under most circumstances, due to their rapid time course, and lower likelihood of synchronization across cells than E/IPSPs. Of note however, this may not hold to account for the generation of some very high-frequency (150 Hz and higher) neural signals with MEG or in the context of epileptiform spike discharges (Lopes da Silva, 2010).

Like EEG and other electrophysiological recording techniques, MEG provides millisecond temporal resolution of neural activity, enabling observations of rapidly changing network dynamics and transient oscillatory phenomena. However, unlike electroencephalographic potentials which derive primarily from extracellular currents and are subject to volume conduction effects (distortion from signal mixing and cerebrospinal fluid, meningeal, skull, and scalp resistance), cortical magnetic fields pass through the skull and other tissues virtually unimpeded (Okada, Lahteenmäki, & Xu, 1999). This "transparence" of the human body to magnetic fields permits localization of the generators of the observed magnetic fields within a reasonable spatial resolution (about 5 mm, depending on source depth) (Leahy, Mosher, Spencer, Huang, & Lewine, 1998), via the additional step of co-registering MEG source imaging with the subject's structural MRI volume (Kaufmann & Lu, 2003). Taken together, the excellent temporal resolution of the raw data, the sensitivity to paroxystic interictal events, and the spatial resolution of magnetic source analysis make MEG a desirable addition to functional mapping studies in the context of presurgical epilepsy evaluations.

MEG Data Collection

Equipment

Most MEG laboratories utilize a common set of components to optimize detection of the magnetic fields of interest. The most important of these is obviously the MEG instrument itself, consisting of a large dewar molded into a helmet-shaped surface at its base, containing approximately 300 magnetic sensors. Different MEG systems involve various combinations of sensors arrays, and the most basic sensor is a magnetometer, consisting of a pickup coil paired with a current detector. Single magnetometers (which measure absolute magnetic fields) and paired magnetometers or "gradiometers" (which measure differences in field strength across short distances, and are thus less sensitive to far-field noise sources) are in turn connected to superconducting current detectors (i.e., superconducting quantum interference devices, or SQUIDs) which ultimately enable detection of the miniscule field strengths generated by neural activity. This superconducting sensing technology is cooled at −269 °C with liquid helium and is necessary to keep instrumental noise levels at less than a few femtotesla per square root hertz.

Working with ultrasensitive sensors requires solving some associated challenges, as they are very good at picking up the nuisances and electromagnetic perturbations generated by external noise sources of environmental noise. A magnetically shielded room (MSR) made of layers of metal alloys (and possibly complemented by active shielding solutions) is employed to attenuate external magnetic fields and in turn makes MEG recordings possible. The attenuation of electromagnetic perturbations through the MSR walls is considerable and facilitates MEG recordings, even in noisy environments like hospitals (even near MRI suites) and in the vicinity of road traffic. Stimulus presentation in the MSR, especially when it requires external devices, needs to be considered carefully to avoid introducing supplementary electromagnetic perturbations. Fortunately, MEG centers can benefit from most of the equipment available to fMRI studies, as it is specified along the same constraints regarding magnetic compatibility. Therefore, audio and video presentations can be performed using electrostatic transducers and mirror systems that beam video projection. Electrical stimulation for somatosensory mapping generates artifacts of short durations that do not overlap with the earliest brain responses (>20 ms latency) or in some instances (e.g., pediatric populations) may be advantageously replaced by air puff delivery.

MEG laboratories are also equipped with safety features such as ventilation systems permitting airflow, maintenance and emergency exhausts for evaporating liquid helium, and audio and video systems enabling constant contact between the subject and experimenter throughout the study. The MEG gantry may be positioned to perform with the subject seated or supine to maximize their comfort or accommodate clinical constraints. Finally EEG, other ancillary electrophysiological recordings (such as electrooculogram, myogram, and cardiogram), various behavioral responses, and even eye tracking can be recorded simultaneously with MEG, allowing detection of complementary physiological and behavioral measures, as well as possible sources of physiological artifacts.

The MEG system is in turn connected to data acquisition software that is run by one or more technicians. Operation of a working MEG lab requires regular delivery and replenishment of liquid helium which is necessary for operation of the sensors, as well as one or more technicians who can maintain consistency in subject preparation and data acquisition. The technology involved in MEG sensing, the weekly helium refills, and the materials building the MSR makes MEG a costly piece of equipment. Exciting recent developments, however, contribute to constant progress in cost-effectiveness, practicality, and the future of MEG sensing science.

Subject Preparation

A unique and challenging aspect of MEG is its sensitivity to multiple possible artifacts. Specifically, MEG data may be contaminated by physiological sources of magnetic fields such as muscles, eye blinks and movements, heartbeats, facial movements, and speech and from any magnetic material moving in the vicinity of the sensors. To permit subsequent detection and attenuation of ocular and cardiac artifacts, subject preparation typically involves application of electrooculogram and electrocardiogram leads. Careful experimental design and data collection is required to either avoid or account for contamination due to speech-related artifacts. Large artifacts due to metallic and magnetic parts (coins, credit cards, some dental retainers, body piercing, bra supports, etc.) or particles (makeup, hair spray, tattoos) can be readily and visually detected as they cause major low-frequency deflections in sensor traces. They are usually emphasized with respiration and/or eye blinks or jaw movements. However, some causes of artifacts may not be easily circumvented. In particular, recent prior participation in an MRI study may result in strong, long-term magnetization of dental retainers, for example, which generally brings the MEG session to a premature close. This may be avoided by scheduling a patient's MRI after their MEG session rather than before. Onsite demagnetization may be attempted using "degaussing" techniques—usually using a conventional magnetic tape eraser, which attenuates

and scrambles magnetization—with limited chances of success, though. As a rule, it is best to ask subjects to refrain from wearing clothing with metallic components, piercings, makeup, or other potentially magnetic materials.

For patient populations, artifacts generated by sources such as ventricular shunts and aneurysm clips may be partially compensated for by filtering out implicated frequencies in the MEG signals or, if necessary, excluding the most affected channels from further analysis. As vagal nerve stimulators create large artifacts (even when turned off), they have generally precluded collection of meaningful data (Makela, 2010). However, the recent development of more sophisticated signal processing techniques has begun to improve correction for more minor, regular artifacts such as heartbeat and eye blinks (Delorme & Makeig, 2004) and has even enabled removal of VNS or DBS artifacts from MEG data in case reports (Carrette et al., 2011; Kringelbach, et al., 2007; Ramirez, et al., 2009; Tanaka, Thiele, Madsen, Bourgeois, & Stufflebeam, 2009). To permit interpretation of the scalp topography within raw MEG data, or accurate source localization, there is also a need to maintain a record of the location of the subject's head with respect the sensor array. This is accomplished by also applying head-positioning coils (HPI) to the subject's head to detect its position with respect to the sensor array while recording. This is critical because although head motion is not encouraged, it is very likely to occur within and between runs, especially with young children and some patients. The HPIs drive a current at some adjustable higher frequency (about 300 Hz) that is readily detected by the MEG sensors at the beginning of each run, permitting their localization within seconds with millimeter accuracy. Some MEG systems feature the possibility for continuous head-position monitoring during the recording as well as offline head movement compensation (Wehner, Hämäläinen, Mody, & Ahlfors, 2008).

If advanced source analysis is required, additional 3D digitization of anatomical fiducial points is necessary to ensure that subsequent registration to the subject's MRI anatomical volume is successful and accurate. A minimum of three fiducial points should be localized using a 3D digitizer device (most commonly near the nasion and left and right periauricular points), and their application should be well-standardized across technicians in a given laboratory. To reduce ambiguity in the detection of these points in the MR volume data, they can be marked using vitamin E pills or any other solid marker that is readily visible in T1-weighted MR images, if an MRI is scheduled immediately after the MEG session. Digitization of EEG electrode locations is also mandatory for accurate, subsequent source analysis (EEG recording is possible concurrently with MEG, without generating increased noise levels). Overall, about 15 min are required for subject preparation for an MEG-only session, which can extend up to about 45 min if simultaneous high-density EEG is required.

Data Acquisition

The time dimension accessible to MEG offers considerable variety in the design of experimental paradigms, enabling collection of various types of event-related brain activity, in addition to measurement of "resting" states, passive stimulation, and oscillatory activity (Salmelin & Baillet, 2009). In the context of presurgical epilepsy evaluations, it is often necessary to obtain "resting-state" data to permit the epileptologist to review the individual sensor traces for epileptiform activity or to apply automated spike-detection algorithms. In contrast, localization of sensory/motor or cognitive functions usually involves collection of event-related data, such as during sustained performance of a task or in the experimental contexts reviewed below.

MEG paradigms commonly utilize automated stimulus presentation to ensure the necessary temporal precision between experimental events and data collection. As with other computer-assisted psychological research, the typical case involves exposure to conditions presented via a succession of individual trials according to blocks or in a randomized or pseudo-randomized order. The number of trials in each condition must be high enough to allow data analysis in single

subjects, accounting for loss of up to 20 % due to artifacts. Practically, this translates into collection of 120 trials for investigators adopting conservative approaches in cognitive paradigms, to 50 or fewer for robust sensory responses to single stimuli (Salmelin & Parkkonen, 2010). The durations of interstimulus intervals are typically much shorter than in fMRI paradigms and range from a few tens of milliseconds to a few seconds. In order to maximize subject comfort and participation (and minimize blink and movement-related artifacts), it is generally advised to divide the MEG session into a series of runs, each lasting less than 10 min, and to minimize the total recording time when possible. In addition to recording the subject's brain activity itself, it is often useful to obtain an empty-room recording for purposes of evaluating the environmental noise levels before subsequent source analysis.

MEG Data Analysis

Quality Control

The raw MEG data is stored as a series of traces, quantifying the continuous time-varying amplitude of the magnetic flux recorded by each sensor. For experimental paradigms and functional tests, the traces are then divided into single trials or "epochs," time locked to an event, which is either the stimulus presentation or the subject's response. Artifact rejection generally proceeds at the level of continuous data or single trials and is accomplished through various means. These include: visually inspecting and manually rejecting contaminated trials, using automated amplitude threshold or other feature-based rejection, or signal classification techniques such as independent component analysis that detects the spatiotemporal "signature" of a given artifact and removes it from the data (Delorme & Makeig, 2004). Most commonly, the epochs are then averaged across trials, to yield a single time-locked average "evoked" response at each given sensor. More recently, computational and conceptual advances have enabled investigation of non-phase-locked oscillatory responses, which are briefly discussed below.

Quality control of the data is recommended to be performed before artifact rejection through the visual examination of the trials themselves, the nature and degree of artifactual contamination, and review of spatial topography of the single trials and averages. This step increases the investigator's familiarity with the responses elicited by the task and ensures that the subsequent analysis proceeds with valid and meaningful data. Two additional steps to further clean the data and facilitate detection of the signals of interest are subtracting the averaged baseline activity from the epochs (baseline correction) and applying filters to frame the detection of signals within a preselected frequency range. While it is perfectly valid in many contexts to restrict the analysis to the averaged evoked responses obtained at the sensor level, the most valuable contribution from MEG in presurgical epilepsy evaluations would typically involve magnetic source analysis. This in turn requires a basic understanding of MEG source estimation (the inverse modeling problem).

The MEG Inverse Problem

Fundamentally, magnetic source estimation and analysis is a modeling problem, which involves the evaluation of the so-called "forward" and "inverse" models. In general terms, solving the forward modeling problem means mathematically modeling unknown observations from a set of known input parameters. In MEG, this translates to predicting the electromagnetic fields generated by any arbitrary neural source distribution, in terms of location, orientation of the current flow, and its amplitude. MEG forward modeling considers that some parameters are known and fixed: the geometry of the head, conductivity of tissues, sensor locations, etc. Generally speaking, forward modeling problems are often considered to be "well-posed," meaning that since the input and other parameters of data generation are assumed to be known, the problem consisting in predicting the experimental measures has a unique solution.

Inverse modeling constitutes the reciprocal situation where we aim to model the sources

(i.e., neural currents) of the MEG observations. This is accomplished by mathematically combining the sensor data with the MEG forward model, thereby enabling estimation of the source parameters (location, orientation of current flow, magnitude time series). Given the approximations of forward modeling, the noise in the data, and the underlying physics of MEG, the inverse modeling problem admits multiple possible solutions that may equivalently predict the observations. This situation is not unique to MEG, and in imaging science, quantitative approaches to dealing with such so-called "ill-posed" inverse problems involve reducing the number of unknown parameters and/or adding supplementary constraints to the estimation of sources, to make it a well-posed problem (Baillet, 2010). Practically in MEG, this means constraining the sources to the cortex, specifying the number of sources in advance, or using fMRI-based spatial weighting (e.g., Henson, Flandin, Friston, & Mattout, 2010).

Models of Neural Generators and Head Tissues

MEG forward modeling consists of two basic models that work together in a complementary manner: a physical model of neural sources and a model that predicts how these sources generate electromagnetic fields outside the head. Regarding the former, the canonical source model of the net primary intracellular currents within a neural assembly can be reduced to an equivalent current dipole (ECD) model (although higher-order models based on multipolar expansions of the current distribution are available) (Jerbi, Mosher, Baillet, & Leahy, 2002). That is, a focal source generating a "dipolar" magnetic field in the scalp topography (see Fig. 9.1 below).

In turn, predicting the electromagnetic fields produced by these source models requires another modeling step. This head modeling process is necessary to address the influence of the head geometry and electromagnetic properties of head tissues on the magnetic fields measured outside the head. Briefly, several well-justified and simplifying assumptions following from MEG physics allow for head geometry to be simplified as a sphere (see: Feynman, Leighton, & Sands, 1964; Hämäläinen, Ilmoniemi, Knuutila, & Lounasmaa, 1993), and hence, the simplest and consequently by far most popular model of head geometry in MEG is a single-layer sphere. In MEG, only the location of the center of the spherical head geometry matters. The respective conductivity and radius of the spherical layers have no influence on the measured MEG fields. This is not the case in EEG, where the location, radii, and respective conductivity of each spherical shell (typically: brain, cerebrospinal fluid, skull, and scalp) influence the distribution and amplitude of surface electrical potentials. Thus, for applications involving simultaneous EEG acquisition (and their source analysis), more complex head modeling approaches such as boundary and finite element head modeling are strongly suggested (Wolters, et al., 2006). These provide more realistic head models via geometric tessellations of the different head tissue envelopes extracted from the subject's individual MRI volume data, though they remain significantly more intensive computationally.

While the topics of forward and inverse modeling are complex and would require an in-depth review per se (see Hansen, Kringelbach, & Salmelin, 2010), this is beyond the scope of this chapter. To a clinical investigator embarking on an MEG evaluation program, it is necessary to be aware that MEG source analysis is fundamentally a *modeling* problem, involving various tradeoffs and approximations, which can be approached in a number of ways. The specific approach taken should be dictated by the goals and constraints of the study. Today, a reasonable degree of technical maturity has been reached by electromagnetic brain imaging using MEG, and the approaches to source estimation reduce to only a handful of well-identified classes.

MEG Source Modeling: Localization vs. Imaging Approaches

The localization approach to MEG source estimation considers that brain activity at any time instant is generated by a relatively small

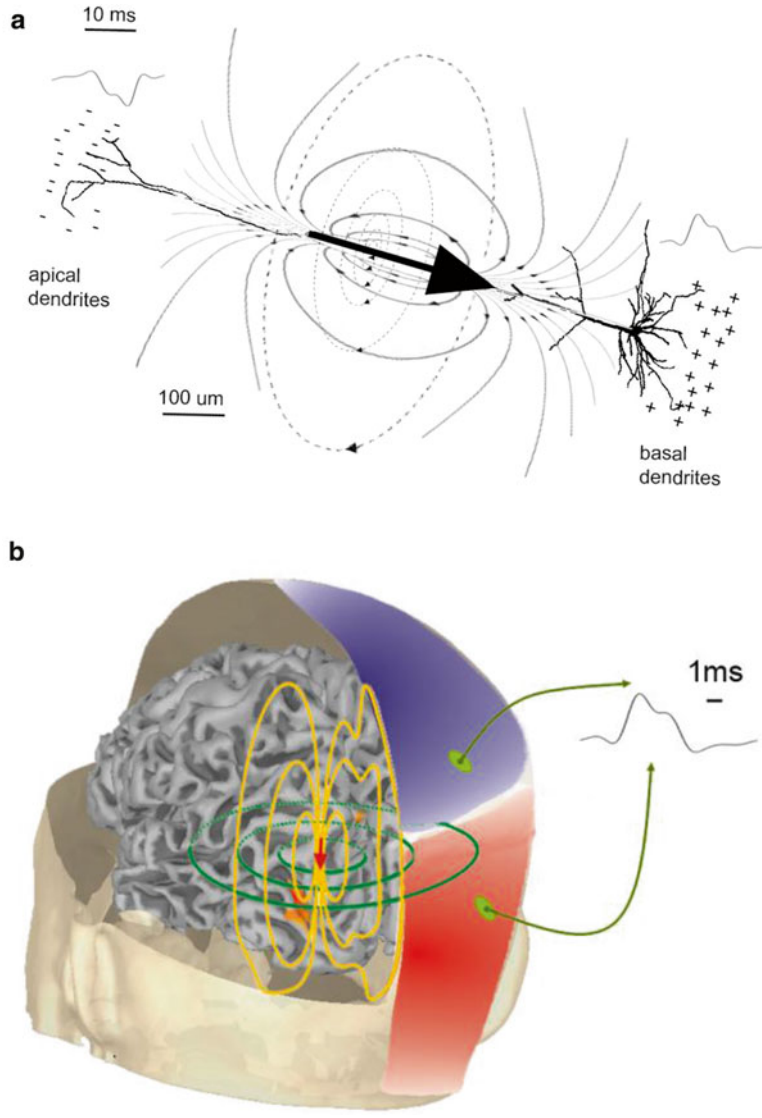

Fig. 9.1 Basic electrophysiological principles of MEG and EEG. (**a**) Large neural cells—just like this pyramidal neuron from cortex layer V—drive ionic electrical currents. These latter are essentially impressed by the difference in electrical potentials between the basal and apical dendrites or the cell body, which is due to a mixture of excitatory and inhibitory postsynaptic potentials, which are slow (>10 ms) relatively to action potentials firing and therefore add up efficiently at the scale of synchronized neural ensembles. These primary currents can be modeled using an equivalent current dipole, here represented by a *large black arrow*. The electrical circuit of currents is closed within the entire head volume by secondary, volume currents shown with the *dark plain lines*. Additionally, magnetic fields are generated by the primary and secondary currents. The magnetic field lines induced by the primary currents are shown using *dashed lines* arranged in *circles* about the dipole source. (**b**) At a larger spatial scale, the mass effect of currents due to neural cells sustaining similar mixtures of postsynaptic potentials add up locally and behave also as a current dipole (shown in *red*). This primary generator induces secondary currents (shown in *yellow*) that travel through the head tissues. They eventually reach the scalp surface, where they can be detected with pairs of electrodes by EEG. Magnetic fields (in *green*) travel more freely within tissues and are less distorted than current flows. They can be captured with arrays of magnetometers by MEG. The distribution of blue and red colors on the scalp illustrates the continuum of magnetic and electric fields and potentials distributed at the surface of the head

number (a handful, at most) of brain regions. Each source is therefore represented by an elementary model, such as an ECD, that captures local distributions of neural currents. Ultimately, each elementary source is back projected or constrained to the subject's brain volume or an MRI anatomical template, for further interpretation. Localization models are essentially compact, in terms of number of generators involved and their surface extension (from point-like to small cortical surface patches).

The early MEG literature is abundant in studies reporting on single-dipole source models. The somatotopic, tonotopic, and retinotopic responses are examples where the single-dipole model contributed to the better temporal characterization of primary sensory area responses. However, later components of evoked fields usually necessitate that more elementary sources be adjusted, and this is detrimental to the numerical stability and robustness of the inverse model. The number of elementary sources in the model is often qualitatively assessed by expert users, which may undermine the reproducibility of the analyses. Hence, special care should be brought to the evaluation of the stability and robustness of the estimated source models. With all that in mind, source localization techniques have proven to be effective, even in complex experimental paradigms (Helenius, Parviainen, Paetau, & Salmelin, 2009). Indeed, as we outline below, dipole-based approaches currently constitute the most widely applied and best-replicated paradigms for presurgical language mapping with MEG. The alternative *imaging* approaches to source modeling were originally inspired by the plethoric research in digital image restoration and reconstruction in other fields of engineering.

In these approaches, dense grids of current dipoles are predefined over the entire brain volume or limited to the cortical gray matter surface. These dipoles are fixed in location and, generally, orientation, and their amplitudes are estimated at once. Thus, the nonlinear parameters (e.g., the elementary source locations) now become fixed priors as provided by anatomical information, and the remaining free parameters are the amplitudes of the elementary source currents distributed on the brain's geometry. The resulting image source models do not yield small sets of local elementary models but rather the distribution of "all" neural currents. As the estimated sources are spatially fixed in this approach, they are homologous to the pixels of a digital image. Hence, the resulting estimations are a set of *images* or maps, representing an estimation of the intensity of neural currents, distributed within the entire brain volume or constrained at the cortical surface. Contrary to the localization model though, there is no intrinsic sense of distinct, active source regions per se. Explicit identification of activity issued from discrete brain regions usually necessitates complementary analysis, such as empirical or inference-driven amplitude thresholding, to discard elementary sources of nonsignificant contribution according to the statistical appraisal. In that respect, MEG source images are very similar in essence to the activation maps obtained in fMRI, with the supplementary benefit of time resolution (Fig. 9.2).

Just like in the context of source localization where, for example, the number of sources is a restrictive prior as a remedy to ill-posedness, imaging models also must be complemented by a priori information. Several academic software packages have addressed this issue by implementing variations of the well-described minimum norm model (Lin, et al., 2006; Lin, Belliveau, Dale, & Hämäläinen, 2006). For present purposes, it is important only that readers be aware of the equivalent need for prior information in both the localization and imaging approaches. These priors are necessary to determine a workable solution to a problem with an infinite number of solutions, in theory.

A final set of approaches involve signal classification and spatial filtering (e.g., "beam forming") to translate the source localization problem into a signal detection issue. In essence these are scanning techniques that systematically sift through the brain space to evaluate how a predetermined elementary source model would fit the data at every voxel of the brain volume. These techniques are efficient alternative approaches in that respect and have gained considerable momentum in the MEG community in the recent years. They have proven especially fruitful in several applications (for both source estimation

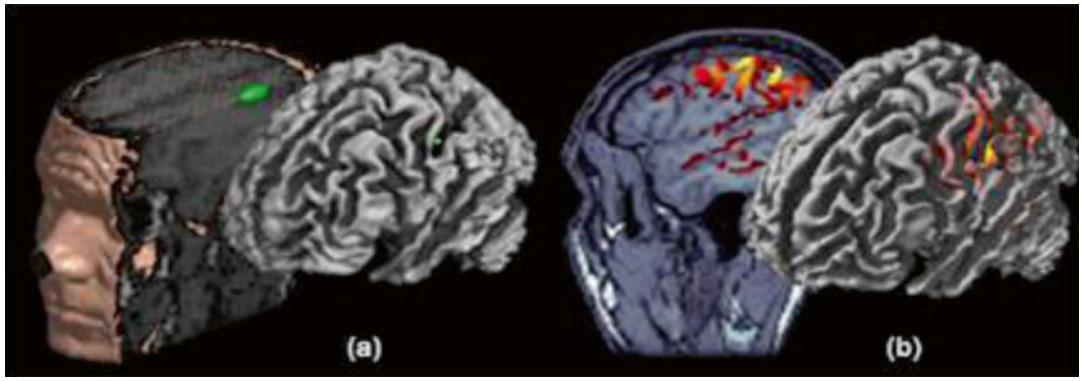

Fig. 9.2 Inverse modeling: localization (**a**) vs. imaging (**b**) approaches. Source modeling through localization consists in decomposing the MEG/EEG generators in a handful of elementary source contributions, the simplest source model in this situation being the ECD. This is illustrated here with experimental data from testing the somatotopic organization of primary cortical representations of hand fingers. The parameters of the single ECD have been adjusted on the 20–40 ms time window following stimulus onset. The ECD was found to localize along the contralateral central sulcus as revealed by the three-dimensional rendering obtained after the source location has been registered to the individual anatomy. In the imaging approach, the source model is spatially distributed on a large number of ECDs. Here, a surface model of MEG-EEG generators was constrained to the individual brain surface extracted from T1-weighted MR images. Elemental source amplitudes are interpolated onto the cortex, which yields an image-like distribution of the amplitudes of cortical currents

and artifact suppression) and the interested reader is referred to a review article by Hillebrand, Singh, Holliday, Furlong, and Barnes (2005) for an introduction to the approach.

Each of these three approaches, MEG source localization, imaging, and scanning, makes use of phenomenally complex methodology and modeling techniques to noninvasively localize the source of magnetic neural activity within the brain. As with any experimental observation, they are subject to error and benefit from explicit assessments of their sensitivity to measure noise and modeling approximations (see, e.g., Darvas, et al., 2005; Mosher, Spencer, Leahy, & Lewis, 1993). Ultimately, an informed consideration of their various assumptions, strengths, and weaknesses, as described above, can guide their optimal application to any given clinical evaluation.

Practical Considerations

Despite the many complex aspects of magnetic source imaging, the preceding exposition can easily be reduced to a handful of essential points to consider before beginning a program of MEG presurgical evaluation. As with fMRI, an efficiently functioning MEG laboratory requires the effort of a multidisciplinary team. The various requirements would ideally be met by a group of individuals with collective expertise in MEG physics, data acquisition, software engineering, task design and development, cognitive evaluation, and neuroanatomy, epileptology, neuro-oncology, etc.

Developing a standardized data acquisition and analysis protocol simply requires explicitly planning through the steps outlined above (e.g., subject preparation, data acquisition, quality control, source modeling, etc). It is important to remember that the tasks, stimuli, and analysis approach in MEG protocols should be designed in a coordinated and complementary fashion and specifically with sensitivity to how the *temporal* aspects of the stimuli, and expected behavioral and neural responses will condition the access to a subset of methods for data analysis. For example, it might be discussed whether or not to collect behavioral data simultaneously with MEG or whether the data should be analyzed as stimulus-locked vs. response-locked epochs. Event-related responses in cognitive tasks most often contain both early components (50–200 ms post-stimulus) reflecting the primary sensory processing and integration of the stimulus and later components (>200 ms

post-stimulus) that are typically thought to reflect activity in association cortices. It has therefore been argued that the mapping of higher cognitive functions with MEG may require restricting analyses to the later components of the brain responses (Simos, Papanicolaou, Castillo, & Buchanan, 2009). Decisions such as duration of stimulus presentation and length and variability of interstimulus intervals (ISIs) need to be guided by the specifics of the task modality and of the underlying scientific hypothesis to be tested (e.g., visual stimuli tend to elicit saccades, auditory stimuli unfold over time, etc.) and the expected nature of the neural responses of interest (Salmelin & Parkkonen, 2010). There are several academic or commercial software packages for MEG data analysis, and the major MEG vendors provide their own software for many aspects of data processing. Additionally, the reference papers for several excellent and freely available software packages can be found at: http://www.hindawi.com/journals/cin/2011/si.ebm/.

As discussed above, MEG recording is greatly facilitated if caution is taken prior to scanning to remove easily eliminated sources of magnetic artifacts (e.g., pieces of metal in garments). To this end, it is a good investment of time to briefly conduct a noise run with the subject sitting or laying under the MEG dewar to help identify any unsuspected artifacts, before subject preparation is completed by applying HPI coils and, optionally, EEG leads. This step has the additional benefit of familiarizing the patient with the MSR environment before the clinical scan per se. For the most part, the prior recommendations regarding behavioral monitoring and testing outside of the instrument in the context of fMRI also apply to MEG. Also like fMRI, it has been reported that language-related activity is impacted by factors such as subject alertness, task compliance, and IQ (Merrifield, Simos, Papanicolaou, Philpott, & Sutherling, 2007; Simos et al., 2009), though there are ongoing efforts to develop MEG language protocols that are better suited for use with pediatric and cognitively lower-functioning individuals. Unlike the highly magnetized MRI environment, patient safety concerns within the MSR primarily relate to clinical concerns. The most important of these is always having appropriately trained personnel ready to rapidly enter and assist the patient within the enclosed MSR, in case of an acute seizure or other medical emergency.

Clinical Use of MEG by Neuropsychologists

For the same reasons outlined in the fMRI chapter of this volume, neuropsychologists can clearly play an appropriate and valuable role in the design, administration, and interpretation of MEG studies of higher cognitive functions. In 2009, the American Academy of Neurology published a policy regarding MEG, including indications to "localize and preserve eloquent cortex during resective surgery," in the context of surgeries for tumors and arteriovenous malformations, in addition to MEG indications for epilepsy surgical planning (see Wu et al., 2010). MEG CPT codes have been issued for these clinical conditions http://acmegs.org/id77.html under "MEG recording and analysis" for localization of language, as well as sensory and motor functions, with the former representing an excellent venue for integrating neuropsychological expertise. As of this writing, we are not aware of any official position statements regarding the role of neuropsychologists in the clinical use of MEG. Given the historical importance that localization of cognitive functions played within the discipline of clinical neuropsychology, as well as ongoing discussions about expanding roles for neuropsychologists (Bilder, 2011; Miller, Elbert, Sutton, & Heller, 2007), this may be a timely topic for discussion within neuropsychological professional organizations and training programs.

Tasks

There are a number of tasks that have been utilized to map language-specific cortical regions with MEG. Fewer studies have examined episodic memory with MEG in ways that are immediately relevant to presurgical epilepsy

evaluations. By far, the most widely studied and best-replicated task for evaluation of the laterality of language functions with MEG is the continuous recognition memory (CRM) paradigm developed by Papanicolaou and colleagues (Frye, Rezaie, & Papanicolaou, 2009). A common version of the task involves presenting the subject with a list of target words (abstract English nouns) immediately prior to the scan, which they are asked to study and accurately repeat. The acquisition scan involves presenting the subject with frequent spoken targets that are randomly interspersed with novel distractor items. Subjects are instructed to immediately issue a manual response (a finger lift) upon presentation of a target and otherwise make no response. Thus, the task essentially represents an auditory verbal recognition memory paradigm.

The analysis stream most often utilized for this task involves identifying the locations of successive dipolar sources that account for the magnetic flux distribution in the "late" (i.e., >200 ms) portion of the post-stimulus period. The acquisition run is often divided into two subsets where the spatial and temporal overlap of the obtained dipoles is assessed, and those which are reliable between the two subsets are retained. The resulting dipole maps depict clusters of reliable source locations. In a manner similar to fMRI, a laterality index can be calculated by taking the difference between the number of right- and left-hemisphere sources divided by their sum, thereby providing a hemispheric dominance index (LI) that varies between 1 and −1 (see Simos et al., 2009 for additional details). This task has been shown to localize activity within posterior language areas (i.e., in the vicinity of the superior and middle temporal gyri) in a number of empirical reports (e.g., Breier et al., 2001; Merrifield et al., 2007; Papanicolaou et al., 1999) including large samples of epilepsy patients (Papanicolaou et al., 2004), in both auditory and visual stimulus modalities (Papanicolaou et al., 2006) and in samples of non-English speakers.

As recently reviewed by Pirmoradi, Béland, Nguyen, Bacon, and Lassonde (2010), many other tasks have also been investigated for functionally mapping language functions with MEG. In addition to variants of the CRM task outlined above, they cite numerous other paradigms designed to either determine hemispheric language dominance or localize systems related to specific functions (Pirmoradi et al., 2010). These include: passive listening and counting paradigms (Kim & Chung, 2008; Martin et al., 1993; Szymanski et al., 2001; Szymanski, Rowley, & Roberts, 1999); grammatical or semantic categorization, matching, or judgment (Härle, Dobe, Cohen, & Rockstroh, 2002; Kamada et al., 2006, 2007; McDonald et al., 2009; Simos, Breier, Zouridakis, & Papanicolaou, 1998); and note/tone vs. vowel comparisons (Gootjes, Raij, Salmelin, & Hari, 1999; Kirveskari, Salmelin, & Hari, 2006).

Other reports have more explicitly examined neural systems involved in language output, via both isolated and combined studies of covert reading and picture naming (Breier et al., 2001; Hirata et al., 2010; Kober et al., 2001), delayed and overt naming (Fisher et al., 2008; Levelt, Praamstra, Meyer, Helenius, & Salmelin, 1998; Salmelin, Hari, Lounasmaa, & Sams, 1994) and reading (Salmelin, Schnitzler, Schmitz, & Freund, 2000), and delayed, covert, and overt word or verb generation tasks (Bowyer et al., 2005; Fisher et al., 2008; Pang, Wang, Malone, Kadis, & Donner, 2011; Ressel et al., 2006; Yamamoto et al., 2006). Despite over a decade of research, and many reliable findings, the MEG language and memory mapping literature is still at somewhat of an earlier stage of development than that of fMRI, owing largely to the smaller MEG community and the more recent maturation of well-delineated source modeling approaches and the availability of software tools.

Activation and Contrast Tasks

The source localization approach has been the dominant paradigm in MEG cognitive mapping for a number of years, with applications of imaging approaches emerging more recently. For studies utilizing ECDs the number of successive dipoles within a region of interest (or their difference between the hemispheres) has generally been utilized as a measure of the

"extent" of neural activation. The report of Bowyer et al. (2005) is one notable exception in that they utilized an imaging approach and the relative *duration* of activity within left- and right-hemisphere regions for calculating LIs, thereby highlighting the diverse metrics available for studying language lateralization with MEG. Given that focal source models necessarily spatially constrain what is presumably distributed activation (at least in the case of higher cognitive functions), source imaging and spatial filtering approaches naturally provide superior indices of the spatial distribution of language-related neural activity.

Contrast tasks have been utilized less frequently in MEG language research than in fMRI, though this trend is changing, especially with the wider application of source imaging models (e.g., Kamada et al., 1998; Kober et al., 2001; McDonald et al., 2009). Whereas changes in the BOLD signal are measured on the order of seconds, in many instances MEG paradigms are designed to detect only the inherently transient changes, which are thought to be more phase locked than time locked to stimulus presentation. This has been suggested as a reason for lack of correspondence with fMRI results (Liljeström, Hultén, Parkkonen, & Salmelin, 2009; Pang et al., 2011). Devising effective MEG contrasts is thus complicated by the additional dimension of time, since the timing of component neural processes might meaningfully differ depending on the features of probe and contrast tasks (Salmelin & Parkkonen, 2010). In such cases, a simple subtraction of contrast and probe task maps could lead to erroneous conclusions if the contrast does not optimally equate for processes peripheral to the study question (e.g., visual processing, attention) and in a way that does not alter their timing. As a solution to this issue, Levelt et al. (1998) argued that if the component processes of a given behavior can be separated into their temporal stages (i.e., object recognition, lexical access, etc., in the case of picture naming), one can manipulate any given stage and only alter the time course of the subsequent stages. The absence of activity in the subtraction maps at early latencies provides some assurance that probe and contrast tasks were well matched in terms of their perceptual attributes (McDonald et al., 2009). Finally, like fMRI, the extent of "activated" cortex detected by an MEG source model strongly depends on the nature of the task, modeling approach, and the statistical thresholds applied (Liljeström et al., 2009).

Behavioral Monitoring

Due to the large magnetic artifacts created by the facial muscles involved in speaking, overt language tasks present a challenge for monitoring spoken responses in MEG. Nonetheless, MEG has been successfully utilized for localizing both receptive and expressive aspects of language functions, including with paradigms that permit behavioral monitoring. A number of studies report localization of language-related activity without recording behavioral data (Hirata et al., 2010; Yamamoto et al., 2006) though most paradigms have utilized covert reading or naming in conjunction with manual responses to ensure accurate task performance. Some groups have utilized vigilance trials which are unrelated to the task, such as a randomly interspersed stimulus prompting a button press, to help ensure attention to the task. Overt and delayed responses have also been successfully collected in MEG studies (Salmelin et al., 1994), including for challenging contexts such as chronic stuttering (Salmelin et al., 2000).

Although behavioral monitoring is clearly desirable to ensure task compliance and/or equate for difficulty between conditions, functional language mapping has been less successful in individuals who are unable to comply with task demands. For this subset of patients, it would be advantageous to have paradigms capable of establishing hemispheric language dominance using tasks requiring minimal behavioral compliance. At least two reports have approached this by examining lateralization of the 100 ms auditory response (N100m) to speech sounds in a simple behavioral condition (Gootjes et al., 1999; Kirveskari et al., 2006). In these studies healthy subjects listened to pairs of tones or spoken vowel sounds and were asked to respond with a finger lift when they perceived that the two

stimuli were identical. This task is arguably minimally cognitively demanding. Nontarget sounds were analyzed and in both reports results demonstrated stronger N100m responses to speech sounds but not pure tones in the left compared to the right hemisphere, in right-handed subjects. The latter report also included weakly right-handed and left-handed subjects, and LIs showed trends for less left-lateralized N100m responses to speech sounds in the those groups; an effect that significantly differed between strong right-handers and left-handers (Kirveskari et al., 2006).

Separately, Kim and Chung (2008) employed an auditory oddball task involving two spoken monosyllabic words, with each being the standard and deviant stimulus, respectively. Participants were epilepsy patients who were merely asked to ignore the auditory stimuli and watch a movie during the recording, making no response to the spoken words. LIs generated from the oscillatory mismatch negativity response to deviant stimuli demonstrated 71 % concordance with Wada results for a posterior superior temporal gyrus ROI and between 76 % and 94 % concordance for a posterior inferior frontal gyrus ROI.

Episodic Memory

There have been relatively few MEG studies that have specifically examined memory functions in epilepsy. One study utilized a variant of the continuous recognition memory paradigm to examine medial temporal lobe activity in a group of healthy subjects and patients with left mesial temporal sclerosis (LMTS) (Ver Hoef, Sawrie, Killen, & Knowlton, 2008). The authors reasoned that since the performance of the CRM task involves both language and memory processes, the paradigm might elicit lateralized medial temporal lobe activity in addition to the robust activation it elicits in posterior temporal areas. A variant of the auditory CRM protocol was investigated in a final sample of six patients with LMTS and seven healthy controls, and a source localization approach involving clusters of dipoles was utilized. Across two runs of the CRM task, left mesial temporal dipole clusters were observed in the majority of control subjects but not LMTS patients (86 vs. 33 %). Conversely, right medial temporal dipole clusters were observed in all LMTS patients (100 %), relative to only 2 of 7 control subjects (28 %), with the difference being statistically significant. The direction of medial temporal LIs also significantly differed between groups, with patients demonstrating rightward mesial temporal laterality, relative to left lateralization in controls. Finally, patients and controls also significantly differed with regard to the number of runs on which each respective group showed right medial temporal activity (67 vs. 7 %).

Speaking to the validity of their findings, the authors noted that medial temporal activity always followed what was presumed to be language-related activity in posterior temporal areas and that both left and right medial temporal sources showed similar time courses. The results of this study are consistent with other research demonstrating abnormal lateralization of memory functions in LMTS (Richardson, Strange, Duncan, & Dolan, 2006) and provide evidence that the CRM elicits both perisylvian and medial temporal lobe activity.

Another report explicitly examined MEG data obtained from successful verbal memory encoding to identify a paradigm for determining hemispheric memory lateralization with MEG. Maestú et al. (2009) examined lateralization of medial temporal activity, along with other regions, in a group of nine epilepsy patients with left hippocampal sclerosis and nine age-matched controls (Maestú et al., 2009). The authors computed event-related averages from encoding trials presenting words later recalled following a delay and utilized a source localization approach to model the data. Among other findings, results demonstrated a group-by-hemisphere interaction for the medial temporal region of interest, where controls exhibited greater numbers of left medial temporal dipoles throughout the analysis window relative to patients. In addition, medial temporal LIs between controls and patients with hippocampal sclerosis significantly differed in a 400–600 ms latency window. Within-group analyses demonstrated significant rightward asymmetry in the patient group in an overlapping time window,

whereas controls showed a nonsignificant tendency toward leftward asymmetry. While just a handful of reports have explicitly investigated medial temporal activation in the context of epilepsy using MEG (Hanlon et al., 2003), these and similar studies are increasingly providing the "proof of principal" supporting a role for MEG in mapping medial temporal memory systems.

MEG Language Mapping in Presurgical Epilepsy Patients

The continuous recognition memory paradigm studied by Papanicolaou and colleagues has been the most widely investigated language task used in functional mapping in epilepsy. The largest of these studies assessed hemispheric dominance using the CRM paradigm in a group of 100 consecutive patients between the ages of 8 and 56 with medically intractable epilepsy (Papanicolaou et al., 2004). The task and analysis were performed according to the usual parameters utilized by this group, with 85 patients included in the final sample. MEG LIs were compared to Wada hemispheric dominance ratings and demonstrated 87 % concordance, with most discordant cases (7/11) being those where MEG showed significant bilateral activity while Wada showed left-hemisphere language dominance. There were no cases where MEG and Wada indicated language dominance solely in opposite hemispheres from one another. Compared to Wada-based ratings of language presence or absence in the operative hemisphere, the CRM procedure demonstrated specificity = 0.83, and sensitivity, and negative and positive predictive values all exceeding 0.91.

Other studies have examined the effect of variations to the CRM analysis procedures in smaller groups of epilepsy patients and controls. In one report, results showed that an average of four different data reduction techniques demonstrated the best sensitivity, specificity, and concordance with Wada (Merrifield et al., 2007). However, the strength of those results was diluted when data from several subjects with IQs below the average range were included. In another report, inter-rater and intersession reliability (separate same-day sessions) was assessed for the auditory CRM paradigm. Findings demonstrated overall inter-rater reliability = 0.88 for LIs derived from two different approaches to epoch selection prior to averaging, whereas intersession reliability ranged from 0.60 to 0.69 across raters (Lee, Sawrie, Simos, Killen, & Knowlton, 2006).

In addition to the numerous reports investigating variants of the CRM paradigm, other studies with substantial sample sizes have employed tasks such as visual word categorization (100 % concordance in 87 patients using combined MEG and fMRI data (Kamada et al., 2007), and silent reading (85 % using a frontal LI in 60 patients (Hirata et al., 2010), and also demonstrated good concordance between MEG hemispheric dominance and Wada. For a detailed review of MEG language studies and concordance with Wada, see Pirmoradi et al. (2010).

Overall, the recognition memory paradigm employed by Papanicolaou et al. (1999) has been the most rigorously validated of available MEG language paradigms. Whereas Wada testing has been considered the "gold standard" against which to compare MEG laterality assessments, the CRM in many ways could be considered the gold standard for MEG assessment of language laterality. It has a number of features to recommend it, including: the relative simplicity of the task, acquisition, and typical analysis protocols; a solid record of replicability within and across instruments and laboratories (Doss, Zhang, Risse, & Dickens, 2009; Lee et al., 2006) and in different stimulus modalities (Papanicolaou et al., 2004); and its high degree of concordance with Wada results in a large clinical sample of epilepsy patients.

While implementing any given mapping procedure involves accepting various tradeoffs, there are some areas in which other tasks could offer advantages over the CRM paradigm. Depending on the clinical needs of the specific context, these might include: stronger differentiation of language from memory processes, greater elicitation of sources outside of posterior temporal areas, more precise manipulation of task difficulty or stimulus features (Salmelin, 2007), and implementation of contrast tasks. Also, while not an inherent feature of the task, it is clear that source imaging and spatial fil-

tering approaches possess an inherent advantage over dipole-based source models for spatiotemporal mapping of language-related activity and other distributed cognitive functions. Finally, of particular importance to the presurgical epilepsy context, it has been reported that certain MEG language tasks elicit strong *bilateral* activation of posterior superior temporal sources, thereby biasing source localization approaches toward neglecting weaker, but lateralized activity in nearby anterior or ventral temporal regions (McDonald et al., 2009). Given the importance of anterior temporal lobe activation in particular to predicting surgical outcomes from functional imaging maps, this is likely to be an especially important direction for future paradigm development in MEG language mapping.

Assessing Postsurgical Change with MEG

Given the relative novelty of MEG language mapping research, little work has been done investigating its utility in predicting cognitive outcomes following surgery, and no large-scale studies have been conducted. However, in one study, Pataraia et al. (2005) examined pre- to postoperative changes in MEG language maps following left anterior temporal lobectomy in a sample of 12 patients with intractable epilepsy. Participants completed the CRM task prior to surgery and at a mean of 40 months postoperatively. Ten of the twelve patients were right-handed, and Wada testing indicated left-hemisphere language dominance in seven of them, with bilateral language representation in the remaining five. Preoperative dominance ratings obtained with the MEG CRM task suggested left-lateralized dominance in eight patients, with bilateral representation in four. MEG and Wada assessments were discordant (suggesting left and bilateral representation, respectively) in a single patient. Reliably obtained perisylvian sources were retained as putatively comprising Wernicke's area, and postoperative change in the location of language-related activity was defined as a 15 mm or greater displacement in the center of the reliable dipole cluster.

Postoperative MEG assessment suggested rightward shift of language representation in three of twelve patients, all of whom had shown bilateral language representation on the basis of preoperative Wada testing (two of whom were rated as having bilateral language dominance on the basis of preoperative MEG). In addition, postoperative MEG suggested an inferior displacement of language-related activity in the left-hemisphere region of interest in a subset (3 of 7) of patients who showed left-hemisphere language dominance based on the Wada, as well as in one patient with bilateral language representation preoperatively (both MEG and Wada). The small sample size precluded formal statistical comparisons of neuropsychological test performance across time points; however, the authors noted that in general those who showed left-hemisphere language dominance on MEG tended to perform better on verbal and performance IQ measures relative to those showing atypical lateralization.

The authors suggested that these findings implicate reorganization of posterior temporal language areas following anterior temporal resections and noted that the obtained displacements exceeded their previous estimates of intraindividual test-retest reliability. While additional research is likely needed to better understand the effects of surgical removal of language-related areas on MEG source localizations, studies such as this provide a foundation for future applications of MEG postoperative assessment.

Future Directions: Investigating Neuronal Connectivity, a Multimodal Approach and Contribution from MEG

Computational and conceptual advances in the last decade or so have greatly expanded MEG/EEG research beyond simply analyzing time-locked, event-related averages (Makeig, Debener, Onton, & Delorme, 2004). Clinical and academic investigators are increasingly recognizing the value that various time-frequency measures (e.g., event-related desynchronization, induced activity, intertrial/regional phase locking, cross-frequency coupling) can add to studies of cognition (for introductions see Canolty & Knight, 2010; Singer, 1999; Varela, Lachaux, Rodriguez &

Martinerie, 2001). These measures have broadened MEG analysis beyond conventional studies of time-locked averages and now enable observations of ongoing neural oscillations, single-trial analysis, and interregional connectivity. The various source modeling approaches outlined above have been integrated with these indices to varying degrees, and several reports listed here have successfully analyzed neural oscillatory activity for functional mapping (e.g., Hirata et al., 2010; Kim & Chung, 2008; Pang et al., 2011). Moving forward, integrating magnetic source analysis with emerging oscillatory measures will enable MEG to increase its contribution to the collaboration with fMRI and clinical neuropsychology in the successful evaluation, counseling, and surgical management of medically intractable epilepsy.

References

Attal, Y., Bhattacharjee, M., Yelnik, J., Cottereau, B., Lefévre, J., Okada, Y., et al. (2009). Modelling and detecting deep brain activity with MEG and EEG. *IRBM, 30*(3), 133–138.

Baillet, S. B. (2010). The dowser in the fields: Searching for MEG sources. In P. C. Hansen, M. L. Kringelbach, & R. Salmelin (Eds.), *MEG: An introduction to methods* (pp. 83–124). New York, NY: Oxford University Press.

Baillet, S., Mosher, J. C., & Leahy, R. M. (2001). Electromagnetic brain mapping. *IEEE Signal Processing Magazine, 18*, 16.

Bilder, R. M. (2011). Neuropsychology 3.0: Evidence-based science and practice. *Journal of the International Neuropsychological Society, 17*, 7–13.

Bowyer, S. M., Moran, J. E., Weiland, B. J., Mason, K. M., Greenwald, M. L., Smith, B. J., et al. (2005). Language laterality determined by MEG mapping with MR-FOCUSS. *Epilepsy and Behavior, 6*(2), 235–241.

Breier, J. I., Simos, P. G., Wheless, J. W., Constantinou, J. E., Baumgartner, J. E., Venkataraman, V., et al. (2001). Language dominance in children as determined by magnetic source imaging and the intracarotid amobarbital procedure: a comparison. *Journal of Child Neurology, 16*(2), 124–130.

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences, 14*(11), 506–515.

Carrette, E., De Tiege, X., De Beeck, M. O., De Herdt, V., Meurs, A., Legros, B., et al. (2011). Magnetoencephalography in epilepsy patients carrying a vagus nerve stimulator. *Epilepsy Research, 93*(1), 44–52.

Darvas, F., Rautiainen, M., Pantazis, D., Baillet, S., Mosher, J. C., Garnero, L., et al. (2005). Investigations of dipole localization accuracy in MEG using the bootstrap. *NeuroImage, 25*, 355–368.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9–21.

Doss, R. C., Zhang, W., Risse, G. L., & Dickens, D. L. (2009). Lateralizing language with magnetic source imaging: validation based on the Wada test. *Epilepsia, 50*(10), 2242–2248.

Feynman, R. P., Leighton, R. B., & Sands, M. L. (1964). *The Feynman lectures on physics* (Vol. 2). Readnig, MA: Addison-Wesley.

Fisher, A. E., Furlong, P. L., Seri, S., Adjamian, P., Witton, C., Baldeweg, T., et al. (2008). Interhemispheric differences of spectral power in expressive language: A MEG study with clinical applications. *International Journal of Psychophysiology, 68*(2), 111–122.

Frye, R. E., Rezaie, R., & Papanicolaou, A. C. (2009). Functional neuroimaging of language using magnetoencephalography. *Physics of Life Reviews, 6*(1), 1–10.

Gootjes, L., Raij, T., Salmelin, R., & Hari, R. (1999). Left-hemisphere dominance for processing of vowels: a whole-scalp neuromagnetic study. *Neuroreport, 10*(14), 2987–2991.

Hämäläinen, M., Hari, R., Ilmoniemi, R., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography – Theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65*, 413–497.

Hanlon, F. M., Weisend, M. P., Huang, M., Lee, R. R., Moses, S. N., Paulson, K. M., et al. (2003). A noninvasive method for observing hippocampal function. *NeuroReport, 14*(15), 1957–1960.

Hansen, P. C., Kringelbach, M. L., & Salmelin, R. (Eds.). (2010). *MEG: An introduction to methods*. Oxford: New York.

Härle, M., Dobe, C., Cohen, R., & Rockstroh, B. (2002). Brain activity during syntactic and semantic processing—A magnetoencephalographic study. *Brain Topography, 15*, 3–11.

Helenius, P., Parviainen, T., Paetau, R., & Salmelin, R. (2009). Neural processing of spoken words in specific language impairment and dyslexia. *Brain, 132*(7), 1918–1927.

Henson, R. N., Flandin, G., Friston, K. J., & Mattout, J. (2010). A parametric empirical Bayesian framework for fMRI-constrained MEG/EEG source reconstruction. *Human Brain Mapping, 31*(10), 1512–1531.

Hillebrand, A., & Barnes, G. R. (2002). A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. *NeuroImage, 16*(3 Pt 1), 638–650.

Hillebrand, A., Singh, K. D., Holliday, I. E., Furlong, P. L., & Barnes, G. R. (2005). A new approach to neuroimaging with magnetoencephalography. *Human Brain Mapping, 25*(2), 199–211.

Hirata, M., Goto, T., Barnes, G., Umekawa, Y., Yanagisawa, T., Kato, A., et al. (2010). Language dominance and mapping based on neuromagnetic

oscillatory changes: Comparison with invasive procedures. *Journal of Neurosurgery, 112*(3), 528–538.

Jerbi, K., Mosher, J. C., Baillet, S. B., & Leahy, R. M. (2002). On MEG forward modelling using multipolar expansions. *Physics in Medicine and Biology, 7*(4), 532–555.

Kamada, K., Kober, H., Saguer, M., Möller, M., Kaltenhäuser, M., & Vieth, J. (1998). Responses to silent Kanji reading of the native Japanese and German in task subtraction magnetoencephalography. *Cognitive Brain Research, 7*(1), 89–98.

Kamada, K., Sawamura, Y., Takeuchi, F., Kuriki, S., Kawai, K., Morita, A., et al. (2007). Expressive and receptive language areas determined by a non-invasive reliable method using functional magnetic resonance imaging and magnetoencephalography. *Neurosurgery, 60*(2), 296–305. discussion 305–306.

Kamada, K., Takeuchi, F., Kuriki, S., Todo, T., Morita, A., & Sawamura, Y. (2006). Dissociated expressive and receptive language functions on magnetoencephalography, functional magnetic resonance imaging, and amobarbital studies. Case report and review of the literature. *Journal of Neurosurgery, 104*(4), 598–607.

Kaufmann, L., & Lu, Z. (2003). Basis of neuromagnetism and magnetic source imaging. In Z. Lu & L. Kaufmann (Eds.), *Magnetic source imaging of the human brain*. Mahwah, NJ: Lawrence Erlbaum Associates, Inc.

Kim, J. S., & Chung, C. K. (2008). Language lateralization using MEG beta frequency desynchronization during auditory oddball stimulation with one-syllable words. *NeuroImage, 42*(4), 1499–1507.

Kirveskari, E., Salmelin, R., & Hari, R. (2006). Neuromagnetic responses to vowels vs. tones reveal hemispheric lateralization. *Clinical Neurophysiology, 117*(3), 643–648.

Kober, H., Moller, M., Nimsky, C., Vieth, J., Fahlbusch, R., & Ganslandt, O. (2001). New approach to localize speech relevant brain areas and hemispheric dominance using spatially filtered magnetoencephalography. *Human Brain Mapping, 14*(4), 236–250.

Kringelbach, M. L., Jenkinson, N., Green, A. L., Owen, S. L. F., Hansen, P. C., Cornelissen, P. L., et al. (2007). Deep brain stimulation for chronic pain investigated with magnetoencephalography. *NeuroReport, 18*(3), 223–228. 210.1097/WNR.1090b1013e328010dc328013d.

Leahy, R. M., Mosher, J. C., Spencer, M. E., Huang, M. X., & Lewine, J. D. (1998). A study of dipole localization accuracy for MEG and EEG using a human skull phantom. *Electroencephalography and Clinical Neurophysiology, 107*(2), 159–173.

Lee, D., Sawrie, S. M., Simos, P. G., Killen, J., & Knowlton, R. C. (2006). Reliability of language mapping with magnetic source imaging in epilepsy surgery candidates. *Epilepsy and Behavior, 8*(4), 742–749.

Levelt, W. J., Praamstra, P., Meyer, A. S., Helenius, P., & Salmelin, R. (1998). An MEG study of picture naming. *Journal of Cognitive Neuroscience, 10*(5), 553–567.

Liljeström, M., Hultén, A., Parkkonen, L., & Salmelin, R. (2009). Comparing MEG and fMRI views to naming actions and objects. *Human Brain Mapping, 30*(6), 1845–1856.

Lin, F.-H., Belliveau, J. W., Dale, A. M., & Hämäläinen, M. S. (2006). Distributed current estimates using cortical orientation constraints. *Human Brain Mapping, 27*(1), 1–13.

Lin, F.-H., Witzel, T., Ahlfors, S. P., Stufflebeam, S. M., Belliveau, J. W., & Hämäläinen, M. S. (2006). Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates. *NeuroImage, 31*(1), 160–171.

Lopes da Silva, F. H. (2010). Electrophysiological basis of MEG signals. In M. L. Kringelbach, P. C. Hansen, & R. Salmelin (Eds.), *MEG: An introduction to methods* (pp. 1–23). New York, NY: Oxford University Press.

Maestú, F., Campo, P., García-Morales, I., del Barrio, A., Paul, N., del Pozo, F., et al. (2009). Biomagnetic profiles of verbal memory success in patients with mesial temporal lobe epilepsy. *Epilepsy and Behavior, 16*(3), 527–533.

Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Science, 8*(5), 204–210.

Makela, A. M. (2010). The use of MEG in clinical settings. In M. L. Kringelbach, P. C. Hansen, & R. Salmelin (Eds.), *MEG: An introduction to methods* (pp. 373–402). New York, NY: Oxford University Press.

Martin, N. A., Beatty, J., Johnson, R. A., Collaer, M. L., Viñuela, F., Becker, D. P., et al. (1993). Magnetoencephalographic localization of a language processing cortical area adjacent to a cerebral arteriovenous malformation. *Journal of Neurosurgery, 79*(4), 584–588.

Martin, T., Houck, J. M., Bish, J. P., Kičić, D., Woodruff, C. C., Moses, S. N., et al. (2006). MEG reveals different contributions of somatomotor cortex and cerebellum to simple reaction time after temporally structured cues. *Human Brain Mapping, 27*(7), 552–561.

McDonald, C. R., Thesen, T., Hagler, D. J., Jr., Carlson, C., Devinksy, O., Kuzniecky, R., et al. (2009). Distributed source modeling of language with magnetoencephalography: Application to patients with intractable epilepsy. *Epilepsia, 50*(10), 2256–2266.

Merrifield, W. S., Simos, P. G., Papanicolaou, A. C., Philpott, L. M., & Sutherling, W. W. (2007). Hemispheric language dominance in magnetoencephalography: Sensitivity, specificity, and data reduction techniques. *Epilepsy and Behavior, 10*(1), 120–128.

Miller, G. A., Elbert, T., Sutton, B. P., & Heller, W. (2007). Innovative clinical assessment technologies: Challenges and opportunities in neuroimaging. *Psychological Assessment, 19*(1), 58–73.

Mosher, J. C., Spencer, M. E., Leahy, R. M., & Lewis, P. S. (1993). Error bounds for EEG and MEG dipole source localization. *Electroencephalography and Clinical Neurophysiology, 86*, 303–321.

Murakami, S., & Okada, Y. (2006). Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *The Journal of Physiology, 575*(Pt 3), 925–936.

Okada, Y. C., Lahteenmäki, A., & Xu, C. (1999). Experimental analysis of distortion of magnetoencephalography signals by the skull. *Clinical Neurophysiology, 110*(2), 230–238.

Pang, E. W., Wang, F., Malone, M., Kadis, D. S., & Donner, E. J. (2011). Localization of Broca's area using verb generation tasks in the MEG: Validation against fMRI. *Neuroscience Letters, 490*(3), 215–219.

Papanicolaou, A. C., Pazo-Alvarez, P., Castillo, E. M., Billingsley-Marshall, R. L., Breier, J. I., Swank, P. R., et al. (2006). Functional neuroimaging with MEG: Normative language profiles. *NeuroImage, 33*(1), 326–342.

Papanicolaou, A. C., Simos, P. G., Breier, J. I., Zouridakis, G., Willmore, L. J., Wheless, J. W., et al. (1999). Magnetoencephalographic mapping of the language-specific cortex. *Journal of Neurosurgery, 90*(1), 85–93.

Papanicolaou, A. C., Simos, P. G., Castillo, E. M., Breier, J. I., Sarkari, S., Pataraia, E., et al. (2004). Magnetocephalography: A noninvasive alternative to the Wada procedure. *Journal of Neurosurgery, 100*(5), 867–876.

Pataraia, E., Billingsley-Marshall, R. L., Castillo, E. M., Breier, J. I., Simos, P. G., Sarkari, S., et al. (2005). Organization of receptive language-specific cortex before and after left temporal lobectomy. *Neurology, 64*(3), 481–487.

Pirmoradi, M., Béland, R., Nguyen, D. K., Bacon, B. A., & Lassonde, M. (2010). Language tasks used for the presurgical assessment of epileptic patients with MEG. *Epileptic Disorders, 12*(2), 97–108.

Ramirez, R. R., Kopell, B. H., Butson, C. R., Gaggl, W., Friedland, D. R., & Baillet, S. (2009). *Neuromagnetic source imaging of abnormal spontaneous activity in tinnitus patient modulated by electrical cortical stimulation*. Minneapolis, MN: Annual International Conference of the IEEE Engineering in Medicine and Biology Society.

Ressel, V., Wilke, M., Lidzba, K., Preissl, H., Krägeloh-Mann, I., & Lutzenberger, W. (2006). Language lateralization in magnetoencephalography: Two tasks to investigate hemispheric dominance. *NeuroReport, 17*(11), 1209–1213. 1210.1097/1201.wnr.0000230506.0000232726.be.

Richardson, M. P., Strange, B. A., Duncan, J. S., & Dolan, R. J. (2006). Memory fMRI in left hippocampal sclerosis. *Neurology, 66*(5), 699–705.

Riggs, L., Moses, S. N., Bardouille, T., Herdman, A. T., Ross, B., & Ryan, J. D. (2009). A complementary analytic approach to examining medial temporal lobe sources using magnetoencephalography. *NeuroImage, 45*(2), 627–642.

Salmelin, R. (2007). Clinical neurophysiology of language: The MEG approach. *Clinical Neurophysiology, 118*(2), 237–254.

Salmelin, R., & Baillet, S. (2009). Electromagnetic brain imaging. *Human Brain Mapping, 30*(6), 1753–1757.

Salmelin, R., Hari, R., Lounasmaa, O. V., & Sams, M. (1994). Dynamics of brain activation during picture naming. *Nature, 368*(6470), 463–465.

Salmelin, R., & Parkkonen, L. (2010). Experimental design. In M. L. Kringelbach, P. C. Hansen, & R. Salmelin (Eds.), *MEG: An introduction to methods* (pp. 75–82). New York, NY: Oxford University Press.

Salmelin, R., Schnitzler, A., Schmitz, F., & Freund, H. J. (2000). Single word reading in developmental stutterers and fluent speakers. *Brain, 123*(6), 1184–1202.

Simos, P. G., Breier, J. I., Zouridakis, G., & Papanicolaou, A. C. (1998). Assessment of functional cerebral laterality for language using magnetoencephalography. *Journal of Clinical Neurophysiology, 15*(4), 364–372.

Simos, P. G., Papanicolaou, A. C., Castillo, E. M., & Buchanan, D. S. (2009). Evoked magnetic fields. In A. C. Papanicolaou (Ed.), *Clinical magnetoencephalography and magnetic source imaging*. Cambridge: Cambridge University Press.

Singer, W. (1999). Neuronal synchrony: A versatile code for the definition of relations? *Neuron, 24*(1), 49–65.

Szymanski, M. D., Perry, D. W., Gage, N. M., Rowley, H. A., Walker, J., Berger, M. S., et al. (2001). Magnetic source imaging of late evoked field responses to vowels: Toward an assessment of hemispheric dominance for language. *Journal of Neurosurgery, 94*(3), 445–453.

Szymanski, M. D., Rowley, H. A., & Roberts, T. P. (1999). A hemispherically asymmetrical MEG response to vowels. *Neuroreport, 10*(12), 2481–2486.

Tanaka, N., Thiele, E. A., Madsen, J. R., Bourgeois, B. F., & Stufflebeam, S. M. (2009). Magnetoencephalographic analysis in patients with vagus nerve stimulator. *Pediatric Neurology, 41*(5), 383–387.

Varela, F., Lachaux, J. P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience, 2*(4), 229–239.

Ver Hoef, L. W., Sawrie, S., Killen, J., & Knowlton, R. C. (2008). Left mesial temporal sclerosis and verbal memory: A magnetoencephalography study. *Journal of Clinical Neurophysiology, 25*(1), 1–6. doi:10.1097/WNP.1090b1013e318163a318166c318160.

Vrba, J., & Robinson, S. E. (2001). Signal processing in magnetoencephalography. *Methods, 25*(2), 249–271.

Wehner, D. T., Hämäläinen, M. S., Mody, M., & Ahlfors, S. P. (2008). Head movements of children in MEG: Quantification, effects on source estimation, and compensation. *NeuroImage, 40*(2), 541–550.

Wolters, C. H., Anwander, A., Tricoche, X., Weinstein, D., Koch, M. A., & MacLeod, R. S. (2006). Influence of tissue conductivity anisotropy on EEG/MEG field and return current computation in a realistic head model: A simulation and visualization study using high-resolution finite element modeling. *NeuroImage, 30*, 813–826.

Wu, J. Y., Salamon, N., Kirsch, H. E., Mantle, M. M., Nagarajan, S. S., Kurelowech, L., et al. (2010). Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex. *Neurology, 74*(5), 392–398.

Yamamoto, M., Ukai, S., Shinosaki, K., Ishii, R., Kawaguchi, S., Ogawa, A., et al. (2006). Spatially filtered magnetoencephalographic analysis of cortical oscillatory changes in basic brain rhythms during the Japanese 'Shiritori' Word Generation Task. *Neuropsychobiology, 53*(4), 215–222.

Evaluation of Psychiatric and Personality Disorders

10

Jana E. Jones

Psychiatric Comorbidity in Epilepsy

Historical Perspective

Throughout history, epilepsy has been viewed as being caused by evil possession, a curse, and even as a divine intervention by God. Hippocrates, in *The Sacred Disease* written in 400 BC, first suggested that epilepsy was a disease with a natural cause, not a divine cause. During the Greco-Roman era, the term "lunatic" was used to describe individuals with epilepsy separate from "maniacs" who were possessed by evil (Hill, 1981). In the Middle Ages, epilepsy was viewed as mystical, magical, or caused by possession of evil spirits, and this view remained as the most prominent cause of epilepsy until the seventeenth and eighteenth centuries (Temkin, 1971).

In the mid- to late nineteenth century with the emergence of neurology from psychiatry (Reynolds & Trimble, 2009), Hughlings Jackson (1931) described epilepsy as "occasional, sudden excessive, rapid and local discharges of gray matter". In France, Briquet (1859) and Morel (1860) identified psychological disturbances as occurring as part of the seizure itself (ictal) and between seizures (interictal) resulting in cognitive and behavioral dysfunction. Gowers (1881) described the difference between epileptic convulsions and nonepileptic convulsions. In Europe with the development of institutions and hospitals for the insane, individuals with epilepsy were sent to these institutions and were treated by psychiatry until the twentieth century (Reynolds & Trimble, 2009). In the 1940s and 1950s after the EEG began to be used clinically, the temporal lobe focus in epilepsy was identified in 1949, and with the increased understanding of the limbic system, it was often anticipated that people with epilepsy would also have psychological problems. By the 1960s the World Health Organization (WHO) classified epilepsy as a neurological disorder, not a psychiatric disorder due to the identification of preictal, ictal, postictal, and interictal psychiatric symptoms (Reynolds & Trimble, 2009).

Around that time, a study in England reported that 29 % of individuals with epilepsy had psychological issues (Pond & Bidwell, 1960). In Iceland, Gudmundsson (1966) found that 50 % of the sample had psychological or personality changes with more psychological problems associated with brain lesions. Similarly Graham and Rutter (1968) reported a higher rate of psychiatric disorders among individuals with brain lesions and/or mental retardation. Currently, it is understood that there are a complex number of factors including biological, medication, and social

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factors that influence the expression of psychopathology in epilepsy (LaFrance, Kanner, & Hermann, 2008; Swinkels, Kuyk, van Dyck, & Spinhoven, 2005). Today, it is commonly understood that people with epilepsy are at a higher risk for psychiatric disorders compared to the general population (LaFrance et al., 2008), and this was exemplified by Fisher et al. (2005) proposing that the definition of epilepsy includes the coexistence of psychiatric disorders.

Axis I Psychiatric Disorders in Epilepsy

The prevalence of psychiatric disorders ranges from 19 % to 80 % (Swinkels et al., 2005). Swinkels and collaborators (2005) attribute the variability in rates to heterogeneity of samples and lack of control groups. Additionally, very few of these studies are population based, and as a result, many studies are based on tertiary care center samples possibly biasing the sample with more severe forms of epilepsy and higher rates of psychiatric disorders (Lacey, Salzberg, Roberts, Trauer, & D'Souza, 2009). Finally, different methodologies have been utilized to measure the presence or absence of psychiatric comorbidity in epilepsy including medical record reviews, self-report measures, psychiatric interviews, and self-identifying as having a particular psychiatric disorder. Davies, Heyman, and Goodman (2003) and Tellez-Zenteno, Patten, Jette, Williams, and Wiebe (2007) utilized community-based samples and similar interview-based methodologies and reported lower rates of psychiatric comorbidity (37 and 23.5 %, respectively).

The most prevalent psychiatric diagnoses in epilepsy include mood disorders, anxiety disorders, and psychotic disorders. Depression is the most common psychiatric disorder in epilepsy with lifetime prevalence rates reported from 20 to 60 %, which is consistently higher than the general population with lifetime prevalence rates of 16–20 % (Kessler et al., 2005). In community-based samples, Ettinger, Reed, and Cramer (2004) used the Center for Epidemiologic Studies Depression Scale (CES-D) and found that 36 % of the sample endorsed symptoms of depression, while Mensah, Beavis, Thapar, and Kerr (2006) used the Hospital Anxiety and Depression Scale (HADS) and reported that 11.2 % endorsed symptoms of depression. Based on the Clinical Interview Schedule (CIS), Edeh and Toone (1987) reported that 22 % of their sample met criteria for depression. Tellez-Zenteno et al. (2007) utilized the Composite International Diagnostic Interview (CIDI) and reported that 17.4 % of their sample had depression. Adding to the complexity of psychiatric comorbidity in epilepsy, Hesdorffer, Hauser, Annegers, and Cascino (2000) and Hesdorffer, Hauser, Olafsson, Ludvigsson, and Kjartansson (2006) reported that individuals with a history of depressive disorders or suicidal behavior were at increased risk to develop epilepsy overtime, indicating that there may be a bidirectional relationship between psychiatric disorders and epilepsy.

When compared to depression, anxiety disorders are less common in the general population with lifetime prevalence rates ranging from 1.9 to 5.1 % (Wittchen et al., 2002; Wittchen, Zhao, Kessler, & Eaton, 1994). However, anxiety disorders are thought to be the second most common psychiatric disorder in epilepsy with prevalence rates ranging from 11 to 40 %. In a multicenter study, 174 consecutive adults were interviewed using the Mini International Neuropsychiatric Interview (MINI), and 30 % of the sample met criteria for an anxiety disorder (Jones et al., 2003). Based on the CIDI, Swinkels, Kuyk, de Graaf, van Dyck, and Spinhoven (2001) reported that in a sample of 209 individuals with epilepsy, 24.9 % had anxiety disorders. Kobau, Gilliam, and Thurman (2006) reported that 39 % of the population-based sample had an anxiety disorder based on self-report.

Psychotic disorders are also more frequent in people with epilepsy compared to the general population (~3 %) (Perala et al., 2007) with some studies reporting rates as high as 10 % (LaFrance et al., 2008). As part of a chart review in a population-based health survey in Sweden, Forsgren (1992) reported that schizophrenia and psychosis were prevalent in 0.8 and 0.7 %, respectively. Utilizing International Classification of Diseases 9 (ICD-9) criteria, Stefansson,

Olafsson, and Hauser (1998) found that 1.2 % of the sample had schizophrenia and 6.2 % had psychosis. Using similar criteria, Gaitatzis, Trimble, and Sander (2004) in the United Kingdom reported the prevalence of schizophrenia as 0.7 % and prevalence of psychosis as 9 %.

In summary, in spite of the fact that different methodologies and samples have been used, there is significant evidence to support the overall conclusion that there are higher rates of Axis I disorders among individuals with epilepsy when compared to the general population.

Axis II Personality Disorders in Epilepsy

In epilepsy, little research has been conducted on the prevalence and types of Axis II disorders or personality disorders common in people with epilepsy. There are a number of studies using the Minnesota Multiphasic Personality Inventory (MMPI) to identify personality dysfunction in epilepsy, but the use of this instrument in epilepsy has been criticized (Provinciali, Franciolini, del Pesce, & Signorino, 1989), and for purposes of this chapter, the MMPI-based literature in epilepsy will not be reviewed. Additionally, very few studies have been conducted utilizing the Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD diagnostic criteria to identify and classify personality disorders in epilepsy. In a small sample of individuals with epilepsy ($n=21$) and controls with other neurological conditions ($n=24$), Schwartz and Cummings (1988) reported that 38 % of the individuals with epilepsy met DSM-III criteria for a personality disorder and only 4 % of controls. Fiordelli, Beghi, Bogliun, and Crespi (1993) evaluated 100 individuals with epilepsy seen in an outpatient clinic compared to 100 controls using the Clinical Interview Schedule (CIS) and DSM-IIIR diagnostic criteria. Only 4 % of individuals with epilepsy and no controls meet criteria for personality disorders. Victoroff, Benson, Grafton, Engel, and Mazziotta (1994) utilized the Structured Clinical Interview for DSM (SCID) to assess 60 surgery candidates and identified 18.33 % as meeting criteria for a personality disorder. Similarly Manchanda et al. (1996) assessed 300 epilepsy surgery candidates using DSM-IIIR criteria and found that 18.3 % had personality disorders with the primary disorders in Cluster C. In a much smaller sample using the SCID, Arnold and Privitera (1996) reported that among 27 people with epilepsy, 18 % were identified with personality disorders, of which avoidant personality disorder was the most common type. Based on the SCID-II, Lopez-Rodriguez et al. (1999) found that 21 % of 52 individuals evaluated for surgery had personality disorders particularly those in Cluster C. In a sample of individuals with epilepsy ($n=35$) and individuals with nonepileptic seizures ($n=10$), Krishnamoorthy, Brown, and Trimble (2001) found that among individuals with epilepsy, 17 % had personality disorders from Cluster A and 17 % from Cluster C.

Similar to the general population, Axis II disorders are less prevalent compared to Axis I disorders. The above studies indicated that approximately 18 % of the samples met criteria for a personality disorder. Additionally, Cluster C personality disorders appear to be a more common personality disorder in epilepsy. In the worldwide population, prevalence estimates indicate that 6.1 % have any personality disorder and of those 3.6 % are Cluster A, 1.5 % are Cluster B, and 2.7 % are Cluster C (Huang et al., 2009). Cluster A personality disorders include odd or eccentric characteristics and correspond to paranoid, schizoid, and schizotypal personality disorders. Cluster B personality disorders are described as dramatic, emotional, and erratic and include antisocial, borderline, narcissistic, and histrionic personality disorders. Cluster C personality disorders are those disorders that are considered anxious or fearful and include avoidant personality disorder, dependent personality disorder, and obsessive-compulsive personality disorder.

In a voxel-based morphometry (VBM) study, using the SCID-II, de Araujo Filho et al. (2009) examined the relationship between personality disorders, specifically Cluster B, juvenile myoclonic epilepsy (JME), and structural brain abnormalities. Significant reductions in the thalamus and increases in the mesioprefrontal and

frontobasal region volumes were reported in individuals with JME and personality disorders. Since the orbitofrontal cortex is believed to be involved in mood reactivity, impulsivity, and social behavior and is considered to be dysfunctional in individuals with Cluster B personality disorders, the authors hypothesized that there is some indication there may be neuronal dysfunction impacting the development of seizures and personality disorders.

There have been a few personality disorder studies that have compared individuals with epilepsy to those individuals with nonepileptic psychogenic events (NES). In a study by Harden et al. (2009) using the SCID-II, individuals with NES were compared to individuals with epilepsy in order to identify the complex personality problems associated with NES and epilepsy. Individuals with NES were significantly more likely to have Cluster A and B diagnoses compared to individuals with epilepsy who were more likely to present with Cluster C diagnoses. Additionally, Kuyk, Swinkels, and Spinhoven (2003), using the CIDI, compared individuals with NES to individuals with NES and epilepsy. Among individuals with NES, somatoform disorders were more common, and those with combined NES and epilepsy were more likely to present with personality disorders with significantly higher rates of Cluster C disorders.

Similar to Axis I disorders, Axis II disorders appear to be common in individuals with epilepsy. However, the research in this area is somewhat limited and additional population-based studies in epilepsy need to be conducted.

Diagnostic Issues in Epilepsy (Preictal, Ictal, Postictal, Interictal, AEDs, Surgery)

When evaluating psychopathology in epilepsy, it is important to determine if there is a relationship between the psychiatric symptoms and the seizure itself. The most common symptoms associated with seizures are depression, anxiety, and psychosis. Typically, preictal depressive symptoms are reported as a dysphoric mood and may be present from hours to 1–3 days before a seizure (Blanchet & Frommer, 1986). Kanner, Soto, and Gross-Kanner (2004) systematically studied postictal symptoms of depression in individuals with refractory partial seizures and found that depressive symptoms were present 50 % of the time and lasted for a median duration of 24 h and occurred in 43 % of the sample. The most frequently reported depressive symptoms in the ictal phase include anhedonia, guilt, and suicidal ideation. Mood changes are typically brief, stereotypical, and followed by a change in consciousness as the ictus moves from a simple to complex partial seizure (LaFrance et al., 2008). Additionally, an interictal form of depression, interictal dysphoric disorder, has been described in the literature and is reported to be present in about 30 % of individuals with epilepsy and mood disorders. The symptoms are often described as chronic dysthymic symptoms that are variable and can be mixed with periods of euphoria, irritability, anxiety, paranoid feelings, and somatic symptoms (Blumer & Altshuler, 1998).

Symptoms of anxiety and fear are the most commonly reported ictal psychiatric symptoms. It can be the sole or predominant clinical symptom of a partial seizure or aura. It is usually believed to originate in the temporal lobe. Ictal panic can also be present. Ictal panic is short in duration lasting only 30 s; it is stereotypical in presentation, is out of context with the situation, and is often associated with confusion, altered consciousness, and automatisms. In 25 % of individuals with ictal panic, interictal panic attacks are also reported (Vazquez & Devinsky, 2003).

Ictal psychotic symptoms typically occur in the context of nonconvulsive status and are often accompanied by automatisms and unresponsiveness. An EEG will assist in confirming that the psychotic symptoms are ictal phenomenon. Postictal psychotic disorders in epilepsy typically have a short duration from hours to a few days and occur in 7 % of individuals with partial epilepsy (Kanner, 2004). The first symptom is often insomnia, and this is followed by symptoms that are often affective and delusional. An increase in secondarily generalized seizures, seizure duration of more than 10 years, and bilateral focus are

risk factors for postictal psychotic episodes associated with epilepsy (LaFrance et al., 2008). Following a temporal lobectomy, new cases of psychotic disorders have been reported in 3.8–35.7 % of the surgical cases (Trimble, 1992), and some have hypothesized that this is related to the concept of "forced normalization" (Akanuma et al., 2005), which is believed to occur following the normalization of the EEG and subsequent appearance of psychotic symptoms.

Antiepileptic drugs (AEDs) can cause psychiatric symptoms (McConnell & Duncan, 1998). The GABAergic properties of some AEDs, like phenobarbital, primidone, benzodiazepines, tiagabine, and vigabatrin, can cause depressive symptoms. Additionally some of the newer AEDs also cause depressive symptoms including felbamate, topiramate, levetiracetam, and zonisamide (Kanner, 2003). Finally, depressive symptoms are associated with the discontinuation of some AEDs, and these medications include carbamazepine, valproic acid, and lamotrigine (Ketter et al., 1994).

Mood and anxiety disorders have been associated with the surgical treatment of epilepsy and primarily with anterior temporal lobectomy. Symptoms often present during the first 3–12 months following surgery. Depressive episodes are more likely to occur in individuals with a history of mood disorders. However, it is possible for there to be a complete remission of a mood disorder associated with a remission of seizures from surgery. Devinsky et al. (2005) reported that depression and anxiety improved after surgery in a group of patients with improved seizure control. Altshuler, Rausch, Delrahim, Kay, and Crandall (1999) reported that among individuals with temporal lobe epilepsy, 77 % had a history of depression prior to surgery, and 50 % had a remission in depressive symptoms following surgery. Only 10 % reported de novo depressive disorders after surgery.

It is important to have a clear understanding of the psychiatric symptoms that are present prior to, during, and after the seizure occurs. The relationship between the psychiatric symptoms and the seizure needs to be identified so that an appropriate diagnosis can be made.

Impact of Psychiatric Disorders in Epilepsy on QOL, Psychosocial Factors, and Healthcare Utilization

Psychiatric disorders can negatively impact overall psychosocial functioning and quality of life among individuals with epilepsy. Several studies have demonstrated the negative effect of depression on quality of life. Using the BDI, Gilliam (2002) reported that the more symptoms of depression independently correlated with lower health-related quality of life when seizure frequency did not. Cramer, Blum, Reed, and Fanning (2003) found that depression, as measured by the CES-D, negatively impacted quality of life regardless of seizure type. Additionally, it was reported that even mild levels of depression had a negative impact on health-related quality of life. Also using the BDI, Boylan et al. (2004) found that in treatment resistant epilepsy, depression was a significant predictor of poorer quality of life compared to seizure variables which had little impact on quality of life. Finally, Johnson, Jones, Seidenberg, and Hermann (2004) reported that depression and anxiety disorders were independently more powerful predictors of lower quality of life than seizure variables like frequency and severity.

When examining psychosocial outcomes, a number of studies have identified a link between symptoms of depression and psychosocial status. Among individuals with epilepsy, Reisinger and DiIorio (2009) reported that unemployment, social support, and stigma were related to higher rates of depressive symptoms, as measured by the CES-D. Lee, Lee, and No (2009) found that social support, unemployment, anxiety, and self-efficacy were predictors of increased depressive symptoms as measured by the BDI. Grabowska-Grzyb, Jedrzejczak, Naganska, and Fiszer (2006) also examined the relationship between depression and psychosocial factors in individuals with epilepsy. They found that unemployment and low educational attainment were significant predictors of depressive symptoms as measured by the BDI and Ham-D. The authors discussed the high prevalence rates of unemployment and depression in people with epilepsy and indicated that it

was difficult to understand if this significant relationship with unemployment was secondary to depression or separate from depression. Depression is known to have a negative impact on all facets of life including family, work, school, and friends, making it difficult to determine which came first.

The impact of psychiatric comorbidity in epilepsy on healthcare utilization has been examined in a few studies. Cramer, Blum, Fanning, and Reed (2004) reported that depression in epilepsy contributed to increased healthcare utilization. Based on the CES-D, depression, not seizure type, increased medical and psychiatric visits but did not increase emergency room visits or total hospital days. In a community-based sample of 652 individuals with epilepsy, Lacey et al. (2009) examined levels of psychological distress in a sample as measured by the Kessler 10 (K10) to see if there was a relationship between psychological distress and healthcare utilization. High levels of distress were reported in 24 % of the sample with epilepsy, and this was elevated compared to the general population (13 %). Individuals with epilepsy and high to very high levels of distress had significantly more visits to the general practitioner, hospital outpatient clinic, and emergency department compared to those with low to moderate distress. Additionally, individuals treated only by a specialist or in combination with a general practitioner had higher levels of distress compared to those who were treated solely by a general practitioner.

Conclusion

In summary, psychiatric comorbidity in epilepsy has adverse consequences on many life outcomes, making it a priority to identify and provide appropriate treatment to individuals with epilepsy who are doubly impacted by seizures and psychiatric disorders. Psychiatric comorbidity has been recognized as a priority and is listed as a Research Benchmark in the National Institute of Neurological Disorders and Stroke (NINDS) (Kelley, Jacobs, & Lowenstein, 2009). Additionally, with the recent alert in 2008 issued by the US Food and Drug Administration (FDA) that indicated that AEDs increased suicidal risk, there is a heightened urgency and awareness to assess and treat individuals with epilepsy and comorbid psychiatric conditions in order to reduce the risk of suicidal ideation and suicide in this population (US Department of Health and Human Services, May 21, 2008). As clinicians working with and providing services to people with epilepsy, it important for us to understand the implications and impact of psychiatric comorbidity in epilepsy. It is increasingly part of our responsibility to assess, identify, and provide recommendations for treatment of psychiatric disorders in this population.

Measures for Identifying Psychiatric and Personality Disorders in Epilepsy

There is a vast array of diagnostic tools available to assess and identify psychiatric disorders. These tools range from self-report measures to structured interviews. A select subset has been used in epilepsy both clinically and in research. In the following summary, a number of instruments used to assess psychiatric disorders are described; reliability and validity of each measure is presented; utility and information regarding how to find each instrument is included.

Semi-structured Interviews for Psychiatric Disorders

Diagnostic Interview Schedule-IV (Robins, Marcus, Reich, Cunningham, & Gallagher, 1996) and Composite International Diagnostic Interview (CIDI) (Robins et al., 1988)

Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). The CIDI is a highly structured interview designed for lay interviewers to assess current and lifetime psychiatric disorders based on the diagnostic criteria. The Diagnostic Interview Schedules (DIS, DIS-IV) were the precursors for the CIDI which was developed to be used across cultures in epidemiological

studies and provides ICD-10 and DSM-IV criteria. CIDI Version 3.0 (Kessler & Üstün, 2004) includes 22 diagnoses, clinical significance criteria, and a clinical severity measure. A screening section is administered first. Both of these instruments are administered by reading verbatim questions with a predetermined set of responses arranged by diagnostic sections. Clinical exploration of responses is limited to probe questions, and interviewers are discouraged from rephrasing misunderstood questions.

Reliability: *DIS-IV*: No reliability studies have been conducted with English-speaking interviewers. There are no reliability studies of the computerized version of the DSI (C-DIS). *CIDI*: Field trials indicated good test-retest reliability with agreement rates over 85 %. Joint reliability for all diagnoses was 97 %.

Validity: *DIS-IV*: Eaton, Neufeld, Chen, and Cai (2000) reported poor agreement between the DIS-IV and Schedules for Clinical Assessment in Clinical Neuropsychiatry (SCAN) in the diagnosis of major depression ($\kappa = 0.20$) and a sensitivity of only 29 %. *CIDI:* The CIDI 3.0 was reported to have high agreement with SCID diagnoses in field trials in France, Italy, Spain, and the United States.

Utility: These instruments may be difficult to use in a clinical setting due to the complexity of the interviews and time required to complete the interviews (90 min to 2 h). These interviews help to identify significant diagnoses and help determine the progression and duration of clinically significant symptoms and disorders. Both of these instruments provide diagnostic reliability.

How to find it: *DIS-IV*: This instrument is no longer available in paper and pencil. It is only available in a computerized format (C-DIS). A license for the C-DIS can be obtained from http://epi.wustl.edu/dis/dishome.htm. A license is required for each project and the license is valid for the duration of the project. *CIDI:* There is a computer-based interview as well as a paper and pencil version. CIDI 3.0 information can be obtained from http://www.hcp.med.harvard.edu/wmhcidi/index.php. Training is required in order to obtain a copy of the CIDI 3.0 Computer-Assisted Personal Interview (CAPI) and to use the Paper and Pencil (PAPI) and its scoring algorithm. Training occurs at the University of Michigan once or twice a year. The website provides costs, contact information, and computer system and software requirements.

Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) is a structured diagnostic interview that was developed in order to provide a brief diagnostic evaluation of the most common mental disorders identified by epidemiological studies. The MINI was designed to be shorter and less intensive than traditional diagnostic interviews used in academic research, and it was to be more thorough than the diagnostic interviews used in primary care settings. It can be used in multicenter clinical trials and epidemiological studies. The MINI utilizes DSM-IV and ICD-10 criteria for diagnoses and as a result can be used internationally. There are two versions: the MINI and the MINI Plus. The MINI contains 19 modules evaluating 17 Axis I disorders (major depressive disorder, dysthymic disorder, mania, panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, generalized anxiety disorder, alcohol dependence and abuse, drug dependence and abuse, psychotic disorder, anorexia nervosa, bulimia, and PTSD). The MINI Plus contains 8 more disorders (hypochondriasis, body dysmorphic disorder, pain disorder, conduct disorder, attention-deficit/hyperactivity disorders, adjustment disorder, premenstrual dysphoric disorder, and mixed anxiety-depressive disorder) and provides rule outs, subtyping, and chronology (Sheehan et al., 1997).

Reliability: A high level of inter-rater reliability has been reported with κ values all above 0.75 and 70 % of the κ values were above 0.90 (Sheehan et al., 1997). The κ values ranged from 0.79 for current mania to 1.00 for major depressive disorder, obsessive-compulsive disorder, current alcohol dependence, anorexia, and bulimia. Test-retest reliability was also good with 61 % of the κ values above 0.75.

Validity: Sheehan et al. (1998) reported that agreement between the MINI and SCID-P was good with 73 % of the κ values 0.60 or greater. Only one disorder had a κ value less than 0.50 (current drug dependence $\kappa = 0.43$). Additionally, agreement between the MINI and CIDI was good with 64 % of the κ values above 0.60. There were two disorders with κ values under 0.50 (simple phobia ($\kappa = 0.43$) and generalized anxiety disorder ($\kappa = 0.36$)).

Utility: The mean time for administration of the MINI is 18 min with a median of 15 min. The MINI takes more time to administer than the PRIME-MD but is significantly shorter than the SCID or CIDI. The MINI has been used in clinical trials, epidemiological investigations, as well as outpatient and inpatient settings. The MINI has been translated into 40 different languages. It requires 2 h of training for psychiatrists and psychologists and 3 h for general practitioners.

How to find it: Free copies of the MINI are available from the MINI website at www.medical-outcomes.com. There is an electronic version of the MINI which can be purchased.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 2002) is a clinician-administered semi-structured interview to be used with nonpatients in the community or psychiatric patients. It was developed to cover a wide range of psychiatric diagnoses based on the DSM-IV. The SCID-I starts with an overview section that addresses demographic information, work history, chief complaint, present and past history of psychiatric illness, treatment history, and current functioning. There are nine diagnostic modules, including Mood Episodes, Psychotic Symptoms, Psychotic Disorders Differential, Mood Disorders Differential, Substance Use, Anxiety, Somatoform Disorders, Eating Disorders, and Adjustment Disorders. Modules can be omitted to focus on areas of diagnostic interest. Two versions of the measure are available: SCID-I Research Version (First et al., 2002) which comes in three editions, SCID-I/P for psychiatric patients, SCID-I/NP for nonpatients, and SCID-I/P with Psychotic Screen for psychiatric patients who do not need a full psychotic disorder assessment, and the SCID-CV Clinical Version (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) which covers only common diagnoses seen in clinical practice with simplified Mood Disorders and Substance Use Disorder modules.

Reliability: The test-retest reliability of the SCID-I for DSM-IV was excellent to good ($\kappa = 0.44$–0.78) with one exception ($\kappa = 0.35$ for dysthymia). Interrater reliability was excellent for alcohol abuse/dependence, other substance abuse/dependence, PTSD, major depressive disorder, eating disorder, and dysthymia and fair to good for generalized anxiety, obsessive-compulsive disorder, panic disorder, and social phobia.

Utility: The SCID-I is a user-friendly clinician-administered interview but can require a significant amount of time to complete. It may take an hour or less to administer the entire SCID-I to individuals with little or no psychopathology. More complicated psychiatric histories will likely extend the interview significantly. The SCID-I requires the interviewer to be trained and have clinical knowledge of psychopathology and psychiatric diagnosis.

How to find it: The Research Version of the SCID-I, user's guide, and training videos can be obtained from www.scid4.org. The SCID-CV is published by American Psychiatric Publishing: voice, 800-368-5777, or Web, www.appi.org.

Questionnaires for Psychiatric Disorders

General Health Questionnaire (GHQ) (Goldberg, 1972; Goldberg & Williams, 1991) is a screening instrument used to assess psychiatric distress related to general medical illness. It does not provide a psychiatric diagnosis but rather a screening instrument to determine if further evaluation is required. The GHQ has a threshold score indicating 95 % probability that criteria will be met for a psychiatric disorder. The GHQ was designed

to evaluate psychological stress and ill health. It assesses the individual's ability to carry out daily functions and identifies the development of new psychiatric symptoms not lifelong personality characteristics. The GHQ is a paper and pencil, self-administered questionnaire. There are four officially recognized versions: 60 items, 30 items, 28 items, and 12 items. The GHQ-30 is considered a better measure of psychological distress because it excludes items present in physical illness. It takes 3–15 min to complete depending upon which version is utilized.

Reliability: Good internal consistency was demonstrated on the 60-, 30-, and 12-item versions with Cronbach α coefficients from 0.82 to 0.93 and split-half coefficients from 0.78 to 0.95. The test-retest reliability appears to be the best for the 28-item version ($r = 0.90$).

Validity: The manual reports adequate content validity with each item having discrimination between those who are psychologically distressed and those who are not. The GHQ scores have been shown to correlate with psychiatric diagnoses based on structured interviews ($r = 0.65$–0.70). All versions demonstrated acceptable sensitivity and specificity with the 60-item version demonstrating the best specificity (89 %).

Utility: The GHQ has been used in a variety of clinical settings. It has been translated into 36 different languages. It is useful in screening for general emotional distress but should not be used for a diagnosing a specific disorder.

How to find it: The four different versions of the GHQ and manual are available from nferNelson: toll free, +44 845 602 1037; email, information@nfer-nelson.co.uk; or Web, www.nfer-nelson.co.uk.

Kessler 10 (K10) and Kessler 6 (K6) (Kessler et al., 2002, 2003) are 10-item and 6-item self-report measures, respectively, that are used to produce a global measure of nonspecific psychological distress. They are based on questions of nervousness, agitation, psychological fatigue, and depression (e.g., feeling so sad that nothing can cheer you up) during the past 30 days. Responses are based on a 5-category Likert scale: all of the time, most of the time, some of the time, a little of the time, and none of the time. These scales were developed based on modern item response theory methods to improve the precision of the scales. This results in a dimensional measure of nonspecific distress in the range found in clinical samples in order to maximize the ability to discriminate cases of serious mental illness from noncases. The K10 and K6 scales were developed to be used in the US National Health Interview Survey (NHIS). The K10 was used in the National Comorbidity Survey Replication as well as in all the national surveys in the World Health Mental Health (WMH) Initiative. The K10 has been translated into 15 different languages.

Reliability: Internal consistency is high for both measures. The Cronbach α is reported to be 0.93 for the K10 and 0.89 for the K6.

Validity: The sensitivity of both measures ranges from 90th to the 99th percentile. A small validation study indicated that the six-item scale is as sensitive as the ten-item scale for distinguishing serious mental illness from noncases. The K10 and K6 have been shown to outperform the GHQ-12 (Furukawa, Kessler, Slade, & Andrews, 2003). The K6 has been shown to be more consistent in samples with physical disabilities.

Utility: It can be easily completed in 2–3 min. The K10 and K6 have been demonstrated to identify cases of anxiety and depression based on DSM-IV criteria. Additionally, the K10 and K6 can be used to measure secondary outcomes of nonspecific impairments as indicated by the Global Assessment of Functioning (GAF).

How to find it: It is one of the projects in the National Comorbidity Survey Harvard Medical School. Web, http://www.hcp.med.harvard.edu/ncs/k6_scales.php.

Minnesota Multiphasic Personality Inventory (MMPI-2) (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989; Butcher, Graham, Ben-Porath,

Tellegen, & Dahlstrom, 2001) is a self-report inventory developed to assess and diagnose psychopathology in adults. The current edition has been restandardized using a contemporary normative sample. The 13 clinical and validity scales are only minimally changed compared to the original version. The MMPI-2 contains 567 true or false items presented in a random order with the first 370 items used for the clinical and validity scales. The basic syndrome scales are as follows: Hypochondriasis (Hs), Depression (D), Hysteria (Hy), Psychopathic Deviate (Pd), Schizophrenia (Sc), Hypomania (Ma), Masculinity-Femininity (MF), Social Introversion (Si), Lie (L), Infrequency (F), and Correction (K). A sixth grade reading level is recommended to complete the MMPI-2, and it typically takes 1–1.5 h to complete.

Reliability: Internal consistency estimates (Cronbach α coefficients) range from 0.34 to 0.87 for the basic scales.

Validity: Over 10,000 references support the validity of the standard scales of the MMPI and MMPI-2 in an array of applications that include psychiatric, general medical, forensics, and vocational assessments. Convergent validity is thought to be stronger than discriminant validity.

Utility: The MMPI has been used most often in psychiatric inpatient and outpatient settings as a screening instrument, but it has also been used quite extensively in medical, neurological, forensic, and vocational settings. The MMPI-2 is quite lengthy and requires a significant amount of time to complete. Additionally, the MMPI is quite complex and may limit its use in busy clinical settings.

How to find it: The manuals, questionnaires, computer versions, scoring, and interpretive services are available from Pearson Assessments: voice, 800-627-7271; email, pearsonassessments@pearson.com; or Web, www.pearsonassessments.com.

Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Zimmerman & Mattia, 1999) is a self-administered 126-item questionnaire developed to screen for 13 of the most common DSM-IV Axis I disorders in outpatient mental health settings. These include eating disorders, mood disorders, anxiety disorders, substance use disorders, and somatoform disorders. It is comprehensive yet can be completed in approximately 15 min before a clinic visit. It has a quick and easy scoring format that can be completed by administrative staff. In order to be used in the most valuable manner, the clinician should review the results prior to the interview with the patient so that the clinician can follow up to confirm any diagnoses identified by the instrument.

Reliability: The PDSQ has a moderate to high internal consistency (mean Cronbach $\alpha = 0.82$ and all subscale $\alpha > 0.70$ with one exception of bulimia [0.69]). Good test-retest reliability was reported with a mean = 0.84 and all subscale r values over 0.70.

Validity: Discriminant and convergent validity were good. High correlations were reported with other measures of the same construct (mean correlation = 0.72).

Utility: This is brief screener that allows for the identification of principal and secondary diagnoses.

How to find it: Western Psychological Services: voice, 800-648-8857; email, customerservice@wpspublish.com; or Web, www.wpspublish.com.

Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1994; Derogatis, Lipman, & Covi, 1973) is a 90-item self-administered questionnaire, and it takes 12–20 min to complete. A sixth grade reading level is recommended. Respondents are instructed to report how much discomfort each item caused them during the past week. The opening stem for each item reads, "How much were you distressed by…" Respondents mark one numbered circle for each item on a Likert-type scale: 0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, and 4 = extremely. Raw scores and *T*-scores are provided for each of the nine dimensions: Somatization, Obsessive-Compulsive,

Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. Global indexes are calculated: Global Severity Index (mean of all items), Positive Symptom Total (number of items with nonzero scores), and Positive Symptom Distress Index (symptom severity). Additionally, there is a shorter 53-item version, Brief Symptom Inventory (BSI), which is derived from the SCL-90-R (Derogatis, 1993; Derogatis & Melisaratos, 1983).

Reliability: Coefficients of internal consistency range from 0.77 to 0.90 in a sample of psychiatric outpatients and symptomatic volunteers.

Validity: Studies have supported better convergent validity than divergent validity. The nine primary symptom dimensions of the SCL-90-R correlated significantly in a convergent fashion with similar score constructs on the MMPI. Correlations between the depression subscale on the SCL-90-R and the Beck Depression Inventory (BDI) ranged from 0.73 to 0.80.

Utility: The SCL-90-R has been used in diverse populations as a screening instrument for global psychological distress and a multidimensional measure of symptom profiles. The questionnaire may be used as a onetime assessment or repeatedly to document changes over time or to quantify pretreatment and posttreatment outcomes. Normative data is available for the following groups: adult nonpatients, adult psychiatric outpatients, and adult psychiatric inpatients. Adolescents as young as 13 can complete this questionnaire, and there are separate norms for this age group.

How to find it: This instrument is copyrighted by Leonard R. Derogatis, Ph.D., with all rights reserved. The manuals, questionnaires, computer versions, scoring, and interpretive services are available from Pearson Assessments: voice, 800-627-7271; email, pearsonassessments@pearson.com; or Web, www.pearsonassessments.com.

Questionnaires for Specific Psychiatric Disorders

Mood Disorders

Beck Depression Inventory (BDI, BDI-II) (Beck, Steer, & Brown, 1996; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was designed to assess behavioral symptoms of depression in adolescents and adults (Beck et al., 1961) and to monitor changes in symptoms over time. It contained a series of statements with a value assigned to each statement. Twenty-one behavioral symptoms were assessed. The BDI-II (Beck et al., 1996) was modified to reflect DSM-IV criteria and simplify wording. Four items were dropped (body image change, work difficulty, weight loss, somatic preoccupation) and four items were added (agitation, worthlessness, loss of energy, concentration difficulties), and the time frame was changed from "right now" to in "the last 2 weeks." It takes 5–10 min to complete. The most recent guidelines suggest the following interpretation of the scores: 0–13 minimal, 13–19 mild, 20–28 moderate, and 29–63 severe. Scores can also be calculated for somatic-affective factor and a cognitive factor. It is available in English and Spanish versions.

Reliability: The BDI-II reports high internal consistency (Cronbach's α of 0.93 in college students and 0.92 in outpatients).

Validity: Beck et al. (1996) reported a correlation of 0.71 with the Ham-D in outpatients. The BDI-II had a sensitivity of 94 % and a specificity of 92 % in diagnosing major depression when a cutoff score of 18 was used (Arnau, Meagher, Norris, & Bramson, 2001).

Utility: The BDI-II is recommended to be used in a previously diagnosed population to monitor depressive symptoms over time. The BDI-II may also be used to screen for depressive symptoms in undiagnosed individuals, but it is recommended that a diagnostic or clinical interview occur to diagnose the individual. It is a very easy to use,

understand, and score. In medical populations it is recommended to use the lower scores as the cutoff scores (13–19 mild).

How to find it: This scale is copyrighted and can be obtained from Harcourt Assessment: voice, 800-211-8378, or Web, http://harcourtassessment.com.

Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) was developed to assess symptoms of depression in community populations. The items were selected to capture major components of depression based on the literature and factor analytic studies and include the following: depressed mood, worthlessness, hopelessness, loss of appetite, poor concentration, and sleep disturbance. The scale is a comprised of 20 items selected primarily from the Zung SDS, BDI, and Minnesota Multiphasic Personality Inventory Depression Scale (MMPI-D). Scores range from 0–60 and scores 16 or higher identify individuals with depressive disorders. It takes 5 min to administer. It has been translated into a number of languages including Chinese (Mandarin and Cantonese), French, Greek, Japanese, and Spanish.

Reliability: Internal consistency was high among different populations with Cronbach α ranging from 0.85 in community samples to 0.90 in psychiatric samples. Split-half reliabilities ranged from 0.77 to 0.92.

Validity: Concurrent validity of the CES-D and the SCL-90-R depression subscale revealed high correlation coefficients ($r = 0.73$–0.89) in several different groups of outpatients. Correlations with the Ham-D were somewhat variable ranging from 0.49 for patients with acute depression to 0.85 for patients with schizophrenia.

Utility: The CES-D was developed to measure depression in community-based samples. Studies do not support its use to assess depression in community populations but rather this measure should be used as a screening instrument with further evaluation needed if the scores are elevated.

How to find it: The CES-D is part of the public domain and was published in its entirety by Radloff (1977).

Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) was designed to assess the severity of depressive symptoms in individuals with primary depression. This measure was designed to quantify symptom severity prior to treatment, monitor the effects of treatment, and identify the recurrence of symptoms. It is the most frequently used observer-rated depressive symptom rating scale. Since validity studies have been conducted on populations with major depressive disorders, applying it to other patient populations could be problematic. The Ham-D has 21 items, but it is recommended that only the first 17 items be scored because the final four symptoms occur infrequently. It takes about 15–20 min to administer. The Ham-D uses a list of items on a scale of 0–4 or 0–2 with 4 indicating greater severity. The scoring thresholds are as follows: >23 very severe, 19–22 severe, 14–18 moderate, 8–13 mild, and <7 normal. The Ham-D is to be administered by physicians, psychologists, and social workers with experience with psychiatric patients. It was originally designed to be scored with two interviewers rating the same subject, but this is rarely used.

Reliability: Reliability of the Ham-D is generally acceptable. Internal consistency ranges from 0.76 to 0.92. Joint reliability ranges from 0.65 to 0.90 for the total score.

Validity: The Ham-D has correlations with global measures of depression ranging from 0.65 to 0.90. Validity is not high in older patients with general medical conditions.

Utility: The total score of the Ham-D is used to gauge the degree of symptom severity among individuals who are depressed. It is useful to monitor change in symptoms after the introduction of an intervention. It should be administered by a trained interviewer. The Ham-D was developed before the DSM-III and thus does not include a number of symptoms that are required for the diagnosis of major depression. It gives

more weight to somatic symptoms than to cognitive symptoms.

How to find it: The most commonly used form of the Ham-D is the ECDEU form, and it is a modified version of the original Ham-D (Guy, 1976).

Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) (Gilliam et al., 2006) is a validated 6-item questionnaire for depression in individuals with epilepsy. It can be used to rapidly and reliably detect depression in a busy clinical setting. Additionally, the NDDI-E has demonstrated an ability to differentiate symptoms of depression from those of medication toxicity and cognitive effects of epilepsy. A Likert scale is used to rate symptom frequency and ratings ranging from always or often, sometimes, rarely to never. A cutoff score of greater than 15 demonstrated optimal sensitivity, specificity, and predictive power. There are no items related to sadness or irritability, and this may be related to the fact that a number of studies have indicated that people with epilepsy often report hopelessness, anhedonia, and frustration, not sadness or a depressed mood.

Reliability: Internal consistency was good (Cronbach $\alpha = 0.85$). Test-retest reliability was also good (0.78).

Validity: Construct validity was high for the BDI ($r = 0.78$) and the CES-D ($r = 0.77$).

Utility: The NDDI-E was found to have a unique role in assessing depression in epilepsy.

How to find it: The NDDI-E is in the public domain. See Gilliam et al. (2006) for questionnaire and scoring instructions.

Zung Self-Rating Depression Scale (Zung SDS) (Zung, 1965) is a self-report measure of depression severity. Items were included to assess affective, cognitive, behavioral, and physiological symptoms of depression. The items were selected based on factor analytic studies and diagnostic criteria. It contains 20 items, ten items negatively worded and ten items positively worded. The time frame used is the present. The Zung SDS takes 5 min but can take additional time to complete depending on the population being assessed. A total severity score is reported, and the scores are interpreted in the following ranges: <50 within the normal range, 50–59 mild depression, 60–69 moderate depression, and ≥70 severe depression.

Reliability: Split-half reliability in psychiatric populations was reported to have a correlation of $r = 0.73$. In a community-based study, Cronbach α was good (0.79).

Validity: The Zung SDS scores discriminate between depressed and nondepressed samples (Zung, 1965). A significant correlation ($r = 0.65$) was reported with the MMPI-D. It is less sensitive to changes in symptoms over time.

Utility: The Zung SDS is often used to rate the severity of depressive symptoms in people with diagnosed depressive illness. The best results are reported in samples with mild to moderate symptoms of depression. It has been used in primary care and the community, but it is not a very good measure to be used as a screening tool for depression.

How to find it: The Zung SDS and instructions are presented in full in the original article (Zung, 1965).

Anxiety Disorders

Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988) is designed to assess anxiety and focuses on somatic symptoms. It was developed to discriminate between anxiety and depression. It is a 21-item self-report measure of symptoms present within the past week, and items include typical symptoms of anxiety, including nervousness, inability to relax, dizziness, light-headedness, and heart pounding or racing. It takes about 5 min to complete. The total score ranges from 0 to 63 and scores 0–9 are normal, 10–18 mild to moderate, 19–29 moderate to severe, and 30–63 severe anxiety.

Reliability: The BAI has high internal consistency with Cronbach α ranging from 0.90 to 0.94 in psychiatric inpatients, outpatients, undergraduates, and adults in the community.

Validity: The BAI correlates highly with the STAI ($r=0.47$–0.58) and the anxiety subscale of the SCL-90-R ($r=0.81$). However, correlations with instruments that measure depressive symptoms are also high: BDI ($r=0.62$) and depression subscale of the SCL-90-R ($r=0.62$). The BAI is able to discriminate between individuals with anxiety disorders and individuals with depression and nonclinical control subjects.

Utility: It is an easily administered and scored instrument. It is typically used to monitor changes with treatment. It has also been used as a screening measure for symptoms of anxiety in the general medical setting.

How to find it: This scale is copyrighted and can be obtained from Harcourt Assessment: voice, 800-211-8378, or Web, http://harcourtassessment.com.

Generalized Anxiety Disorder 7 (GAD-7) (Spitzer, Kroenke, Williams, & Lowe, 2006) is a brief seven-item self-report measure used to identify one of the most common anxiety disorders—generalized anxiety disorder (GAD). This is one of only a few anxiety measures that is specifically related to the DSM-IV criteria. Responses are based on a 4-category Likert scale: not at all, several days, more than half the days, and nearly every day. A cutoff score of greater than 10 identifies cases of GAD. A score of 5 indicates mild, 10 moderate, and 15 severe levels of anxiety. Additionally, a statement assessing the level of impairment at work, home, and people is included.

Reliability: The GAD-7 internal consistency was excellent with a Cronbach $\alpha=0.92$. Test-retest reliability was also good with an intraclass correlation of 0.83.

Validity: Convergent validity was good as demonstrated by the significant correlations with the BAI and the anxiety subscale of the SCL-90-R ($r=0.72$ and $r=0.74$, respectively). The GAD-7 was strongly associated with functional impairments with increasing scores, demonstrating good construct validity.

Utility: The GAD-7 allows for identification of cases of GAD. It also allows for the assessment of symptom severity, and increasing scores are associated with functional impairment and disability days. The GAD-7 can also be used to monitor change over time, but there is limited evidence of its ability to detect change over time.

How to find it: The GAD-7 is in the public domain. See Spitzer et al. (2006) for questionnaire and scoring instructions.

Penn State Worry Questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990) was developed to assess trait symptoms of pathological worry. It was designed to evaluate the propensity of an individual to worry, the excessiveness of the worry, and the tendency for the worry to be generalized and not focused on a small number of situations. This scale assesses the three DSM-IV criteria for generalized anxiety disorder, including the duration of the worry at least 6 months, excessiveness of the worry, and generalized symptoms. It contains 16 items and measures the frequency and intensity of worry symptoms. It can be administered in 5 min. It utilizes a Likert scale from 1 = not at all typical to 5 = very typical. Individuals with generalized anxiety typically score ≥ 60, and individuals with anxiety disorders score about 10 points lower, and their score is higher than individuals who are not anxious. Notably, individuals in a major depressive episode score as high as those with generalized anxiety.

Reliability: A high degree of internal consistency has been demonstrated in several populations with Cronbach α ranging from 0.86 to 0.93 for individuals diagnosed with anxiety and 0.91 to 0.95 for community samples.

Validity: In clinical samples, the PSWQ was weakly correlated with Hamilton Anxiety Rating

Scale, the trait scale of the STAI and the Zung SDS; the correlation coefficients ranged from 0.02 to 0.18. The PSWQ has demonstrated to measure worry symptoms distinctly different from obsessive-compulsive symptoms measured by the Padua Inventory (PI).

Utility: The PSWQ is a brief measure of worry in generalized anxiety. It is used as a measure of severity of pathological worry, and it can be used to monitor change over time. It can be used as a screen for pathological worry, but it should not be used to diagnose generalized anxiety disorder because worry can accompany other disorders (OCD, depression). It also does not assess frequency, intensity, content, or degree of control of the worry or anxiety, which are required for a diagnosis.

How to find it: The PSWQ is in the public domain and may be obtained by contacting Thomas Borkovec, Ph.D., Department of Psychology, Pennsylvania State University. Voice, 814-863-1725, or email, tdb@psu.edu.

State Trait Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970) Form *Y* is used to measure anxiety in adults. Form *X* was the first version of the measure. There is a child form available. The STAI differentiates between the temporary "state anxiety" and more long-standing "trait anxiety." The STAI contains forty questions and is written on a sixth grade reading level. It utilizes a 4-point Likert scale and provides three scores: state anxiety, trait anxiety, and overall anxiety. It has been translated into 48 languages and is one of the most commonly used instruments to measure anxiety.

Reliability: According to the test-retest correlations provided by Spielberger et al. (1970), the correlations are as follows: $r = 0.54$ (state) and 0.86 (trait).

Validity: In terms of concurrent validity, the STAI-state and STAI-trait were found to be positively correlated with the Taylor Manifest Anxiety Scale ($r = 0.80$) and the Multiple Affect Checklist (0.52).

Utility: The STAI can assist in the clinical diagnosis of anxiety, and it can help differentiate anxiety from depression. It has been used in psychological and health research. It has been used in a wide array of settings, including medical, surgical, and psychiatric.

How to find it: Mind Garden Inc. 855 Oak Grove Ave., Suite 215, Menlo Park, CA 94025. Voice, (650) 322-6300, or Web, http://www.mindgarden.com.

Semi-structured Interviews for Personality Disorders

Diagnostic Interview for the DSM-IV Personality Disorders (DIPD-IV) (Zanarini, Frankenburg, Chauncey, & Gunderson, 1987; Zanarini, Frankenburg, & Sickel, 1996) categorically assesses personality disorders based on the DSM-IV, and it is organized based on the criteria for each personality disorder. The interview also contains 108 sets of yes/no and open-ended questions, and each criterion is indicated by 0 = absent or clinically insignificant, 1 = present but uncertain clinical significance, 2 = present and clinically significant, or NA if not applicable. Traits or behaviors must be characteristic of the person throughout the person's adulthood.

Reliability and validity: The DIPD-IV appears to have good psychometric data. It has been used in a multisite study on the validity of personality disorder diagnosis. Inter-rater reliability kappa coefficients ranged from $\kappa = 0.58$ to 1.00 (Zanarini et al., 2000). Few studies have been conducted to examine the reliability and validity of this instrument.

Utility: The DIPD-IV requires 90 min to complete. This instrument requires the interviewer to be trained and have clinical knowledge of psychopathology, psychiatric diagnosis, and personality disorders and can be administered by someone with a bachelor's degree with at least one year of clinical training. The manual has limited information on administration and scoring. A Spanish version of this instrument is available.

How to find it: The DIPD-IV, training videos, and workshops are available by contacting Mary C. Zanarini, Ed.D., Director, Laboratory for the Study of Adult Development, McLean Hospital, (voice 617-855-2660; email zanarini@mclean.harvard.edu).

International Personality Disorder Examination (IPDE) (Loranger, Sartorius, Andreoli, & Berger, 1994) is a semi-structured interview that categorically and/or dimensionally assesses personality disorders based on DSM-IV and/or ICD-10. The IPDE was developed based on the World Health Organization and National Institutes of Health field trials on personality disorders. It contains two versions: a DSM-IV-based version that contains 99 sets of questions and an ICD-10 module that contains 67 sets of questions. The questions are organized in the following domains: work, self, interpersonal relationships, affect, reality testing, and impulse control. A true/false screening questionnaire is available for both versions to help reduce interview time by omitting items that are less likely to be present. The IPDE is a well-established Axis II semi-structured interview.

Reliability: The IPDE has demonstrated good inter-rater reliability and temporal stability.

Utility: The average administration time is 90 min. The self-administered screening questionnaire is written on a 4th grade reading level and takes less than 15 min to complete, reducing the overall interview time. It is recommended that the IPDE be administered by experienced clinicians. Training workshops are available. The thematic format of the IPDE may be easier for patients because there are fewer redundancies since it is organized by common issues and themes rather than diagnostic criteria.

How to find it: The DSM-IV module, ICD-10 module, screen, manual, scoring sheets, and optional computer scoring program can be obtained from Psychological Assessment Resources: voice, 800-331-8378, or Web, www.parinc.com.

Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First et al., 1997) is a clinician-administered semi-structured interview to assess DSM-IV personality disorders. The SCID-II starts with a screening questionnaire with 119 yes/no questions to identify the personality disorders that need to be examined further in the SCID-II interview. Each criterion is indicated by 1 = absent/false, 2 = subthreshold, 3 = threshold/true, or ? = inadequate information. Personality disorders are assessed categorically and/or dimensionally.

Reliability: The reliability coefficients reported are good. However, there is some concern that the queries used are insufficient compared to other instruments that assess personality disorders.

Utility: The SCID-II is a user-friendly clinician-administered interview and requires 90 min to complete. The SCID-II requires the interviewer to be trained and have clinical knowledge of psychopathology, psychiatric diagnosis, and personality disorders.

How to find it: The SCID-II manual is published separately from the SCID-I. The manual, interview, screen, and scoring sheets can be obtained from American Psychiatric Publishing: voice, 800-368-5777; email, appi@psych.org; or Web, www.appi.org. A computer-administered version is available through Multi-Health Systems: voice, 800-456-3003, or Web, www.mhs.com.

Questionnaires for Personality Disorders

Minnesota Multiphasic Personality Inventory-2 Personality Disorder Scales (MMPI-2 PD) (Somwaru & Ben-Porath, 1995) were developed to assess symptoms of personality disorders that could be extracted from the MMPI-2. These scales would allow for a dimensional assessment of the 10 DSM-IV personality disorders using the standard MMPI-2. Morey, Waugh, and Blashfield (1985) created 11 scales to assess each of the

personality disorders in the DSM-III, and when the MMPI-2 was published, several items in these scales were deleted. Somwaru and Ben-Porath (1995) developed a new set of subscales based on the DSM-IV; over 60 % of the items in these new subscales were not included in the Morey et al. (1985) scales.

Reliability: The internal consistency is reported to be above 0.85, which is an improvement over the Morey et al. (1985) scales which were reported to be 0.74 (Hicklin & Widiger, 2000).

Validity: Hicklin and Widiger (2000) reported that the Somwaru and Ben-Porath scales are as valid as the Morey et al. (1985) scales with stronger convergent validity reported for Antisocial, Borderline, and Schizoid dimensions. Additionally, Rossi, Van den Brande, Tobac, Sloore, and Hauben (2003) found that the MMPI-2 PD scales had comparable convergent validity with similar scales on the Millon Clinical Multiaxial Inventory-III (MCMI-III).

Utility: The MMPI-2 PD scales provide dimensional assessment of 10 DSM-IV personality disorders including the following: paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, and obsessive-compulsive. Since the MMPI-2 PD is derived from the standard MMPI-2, a significant amount of data can be obtained by using this one instrument.

How to find it: In order to obtain the MMPI-2 items and scoring instructions for the MMPI-2 PD, contact: Yossef S. Ben-Porath, Ph.D., Kent State University, voice, 330-672-2684, or email, ybenpora@kent.edu.

NEO Personality Inventory-Revised (NEO-PI-R) (Costa & MCCrae, 1992) was designed to assess the five major domains of personality from the five-factor model of personality which includes: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. Within each domain there are six facets of personality and each facet is measured by eight items on a 5-point scale. This is a 240-item self-administered questionnaire, and it also has a parallel form that can be completed by a peer, spouse, or expert rater. There is also a short form that contains 60 items and provides scores for the five domains only. Profiles are based on gender and age. There are two age groups based on the normative samples: college age (17–20 years) and adults (21 years and older).

Reliability: Internal consistency coefficients (Cronbach's α) for both forms ranged from 0.86 to 0.95. Test-retest reliability ranged from 0.63 to 0.83 for the five domains on both forms.

Validity: High correlations between the domain scores and facet scores (0.89–0.95) were reported by the authors.

Utility: It takes 35–40 min to complete. A Spanish version is available. The NEO-PI-R is a measure of the five factors of normal personality traits. It can be used to assess personality attributes and their impact on overall functioning. The manual suggests that the NEO-PI-R can be used in selecting treatments, vocational counseling, and industrial and organizational consulting.

How to find it: The NEO-PI-R is copyrighted and can be purchased by contacting Psychological Assessment Resources: voice, 800-331-8378, or Web, www.parinc.com.

Personality Assessment Inventory (PAI) (Morey, 1991) was developed to assess clinical syndromes, personality features, and treatment complications. The PAI contains 344 items producing 22 scales, of which 10 are divided into 31 subscales. There are 4 validity scales, 11 clinical, 2 interpersonal, and 5 treatment related. The 11 clinical scales contain 2 scales that assess personality features including the following: borderline features (affective instability, identity problems, negative relationships with others, and impulsive self-harm) and antisocial features (antisocial behaviors, egocentricity, and poor empathy).

Reliability: Internal consistency coefficients in various samples were all reported to be above 0.80 for full scales and 0.70 for subscales.

Median test-retest reliability coefficients range from 0.77 to 0.80.

Validity: Morey (1991) reported that the Dominance scale correlated ($r = 0.71$) highly with the Assertiveness Facet of the NEO-PI. Differences between gender, race, and age were reported to be small.

Utility: It takes 40–50 min to complete the PAI. It was developed for adults 18 years and older with a 4th grade reading level. There is a Spanish version. The PAI has a limited number of personality scales, but the reliability, validity, and clinical utility of the scales appear to be good. It also assesses many Axis I disorders including depression, anxiety, and substance abuse.

How to find it: The PAI is copyrighted and can be purchased by contacting Psychological Assessment Resources: voice, 800-331-8378, or Web, www.parinc.com.

References

Akanuma, N., Kanemoto, K., Adachi, N., Kawasaki, J., Ito, M., & Onuma, T. (2005). Prolonged postictal psychosis with forced normalization (Landolt) in temporal lobe epilepsy. *Epilepsy and Behavior, 6*(3), 456–459.

Altshuler, L., Rausch, R., Delrahim, S., Kay, J., & Crandall, P. (1999). Temporal lobe epilepsy, temporal lobectomy, and major depression. *The Journal of Neuropsychiatry and Clinical Neurosciences, 11*(4), 436–443.

Arnau, R. C., Meagher, M. W., Norris, M. P., & Bramson, R. (2001). Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. *Health Psychology, 20*(2), 112–119.

Arnold, L. M., & Privitera, M. D. (1996). Psychopathology and trauma in epileptic and psychogenic seizure patients. *Psychosomatics: Journal of Consultation Liaison Psychiatry, 37*(5), 438–443.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*(6), 893–897.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck Depression Inventory-II manual*. San Antonio, TX: Psychological Corporation.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571.

Blanchet, P., & Frommer, G. P. (1986). Mood change preceding epileptic seizures. *Journal of Nervous and Mental Disease, 174*(8), 471–476.

Blumer, D., & Altshuler, L. (1998). Affective disorders. In J. Engel Jr. & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (pp. 2083–2099). Philadelphia, PA: Lippincott-Raven.

Boylan, L. S., Flint, L. A., Labovitz, D. L., Jackson, S. C., Starner, K., & Devinsky, O. (2004). Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology, 62*(2), 258–261.

Briquet, P. (1859). *Traité Clinique et therapeutique de l'hysteric*. Paris: Plou, Nourit et Co.

Butcher, J. N., Dahlstrom, W. G., Graham, J. R., Tellegen, A., & Kaemmer, B. (1989). *Minnesota multiphasic personality inventory-2 (MMPI-2): Manual for administration and scoring*. Minneaoplis, MN: University of Minnesota Press.

Butcher, J. N., Graham, J. R., Ben-Porath, Y. S., Tellegen, A., & Dahlstrom, W. G. (2001). *Minnesota multiphasic personality inventory – 2 (MMPI-2): Manual for administration and scoring* (Revisedth ed.). Minneapolis, MN: University of Minnesota Press.

Costa, R. M., & MCCrae, R. R. (1992). *NEO-PI-R professional manual*. Odessa, FL: Psychological Assessment Resources.

Cramer, J. A., Blum, D., Fanning, K., & Reed, M. (2004). The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy. *Epilepsy and Behavior, 5*(3), 337–342.

Cramer, J. A., Blum, D., Reed, M., & Fanning, K. (2003). The influence of comorbid depression on quality of life for people with epilepsy. *Epilepsy and Behavior, 4*(5), 515–521.

Davies, S., Heyman, I., & Goodman, R. (2003). A population survey of mental health problems in children with epilepsy. *Developmental Medicine and Child Neurology, 45*(5), 292–295.

de Araujo Filho, G. M., Jackowski, A. P., Lin, K., Guaranha, M. S., Guilhoto, L. M., da Silva, H. H., et al. (2009). Personality traits related to juvenile myoclonic epilepsy: MRI reveals prefrontal abnormalities through a voxel-based morphometry study. *Epilepsy and Behavior, 15*(2), 202–207.

Derogatis, L. R. (1993). *Brief symptom inventory (BSI): Adminstration, scoring and procedures manual* (3rd ed.). Minneapolis, MN: National Computer Systems.

Derogatis, L. R. (1994). *The SCL 90-R: Administration, scoring, and procedures manual* (3rd ed.). Minneapolis, MN: National Computer Systems.

Derogatis, L. R., Lipman, R. S., & Covi, L. (1973). SCL-90: An outpatient psychiatric rating scale–preliminary report. *Psychopharmacology Bulletin, 9*(1), 13–28.

Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory: An introductory report. *Psychological Medicine, 13*(3), 595–605.

Devinsky, O., Barr, W. B., Vickrey, B. G., Berg, A. T., Bazil, C. W., Pacia, S. V., et al. (2005). Changes in depression and anxiety after resective surgery for epilepsy. *Neurology, 65*(11), 1744–1749.

Eaton, W. W., Neufeld, K., Chen, L.-S., & Cai, G. (2000). A comparison of self-report and clinical diagnostic interviews for depression: Diagnostic Interview Schedule and Schedules for Clinical Assessment in Neuropsychiatry in the Baltimore Epidemiologic Catchment Area follow-up. *Archives of General Psychiatry, 57*(3), 217–222.

Edeh, J., & Toone, B. (1987). Relationship between interictal psychopathology and the type of epilepsy. Results of a survey in general practice. *British Journal of Psychiatry, 151*, 95–101.

Ettinger, A., Reed, M., & Cramer, J. (2004). Depression and comorbidity in community-based patients with epilepsy or asthma. *Neurology, 63*(6), 1008–1014.

Fiordelli, E., Beghi, E., Bogliun, G., & Crespi, V. (1993). Epilepsy and psychiatric disturbance: A cross-sectional study. *British Journal of Psychiatry, 163*, 446–450.

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured clinical interview for DSM-IV axis II personality disorders (SCID-II)*. Washington, DC: American Psychiatric Press.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version (SCID-I)*. New York, NY: Biometrics Research, New York State Psychiatric Institute.

Fisher, R. S., van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., et al. (2005). Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia, 46*(4), 470–472.

Forsgren, L. (1992). Prevalence of epilepsy in adults in northern Sweden. *Epilepsia, 33*(3), 450–458.

Furukawa, T. A., Kessler, R. C., Slade, T., & Andrews, G. (2003). The performance of the K6 and K10 screening scales for psychological distress in the Australian National Survey of Mental Health and Well-Being. *Psychological Medicine, 33*(2), 357–362.

Gaitatzis, A., Trimble, M. R., & Sander, J. W. (2004). The psychiatric comorbidity of epilepsy. *Acta Neurologica Scandinavica, 110*(4), 207–220.

Gilliam, F. (2002). Optimizing health outcomes in active epilepsy. *Neurology, 58*(8 Suppl 5), S9–S20.

Gilliam, F. G., Barry, J. J., Hermann, B. P., Meador, K. J., Vahle, V., & Kanner, A. M. (2006). Rapid detection of major depression in epilepsy: A multicentre study. *Lancet Neurology, 5*(5), 399–405.

Goldberg, D. P. (1972). *The detection of psychiatric illness by questionnaire*. Oxford: Oxford University Press.

Goldberg, D. P., & Williams, P. (1991). *A user's guide to the general health questionnaire*. Berkshire: Nfer-Nelson.

Gowers, W. R. (1881). *Epilepsy and other chronic convulsive diseases: Their causes, symptoms, and treatment*. London: J & A Churchill.

Grabowska-Grzyb, A., Jedrzejczak, J., Naganska, E., & Fiszer, U. (2006). Risk factors for depression in patients with epilepsy. *Epilepsy and Behavior, 8*(2), 411–417.

Graham, P., & Rutter, M. (1968). Organic brain dysfunction and child psychiatric disorder. *BMJ [British Medical Journal], 3*(5620), 695–700. doi:10.1136/bmj.3.5620.695.

Gudmundsson, G. (1966). Epilepsy in Iceland. A clinical and epidemiological investigation. *Acta Neurologica Scandinavica, 43*(Suppl 25), 21–124.

Guy W. (1976). ECDEU Assessment Manual for Psychopharmacology, Revised Edition (DHEW Publ No ADM 76–388). Washington, DC, US Dept of Health, Education and Welfare.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56–62.

Harden, C. L., Jovine, L., Burgut, F. T., Carey, B. T., Nikolov, B. G., & Ferrando, S. J. (2009). A comparison of personality disorder characteristics of patients with nonepileptic psychogenic pseudoseizures with those of patients with epilepsy. *Epilepsy and Behavior, 14*(3), 481–483.

Hesdorffer, D. C., Hauser, W. A., Annegers, J. F., & Cascino, G. (2000). Major depression is a risk factor for seizures in older adults. *Annals of Neurology, 47*(2), 246–249.

Hesdorffer, D. C., Hauser, W. A., Olafsson, E., Ludvigsson, P., & Kjartansson, O. (2006). Depression and suicide attempt as risk factors for incident unprovoked seizures. *Annals of Neurology, 59*(1), 35–41.

Hicklin, J., & Widiger, T. A. (2000). Convergent validity of alternative MMPI-2 personality disorder scales. *Journal of Personality Assessment, 75*(3), 502–518.

Hill, D. (1981). Historical review. In E. Reynolds & M. Trimble (Eds.), *Epilepsy and psychiatry* (pp. 1–11). Edinburgh: Churchill Livingstone.

Huang, Y., Kotov, R., de Girolamo, G., Preti, A., Angermeyer, M., Benjet, C., et al. (2009). DSM-IV personality disorders in the WHO World Mental Health Surveys. *British Journal of Psychiatry, 195*(1), 46–53.

Jackson, J. (1931). Selected writings. In J. Taylor (Ed.), *On epilepsy and epileptiform convulsions* (Vol. 1). London: Hodder & Stoughton.

Johnson, E. K., Jones, J. E., Seidenberg, M., & Hermann, B. P. (2004). The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. *Epilepsia, 45*(5), 544–550.

Jones, J. E., Hermann, B. P., Barry, J. J., Gilliam, F. G., Kanner, A. M., & Meador, K. J. (2003). Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. *Epilepsy and Behavior, 4*(Suppl 3), S31–S38.

Kanner, A. M. (2003). Depression in epilepsy: Prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biological Psychiatry, 54*(3), 388–398.

Kanner, A. M. (2004). Recognition of the various expressions of anxiety, psychosis, and aggression in epilepsy. *Epilepsia, 45*(Suppl 2), 22–27.

Kanner, A. M., Soto, A., & Gross-Kanner, H. (2004). Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology, 62*(5), 708–713.

Kelley, M. S., Jacobs, M. P., & Lowenstein, D. H. (2009). The NINDS epilepsy research benchmarks. *Epilepsia, 50*(3), 579–582.

Kessler, R. C., Andrews, G., Colpe, L. J., Hiripi, E., Mroczek, D. K., Normand, S. L., et al. (2002). Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological Medicine, 32*(6), 959–976.

Kessler, R. C., Barker, P. R., Colpe, L. J., Epstein, J. F., Gfroerer, J. C., Hiripi, E., et al. (2003). Screening for serious mental illness in the general population. *Archives of General Psychiatry, 60*(2), 184–189.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602.

Kessler, R. C., & Üstün, T. B. (2004). The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research, 13*(2), 93–121.

Ketter, T. A., Malow, B. A., Flamini, R., White, S. R., Post, R. M., & Theodore, W. H. (1994). Anticonvulsant withdrawal-emergent psychopathology. *Neurology, 44*(1), 55–61.

Kobau, R., Gilliam, F., & Thurman, D. J. (2006). Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: Results from the 2004 HealthStyles Survey. *Epilepsia, 47*(11), 1915–1921.

Krishnamoorthy, E. S., Brown, R. J., & Trimble, M. R. (2001). Personality and Psychopathology in Nonepileptic Attack Disorder and Epilepsy: A Prospective Study. *Epilepsy and Behavior, 2*(5), 418–422.

Kuyk, J., Swinkels, W. A. M., & Spinhoven, P. (2003). Psychopathologies in patients with nonepileptic seizures with and without comorbid epilepsy: How different are they? *Epilepsy and Behavior, 4*(1), 13–18.

Lacey, C. J., Salzberg, M. R., Roberts, H., Trauer, T., & D'Souza, W. J. (2009). Psychiatric comorbidity and impact on health service utilization in a community sample of patients with epilepsy. *Epilepsia, 50*(8), 1991–1994.

LaFrance, W. C., Jr., Kanner, A. M., & Hermann, B. (2008). Psychiatric comorbidities in epilepsy. *International Review of Neurobiology, 83*, 347–383.

Lee, S. A., Lee, S. M., & No, Y. J. (2009). Factors contributing to depression in patients with epilepsy. *Epilepsia, 20*, 20.

Lopez-Rodriguez, F., Altshuler, L., Kay, J., Delarhim, S., Mendez, M., & Engel, J., Jr. (1999). Personality disorders among medically refractory epileptic patients. *The Journal of Neuropsychiatry and Clinical Neurosciences, 11*(4), 464–469.

Loranger, A. W., Sartorius, N., Andreoli, A., & Berger, P. (1994). The International Personality Disorder Examination: The World Health Organization/ Alcohol, Drug Abuse, and Mental Health Administration international pilot study of personality disorders. *Archives of General Psychiatry, 51*(3), 215–224.

Manchanda, R., Schaefer, B., McLachlan, R. S., Blume, W. T., Wiebe, S., Girvin, J. P., et al. (1996). Psychiatric disorders in candidates for surgery for epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 61*(1), 82–89.

McConnell, H. W., & Duncan, P. W. (1998). Treatment of psychiatric comorbidity in epilepsy. In H. W. McConnell & P. J. Snyder (Eds.), *Psychiatric comorbidity in epilepsy: Basic mechanisms, diagnosis, and treatment* (pp. 245–361). Washington, DC: American Psychiatric Association.

Mensah, S. A., Beavis, J. M., Thapar, A. K., & Kerr, M. (2006). The presence and clinical implications of depression in a community population of adults with epilepsy. *Epilepsy and Behavior, 8*(1), 213–219.

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy, 28*(6), 487–495.

Morel, B. (1860). *Traité des malades metales*. Paris: Masson et Cie.

Morey, L. C. (1991). *Personality assessment inventory: Professional manual*. Odessa, FL: Psychological Assessment Resources.

Morey, L. C., Waugh, M. H., & Blashfield, R. K. (1985). MMPI scales for DSM-III personality disorders: Their derivation and correlates. *Journal of Personality Assessment, 49*(3), 245–251.

Perala, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., et al. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry, 64*(1), 19–28.

Pond, D. A., & Bidwell, B. H. (1960). A survey of epilepsy in fourteen general practices. II. Social and psychological aspects. *Epilepsia, 1*, 285–299.

Provinciali, L., Franciolini, B., del Pesce, M., & Signorino, M. (1989). Influence of neurological factors on the personality profile of patients with temporal lobe epilepsy. *Journal of Epilepsy, 2*(4), 239–244.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385–401.

Reisinger, E. L., & DiIorio, C. (2009). Individual, seizure-related, and psychosocial predictors of depressive

symptoms among people with epilepsy over six months. *Epilepsy and Behavior, 15*(2), 196–201.

Reynolds, E. H., & Trimble, M. R. (2009). Epilepsy, psychiatry, and neurology. *Epilepsia, 50*(Suppl 3), 50–55.

Robins, L. N., Marcus, W., Reich, W. C., Cunningham, R., & Gallagher, T. (1996). *NIMH diagnostic interview schedule, version IV (DIS-IV)*. St. Louis, MO: Department of Psychiatry, Washington School of Medicine.

Robins, L. N., Wing, J., Wittchen, H. U., Helzer, J. E., Babor, T. F., Burke, J., et al. (1988). The composite international diagnostic interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry, 45*(12), 1069–1077.

Rossi, G., Van den Brande, I., Tobac, A., Sloore, H., & Hauben, C. (2003). Convergent validity of the MCMI-III personality disorder scales and the MMPI-2 scales. *Journal of Personality Disorders, 17*(4), 330–340.

Schwartz, J., & Cummings, J. L. (1988). Psychopathology and epilepsy: An outpatient consultation-liaison experience. *Psychosomatics: Journal of Consultation Liaison Psychiatry, 29*(3), 295–300.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-international neuropsychiatric interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*(Suppl 20), 22–33. quiz 34–57.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Janavs, J., Weiller, E., Keskiner, A., et al. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry: The Journal of the Association of European Psychiatrists, 12*(5), 232–241.

Somwaru, D. P., & Ben-Porath, Y. S. (1995) *Development and reliability of MMPI-2 based personality disorder scales*. Paper presented at the 30th Annual Workshop and Symposium on Recent Developments in the Use of the MMPI-2 and MMPI-A, St. Petersburg Beach, FL.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine, 166*(10), 1092–1097.

Stefansson, S. B., Olafsson, E., & Hauser, W. A. (1998). Psychiatric morbidity in epilepsy: A case controlled study of adults receiving disability benefits. *Journal of Neurology, Neurosurgery, and Psychiatry, 64*(2), 238–241.

Swinkels, W. A. M., Kuyk, J., de Graaf, E. H., van Dyck, R., & Spinhoven, P. (2001). Prevalence of psychopathology in Dutch epilepsy inpatients: A comparative study. *Epilepsy and Behavior, 2*(5), 441–447.

Swinkels, W. A. M., Kuyk, J., van Dyck, R., & Spinhoven, P. (2005). Psychiatric comorbidity in epilepsy. *Epilepsy and Behavior, 7*(1), 37–50.

Tellez-Zenteno, J. F., Patten, S. B., Jette, N., Williams, J., & Wiebe, S. (2007). Psychiatric comorbidity in epilepsy: A population-based analysis. *Epilepsia, 48*(12), 2336–2344.

Temkin, O. (1971). *The falling sickness: A history of epilepsy from the Greeks to the beginnings of modern neurology* (2nd ed.). Baltimore, MD: Johns Hopkins Press.

Trimble, M. R. (1992). Behaviour changes following temporal lobectomy, with special reference to psychosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 55*(2), 89–91.

US Department of Health and Human Services, F. a. D. A., Center for Drug Evaluation and Research, Office of Translation Science, Office of Biostatistics. (May 21, 2008). *Statistical review and evaluation :Antiepileptic drugs and suicidality.*

Vazquez, B., & Devinsky, O. (2003). Epilepsy and anxiety. *Epilepsy and Behavior, 4*(Suppl 4), S20–S25.

Victoroff, J. I., Benson, F., Grafton, S. T., Engel, J., Jr., & Mazziotta, J. C. (1994). Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. *Archives of Neurology, 51*(2), 155–163.

Wittchen, H. U., Kessler, R. C., Beesdo, K., Krause, P., Hofler, M., & Hoyer, J. (2002). Generalized anxiety and depression in primary care: Prevalence, recognition, and management. *Journal of Clinical Psychiatry, 63*(Suppl 8), 24–34.

Wittchen, H. U., Zhao, S., Kessler, R. C., & Eaton, W. W. (1994). DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 51*(5), 355–364.

Zanarini, M. C., Frankenburg, F. R., Chauncey, D. L., & Gunderson, J. G. (1987). The diagnostic Interview for Personality Disorders: Interrater and test-retest reliability. *Comprehensive Psychiatry, 28*(6), 467–480.

Zanarini, M. C., Frankenburg, F. R., & Sickel, A. E. (1996). *Diagnostic interview for DSM-IV personality disorders (DIPD-IV)*. Belmont, MA: Laboratory for the Study of Adult Develpment, McLean Hospital, and Department of Psychiatry, Harvard Medical School.

Zanarini, M. C., Skodol, A. E., Bender, D., Dolan, R., Sanislow, C., Schaefer, E., et al. (2000). The Collaborative Longitudinal Personality Disorders Study: Reliability of axis I and II diagnoses. *Journal of Personality Disorders, 14*(4), 291–299.

Zimmerman, M., & Mattia, J. I. (1999). The reliability and validity of a screening questionnaire for 13 DSM-IV Axis I disorders (the Psychiatric Diagnostic Screening Questionnaire) in psychiatric outpatients. *Journal of Clinical Psychiatry, 60*(10), 677–683.

Zung, W. W. (1965). A self-rating depression scale. *Archives of General Psychiatry, 12*(1), 63–70.

Psychotherapeutic and Cognitive Remediation Approaches

11

Luba Nakhutina

As the medical management of epilepsy advanced, it became evident that a considerable number of patients with epilepsy (PWE), including those with well-controlled seizures, have psychological and cognitive problems and are in need of further support. The lifetime prevalence of depressive disorders, anxiety disorders, and suicidal thoughts is all significantly higher in PWE than in the general public (Hermann, Seidenberg, & Jones, 2008). There are numerous psychosocial consequences associated with epilepsy, including stigmatization and social isolation (Morrell, 2002), which contribute to distress and poor coping with the disease. Cognitive impairment, particularly memory dysfunction, is experienced by many epilepsy patients, and these deficits negatively impact their functional and social independence. While ictal and postictal cognitive and behavioral disturbances have been long recognized and targeted in treatment, interictal disturbances in cognition and mood remain largely unaddressed, although in some individuals these problems may be more disabling than the seizures themselves.

Emotional distress and persistent cognitive disturbance associated with epilepsy are major causes of disability and poor quality of life (QOL) in this population. Epilepsy patients consistently report lower education, higher rates of unemployment, lower income, and being single compared with people without epilepsy (Hermann et al., 2008). Unemployment or reduced employment options and earning potential of PWE are much more frequent than in the general population, and according to some studies, as much as double that of the general population (Smeets, van Lierop, Vanhoutvin, Aldenkamp, & Nijhuis, 2007). Patients' abilities to manage their epilepsy treatment and adhere to medication regimens are also impacted by emotional and cognitive problems. In fact, treatment nonadherence is PWE is high, with estimates ranging from 20 to 60 %. Nonadherence naturally results in increased seizures and increased health-care utilization costs and is the most significant risk for sudden unexplained death in epilepsy or SUDEP (Faught, Duh, Weiner, Guerin, & Cunnington, 2008, 2009, Faught, Weiner, et al., 2009). Finally, studies have shown that epilepsy patients report lower QOL compared to persons with other chronic illnesses and disabilities (e.g., Hermann et al., 1996). Symptoms of depression and seizure worry were shown to be the most important factors affecting QOL in patients with intractable epilepsy (Loring, Meador, & Lee, 2004), and cognitive impairment is one of the most frequently identified factors in reducing the overall QOL (Bishop & Allen, 2003; Leidy et al., 1999).

As awareness of these problems has increased, it has become evident that management of

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epilepsy with AEDs and neurosurgery is insufficient, and comprehensive care that includes behavioral interventions is necessary. Yet, while the literature on the medical management of epilepsy is extensive, there remains a paucity of psychotherapeutic and cognitive remediation approaches that have been validated empirically for use in the comprehensive management of PWE. Available research in this area is complicated by methodological pitfalls, such as small sample sizes, sample selection bias, absence of adequate control group and randomization procedures, and controversies as to measures of outcome. Despite these limitations, there is evidence to suggest that behavioral interventions can reduce emotional distress and cognitive morbidity, increase treatment compliance, and possibly reduce seizure frequency and severity. By targeting the psychological and cognitive symptoms of PWE, effective behavioral interventions also have the potential to increase patients' independence, reduce epilepsy-related disability and the associated costs, as well as enhance patients' overall QOL.

The purpose of this chapter is to (1) briefly discuss prevalent emotional and cognitive problems associated with epilepsy, (2) summarize evidence-based strategies and guidelines offered for interventions in other patient groups (e.g., TBI, stroke), (3) review the limited empirical information available from behavioral intervention studies in epilepsy, and (4) provide guidance to neuropsychologists who are looking to design and implement psychotherapeutic and cognitive remediation treatments for PWE.

Psychotherapeutic Interventions

Emotional Distress and Psychosocial Factors in Patients with Epilepsy

In management of epilepsy, it is important to consider the high rates of emotional distress and psychosocial problems, which negatively impact patients' ability to cope with disease and their QOL. The lifetime prevalence of depression and anxiety disorders is significantly higher in PWE than in the general public or in patients with several other chronic conditions, such as asthma (Ettinger, Reed, Cramer, & Epilepsy Impact Project Group, 2004; Kanner, 2007). Depression is the most common emotional concern in epilepsy, with the rates of depression reported to be as high as 55 % among patients treated in specialized medical centers (Dodrill, 2008). The level of depression is not usually well accounted for by seizure variables, suggesting that psychological, social, and medication variables play a significant part in this relationship (Bishop & Allen, 2007). It has been shown that depression but not seizure frequency predicts QOL in treatment resistant epilepsy, and this has led many investigators to conclude that treatment of depression may be inadequately prioritized in the epilepsy management in these patients (e.g., Boylan et al., 2004; Thapar, Kerr, & Gordon, 2009).

Anxiety disorders are also commonly comorbid with epilepsy, with reported prevalence rates ranging from 19 % to over 50 % across studies and the different settings where epilepsy patients were assessed (Beyenburg, Mitchell, Schmidt, Elger, & Reuber, 2005). The unpredictable timing and intrusive nature of seizures demand constant vigilance and often result in chronic and disabling anxiety, which can have a profound influence on the QOL of epilepsy patients. Seizure frequency has been linked to anxiety in some but not all studies. In older adults, including those with infrequent seizures (i.e., less than one per year), the fear induced by the possibility of a seizure may be sufficient to significantly reduce QOL (McLaughlin, Pachana, & Mcfarland, 2008).

The level of distress in PWE is also increased by cognitive problems, and distress in turn exacerbates cognitive dysfunction. At the same time, distressed patients are more prone to overreactions to memory failures, some of which may be normal forgetfulness. It has been shown that perceived cognitive functioning was strongly correlated with mood and weakly correlated with memory performance scores (Elixhauser, Kline Leidy, Meador, Means, & Willian, 1999).

Living with epilepsy also implies psychosocial challenges. Psychosocial functioning in PWE has to do with the level of effectiveness with which individuals are able to function in their social environment, including situations pertaining to education, employment, interpersonal relationships, as well as relationships with their physicians, adjustment to seizures, and medical management of epilepsy. For instance, psychosocial factors that have been implicated in the high unemployment rate among PWE include social isolation, lack of information, social skills deficits, and lack of family support (Bishop & Allen, 2007). Some of the psychosocial problems may be related to the perceived social stigma associated with epilepsy. In fact, epilepsy in many cultures has often been regarded as one of the most stigmatizing conditions. The negative attitudes that PWE encounter typically result from lack of information and understanding of epilepsy; however, feeling stigmatized does not always correlate with the presence of prejudice but relies heavily on individuals' perceptions. Stigma can be one of the most distressing consequences of having seizures, and it can lead to social isolation and have a negative impact on QOL (Prus, Nakhutina, & Grant, 2009). Perceptions of lower self-efficacy to manage epilepsy and poorer adherence to treatment were found in PWE who report higher levels of stigma (DiIorio, Osborne Shafer, Letz, et al., 2003), and lower levels of stigma were associated with finding and maintaining employment (Smeets et al., 2007). Smith et al. (2009) found complex interactions between demographic, clinical, and psychosocial factors at play with the perception of stigma and suggested that perceptions of self-efficacy in managing epilepsy are a point of intervention to improve stigma.

Compounding the emotional and psychosocial problems is the fact that epilepsy patients often have inadequate knowledge and misconceptions about their illness and its treatment. They may also possess poor understanding of the cognitive and emotional problems they may be experiencing and the way these problems may be impacting their daily lives. Lack of information and erroneous beliefs can result in dangerous consequences of AEDs misuse, with resultant increase in seizure frequency, misguided medication changes or emergency room visits, as well as heightened perceptions of stigma, social withdrawal, and depression.

To address emotional distress, psychosocial problems, and lack of disease-related information among PWE, a number of educational and psychotherapeutic interventions have been developed. These interventions have been provided by various types of professionals, including specialist epilepsy nurses, social workers, health psychologists, and only infrequently neuropsychologists. Infrequent participation of neuropsychologists is surprising given the need for understanding of cognitive deficits in PWE when attempting to effect behavior change in these patients and to teach them new information. In the next section, empirical evidence from psychoeducational and psychotherapeutic programs for PWE will be reviewed. It should be noted that differentiation among these interventions is difficult to make, as there is usually much overlap, whereby psychotherapy commonly includes patient education and psychoeducational programs often instruct patients in coping skills.

Psychoeducational Programs

The focus of psychoeducation has been to impart knowledge about epilepsy and its treatment, improve coping skills and QOL, and increase compliance with treatment and seizure control. The educational programs have varied in their approach, and only a few have been evaluated using randomized, controlled methodology (May & Pfafflin, 2005). The results of studies conducted thus far are promising, and the need for educational interventions has been highlighted (Bradley & Lindsay, 2008).

Programs Targeting Epilepsy-Related Knowledge and Attitudes

Reviews by the Cochrane group (Bradley & Lindsay, 2008; Shaw et al., 2007) identified only two randomized controlled studies, evaluating

programs that have targeted epilepsy-related knowledge and attitudes (Helgeson, Mittan, Tan, & Chayasirisobhon, 1990; May & Pfafflin, 2002). Seizures and Epilepsy Education (SEE; Helgeson et al., 1990) is a 2-day psychoeducational intervention for adults with epilepsy aimed at improving understanding of epilepsy and viewed essential to effective coping with the disease and related disability. The program covers the medical aspects of epilepsy, placing an emphasis on improving medication adherence, as well as on the social and emotional aspects of the disease. Helgeson et al. (1990) found that, in comparison to the wait-list control group ($n=18$), the treatment group ($n=20$) demonstrated significant improvements in disease-related knowledge and reduction in epilepsy-related fears (e.g., fear that a single seizure will lead to brain damage or death). They also demonstrated improvement in compliance with medication regimens, as measured by drug serum levels. However, there were no significant changes in anxiety, depression, QOL, self-efficacy, or seizure frequency.

Modular Service Package Epilepsy (MOSES; Reid, Specht, Thornbecke, Goecke, & Wohlfarth, 2001) is designed for group education and aims to engage patients in an active role in managing their disability and become experts in dealing with epilepsy. The program consists of multiple modules with goals of improving individual participants' understanding of epilepsy, its treatment, and its psychosocial consequences and, thus, increasing their self-confidence, teaching them to cope with the disease, and enabling them to become more autonomous. May and Pfafflin (2002) investigated the efficacy of MOSES, given as a 2-day course, in a randomized controlled study. The findings indicated that the program was particularly effective in providing information and self-management strategies. Patients in the treatment group ($n=113$) reported reduction in seizure frequency and better tolerability of AED treatment. The program did not have a significant impact on QOL, epilepsy-related fears, or emotional disturbances, such as depression.

Programs Aimed at Increasing Medication Compliance

Despite the recognized importance of treatment adherence in determining health and disability outcomes in PWE, research on interventions aimed specifically at improving adherence in these patients has been lacking (Bradley & Lindsay, 2008). The one existing randomized controlled trial (RCT) showed that a brief intervention focusing on patient education about the importance of compliance and training in behavioral strategies (e.g., medication container, prescription refill reminder cards sent by mail) can be effective in improving medication adherence and self-reported seizure control (Petersen, McLean, & Millingen, 1984). These results are encouraging; however, the research in this area unfortunately has not progressed much beyond this study, and a handful of additional interventions conducted since had many methodological limitations. Recently, DiIorio and colleagues have published descriptions of two interventions, one telephone based and one web based, that are under investigation in RCTs (DiIorio et al., 2009, DiIorio, Reisinger, Yeager, & McCarty, 2009). These nurse-delivered interventions focus on medication adherence strategies, information about epilepsy and seizures, and stress management. Based on constructs from social cognitive theory and motivational interviewing, these interventions focus on identifying and addressing barriers to adherence through a collaborative, confidence-enhancing approach.

Psychotherapy Approaches

Psychotherapeutic interventions include cognitive behavioral therapy, relaxation therapy, and EEG biofeedback, as well as patient education. These interventions have been used alone or in combination in treatment of epilepsy patients, with the aim of reducing depression and anxiety symptoms, decreasing seizure frequency, and improving QOL.

Cognitive Behavioral Therapy

A major focus of interventions that have applied cognitive behavioral therapy (CBT) to treatment of PWE has been on cognitive restructuring to improve patients' coping and stress management skills in order to reduce depression and anxiety and enhance their overall QOL. Using CBT techniques, patients are taught to confront cognitive distortions, irrational beliefs, and negative thoughts related to epilepsy and self-perception. Another major application of CBT with epilepsy patients has been to teach self-management techniques for improvement of seizure control. These strategies have included observation of seizure triggers and initiation of countermeasures, such as breathing techniques or coping statements. The methods employed in CBT interventions for PWE have varied widely and have included treatment protocols of varying length, individual or group format, with different types of professionals administering treatment. While only a limited number of RCTs have been conducted, with mixed findings, possibly attributable to varying methodologies, they suggest that CBT can be a valuable approach in treatment of epilepsy patients.

In earlier studies, Davis, Armstrong, Donovan, & Temkin (1984) reported positive results from an RCT evaluating a 6-week treatment with 13 adults with epilepsy, designed to increase participants' skills in managing depression. Cognitive behavioral techniques included maximizing pleasant events and physical exercise, increasing assertiveness, identifying faulty belief systems, and increasing positive cognitions and self-reinforcing statements. The treatment group was reported to evidence marked reduction in depression, as assessed by self-report measures. There was also a significant decrease in self-reported anxiety/stress and anger and increased involvement in social activities.

Subsequently, Au et al. (2003) evaluated effectiveness of cognitive behavioral intervention (eight 2-h sessions) focused particularly on cognitive restructuring and seizure control. The sessions were led by two clinical psychologists and included information about the relationship of stress and seizures, identification of seizure-provoking situations, cognitive restructuring, and training in relaxation and stress management techniques. The patients in the treatment group (eight adults) were reported to show significant gains in self-efficacy or the ability to manage seizures and stress, as was assessed by a modified Epilepsy Self-Efficacy Scale (ESES; DiIorio & Yeager, 2003) and in QOL (QOLIE-31; Cramer et al., 1998) when evaluated at 3-month follow-up. These changes were not observed in the wait-list control group (nine adults), and no significant reduction in seizure frequency was noted following treatment.

Goldstein, McAlpine, Deale, Toone, and Mellers (2003) reported positive results of CBT (12 sessions) led by a nurse specialist and designed to address epilepsy-related problems and the associated psychopathology. Treatment focused on decreasing psychiatric symptoms by assisting patients in adjustment and introducing countermeasures, such as coping statements, shifting attention, and deep breathing, to reduce seizures. Upon completion of treatment, patients rated their epilepsy-related problems as having less impact on their daily lives than previously. At 1-month follow-up, patients also reported decreased use of escape-avoidance coping strategies, as well as improved self-rated work and social adjustment. These results were observed despite the absence of a significant decrease in seizure frequency.

Cognitive behavioral techniques have also been used in attempts to prevent depression in those determined to be at risk for the development of depression. Martinovic, Simonovi, and Djoki (2006) randomized 30 adolescent patients with equivalent levels of depressive symptoms prior to treatment to receive either CBT or counseling as usual. Depressive symptoms improved in patients who received CBT, and patient QOL ratings correlated with mood improvement. In contrast, a few of the patients in the control group developed depression at follow-up.

Studies evaluating interventions that specifically targeted seizure frequency, severity, or duration have yielded mixed results. In a

study by Tan and Bruni (1986), patients were randomized to CBT, supportive counseling, or wait-list control. The treatment did not result in significant reduction in seizure frequency. Moreover, improvements in psychosocial adjustment were observed in both therapy groups, and thus, no specific advantage of CBT was demonstrated. In contrast, Gillham (1990) reported an improvement in seizure control and psychological symptoms after individual CBT that involved monitoring of symptoms and initiation of countermeasures, such as breathing techniques. Spector, Tranah, Cull, and Goldstein (1999) reported positive efficacy results of a group intervention (8 weekly sessions) designed to improve seizure control in seven adult patients with intractable seizures. Treatment included psychoeducation and cognitive behavioral techniques. Seizure frequency was significantly reduced in intervention participants, and the treatment effects persisted at 2-month follow-up. However, no significant improvement in psychosocial functioning in these patients was observed. Finally, Lundren, Dahl, Melin, and Kies (2006) reported that a short-term acceptance and commitment therapy, combined with seizure behavior management techniques, had significant effects on seizure frequency, duration, and QOL, as compared to supportive therapy. Treatment was distributed in two individual and two group sessions during a 4-week period.

In summary, the evidence from a number of studies suggests that CBT may be effective in helping PWE manage depression and anxiety symptoms, improve their ability to control seizures, as well as improve their overall QOL. However, the validity of reported results is limited by methodological problems, including a small number of participants, lack appropriate control groups or randomization procedures, and insufficient information with regard to seizure type and concomitant antidepressant therapy (Ramaratnam, Baker, & Goldstein, 2008). While it is difficult to draw definitive conclusions about the efficacy of CBT in treatment of PWE in view of these methodological limitations, the evidence gathered thus far suggests that CBT may prove to be an effective method in addressing epilepsy-related emotional and psychosocial problems. Continued research evaluating this approach in epilepsy is needed.

Progressive Relaxation Training

It is widely accepted that stress is a common precipitant of seizures in PWE, and it has been inferred that behavioral approaches used to minimize stress would therefore improve seizure control. A number of studies have tested this hypothesis employing different relaxation training protocols and have reported positive results, although the mechanisms by which relaxation training appears to reduce seizure frequency are unclear. Dahl, Melin, and Lund (1987) found a significant advantage of relaxation therapy in decreasing seizure frequency in 18 adults treated over 6 weeks (1 h weekly), as compared to supportive therapy attention control or no treatment. The treatment effects were maintained at 10- and 30-week follow-up. Rousseau, Hermann, and Whitman (1985) reported that implementing progressive relaxation training over 3 weeks in eight adults with uncontrolled epilepsy resulted in 30 % reduction in median seizure frequency. Similarly, in a study examining the efficacy of progressive muscle relaxation (six sessions conducted over 4–8 weeks) in reducing seizure activity, Puskarich et al., 1992 found that the treatment resulted in 29 % reduction in mean seizure frequency, whereas there was only 3 % decrease for the control (i.e., quiet sitting) group. The effects of relaxation therapy on psychosocial functioning have also been investigated (Snyder, 1983); however, no significant difference in scores on the Washington Psychosocial Seizure Inventory (WPSI; Dodrill, Batzel, Queisser, & Temkin, 1980) were found between treatment and control groups after relaxation therapy, and no information regarding the seizure frequency was provided.

These studies indicate possible beneficial effects of relaxation training on seizure frequency; however, due to methodological deficiencies, including considerable difference in the seizure frequencies at baseline among patients in the control and treatment groups, definitive conclusions

cannot be made, and further studies are needed (Ramaratnam et al., 2008).

Use of Biofeedback in Treatment of Epilepsy Patients

The biofeedback technique involves monitoring of physiological responses, such as heart rate, galvanic skin response (GSR), or brain wave pattern (EEG), and providing feedback to the individual to help him or her actively control the physiological response. The effects of biofeedback on seizure frequency have been explored in numerous studies, and there is a significant body of literature on EEG biofeedback (see review by Sterman, 1990). Ramaratnam et al. (2008) critically reviewed this literature and identified only one trial where randomized controlled procedures were employed (Lantz & Sherman, 1988). In this study, the authors investigated the effects of EEG biofeedback (6-week treatment) on 24 adults with uncontrolled epilepsy who were randomized to contingent EEG biofeedback, noncontingent feedback, and no intervention control. Significant seizure frequency reduction (61 %) following contingent EEG biofeedback at 6 weeks follow-up was reported (Lantz & Sherman, 1988).

Nagai, Goldstein, Fenwick, and Trimble (2004) studied the effects of GSR biofeedback training or sham feedback on seizure frequency in 18 adult patients with treatment resistant epilepsy in a single blind RCT. These investigators reported 50 % greater reduction in seizure frequency in the treatment group relative to patients in the control group.

Cognitive Remediation Approaches

Cognitive Deficits in Patients with Epilepsy

Epilepsy patients can present with cognitive deficits in various domains, including intellectual abilities, attention and concentration, memory, executive functions (e.g., organization, mental flexibility, problem-solving), language, visuospatial skills, processing and motor speed, as well as in social and emotional cognition. Memory impairment, attention and concentration deficits, and mental slowing are the most frequent cognitive problems associated with epilepsy (Aldenkamp, 2006; Jokeit & Ebner, 1999) and are commonly reported subjective complaints of PWE. Cognitive impairment in PWE appears to result from multiple factors, including the underlying etiology, neuronal dysfunction or loss, seizure-related variables, localization of the epileptogenic zone, adverse effects of antiepileptic drugs (AEDs), and comorbid psychiatric conditions, such as depression and anxiety (Aldenkamp, Baker, & Meador, 2004; Hermann & Whitman, 1984). These factors interrelate, resulting in heterogeneous nature of cognitive profiles that range widely in severity of deficits. Early seizure onset, long duration of the disease, and poor seizure control are associated with poor cognitive outcome (Elger, Helmstaedter, & Kurthen, 2004). While epilepsy surgery is an important treatment option allowing many patients to achieve seizure freedom, the surgical intervention carries the risk of causing additional cognitive impairments.

Patients often list memory problems as their greatest concern (Hendriks, 2001) with memory deficits, in varying degrees of severity, being the most common finding in objective neuropsychological evaluations. Seizures often originate in mesiotemporal structures that are essential for memory processes (Squire, Stark, & Clark, 2004), and NMDA receptors, critical in learning and memory, appear to play a prominent role in the neuropathology of epilepsy (Engel, Pedley, Aicardi, & Dichter, 2007). Learning and memory difficulties are the most frequent cognitive changes in patients with temporal lobe epilepsy (TLE), irrespective of the presence of overt damage in temporal lobe structures (Giovagnoli & Avanzini, 1999). Frontal lobe epilepsy (FLE) may affect an array of cognitive abilities, including memory, attention, and executive functions (Helmstaedter, Kemper, & Elger, 1996). The overall prevalence of memory problems in patients with refractory epilepsy has been estimated as high as 20–50 % (Halgren et al., 1991).

Deficits in cognitive functions are considered more debilitating than the actual seizures by some patients. Cognitive functioning may be a significant factor in determining educational attainment and employment status, and even subtle deficits may manifest themselves in demanding professional or academic settings. Cognitive deficits are also likely to negatively impact patients' ability to adhere to their treatment regimens, especially when the regimens are complex and, thus, reliant on many cognitive abilities. In a study focused on medication adherence, study, 56 % of epilepsy patients reported forgetfulness as a reason for poor medication adherence, and the overall nonadherence rate was 68 % (Nakhutina, Gonzalez, Prus, & Grant, 2009). Finally, cognitive dysfunction is also one of the most frequently identified factors in reducing QOL (Bishop & Allen, 2003), even in patients with well-controlled epilepsy. In particular, individuals with impaired memory were found to have significantly worse QOL than the ones with unimpaired memory (Leidy et al., 1999).

Evidence-based cognitive remediation has the potential to improve cognitive status, functional abilities, and QOL in PWE. The interest in the possibility of rehabilitation of cognitive problems has greatly expanded in the last decades, and there is now a considerable amount of literature on cognitive rehabilitation (e.g., Sohlberg & Mateer, 2001; Wilson, 1987); however, the focus of this literature remains primarily on traumatic brain injury (TBI) and stroke, whereas applications to epilepsy patients have been very limited (Shulman & Barr, 2002). The attempts to investigate the efficacy of cognitive rehabilitation in PWE with adequate study of outcomes have been very few, and RCTs are grossly lacking. In the following section, (1) definition of cognitive remediation will be provided, (2) select remediation strategies with supportive evidence for use with brain injury and stroke patients will be summarized, and (3) limited empirical evidence from studies of cognitive interventions in PWE will be reviewed. The focus will be on rehabilitation of memory and attention problems, the most prevalent complaints in PWE and key domains targeted by existing remediation interventions in epilepsy patients.

Cognitive Rehabilitation: Definition

Cognitive rehabilitation has been defined as a "systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioral deficits" (Cicerone et al., 2000). Wilson has defined cognitive rehabilitation as "any intervention strategy or technique which intends to enable clients or patients, and their families, to live with, manage, by-pass, reduce or come to terms with cognitive deficits precipitated by injury to the brain" (Wilson, 1997). A comprehensive neuropsychological evaluation plays an important role in guiding cognitive remediation based on detailed information about patients' level of intellectual functioning, cognitive profile (e.g., areas of cognitive deficits and preserved abilities), and severity of cognitive impairment. Cognitive remediation is also guided by patients' functional goals or what is expected of them (e.g., return to work or school, participation at home).

Rehabilitation of Memory

Memory rehabilitation is a component of cognitive rehabilitation. Two broad approaches to memory rehabilitation have been employed: (1) *restitution* training and (2) *strategy* training. Using the restitution training approach, memory rehabilitation programs rely heavily on repetitive drills and practice of cognitive skills in attempts to restore the underlying impaired function. Tasks utilized for this purpose are often computerized, and software packages have been made commercially available. This approach has not been found to lead to general improvements in memory functioning (Prigatano et al., 1984). The *strategy* training approach to rehabilitation has received more research support, especially when targeting memory problems (Cicerone et al., 2000, 2005). This approach focuses on teaching patients compensatory strategies to circumvent difficulties that arise as a result of their memory impairment (Sohlberg & Mateer, 1989). Patients are taught the use of *internal*

memory aids, such as mnemonics, visual imagery, and rehearsal, to help them remember and recall information and/or *external* memory aids, such as notebooks, voice organizers (Van den Broek, Downes, Johnson, Dayus, & Hilton, 2000), alarms, pagers (Wilson, Emslie, & Evans, 2001), mobile phones (Wade & Troy, 2001), and other assistive devices and environmental manipulations, to help reduce memory failures and executive functioning problems. The generalizability of internal memory aid use to natural settings has also been questioned. These techniques have been found ineffective for many patients with significantly compromised intellectual functioning and may be useful only for acquisition of specific and small bodies of information (Sohlberg & Mateer, 1989). The external memory aids can be very effective, particularly when dealing with severe memory impairment; however, these aids are often given with minimal instruction or formal training (Sohlberg & Mateer, 1989).

Cicerone and colleagues (2000) provided evidence-based recommendations for cognitive rehabilitation with TBI and stroke patients. Based on the review of findings from well-designed prospective RCTs, along with supportive evidence from less rigorous trials, Cicerone et al. (2005) suggested that the evidence for memory strategy training (including the use of internalized strategies and external memory compensations) for individuals with mild memory problems was "compelling enough" to recommend it as a *practice standard*. Teaching external memory aids with direct application to functional activities was offered as *practice guidelines* for patients with moderate to severe memory impairment, based on evidence of probable effectiveness (e.g., as seen in nonrandomized cohort studies or case-control studies).

Remediation of Mild to Moderate Memory Deficits

Johanson, Chaplin, and Wedlund (2001) conducted memory training for PWE as part of a holistic neurorehabilitation program that integrated psychotherapy and aimed at addressing poor self-image and education about epilepsy and brain functioning. Twenty-one participants, in groups of five, attended 16-day treatment over a period of 8 weeks. Memory training with participants focused on increasing understanding of memory functioning and on teaching strategies (e.g., diary) for improving memory, while targeting their individual cognitive problems, as identified by the neuropsychological evaluation. A few meetings were also conducted with a parallel group of participants' significant others. The results included improvements in the overall QOL, as assessed by QOLIE-89 (Devinsky et al., 1995), administered prior to enrollment, immediately after completion of the program and at 6 months posttreatment. Qualitative assessments of treatment outcome revealed improved understanding and control of memory problems (as reported by 10 of 21 participants), increased knowledge about epilepsy, and improved self-confidence. Although patients derived benefit from the holistic approach, their feedback also indicated that the time devoted to memory training was insufficient for participants whose memory problems were more severe.

Barr, Morrison, Isaacs, and Devinsky (2004) developed and evaluated a group-based intervention focused specifically on treatment of memory difficulties in PWE. Twenty-three patients were enrolled in treatment, consisting of six 75-min-long sessions led by two neuropsychologists. Sixteen patients had previously received surgical intervention. Each session included educational presentations about epilepsy and memory, followed by instruction in the use of memory aids (e.g., calendar, electronic organizers, pagers) and mnemonic techniques (e.g., imagery and association). Participants shared personal experiences and strategies they found helpful for managing memory problems. They were provided with informational handouts and given homework assignments utilizing concepts introduced in the group. The treatment outcome was assessed by self-report inventories (i.e., QOLIE-10, Cramer, Perrine, Devinsky, & Meador, 1996; modified Memory Complaints Inventory or MCI; Green & Allen, 1997), given at baseline and at 1–2-month follow-up.

While no significant changes in global ratings of QOL were observed, patient responses suggested improvements in subjective ratings of verbal memory and word finding. Patients also reported an increase in medication side effects which, as the authors suggested, may have been due to increased awareness of these issues through educational presentations.

Ponds and Hendriks (2006) described a treatment program also focused on memory rehabilitation, reporting positive results. Participants were epilepsy patients with objectively defined memory deficits, as determined by the diagnostic neuropsychological assessment. Everyday memory problems were assessed with questionnaires completed by patients and their significant others, who were also asked to monitor patients' memory problems on a daily basis for 2 weeks. Information gleaned from these assessments resulted in a list of ten concrete memory problems, formulated as individual treatment goals. In six to eight sessions, scheduled every 2 weeks, patients learned compensatory strategies for their personally formulated treatment goals. Rather than prescribing strategies, participants were encouraged to choose strategies for the memory problems they were experiencing, apply them to everyday life situations, and discuss in group their experience using these strategies. Participants were also provided with information about epilepsy and memory functioning. Three months after finishing treatment, participants returned for "brush-up" session and a neuropsychological reevaluation to measure treatment effects. The authors reported positive results of this treatment approach, as assessed with subjective rating scales completed by 21 patients and their relatives. The participants reported being more acquainted with strategies to support memory problems and better ability to cope with memory problems in their daily lives. In addition, significant improvements were observed on verbal memory tasks (Hendriks, 2001; Ponds & Hendriks, 2006).

The question has been raised by some investigators whether postsurgical memory decline can be counteracted with a cognitive intervention. In a study investigating the effectiveness of visual imagery as a mnemonic technique in aiding the recall of verbal information in patients after unilateral temporal lobectomy (TL) for treatment of refractory epilepsy, Jones (1974) showed that on a paired-associate learning task, patients with left TL could partially compensate for their verbal memory deficits by using visual imagery, and thus improve their recall. In contrast, patients with amnestic syndromes (resulting from bilateral damage to the mesial temporal structures) derived no benefit from this strategy, and patients with right TL performed similarly to normal controls.

The effects of cognitive remediation on memory outcome after temporal lobe epilepsy (TLE) surgery were also evaluated by Helmstaedter et al. (2008). Patients began treatment 3–15 days after surgery, and the average duration of treatment was 29.3 days. The intervention aimed to strengthen compensation strategies for coping with cognitive impairment and involved repeated practice of computer-based exercises for attention, memory, and executive functioning, with difficulty level adjusted to each patient. The software employed was intended for general use with individuals with compromised brain functioning. The intervention was conceptualized as holistic and included psychoeducation into the effects of brain functioning, cognitive deficits, impact of personality and emotional reactions, as well as individual counseling and occupational and physical therapy. Baseline and outcome assessments included attention measures (letter cancellation) and tests of verbal and figural memory.

Helmstaedter et al. (2008) reported that left TL patients profited less from the rehabilitation than those post-right TL patients. Figural memory was not affected by the rehabilitation, and attention improved independent of treatment. The authors concluded that rehabilitation can counteract the verbal memory decline after temporal lobe resection, particularly in right TL patients with verbal memory problems. However, these results should be interpreted with caution due to methodological limitations, given that

there was no randomization, with patients from another center serving as a control group. In addition, strategies similar to those covered in cognitive rehabilitation were also taught in occupational therapy, making it difficult to tease out the independent effects of the cognitive intervention. Finally, it is unclear whether the benefits of the intervention generalized, as the effects on everyday functioning and on daily living were not investigated.

Other reports in the area of cognitive remediation in epilepsy patients are case studies (e.g., Gupta & Naorem, 2003; Langenbahn, Peery, Rodriguez, Payton, & Dams-O'Connor, 2008). Gupta and Naorem (2003) described cognitive retraining with an epilepsy patient who was taught compensatory strategies (e.g., chunking, imagery) for memory and given exercises for attention (e.g., cancellations). The patient was also instructed in deep breathing relaxation techniques. There was a parallel home-based intervention program under the supervision of a trained family member. Assessment included neuropsychological measures of memory (Rivermead Behavioral Memory Test; Wilson, Cockburn, & Baddeley, 1985) and attention (e.g., digit cancellation task), a self-report questionnaire, and observer ratings of patient's emotional status, administered pre- and post-training. The training was reported to be effective in improving attentional and memory capacities, as well as the emotional status of the patient. However, the issue of practice effects was not addressed, and it is unclear whether the training effects generalized to everyday functioning.

Langenbahn et al. (2008) reported positive results of rehabilitation of a 39-year-old, predominantly Spanish-speaking, Hispanic woman with seizure disorder and left TL. The patient was treated in individual cognitive remediation, psychotherapy, and psychosocial group sessions, once weekly, over a period of 17 months. Treatment was conducted in Spanish by staff with the knowledge about acculturation, patient family structure and values, spiritual beliefs, and cultural beliefs about treatment and recovery. Utilizing techniques used with acquired brain injury patients, initial cognitive remediation goals were to improve attention and memory for auditory and written information. Exercises included visual search for targets of increasing complexity, listening to and reading news articles, and providing a summary of this information. Subsequent treatment goals targeted more complex functions, including verbal conceptualization and flexibility. The treatment approach cognitive flexibility emphasized functional goals (e.g., to attend classes toward a certificate in child care) and provided guided practice in use of strategies in daily life, employing task analysis, structure, graduated cuing, and shaping (Langenbahn et al., 2008).

Cognitive Interventions for Patients with Severe Memory Disturbance

Sohlberg and Mateer (1989) provided a training protocol for teaching individuals with severe memory impairments to independently utilize a compensatory memory notebook. This portable notebook is personalized to the functional needs of the patient. It serves as a means to organize and store information (e.g., calendar, names and phone numbers of important contacts) and can be adapted to patients at various levels of cognitive functioning. The training of patients in functional memory book system incorporates principles of learning theory and consists of three steps. First, during the *acquisition* stage, the patient becomes familiar with the names and functions of each notebook section. Then, the *application* stage involves training in applying the use of the notebook to the appropriate situations. Finally, during the *adaptation* stage, the individual demonstrates the ability to adapt and modify skill when faced with novel situations. Each level of instructions incorporates an *efficiency building* learning parameter, consisting of accuracy and consistency measures that result in skill maintenance and use. Using this protocol, Sohlberg and Mateer (1989) found that an intensive, systematic approach to training in memory book system utilization may improve may improve functional capacity in individuals with severe memory deficits and that many patients went on to independent living.

Aldenkamp and Vermeulen (1991) described memory training efforts with amnestic epilepsy

patients. The training of compensatory memory aids was the primary objective. Patients were also taught specific information, relevant to their jobs (e.g., as a phone operator in a sheltered workshop). The group treatment approach was chosen as most patients found this motivating and a source of support. The training, conducted in six sessions, was co-led by a neuropsychologist and a vocational trainer, both with expertise in epilepsy. Patients underwent a neuropsychological assessment prior to participation in treatment and at 2 months after completion of the program. Based on their observations, the authors concluded that external memory aids can be used to bypass some of the problems in severely amnestic epilepsy patients. They also concluded that it is possible to teach epilepsy patients with memory impairment specific bits of information, skills, or behaviors that are important to their daily needs.

Rehabilitation of Attention Deficits

Rehabilitation programs to address attention impairments have been developed for patients with head injury (Fasotti, Kovacs, Eling, & Brouwer, 2000; Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000), schizophrenia (Hayes & McGrath, 2000), and multiple sclerosis (Plohmann, Kappos, & Brunnschweiler, 1994); however, very few studies have specifically targeted attention problems in epilepsy patients (e.g., Engelberts et al., 2002a). Based on their review of evidence-based cognitive remediation of attention deficits in TBI and stroke patients, Cicerone et al. (2000, 2005) recommended *compensation* strategy training as a *practice standard* during postacute period of rehabilitation.

Engelberts et al. (2002a) evaluated the effectiveness of cognitive rehabilitation for attention deficits in adults with focal seizures, specifically comparing the *retraining* and the *compensation* methods in a randomized controlled study. Fifty patients with no psychiatric comorbidity, IQ over 80, and receiving carbamazepine monotherapy were randomly assigned to the retraining method, the compensation method, or the wait-list control group. Both methods of rehabilitation consisted of six weekly, individual, 1-h sessions. Patients in the retraining method had to rehearse responses on tasks, as task complexity increased automatically with improved performance. During treatment using the compensation method, patients were made aware of their attention and memory failures in daily life and then taught compensatory strategies to target these failures. All patients were evaluated with neuropsychological measures and self-report inventories at pre-training, post-training, and a 6-month follow-up. The results suggested improvements on objective neuropsychological outcome measures, self-reported cognitive outcomes, and QOL at 6-month follow-up both, in the retraining and the compensation method groups relative to the wait-list control group. However, the compensation method was more effective in improving self-reported neuropsychological outcomes and QOL, especially for patients with less education (Engelberts et al. 2002a).

Evaluation of Outcome in Behavioral Interventions for PWE

Measurement of outcome in psychotherapy and cognitive remediation is a major challenge. Methodological issues in outcome measurement have been discussed previously by many authors (e.g., Neuropsychological Rehabilitation Special Issue, Fleminger & Powell, 1999) and, thus, will not be addressed here. In the epilepsy literature, intervention outcomes have been evaluated by objective tests, subjective measures, and observer ratings. In addition, functional measures, such as QOL ratings (QOLIE, Devinsky et al., 1995), aimed at understanding perceptions of PWE in a broad sense have become the "standard of care" in recent years (Gilliam, 2002).

In cognitive remediation interventions, the biggest treatment effects are found when subjective patient report measures are used, and evaluations of results with objective measures have generally been disappointing (Hendriks, 2001). It has also been noted that responses on subjective measures may correlate poorly with objective findings. For example, only moderate correlations (i.e., 0.30–0.40) were found between

self-reported memory problems and the results of assessments using neuropsychological tests (Brown, Dodrill, Clark, & Zych, 1991). When objective neuropsychological measures were used and positive results were reported, the limitations due to practice effects, overlap between the outcome measures and the intervention, and the ecological validity of most measures often were not addressed.

In psychotherapeutic interventions and those providing psychoeducation, outcomes have been measured primarily by self-report ratings. Positive effects of interventions were reported when using patient ratings of disease-related knowledge (e.g., Helgeson et al., 1990), perceptions of self-efficacy in managing epilepsy (DiIorio, Escoffery, et al., 2009), work and social adjustment (Goldstein et al., 2003), as well as symptoms of depression (e.g., Martinovic et al., 2006), anxiety (e.g., Davis et al., 1984), and epilepsy-related fears (Helgeson et al., 1990). Positive outcomes were also observed in studies where self-reported seizure frequency and seizure control were the dependent measures (May & Pfafflin, 2002; Petersen et al., 1984). Unfortunately, objective confirmation of improvement was generally lacking, with the exception of studies investigating patient adherence to medication regimens, where drug serum levels were obtained (Helgeson et al., 1990; Petersen et al., 1984).

It is evident that in order to demonstrate benefits of behavioral interventions for PWE, selecting appropriate outcome measures is critical. In cognitive remediation, standardized neuropsychological measures may not necessarily measure what is expected to change, or these tests may not be sensitive to changes that do take place as a result of an intervention. Wilson (1997) has pointed out that most interventions target impairments, identified by scores on tests, rather than disabilities or manifestation of problems in everyday life, yet rehabilitation is concerned with the treatment of disabilities. Focusing on health and functional outcomes has also been recommended by others in the field (e.g., Fleminger & Powell, 1999). Future studies will need to evaluate the efficacy of these approaches. Studies using appropriate, well-validated outcome assessment instruments will give insight into the benefits of psychological and cognitive interventions for PWE and into the generalizability of intervention training to everyday life. In addition, long-term follow-up with these assessments would shed light on the durability of treatment effects over time.

Recommendations for Educational and Psychotherapeutic Interventions for PWE

The general recommendations for educational programs and psychotherapy provided below are based on the findings of intervention studies in PWE. Due to the very limited number of studies with randomized controlled methodologies thus far, definitive guidelines for practice cannot be made. Given the promising results of many of the interventions discussed above and the dire need for such interventions for PWE, treatment programs that are adequately evaluated and can provide evidence of improved outcomes in PWE are necessary.

The content of psychoeducation interventions for PWE should aim to address the following goals:

(a) Improve knowledge about epilepsy (e.g., etiology, types of seizures)
(b) Improve understanding of treatment options and possible adverse effects of treatment
(c) Improve understanding of the importance of treatment adherence
(d) Improve seizure management (e.g., first aid practices, understanding precipitating factors)
(e) Improve awareness of safety issues (e.g., as pertains to driving)
(f) Instruct in careful recording of seizures and adverse events (e.g., to better guide medication changes)
(g) Teach basics about brain functioning and commonly experienced cognitive problems
(h) Increase awareness of commonly experienced emotional disturbances

(i) Discuss common psychosocial problems, including perceptions of stigma
(j) Discuss other medical conditions (e.g., cerebrovascular disease) that are frequently comorbid with epilepsy and can impact cognition
(k) Improve coping skills
(l) Provide support
(m) Educate family members about epilepsy and its consequences
(n) Provide professional referrals for patients with severe emotional and cognitive problems
(o) Provide information about local resources for PWE

In addition, educational programs that encompass group discussion provide patients with an opportunity to share their experiences and receive feedback from others. Furthermore, interventions that span over a longer period of time allow a bond among group members to develop, and a social network can be formed, which has been described by participants in previous studies as one of the most valuable components of interventions (Johanson et al., 2001). During sessions, group members should also be given opportunities to ask questions, so that the necessary clarifications can be provided and misconceptions about epilepsy and its treatment can be targeted. Patients at different points in the course of having epilepsy can benefit from educational programs; however, it is likely that more benefit could be derived by patients who receive education early on after receiving epilepsy diagnosis. Moreover, educational programs after the first seizure could be valuable as a preventive measure against developing epilepsy.

Given the findings of limited efficacy of educational programs in reducing emotional distress, as neither SEE (Helgeson et al., 1990) nor MOSES (May & Pfafflin, 2002) showed a significant impact on QOL or mood symptoms, appropriate referrals and recommendations for psychotherapy (group or individual) will need to be made, and problems of patients with severe psychopathology may require immediate attention. Similarly, patients evidencing notable cognitive problems will require referrals for cognitive remediation where those problems can be addressed more specifically. In general, it is important for group leaders to be aware of patients' cognitive problems and ensure that education materials and handouts are appropriate to their level of cognitive and intellectual functioning.

With regard to psychotherapy, the task is to adapt an approach shown effective in RCTs in order to meet the needs of PWE in an evidence-based treatment. Extensive research has been conducted with other chronic disease patients, such as HIV and diabetes, specifically evaluating behavioral interventions that promote effective coping and examining the various mechanisms of coping. In contrast, there has not been similar progress in research of this area in epilepsy. In epilepsy there has not been similar progress in research of this area. Findings from studies with other chronic disease patients can inform intervention efforts with epilepsy patients; however, more studies are needed to determine the applicability of these techniques. In the epilepsy literature, among specific coping strategies, cognitive restructuring and problem-solving were identified as strategies that appear to be associated with lower levels of anxiety, depression, and other indicators of psychosocial well-being in PWE (Bishop & Allen, 2007).

Psychotherapy approach will likely depend on the baseline psychological functioning, the level of education and intellectual functioning, as well as seizure variables. Among the various approaches, cognitive behavioral therapy (CBT) appears to have a significant potential for alleviating epilepsy patients' emotional distress and improving their psychosocial functioning, self-efficacy, and possibly seizure control. Cognitive therapy (Beck, 1976) has been studied in more RCTs than any other psychosocial treatment and has been shown to provide effective treatment for numerous clinical problems and disorders, including those in the context of chronic illnesses. Psychotherapy can be based on traditional CBT approaches to the treatment of depression and anxiety, combined with intervention techniques most applicable to patients with chronic illness in general, and with

the knowledge of issues relevant specifically to epilepsy patients. Therapy can be conducted in individual sessions or in groups, as there is no definitive evidence in the epilepsy literature that either one format is more beneficial to patients than the other.

Cognitive behavioral therapy, while structured, allows for flexibility, whereby treatment can be adapted to the specific needs of PWE. Therapists working with epilepsy patients need to make sure that patients are able to adequately attend, engage in, and benefit from the intervention provided, given that patients may present with cognitive deficits, including problems with attention, executive functions, memory, and mental slowing. For example, it may be necessary to adjust the pace of the intervention, include concrete examples, and incorporate strategies, such as memory notebook to ensure carryover. Memory aids and informational handouts will also help patients when epilepsy-related psychoeducation is provided as part of therapy.

In formulating hypotheses in treatment about factors causing and maintaining patients' problems, specific attention needs to be paid to epilepsy-related issues. Cognitive restructuring strategies can be targeted at patients' negative automatic thoughts and beliefs about epilepsy, its treatments, and themselves, as individuals who have a seizure disorder. Integrating progressive relaxation techniques is often beneficial (Puskarich et al., 1992), particularly in patients for whom stress is a frequent precipitant of seizures or those with other identifiable seizure triggers. Other special considerations in therapy with epilepsy patients include attention to safety when introducing the idea of maximizing pleasurable activities. Specific discussions of the effects of mood symptoms on ability to manage epilepsy and regular monitoring of their functioning in this area are particularly important. Of critical importance is the evaluation of suicide risks throughout treatment, given that epilepsy is associated with higher prevalence of suicidal ideation (Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007).

The problem-solving component of therapy can be informed by interventions shown to be effective in patients with other chronic illnesses, specifically by work of Nezu and colleagues (Nezu, Nezu, Friedman, Faddis, & Houts, 1998, Nezu, Nezu, Felgoise, McClure, & Houts, 2003) conducted with cancer patients. Using the techniques they describe, aimed at lessening emotional distress and improving QOL, epilepsy patients can be taught to define the problem, generate alternatives, implement the solution, and review the outcome. Problem-solving techniques also include teaching patients to take an overwhelming task and break it into manageable steps. A problem list can be collaboratively arrived at with the epilepsy patient. Targets for problem-solving with epilepsy patients can include obtaining information about treatment options, planning and organizing to ensure AED compliance, addressing treatment side effects, and confronting social isolation.

Recommendations for Cognitive Remediation for PWE

The following section is intended to provide guidance to clinicians when designing and implementing cognitive rehabilitation interventions for PWE. It would be premature to propose any definitive guidelines for this type of treatment, given that the cognitive remediation literature as applied to epilepsy is in its infancy, with very few randomized controlled studies conducted. The design of cognitive remediation interventions for PWE can be informed from multiple sources, including neuropsychology, learning theory, interventions with demonstrated efficacy conducted with other patient groups, and by the findings from existing interventions with epilepsy patients.

As a first step, a thorough neuropsychological assessment can guide cognitive remediation by providing the necessary information about the nature and the severity of cognitive impairment and about the overall level of intellectual functioning. Detailed understanding of individual's

cognitive strengths and weaknesses and an appreciation of his or her functional goals (e.g., return to work or studies, participation at home) will help to identify relevant areas for rehabilitation. Treatment goals can be identified collaboratively with a patient and, whenever possible, their family member or significant other. These goals must be concrete and adjusted to the specific needs of patients. It is also important to assess patient's level of awareness of deficits and their willingness to engage in the intervention, as lack of awareness is a significant barrier to remediation (Prigatano, 1999). Improving patients' understanding of their cognitive strengths and weaknesses and the effects of cognitive deficits in their daily lives can make them more likely to engage in the intervention and learn compensatory behaviors.

While memory problems are the dominant complaint in the clinical practice of epilepsy care (Hendriks, 2001) and are the key domain targeted by most existing interventions for PWE, attention problems often underlie memory difficulties, as well as problems with other higher order functions. Attentional disturbances can obscure intact cognitive abilities and constitute a major obstacle to rehabilitation (Ben-Yishai, Piasetsky, & Rattock, 1987). Thus, in patients with primary deficits in attention-concentration, it is important to ameliorate these problems before proceeding with attempts to remediate other functions, such as memory (Ben-Yishai et al., 1987). Specific techniques can include Attention Process Training (APT; Sohlberg & Mateer, 1987), designed to remediate and improve attentional systems, including sustained, alternating, selective, and divided attention. While this technique has not been evaluated specifically in PWE, it has been shown to be effective in other patient populations, such as those with acquired brain injury (Sohlberg et al., 2000) and cancer (Butler & Copeland, 2002). In epilepsy patients, while both retraining and compensation methods for attention deficits were shown to be effective, the use of compensatory techniques was more effective with patients who have low levels of education (Engelberts et al., 2002a), and this approach has been recommended as a practice standard based on findings of studies in TBI and stroke (Cicerone et al., 2000, 2005). Compensatory strategies for attention deficits can include modifications to the environment and the use of external aids to help track and organize information (Sohlberg & Mateer, 2001).

Interventions targeting memory problems in PWE can focus on memory strategy training, as this approach has received the most research support (Cicerone et al., 2000, 2005). In cognitive remediation for participants with *mild* memory problems, strategies can include external and internal compensatory aids. External memory strategies can include: (1) means to organize and store information (e.g., calendar, diary, mobile phone), (2) methods to remind patients to perform a particular activity at a specified time in the future (e.g., pagers, alarms), and (3) environmental modifications to decrease the impact of memory deficit on daily life.

Internal aids can include verbal strategies (e.g., forming acronyms) and visual imagery (e.g., constructing visual images for information that is to be remembered; loci method). Many of these techniques have been around for centuries, and detailed discussions of the various strategies have been offered by many authors (e.g., Sohlberg & Mateer, 2001; Wilson, 1987). Selection of cognitive remediation strategies for patients can be guided by the findings of their neuropsychological evaluation. In PWE, the lateralization and localization of the epileptogenic focus are important factors to consider when offering strategies. Patients with left temporal lobe lesions have been found to be able to partially compensate for their verbal memory deficits using visual imagery (Jones, 1974). In contrast, patients with right temporal lobe lesions have been observed to resort to verbal labeling in attempts to partially compensate for their memory deficits for certain kinds of nonverbal material, such as unfamiliar faces (Kimura, 1963; Milner, 1968).

In terms of localization of seizure focus and cognitive dysfunction, patients with deficits in executive functioning, which may be prominent with seizures originating in the frontal lobe, but also present in TLE and other types of epilepsy,

may not be able to initiate and apply internal aid strategies. Depending on the extent of their deficits, they may also require additional assistance with organization and execution of external procedures. Many individuals, including those with minimal executive dysfunction, benefit from organizational strategies, including category formation, chunking, simplifying, and reducing the amount of information to be remembered. Strategies to improve problem-solving, which are sometimes incorporated in psychotherapeutic interventions, as discussed above, can also be used to target deficits in executive functioning. For example, Rath, Simon, Langenbahn, Sherr, and Diller (2003) described group treatment for problem-solving deficits for patients with TBI and reported positive results of this intervention as compared to conventional group neuropsychological rehabilitation. Patients demonstrated improvements in problem-solving, as assessed by various measures, including tests of executive functions, self-appraisal ratings, and objective observer ratings. Future studies can evaluate the efficacy of interventions for problem-solving in PWE.

Epilepsy patients with *severe* memory impairment require external memory aids with direct application to functional activities and needs. Training in the use of a compensatory memory notebook can be conducted according to the procedure detailed by Sohlberg and Mateer (1989). Possible memory notebook sections can include pertinent autobiographical data, calendar, to-do lists, medications list and schedule, names, and journal of daily events. Thus, the notebook can include sections to record past events (i.e., retrospective memory support) and intended actions or future events (i.e., prospective memory support). Neuropsychological evaluation results can be used to determine the level of complexity of the notebook system. Alternatively, electronic memory aids may be more useful for some individuals. Regardless of the method used, family members need to understand the system and assist in implementing it (Sohlberg & Mateer, 1989).

Patients with severe memory impairment can also be taught specific bits of information, skills, or behaviors that are important to their daily needs. Sohlberg and Mateer (1989) describe techniques for teaching domain-specific knowledge, which include mnemonic strategies, expanded rehearsal, and use of priming. Tasks considered domain specific can include procedures for operating a computer and learning one's medication schedule, orientation information, and names of people. In their intervention for amnestic epilepsy patients, Aldenkamp and Vermeulen (1991) employed external memory aids and verbal mnemonic strategies to teach an amnestic patient key phone numbers, enabling her to perform a job as a telephone operator in a sheltered workshop. Her job was also organized with a fixed, step-by-step scheme. While the techniques employed in their intervention to confront memory problems in severely amnestic patients were not specific for epilepsy, given their positive results, these techniques were deemed "sufficiently operational to be applicable in a clinical group such as epilepsy" (Aldenkamp & Vermeulen, 1991).

In addressing cognitive deficits in PWE, the possible contribution of emotional disorder needs to be considered. Patients' cognitive deficits may be exacerbated by their emotional distress, and they may be unable to benefit from cognitive remediation unless their mood symptoms are addressed. Depending on the severity of emotional distress, decisions about an appropriate course of action and referrals will need to be made. Effective interventions targeting cognitive problems require a clinician to attend to patients' emotional states and provide the necessary support, education, and strategies for managing distress.

The educational component, as part of cognitive remediation interventions, can be devoted to providing PWE with information about the effects of epilepsy, its treatment, commonly experienced cognitive and mood problems, and the effect of mood on cognition. In discussing memory, realistic expectations. About possibilities for improvement in memory functioning will need to be set. Patients should also be made aware that there is no single technique that can produce positive effects on memory and that

the best method is likely to differ for each individual. Information provided in psychoeducation for PWE should be accompanied by handouts to aid learning. In fact, participants often report that being given informational handouts is one of the most valuable components of an intervention (e.g., Barr et al., 2004).

When designing a cognitive remediation intervention for PWE, decisions will need to be made regarding the timing, length, and format of an intervention. With regard to timing, it is unclear when during the course of epilepsy cognitive remediation can be most effective for patients. Questions have been raised whether interventions prior to surgery would be beneficial, and at which point postsurgery interventions can be used to counteract possible postsurgical memory decline (Helmstaedter et al., 2008). The epilepsy literature does not yet provide definitive answers to these questions, and well-designed trials of pre- versus postoperative rehabilitation would be informative. With regard to the length of an intervention, Aldenkamp and Vermeulen (1991) found short training periods beneficial and observed a plateau in improvement after four or five sessions. Other interventions have been more intensive and/or spanning a number of weeks (e.g., Helmstaedter et al., 2008; Langenbahn et al., 2008), with positive results reported. This approach allows more opportunity for skill practice.

The choice of treatment format (i.e., group or individual) will likely be guided by the criteria used in selecting participants. In general, the group format in prior studies has been found by participants to be more motivating than individual training sessions, and participants tend to form a supportive network (Aldenkamp, Hendriks, & Vermeulen, 2000). The role of social support cannot be underestimated, and in PWE it has been found to relate to QOL, irrespective of seizure control (Amir, Roziner, Knoll, et al., 1999). Interventions conducted in the form of group training also have the advantages of being cost-effective. On the other hand, cognitive remediation conducted with a patient one-on-one allows for more individualized work toward treatment goals, which may be particularly important when dealing with a heterogeneous patient population. Given the individual differences among cognitive profiles and functional needs in epilepsy patients, there is a clear need for flexible approach in treatment. This is easier to accomplish in individualized treatment rather than in groups; however, flexibility of approach is an essential consideration regardless of the format chosen.

Conclusion

Comprehensive care of epilepsy patients requires that emotional, cognitive, and psychosocial problems be addressed, given their high prevalence in this patient population. Despite the increased awareness of these problems, few psychotherapeutic and cognitive remediation treatments for PWE have been developed, and these are infrequently utilized and evaluated using proper methodology. The findings of studies reviewed in this chapter suggest that behavioral interventions can reduce emotional distress and cognitive morbidity, increase treatment compliance, and improve psychosocial functioning and QOL, as well as seizure control in epilepsy patients. The results are encouraging not only in studies of patients with refractory seizures, but also when psychological interventions were administered to patients with well-controlled epilepsy (Engelberts et al., 2002a, 2002b). Thus, there is a clear need for behavioral intervention development in epilepsy and for robust and well-designed trials evaluating the various approaches.

Until epilepsy-specific intervention strategies are available, treatment techniques supported by research with other patient groups can be utilized. However, epilepsy-specific factors will have to be taken into account, and the applicability of these techniques examined. In contrast to TBI or stroke where after an acute phase, patients will generally improve, epilepsy is chronic, and concerns about cognitive, psychological, and social functioning deteriorating over time have been voiced. Given that not all patients with epilepsy will necessarily show cognitive deterioration (Hermann et al., 2008), the findings from inter-

ventions literature in TBI and stroke are likely applicable. In addition, findings from behavioral treatment studies conducted with other chronic disease patients can also inform the treatment of PWE.

Finally, it should be noted that while the importance of considering cultural relevance when providing an intervention has been recognized (Gupta & Naorem, 2003), there are very few reports of such interventions. More efforts to gain better understanding of cultural beliefs about epilepsy and its treatment are necessary, as these beliefs influence the treatment process and outcome. In addition, better understanding of factors impacting QOL in epilepsy patients from different cultural, ethnic, and socioeconomic backgrounds is needed in order to provide effective treatment to diverse patient groups.

In summary, successful interventions have the potential to greatly impact the quality of care for PWE and could lead to improved outcomes and lowered disability and health-care costs.

Future randomized controlled studies with adequate sample sizes and employing well-validated outcome assessment instruments will give insight into the benefits of behavioral interventions in epilepsy and will be in the position to evaluate the empirical evidence for the recommendations made in this chapter.

References

Aldenkamp, A. P. (2006). Cognitive impairment in epilepsy: state of affairs and clinical relevance. *Seizure, 15*, 219–220.

Aldenkamp, A. P., Baker, G. A., & Meador, K. (2004). The neuropsychology of epilepsy: What are the factors involved? *Epilepsy and Behavior, 5*, S1–S2.

Aldenkamp, A. P., Hendriks, M., & Vermeulen, J. (2000). Cognitive deficits in epilepsy: is there a treatment? In D. Schmidt & S. C. Schachter (Eds.), *Epilepsy: Problem solving in clinical practice*. London: Martin Dunitz, Ltd.

Aldenkamp, A. P., & Vermeulen, J. (1991). Neuropsychological rehabilitation of memory function in epilepsy. *Neuropsychological Rehabilitation, 3*, 199–214.

Amir, M., Roziner, I., Knoll, A., et al. (1999). Self efficacy and social support as mediators in the relation between disease severity and quality of life in patients with epilepsy. *Epilepsia, 40*, 216–224.

Au, A., Chan, F., Li, K., Leung, P., Li, P., & Chan, J. (2003). Cognitive-behavioral group treatment program for adults with epilepsy in Hong Kong. *Epilepsy & Behavior, 4*, 441–446.

Barr, W. B., Morrison, C., Isaacs, K., & Devinsky, O. (2004). Group treatment of memory disorders in patients with epilepsy. *Epilepsia, 45*(S7), 171.

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. New York, NY: International Universities Press.

Ben-Yishai, Y., Piasetsky, E. B., & Rattock, J. (1987). A systematic method for ameliorating disorders of basic attention. In M. J. Meyer, A. L. Benton, & L. Diller (Eds.), *Neuropsychological Rehabilitation*. Edinburgh: Churchill Livingstone.

Beyenburg, S., Mitchell, A. J., Schmidt, D., Elger, C. E., & Reuber, M. (2005). Anxiety in patients with epilepsy: Systematic review and suggestions for clinical management. *Epilepsy & Behavior, 7*, 161–171.

Bishop, M., & Allen, C. A. (2003). The impact of epilepsy on quality of life: a qualitative analysis. *Epilepsy and Behavior, 4*, 226–233.

Bishop, M., & Allen, C. A. (2007). Coping with epilepsy: Research and interventions. In E. Martz, H. Livneh, & B. A. Wright (Eds.), *Coping with chronic illness and disability: Theoretical, empirical, and clinical aspects* (pp. 241–266). New York, NY: Springer.

Boylan, L. S., Flint, L. A., Labovitz, D. L., Jackson, S. C., Starner, K., & Devinsky, O. (2004). Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology, 62*, 258–261.

Bradley, P. M., & Lindsay, B. (2008). Care delivery and self-management strategies for adults with epilepsy. *Cochrane Database of Systematic Reviews*, *Issue 1*, Art. No.: CD006244. doi:10.1002/14651858.CD006244.pub2.

Brown, F. H., Dodrill, C. B., Clark, T., & Zych, K. (1991). An investigation of the relationship between self-report of memory functioning and memory test performance. *Journal of Clinical Psychology, 47*, 772–777.

Butler, R. W., & Copeland, D. R. (2002). Attentional processes and their remediation in children treated for cancer: a literature review and the development of a therapeutic approach. *Journal of International Neuropsychological Society, 8*, 115–124.

Cicerone, K. D., Dahlberg, C., Kalmar, K., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., et al. (2000). Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Archives of Physical Medicine and Rehabilitation, 81*, 1596–1615.

Cicerone, K. D., Dahlberg, C., Malec, J. F., Langenbahn, D. M., Felicetti, T., Kneipp, S., et al. (2005). Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Archives of Physical Medicine and Rehabilitation, 86*, 1681–1692.

Cramer, J. A., Perrine, K., Devinsky, O., Bryant-Comstock, L., Meador, K., & Hermann, B. P. (1998). Development and cross-cultural translation of a

31-item quality of life questionnaire (QOLIE-31). *Epilepsia, 39*, 81–88.

Cramer, J. A., Perrine, K., Devinsky, O., & Meador, K. (1996). A brief questionnaire to screen for quality of life in epilepsy The QOLIE-10. *Epilepsia, 37*(6), 577–582.

Dahl, J., Melin, L., & Lund, L. (1987). Effects of a contingent relaxation treatment program on adults with refractory epileptic seizures. *Epilepsia, 28*(2), 125–132.

Davis, G. R., Armstrong, H. E., Jr., Donovan, D. M., & Temkin, N. R. (1984). Cognitive-behavioral treatment of depressed affect among epileptics: Preliminary findings. *Journal of Clinical Psychology, 40*(4), 930–935.

Devinsky, O., Vickrey, B. G., Cramer, J., Perrine, K., Hermann, B., Meador, K., et al. (1995). Development of the quality of life in epilepsy inventory. *Epilepsia, 36*, 1089–1104.

DiIorio, C., Escoffery, C., Yeager, K. A., McCarty, F., Henry, T. R., Koganti, A., et al. (2009). WebEase: Development of a Web-based epilepsy self-management intervention. *Preventing Chronic Disease, 6*(1), 1–7.

DiIorio, C., Osborne Shafer, P., Letz, R., et al. (2003). The association of stigma with self-management and perceptions of health care among adults with epilepsy. *Epilepsy & Behavior, 4*, 259–267.

DiIorio, C., Reisinger, E. L., Yeager, K. A., & McCarty, F. (2009). A telephone-based self-management program for people with epilepsy. *Epilepsy & Behavior, 14*, 232–236.

DiIorio, C., & Yeager, K. (2003). The epilepsy self-efficacy scale. In O. L. Strickland & C. DiIorio (Eds.), *Measurement of nursing outcomes: Self care and coping* (2nd ed., Vol. 3, pp. 40–51). New York, NY: Springer Publishing Company.

Dodrill, C. (2008). Emotional and psychosocial factors in epilepsy. In J. E. Morgan & J. H. Ricker (Eds.), *Textbook of clinical neuropsychology*. New York, NY: Taylor and Francis.

Dodrill, C. B., Batzel, L. W., Queisser, H. R., & Temkin, N. (1980). An objective method for the assessment of psychological and social problems among epileptics. *Epilepsia, 21*, 123–135.

Elger, C. E., Helmstaedter, C., & Kurthen, M. (2004). Chronic epilepsy and cognition. *Lancet Neurology, 3*(11), 663–672.

Elixhauser, A., Kline Leidy, N., Meador, K., Means, S., & Willian, M. K. (1999). The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. *Epilepsy Research, 37*, 13–24.

Engel, J., Pedley, T. A., Aicardi, J., & Dichter, M. A. (2007). *Epilepsy: A comprehensive textbook*. Philadelphia, PA: Lippincott Williams & Wilkins.

Engelberts, N. H. J., Klein, M., Ader, H., Heimans, J. J., Kasteleijn-Nolst Trenite, D. G. A., & van der Ploeg, H. M. (2002a). The effectiveness of cognitive rehabilitation for attention deficits in focal seizures: A randomized controlled study. *Epilepsia, 43*, 587–595.

Engelberts, N. H. J., Klein, M., Kasteleijn-Nolst Trenite, D. G. A., Heimans, J. J., & van der Ploeg, H. M. (2002b). The effectiveness of psychological interventions for patients with relatively well-controlled epilepsy. *Epilepsy and Behavior, 3*, 420–426.

Ettinger, A., Reed, M., Cramer, J., & Epilepsy Impact Project Group. (2004). Depression and comorbidity in community-based patients with epilepsy or asthma. *Neurology, 63*, 1008–1014.

Fasotti, L., Kovacs, F., Eling, P. A., & Brouwer, W. H. (2000). Time pressure management as a compensatory strategy training after closed head injury. *Neuropsychological Rehabilitation, 10*, 47–65.

Faught, E., Duh, M. S., Weiner, J. R., Guerin, A., & Cunnington, M. C. (2008). Nonadherence to antiepileptic drugs and increased mortality: Findings from the RANSOM study. *Neurology, 71*, 1572–1578.

Faught, E., Weiner, J. R., et al. (2009). Impact of nonadherence to antiepileptic drugs on health care utilization and costs: Findings from the RANSOM study. *Epilepsia, 50*, 501–509.

Fleminger, S., & Powell, J. (1999). Editorial. *Neuropsychological Rehabilitation, 9*, 225–230.

Gillham, R. (1990). Refractory epilepsy: An evaluation of psychological methods in out-patient management. *Epilepsia, 31*, 427–432.

Gilliam, F. G. (2002). Optimizing health outcome in active epilepsy. *Neurology, 58*(Suppl. 5), S9–S19.

Giovagnoli, A. R., & Avanzini, G. (1999). Learning and memory impairment in patients with temporal lobe epilepsy: Relation to the presence, type, and location of brain lesion. *Epilepsia, 40*(7), 904–911.

Goldstein, L. H., McAlpine, M., Deale, A., Toone, B. K., & Mellers, J. D. C. (2003). Cognitive behavioral therapy with adults with intractable epilepsy and psychiatric co-morbidity: Preliminary observations on changes in psychological state and seizure frequency. *Behaviour Research and Therapy, 41*(4), 447–460.

Green, P., & Allen, L. (1997). *Memory complaints inventory*. Durham, NC: CogniSyst.

Gupta, A., & Naorem, T. (2003). Case study. *Cognitive retraining in epilepsy. Brain Injury, 17*(2), 161–174.

Halgren, E., Stapleton, J., Domalski, T., Swartz, B. E., Delgado-Excueta, A. V., & Walsh, G. O. (1991). Memory dysfunction in epilepsy: patient as a derangement of normal physiology. In D. Smith, D. Treiman, & M. Trumble (Eds.), *Advances in neurology; Neurobehavioral problems* (Vol. 55). New York, NY: Raven Press.

Hayes, R. L., & McGrath, J. J. (2000). Cognitive rehabilitation for people with schizophrenia and related conditions. *Cochrane Database of Systematic Reviews*, *Issue 3*, Art. No.: CD000968.

Helgeson, D. C., Mittan, R., Tan, S. Y., & Chayasirisobhon, S. (1990). Sepulveda epilepsy education: The efficacy of a psychoeducational treatment program in treating medical and psychosocial aspects of epilepsy. *Epilepsy, 31*, 75–82.

Helmstaedter, C., Kemper, B., & Elger, C. E. (1996). Neuropsychological aspects of frontal lobe epilepsy. *Neuropsychologia, 34*, 399–406.

Helmstaedter, C., Loer, B., Wohlfahrt, R., Hammen, A., Saar, J., Steinhoff, B. J., et al. (2008). The effects of cognitive rehabilitation on memory outcome after temporal lobe epilepsy surgery. *Epilepsy & Behavior, 12*, 402–409.

Hendriks, M. P. H. (2001). Neuropsychological compensatory strategies for memory deficits in patients with epilepsy. In M. Pfafflin, R. T. Fraser, R. Thorbecke, U. Specht, & P. Wolf (Eds.), *Comprehensive* (pp. 87–94). Herts: John Libbey & Company Ltd.

Hermann, B. P., Seidenberg, M., & Jones, J. (2008). The neurobehavioral comorbidities of epilepsy: Can a natural history be developed. *Lancet of Neurology, 7*, 151–160.

Hermann, B. P., Vickrey, B., Hays, R. D., Cramer, J., Devinsky, O., Meador, K., et al. (1996). A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Research, 113–118*.

Hermann, B. P., & Whitman, S. (1984). Behavioral and personality correlates of epilepsy: a review, methodological critique, and conceptual model. *Psychological Bulletin, 95*(3), 451–497.

Johanson, M., Chaplin, J. E., & Wedlund, J. (2001). A holistic neurorehabilitation programme for people with epilepsy: Theoretical approach, evaluation and long-term follow up. In M. Pfafflin, R. T. Fraser, R. Thorbecke, U. Specht, & P. Wolf (Eds.), *Comprehensive care for people with epilepsy* (pp. 203–211). Herts: John Libbey & Company Ltd.

Jokeit, H., & Ebner, A. (1999). Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. *Journal of Neurosurgery and Psychiatry, 67*, 44–50.

Jones, M. K. (1974). Imagery as a mnemonic aid after left temporal lobectomy: contrast between material-specific and generalized memory disorders. *Neuropsychologia, 12*, 21–30.

Kanner, A. M. (2007). Epilepsy and mood disorders. *Epilepsia, 48*(Suppl. 9), 20–22.

Kimura, D. (1963). Right temporal lobe damage. *Archives of Neurology, 8*, 264–271.

Langenbahn, D. M., Peery, S., Rodriguez, I. A., Payton, G., & Dams-O'Connor, K. (2008). *Neuropsychological rehabilitation of a hispanic woman and seizure disorder*. New York, NY: National Academy of Neuropsychology. Presented at the Annual Conference of the National Academy of Neuropsychology.

Lantz, D. L., & Sherman, M. B. (1988). Neuropsychological assessment of subjects with uncontrolled epilepsy: effects of EEG biofeedback training. *Epilepsia, 29*(2), 163–171.

Leidy, N. K., Elixhauser, A., Rentz, A. M., Beach, R., Pellock, J., Schachter, S., et al. (1999). Telephone validation of the quality of life in epilepsy inventory – 89 (QOLIE-89). *Epilepsia, 40*(1), 97–106.

Loring, D. W., Meador, K. J., & Lee, G. P. (2004). Determinants of quality of life in epilepsy. *Epilepsy and Behavior, 5*, 976–980.

Lundren, T., Dahl, J., Melin, L., & Kies, B. (2006). Evaluation of acceptance and commitment therapy for drug refractory epilepsy: A randomized controlled trial in South Africa – A pilot study. *Epilepsia, 47*, 2173–2179.

Martinovic, Z., Simonovi, P., & Djoki, R. (2006). Preventing depression in adolescents with epilepsy. *Epilepsy & Behavior, 9*, 619–624.

May, T. W., & Pfafflin, M. (2002). The efficacy of an educational treatment program for patients with epilepsy (MOSES): Results of a controlled, randomized study. *Epilepsia, 43*(5), 539–549.

May, T. W., & Pfafflin, M. (2005). Psychoeducational programs for patients with epilepsy. *Disease Management and Health Outcomes, 13*(3), 185–199.

McLaughlin, D. P., Pachana, N. A., & Mcfarland, K. (2008). Stigma, seizure frequency, and QOL: The impact of epilepsy in late adulthood. *Seizure, 17*(3), 281–287.

Milner, B. (1968). Visual recognition and recall after right temporal-lobe excision in man. *Neuropsychologia, 6*, 191–209.

Morrell, M. J. (2002). Stigma and epilepsy. *Epilepsy and Behavior, 3*(6(S2)), 21–25.

Nagai, Y., Goldstein, L. H., Fenwick, P. B. C., & Trimble, M. R. (2004). Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: A preliminary randomized controlled study. *Epilepsy & Behavior, 3*, 216–223.

Nakhutina, L., Gonzalez, J., Prus, N., & Grant, A. C. (2009). Adherence to antiepileptic drugs and beliefs about medication among patients with epilepsy. *Epilepsia, 50*, 115.

Nezu, A. M., Nezu, C. M., Felgoise, S. H., McClure, K. S., & Houts, P. S. (2003). Project genesis: Assessing the efficacy of problem-solving therapy for distressed adult cancer patients. *Journal of Consulting and Clinical Psychology, 71*, 1036–1048.

Nezu, A. M., Nezu, C. M., Friedman, S. H., Faddis, S., & Houts, P. S. (1998). *Helping cancer patients cope: A problem-solving approach*. Washington, DC: American Psychological Association.

Petersen, G. M., McLean, S., & Millingen, K. S. (1984). A randomized trial of strategies to improve patient compliance with anticonvulsant therapy. *Epilepsia, 25*, 412–417.

Plohmann, A., Kappos, L., & Brunnschweiler, H. (1994). Evaluation of a computer-based attention retraining program for patients with multiple sclerosis. *Swiss Archives of Neurology and Psychiatry, 145*, 35–36.

Ponds, R., & Hendriks, M. (2006). Cognitive rehabilitation of memory problems in patients with epilepsy. *Seizure, 15*, 267–273.

Prigatano, G. P. (1999). *Principles of neuropsychological rehabilitation*. New York, NY: Oxford University Press.

Prigatano, G., Fordyce, D., Zeiner, H., Roueche, J., Pepping, M., & Wood, B. (1984). Neuropsychological rehabilitation after closed head injury in young adults. *Journal of Neurology, Neurology, Neurosurgery and Neuropsychiatry, 47*, 505–513.

Prus, N., Nakhutina, L., & Grant, A. C. (2009). Perceived epilepsy stigma and quality of life in epilepsy. *Epilepsia, 50*(Suppl 11), p219.

Puskarich, C. A., Whitman, S., Dell, J., Hughes, J. R., Rosen, A. J., & Hermann, B. P. (1992). Controlled examination of effects of progressive muscle relaxation training on seizure reduction. *Epilepsia, 33*(4), 675–680.

Ramaratnam, S., Baker, G. A., & Goldstein, L. H. (2008). Psychological treatments for epilepsy. *Cochrane Database of Systematic Reviews*, *Issue 3*, Art. No.: CD002029. doi:10.1002/14651858.CD002029.pub3.

Rath, J. F., Simon, D., Langenbahn, D. M., Sherr, R. S., & Diller, L. (2003). Group treatment of problem-solving deficits in outpatients with traumatic brain injury: A randomized outcome study. *Neuropsychological Rehabilitation, 13*(4), 461–488.

Reid, S., Specht, U., Thornbecke, R., Goecke, K., & Wohlfarth, R. (2001). MOSES: An educational program for patients with epilepsy and their relatives. *Epilepsia, 42*(Suppl 3), 76–80.

Rousseau, A., Hermann, B., & Whitman, S. (1985). Effects of progressive relaxation on epilepsy: Analysis of a series of cases. *Psychological Reports, 57*, 1203–1212.

Shaw, E. J., Stokes, T., Camosso-Stefinovic, J., Baker, R., Baker, G. A., & Jacoby, A. (2007). A self-management education for adults with epilepsy. *Cochrane Database of Systematic Reviews*, *Issue 2*, Art. No.: CD004723. doi:10.1002/14651858.CD004723.pub2.

Shulman, M. B., & Barr, W. B. (2002). Treatment of memory disorders in epilepsy. *Epilepsy & Behavior, 3*, S30–S34.

Smeets, V. M., van Lierop, B. A., Vanhoutvin, J. P., Aldenkamp, A. P., & Nijhuis, F. J. (2007). Epilepsy and employment: Literature review. *Epilepsy & Behavior, 10*, 354–362.

Smith, G., Ferguson, P. L., Saunders Lee, L., Wagner, J. L., Wannamaker, B. B., & Selassie, A. W. (2009). Psychosocial factors associated with stigma in adults with epilepsy. *Epilepsy & Behavior, 16*, 484–490.

Snyder, M. (1983). Effect of relaxation on psychological functioning in persons with epilepsy. *Journal of Neuroscience Nursing, 15*(4), 250–254.

Sohlberg, M., & Mateer, C. A. (1987). Effectiveness of an attention training program. *Journal of Clinical and Experimental Neuropsychology, 9*, 117–130.

Sohlberg, M., & Mateer, C. A. (1989). Training use of compensatory memory books: A three stage behavioral approach. *Journal of Clinical and Experimental Neuropsychology, 11*(6), 871–891.

Sohlberg, M., & Mateer, C. A. (2001). *Cognitive rehabilitation. An integrative neuropsychological approach*. New York, NY: The Guilford Press.

Sohlberg, M., McLaughlin, K. A., Pavese, A., Heidrich, A., & Posner, M. I. (2000). Evaluation of attention process training and brain injury education in persons with acquired brain injury. *Journal of Clinical and Experimental Neuropsychology, 22*, 656–676.

Spector, S., Tranah, A., Cull, C., & Goldstein, L. H. (1999). Reduction in seizure frequency following a short-term group intervention for adult with epilepsy. *Seizure, 8*(5), 297–303.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*, 279–306.

Sterman, M. B. (1990). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operantconditioning. *ClinicalElectroencephalography, 32*(1), 45–55.

Tan, S. Y., & Bruni, J. (1986). Cognitive behavioral therapy with adult patients with epilepsy: A controlled outcome study. *Epilepsia, 27*(3), 225–233.

Tellez-Zenteno, J. F., Patten, S. B., Jette, N., Williams, J., & Wiebe, S. (2007). Psychiatric comorbidity in epilepsy: A population-based analysis. *Epilepsia, 48*(12), 2336–2344.

Thapar, A., Kerr, M., & Gordon, H. (2009). Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. *Epilepsy & Behavior, 14*, 134–140.

Van den Broek, M. D., Downes, J., Johnson, Z., Dayus, B., & Hilton, N. (2000). Evaluation of an electronic memory aid in the neuropsychological rehabilitation of prospective memory deficits. *Brain Injury, 14*(5), 455–462.

Wade, T. K., & Troy, J. C. (2001). Mobile phones as a new memory aid: A preliminary investigation using case studies. *Brain Injury, 15*(4), 305–320.

Wilson, B. (1987). *Rehabilitation of memory*. New York, NY: Guilford Press.

Wilson, B. (1997). Cognitive rehabilitation: How it is and how it might be. *Journal of the International Neuropsychological Society, 3*, 487–496.

Wilson, B. A., Cockburn, J., & Baddeley, A. (1985). *The Rivermead Behavioral Memory Test. Thames Valley Test Co*. Gaylord, MI: National Rehabilitation Services.

Wilson, B. A., Emslie, H. C., & Evans, J. J. (2001). Reducing everyday memory and planning problems by means of a paging system: a randomized control crossover study. *Journal of Neurology, Neurosurgery, and Psychiatry, 70*, 477–482.

Evaluation and Management of Psychogenic Nonepileptic Attacks

12

John T. Langfitt and William Watson

Introduction

Psychogenic nonepileptic attacks (PNEAs) are paroxysmal behaviors that look like epileptic seizures but an EEG recorded during the event does not show epileptiform activity. Unlike organically based, nonepileptic events that resemble seizures (e.g., syncope, transient ischemic attacks), there are no physical findings that explain the symptoms. PNEAs also are distinguished from normal-range behaviors that may be mistaken for seizures by educated observers (e.g., brief episodes of staring or inattention, startle or other reflexes in infants, nocturnal myoclonus). PNEAs are further characterized by aspects of the patient's history and behavior that suggest a psychological cause.[1] Some object to the term "psychogenic," because it implies a known, causal link between unobservable mental events and behaviors. Nevertheless, the term is heuristically useful as long as one is clear that it reflects evolving theories about mind-body interactions that are supported by a large body of data.

Clinical psychologists (including clinical neuropsychologists) often are asked to consult on PNEA patients seen by neurology or epilepsy services. It is not enough to tell patients what they do not have (i.e., ruling out epilepsy and other causes). Patients also need to know what they *do* have, so they can understand it and begin to manage it more effectively. Most neurologists do not have the time or expertise to provide psychiatric diagnosis, education, or management. Guidelines for establishing specialized epilepsy centers recommend an integrated approach to comprehensive management of PNEA that involves

Dr. Langfitt, a clinical neuropsychologist, and Dr. Watson, a family psychologist, have evaluated and treated patients with PNEA admitted to the Strong Epilepsy Center for 30 years combined.

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[1] A number of terms have been used to describe these events, including "pseudoseizures," "psychogenic nonepileptic seizures," "nonepileptic attacks," or "stress seizures" (Benbadis, 2010; LaFrance, 2010). We prefer the term "psychogenic nonepileptic attacks" (PNEA), because it clearly communicates the assumption that the events are generated from the mind and unequivocally distinguishes them from "seizures" (which most people associate with epilepsy).

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doctoral-level psychologists with appropriate training (Gumnit RJ, Walczak TS, National Association of Epilepsy Centers, 2001). Psychologists can play a critical role in these settings by (1) formulating an underlying psychiatric diagnosis, (2) ensuring that the psychological etiology of the symptoms is clearly communicated in terms that are easily understood, (3) promoting acceptance of the diagnosis and the treatment plan by the patient and family, and (4) providing treatment.

By virtue of their training, psychologists are well positioned to evaluate the intra- and interpersonal characteristics that predispose a patient to develop PNEA, precipitate their onset, and perpetuate their occurrence. These characteristics also may become barriers to their understanding and acceptance of the diagnosis that require psychotherapeutic communication skills to overcome, skills that are central to psychologists' training. Psychologists can speak authoritatively to health-care providers, the patient, and the family about how psychological factors contribute to the experience of physical symptoms in ways that many physicians cannot.

In this chapter, we review the diagnostic approach to PNEA and their epidemiology, risk factors, etiologic theories, treatments, and prognosis. We then describe a multidisciplinary, collaborative approach for evaluating patients and presenting the diagnosis, illustrated by case vignettes.

Relevant Clinical Literature

Approach to Diagnosis

The physical signs of PNEA are as variable as epileptic seizures themselves. They can range from mild tremulousness to full convulsions. Patients may remain aware, may be partially responsive, or may be unaware, unresponsive, and amnestic. Like epileptic seizures, PNEAs are difficult to diagnose just based on the history. Physicians rarely see them and typically have to rely on descriptions from untrained (and often distressed) witnesses.

Certain behaviors are more common in PNEA and less common in epileptic seizures (Reuber & Elger, 2003).These include undulating, rhythmic, asynchronous, purposeful, or goal-directed movements, pelvic thrusting, side-to-side head movements, crying, closed eyes and resistance to opening, verbal responses, lack of cyanosis during a prolonged "tonic" phase, and rapid reorientation postictally. These behaviors should raise suspicions of PNEA, but they sometimes can be misleading. For example, directed aggression during the ictus is almost always considered a sign of nonepileptic activity. However, in a recently reported case, a young man repeatedly made focused verbal threats to physicians that were accompanied by profanity and "shooting" them with his index finger. The events were associated with bifrontal epileptiform activity and hyperperfusion in the right lateral and orbitofrontal cortex on SPECT imaging (Shih, LeslieMazwi, Falcao, et al., 2009). One of our patients was partly responsive during his seizures and had a remote history of drug abuse. He was repeatedly barred from the local emergency room and eventually assaulted and incarcerated by police because staff assumed he was faking seizures to obtain drugs. He was later shown by video-EEG monitoring to have frontal lobe seizures. Major injuries during PNEA are rare but not unheard of. One of our PNEA patients had broken an arm during an attack. It later came out that she had intentionally and repeatedly broken her hand with a hammer or bat on several occasions as a child, in response to severe family dysfunction and abuse.

Because of the significant risk for misdiagnosis based on clinical signs, the "gold-standard" diagnostic method for PNEA is to show absence of epileptiform discharges during the patient's typical event(s) which usually requires inpatient, video-EEG scalp monitoring. In rare cases, PNEAs diagnosed based on scalp monitoring later have been shown to be epileptic with invasive monitoring, but all these cases had simple partial or complex partial events and interictal EEG abnormalities or other evidence of neurologic involvement (Wyler, Hermann, Blumer, et al., 1993). Inpatient evaluation also allows a

thorough medical and psychological evaluation to rule out nonepileptic, organic causes of seizures and to evaluate risk factors for PNEA. Unfortunately, definitive diagnosis is often delayed, by an average of 7 years in one study (Reuber, Fernandez, Bauer, et al., 2002). During this time, patients are exposed to side effects of antiepilepsy drugs (AEDs), social stigma, and activity restrictions, often resulting in an intractable, disabled lifestyle. In our experience, the longer the patient has carried an epilepsy diagnosis, the harder it is for them to understand and accept that the events are psychogenic. This is particularly important in light of data indicating that successful recovery from PNEA is directly correlated with the patient's understanding and acceptance of the diagnosis (Carton, Thompson, & Duncan, 2003).

Psychiatric Diagnosis

PNEAs are symptoms of one of a number of psychiatric diagnoses. Most commonly, PNEAs are manifestations of an underlying somatoform disorder. The most recent version of psychiatric nomenclature (DSM-V) refers to these as somatic symptom disorders (American Psychiatric Association, 2013). These patients have physical symptoms that suggest a general medical condition but cannot be explained on the basis of the physical findings. Patients show undue worry and concerns about their symptoms, even in the face of reassurance. In severe cases, symptoms become the focus of the patient's life and may dominate their relationships with others.

PNEAs that occur as the lone unexplained symptom reflect a conversion disorder. When PNEAs are one of a number of medically unexplained symptoms, these patients should be diagnosed with somatic symptom disorder, with different specifiers, depending on the role of pain in the presentation, duration, and severity. Severity is based on the degree of associated behavioral disturbance and the number and severity of symptoms. PNEAs that appear as paroxysmal changes in mood, sensation, or cognition may be symptoms of other psychiatric diagnoses (e.g., panic disorder, PTSD, dissociative disorders). There are few studies where psychiatric diagnosis has been prospectively established by standard psychiatric interviews. The majority of diagnoses were conversion disorder (36–63 %) or other somatoform disorder (16–23 %), with other diagnoses including anxiety disorders (7–15 %) and dissociative disorders (4–7 %) (Galimberti, Ratti, Murelli, et al., 2003; Marchetti, Kurcgant, Neto, et al., 2008).

PNEAs as an expression of malingering or factitious disorder are rare, in our experience.[2] These diagnoses should be suspected in forensic and other settings where there is an external incentive (injury compensation, avoidance of major role responsibility, or culpability) or other evidence that suggests deliberate attempts to deceive (e.g., significant inconsistencies in the history and examination). Rarely, children have admitted to manufacturing attacks to draw attention to ongoing abuse or neglect. Certain results of psychometric assessment may be useful in supporting these diagnoses (see "Utility of Psychometric Assessment," below).

Epidemiology

Medically unexplained symptoms are the most common symptoms in primary care settings. Prevalence ranges from 8 to 25 %, depending of the severity and number of symptoms (Escobar, Waitzkin, Silver, et al., 1998; Kroenke, Spitzer, deGruy, et al., 1997). Prevalence of conversion in neurology clinics has been estimated at 20 % (Mace & Trimble, 1996). The exact incidence and prevalence of PNEA is not known. There are no community-based studies, no doubt, because of the expense of obtaining video-EEG monitoring as a gold-standard diagnosis in a community-based sample. PNEA patients represent ~10–20 % of patients referred to epilepsy centers and a somewhat higher percentage of monitored

[2] Of course, they may be more common than we believe. Only when the patient admits that the symptoms are voluntarily produced can these diagnoses be made with absolute certainty.

patients. This has led to an estimated prevalence of 2–33/100,000 (Benbadis & Hauser, 2000). PNEA usually onsets between 20 and 30 years of age, but there have been cases as young as 4 and as old as 70. Ten to 50 % of patients also have current or past epileptic seizures, making diagnosis and treatment even more difficult.

Risk Factors

The characteristics that distinguish patients with PNEA from patients with epilepsy and healthy controls have been reviewed extensively (Bodde, Brooks, Baker, et al., 2009, Reuber & Elger, 2003). Since antiquity, PNEAs have been seen more often in women, such that they were often felt to be a uniquely female problem. Modern studies suggest that 75 % of patients are women (Lesser, 1996). PNEA patients are more likely than epilepsy patients to have other psychiatric diagnoses, particularly personality disorders with borderline features (Bowman & Markand, 1996; Reuber, Pukrop, Bauer, et al., 2004). High rates of clinically significant depressive symptoms (52 %), suicidal ideation (40 %), and prior suicide attempts (20 %) have also been reported (Ettinger, Devinsky, Weisbrot, et al., 1999). PNEA patients have high levels of psychopathology, as measured by the MMPI. The variety of profile types is felt to represent the diversity of psychopathology underlying the symptoms (Cragar, Berry, Schmitt, et al., 2005; Dodrill, Wilkus, & Batzel, 1993). PNEA patients are more likely to have difficulty describing their own emotional states or recognizing them in others (alexithymia) (Bewley, Murphy, Mallows, et al., 2005).

PNEA patients often have a past history of trauma and recent social stress, particularly involving family. They report a higher frequency of past traumatic experiences in general (Rosenberg, Rosenberg, Williamson, et al., 2000). Reported childhood sexual or physical abuse is more common in PNEA (33 %) than in epilepsy patients (9 %) (Alper, Devinsky, Perrine, et al., 1993). PNEA patients experienced more adverse or traumatic events in the 12 months prior to diagnosis than patients with epilepsy (Binzer, Stone, & Sharpe, 2004). Their family members have higher levels of concerns about their own health. They perceive their families as more hostile and critical than family members of patients with epilepsy (Wood, McDaniel, Burchfiel, et al., 1998).

Risk factors for the broader range of somatoform disorders are also of interest, since many PNEA patients carry these diagnoses. In a large, German population-based cohort, somatoform symptoms were associated with female gender, older age, lower education, lower income, and rural residence (Hiller, Rief, & Brahler, 2006). In a prospectively followed, population-based cohort of adolescents, the new onset of a somatoform diagnosis was predicted by female gender, lower social class, substance use, anxiety or affective disorder, and the experience of traumatic sexual or physical threat events (Lieb, Zimmermann, Friis, et al., 2002). Severe illness in a parent predicted later somatoform symptoms in a population-based birth cohort (Hotopf, 2002). Patients with somatoform disorder and histrionic personality disorder also are more likely to have a first-degree relative with antisocial personality disorder (Lilienfeld, Van, Larntz, et al., 1986). Somatoform patients also are more susceptible to hypnotic suggestion (Roelofs, Hoogduin, Keijsers, et al., 2002).

An important limitation of the literature on PNEA risk factors is that most studies compared patients with PNEA to patients with epileptic seizures. Comparisons to psychiatric samples without seizure-like events are rare. Therefore, some of these risk factors may reflect risk for psychopathology in general and not specifically for PNEA. In one of the few studies to include other psychiatric patients, a history of childhood sexual abuse was more frequent in PNEA patients than in inpatients with other psychiatric diagnoses (Betts & Boden, 1992). In another study, PNEA patients and patients with other somatoform disorders had similar rates of comorbid psychiatric disorders and levels of anxiety, depression, and anger. These rates were higher than in healthy controls (Mokleby, Blomhoff, Malt, et al., 2002). However, PNEA patients were more likely than other somatoform patients and controls to report

a history of minor head injuries, have more subtle EEG abnormalities, and express higher levels of hostility.

Etiology

Pre-modern Theories: Many premodern writers recognized that PNEAs were more common in women and were associated with emotionality and psychosocial stressors, but their theories to explain these observations were naturally constrained by the knowledge of the time (Temkin, 1971). The Hippocratic writers saw hysterical seizures as a form of epilepsy. The Roman physician Celsus wrote that "a disease originating from the uterus sometimes made women so weak it prostrated them as in epilepsy." Renaissance physicians explained all hysterical phenomena as the effect of vapors rising from the uterus to the brain. Recognizing the interplay of constitutional and environmental factors, Todd, a nineteenth-century physician, described a "highly excitable" hysteric who had been "subjected to moral, and perhaps physical influences also, well-calculated to keep up that state." Briquet theorized that *hystero-epilepsy* embodied painful emotions that prompted reactions of the emotional centers of the brain. Women were more prone, due to an innate emotionality that allowed them to fulfill their "noble mission in life." Breuer's description of the hysterical pregnancy of Anna O., "a young woman of exceptional cultivation and talents," played a key role in initially convincing Freud that repression of unpleasant memories and emotions (especially sexual ones) led to "conversion" into physical symptoms that symbolized the original trauma (Gay, 1988). Janet's concept of dissociation was one of the first purely cognitive theories. It held that psychosomatic symptoms reflect a narrowing or fragmenting of attention in response to extreme emotional stress. This caused symptoms ranging from over-attending to subjective sensations to unresponsiveness and amnesia (Janet, 1907).

Despite continued heuristic value in lay and clinical circles, older conceptualizations of conversion and dissociation are limited as explanatory theories, from a strictly scientific point of view. Both hold that sensory and motor changes are caused by subjective, unobservable mental processes whose neurologic basis is not specified. The psychoanalytic concepts of repression and symbolic representation of past events in the unconscious are not falsifiable. Modern explanations of the phenomenon of PNEA rely on objective observations, are potentially falsifiable, and invoke mechanisms by which sensation and behavior might plausibly emerge from the central nervous system.

Psychological Theories: Attachment theory has been invoked to explain observed associations between over-reporting of physical symptoms and early traumatic experiences (Lamberty, 2008). Attachment theory holds that early experiences with caretakers have an enduring influence on how people perceive themselves and how they form relationships as adults (Bowlby, 1969). Validated measures allow researchers to classify various attachment "styles" (e.g., "secure," "anxious/attached," "anxious/avoidant," "dismissing," "preoccupied," and "fearful") that reflect interest in, and comfort with, engagement in intimate and autonomous relationships (Ainsworth, 1967; Bartholomew & Horowitz, 1991). Preoccupied and fearfully attached persons report more physical symptoms than securely attached persons (Ciechanowski, Walker, Katon, et al., 2002). Preoccupied persons also used more health care than fearful ones, suggesting that attachment style also influences strategies for managing symptoms. In a community-based sample, persons with a history of childhood trauma were more likely to report physical symptoms and to have an insecure attachment style (Waldinger, Schulz, Barsky, et al., 2006). Patients with insecure or preoccupied attachment styles may over-report physical symptoms because they are hypervigilant to a range of perceived threats. Over-reporting also may elicit concerns and support that strengthen their attachment in key relationships.

In a similar way, somatoform symptoms have been described as a "bodily idiom of distress," a way to acceptably communicate emotions that might otherwise disrupt important relationships. In one case series, in-depth interviews revealed

that 13/14 conversion patients had been experiencing intolerable family situations that they felt unable to address openly (Griffith, Polles, & Griffith, 1998). The authors described these as "unspeakable dilemmas" where "family, social, religious or political circumstances… have imposed forced choices… and consequent suffering must remain hidden from important persons involved in the situation." Many of the patients were the least expressive family members during the family interviews. They later confided that they presently were feeling threatened by physical or sexual assault or were having difficulty coping with a psychiatrically disabled family member. Social communication theories may also explain some of the many outbreaks of "mass hysteria" that have occurred across cultures and over time (Evans & Bartholomew, 2009). For example, episodes of mass hysteria in Malaysia were virtually unheard of prior to the imposition of strict Islamic codes of female behavior in 1960. Subsequent episodes often involved female students or sweatshop workers and were accompanied by outspoken criticism of authorities. Interpreting them as signs of a physical problem provided a culturally acceptable explanation for an otherwise intolerable breach of the social order (Bartholomew, 1997).

Attachment and social communication theories have been combined to explain conversion symptoms presenting in "good" children in the absence of the usual risk factors (e.g., abuse, overt stressors, family dysfunction) (Kozlowska, 2001). These children often do very well in school, are admired by peers, and generally lack recognizable psychopathology. Their families tend to be "supernormal" and expect a high degree of academic and athletic achievement, social propriety, and family cohesion. Providers tend to find these parents mildly intimidating. According to Kozlowska, children become "compulsively compliant" in order to bolster insecure attachments in the face of mounting expectations. They anticipate parents' needs and expectations. They focus on performing tasks instead of attending to relationships. In this setting, conversion symptoms are seen as passive resistance that secures attachment by avoiding conflict. Symptoms elicit functional and emotional support from the parents in a face-saving way that also provides relief from overwhelming demands. Adults also may use a compulsively compliant strategy to manage "unspeakable dilemmas" where they feel they have to comply with intolerable demands and suppress their own needs out of a fear of threatening important attachments (e.g., the abused spouse, the overworked single parent).

Neurobiological Theories: Attachment and social communication theories point to testable hypotheses about how a person's history of relationships might predispose them to develop PNEA. However, they do not address a central question: how does the central nervous system produce such dramatic changes in sensation or behavior without apparent awareness or voluntary control? Watching some of these events, it is difficult to imagine that they are not done on purpose, yet patients' protestations typically seem credible. There also are so many other less painful symptoms that would have a similar effect. Updating the concept of dissociation, Brown (2004) has proposed that medically unexplained symptoms reflect disruption of normal attention systems. These systems shape the contents of consciousness and control behavior via spreading activation of hierarchically organized, neural networks. According to one such model, primary attention systems (PAS) govern sensory and motor representations instantiated in neural networks that are activated rapidly and efficiently (e.g., sensory perception, skilled motor movements, implicit memory) (Norman & Shallice, 1986). Behaviors activated by PAS are typically experienced as occurring without conscious effort (e.g., walking, some aspects of driving), while perceptions and thoughts are experienced as intuitive, self-evident, or automatic (e.g., simple visual discrimination, "realizing" that you forgot to put out the trash). Secondary attention systems (SAS) activate sensory, cognitive, and motor representations that subserve higher-level, goal-directed behaviors. These are experienced as effortful and associated with feelings of conscious volition and self-awareness.

Within this framework, medically unexplained symptoms reflect inappropriate PAS activation of chronically overactive "rogue representations." These have been acquired during prior experiences

(e.g., trauma) or strengthened by chronic over-attention to bodily sensations (e.g., in somatically focused persons). In the sensory realm, inappropriate activation of "rogue" representations amplifies normal sensory inputs (e.g., psychogenic pain or discomfort) or suppresses them (e.g., psychogenic anesthesia or amnesia). These experiences feel "real" to the person but are inconsistent with sensory inputs (i.e., medically unexplained). Activation of "rogue" motor representations by PAS produces behaviors that are inappropriate to the goals subserved by representations activated by SAS. Behaviors are experienced as "real" but involuntary and outside awareness (e.g., PNEA).

Brown's theory extends more modern theories of dissociative behavior (such as occurs during hypnosis) that posit an "amnesic barrier" between executive systems and lower-level perceptual and motor systems (Hilgard, 1977). Evidence that an amnesic barrier can be affected by suggestion in PNEA comes from a study of patients with ictal amnesia. Under hypnotic suggestion designed to facilitate recall, 85 % of PNEA patients, but no epilepsy patients, were able to recall what had occurred during a prior event (Kuyk, Spinhoven, & van Dyck, 1999). The idea that PNEA patients have aberrant, unconscious attention mechanisms is supported by a recent study where subjects were asked to view and rapidly name colors under interference conditions, similar to the Stroop task (Bakvis, Roelofs, Kuyk, et al., 2009). The colors were preceded by a picture of a face that was flashed for 14 ms and backward masked in order to prevent conscious processing. PNEA patients were slower than healthy controls to name colors when the colors were preceded by angry faces, but not by happy ones. This suggests that PNEA patients have a preconscious attentional bias to threatening stimuli that places demands on information processing and affects subsequent behavior. Interestingly, PNEA patients with a greater attentional bias were more likely to report a history of sexual trauma and to have higher basal cortisol levels, indicating HPA axis dysfunction (Bakvis, Spinhoven, & Roelofs, 2009). Whether these findings are specific to PNEA or are seen with other psychiatric disorders remains to be determined. In functional imaging studies, patients with conversion paralysis show decreased activity in primary motor areas and increased activity in functionally related, inhibitory areas that also are involved in attention networks (Halligan, Athwal, Oakley, et al., 2000; Marshall, Halligan, Fink, et al., 1997). In studies of conversion anesthesia, peripheral stimulation that was not perceived resulted in deactivation of contralateral, primary sensory cortex and corresponding activation of limbic structures (Mailis-Gagnon, Giannoylis, Downar, et al., 2003; Vuilleumier, 2005). Brown's attentional theory and these neuroimaging findings are far from definitive, but they do provide a neurologically plausible framework for testing hypotheses about the neural correlates of abnormal perceptual processing in these patients.

Multi-factorial Models: Recently, two groups have proposed similar multifactorial models to explain the wide range of risk factors for PNEA (Bodde et al., 2009; Reuber, 2009). Each model suggests that PNEAs arise from a complex interplay of predisposing, precipitating, and perpetuating factors that varies from patient to patient. Predisposing factors include constitutional factors (e.g., genetics, temperament, learning disabilities, subtle structural brain abnormalities) and early experiences (e.g., abuse, neglect, other sources of insecure attachment). Later exposure to stressful experiences (e.g., actual or recalled trauma, actual or perceived threats, unspeakable dilemmas, or physical illness) precipitates the onset of events. Events are perpetuated by distress over social stigma, isolation, dependency and diagnostic uncertainty, and by factors that reinforce the "sick role" (e.g., increased family concern or support, avoidance of conflicts or burdensome responsibilities, disability benefits). The main advantage of these models is that they account for (1) the heterogeneity in the history and presentation of PNEA patients, (2) no single risk factor being either necessary or sufficient to cause PNEA, and (3) PNEA risk factors being risk factors for many other psychiatric conditions. They provide a clinically useful framework for thinking about how the many facets of an individual patient's

constitution and experience may interact to produce PNEA. They remain somewhat limited from a scientific standpoint. Predisposing, precipitating, and perpetuating factors are quite common and how some factors (and not others) interact to produce PNEA is not highly specified. Therefore, almost any set of factors can be retrospectively invoked to explain PNEA in a given patient. They also do not propose mechanisms that explain how PNEAs are experienced as "real" by the patient yet involuntary and outside awareness.

Summary: It is apparent at this point that no single theory or model sufficiently explains how biological vulnerabilities, environmental stressors, and psychological and physiological processes give rise to PNEA. On the other hand, it is clear that many PNEA patients experience early environments that make it very difficult for them to manage stress in their relationships later in life. They may also have aberrant cognitive and physiological functioning that plausibly play a role in creating changes in sensation and behavior that they experience as abnormal, unconscious, and involuntary. The neurologic basis for this remains unclear. It is perhaps unreasonable to expect that any one theory could explain the wide variety of PNEA behaviors and their causes. As we shall see, the clinical challenge is to engage the patient in examining their own history and present circumstances so that they can develop a personalized, plausible theory that leads to cognitive and behavioral strategies that make their events stop.

Prognosis

In some cases, simply making the diagnosis leads to an abrupt cessation of events (Farias, Thieman, & Alsaadi, 2003), but there are few well-controlled studies of long-term outcome. Remission rates in case series vary widely (Bodde et al., 2009; Reuber, Pukrop, Bauer, et al., 2003). Follow-up studies vary greatly in sample sizes, duration, and completeness of follow-up and treatments. Most studies report long-term remission rates <50 %, and relapse is common if patients are followed long enough. Studies of other outcomes suggest that psychosocial disability often persists. On the other hand, definitive diagnosis of PNEA has been associated with an 85 % reduction in healthcare costs in the following 6 months, including virtual elimination of emergency room visits (Martin, Gilliam, Kilgore, et al., 1998). Outcome in children appears to be more favorable, with 80 % in remission at three years in one study (Wyllie, Friedman, Luders, et al., 1991).

Others have reviewed a wide range of patient characteristics that has been associated with prognosis (Bodde et al., 2009, Reuber et al., 2003). Favorable outcomes are associated with female gender, younger age, higher intelligence and socioeconomic status, living independently, mild or no other psychiatric history, an identifiable psychological precipitant to the onset of the illness, shorter duration of illness, milder or less dramatic attacks, no ongoing use of AEDs, and lower scores on personality measures reflecting inhibitedness, emotional dysregulation, and compulsiveness. There have been few studies of the effect of psychiatric diagnosis on outcome. It is our experience that patients with conversion disorder do better that those with other somatoform disorders. Conversion patients often are more recently diagnosed and have fewer unexplained symptoms. For patients with somatic symptom disorder, the attacks often are the latest in a series of medically unexplained symptoms going back many years.

Treatment

A number of treatment modalities for somatoform disorders in general have been studied with appropriate research designs (Kroenke, 2007), but there have been very few well-controlled studies of treatment specifically for PNEA. A 2006 National Institutes of Health symposium concluded that the field had "not progressed much beyond anecdotal reports of treatments… and no blinded, randomized, controlled trials of treatment for (PNEA) have been completed" (LaFrance, Alper, Babcock, et al., 2006). A Cochrane systematic review of non-pharmacologic treatment identified 23 treatment studies, only three of which were blinded, randomized, controlled trials (RCTs) (Brooks, Goodfellow, Bodde, et al., 2007). Hypnosis in general conversion patients did not provide any

symptomatic benefit over and above an intensive inpatient behavioral program but was superior to being on a treatment waiting list when used in an outpatient setting (Moene, Spinhoven, Hoogduin, et al., 2002, 2003). Outcomes for PNEA patients were not reported separately. After twice-daily sessions of paradoxical intention (imagining anxiety-provoking experiences) during a 3-week inpatient stay versus outpatient treatment with diazepam, 93 % of the paradoxical intention group and 60 % of the diazepam group were in remission in the final two weeks of the study (Ataoglu, Ozcetin, Icmeli, et al., 2003).

More recently, a double-blind, placebo-controlled RCT of sertraline showed no significant effect of treatment on the primary outcome measure (relative change in attack rates), but treated patients experienced a 45 % reduction in attack frequency, compared to an 8 % increase in the placebo group (LaFrance, Keitner, Papandonatos, et al., 2010). There were no group differences in secondary outcomes (depression, anxiety, impulsivity, somatic symptoms, quality of life, and psychosocial functioning). In an RCT of supportive treatment (ST) versus supportive treatment plus cognitive behavioral therapy (CBT) for 12 weeks, median monthly attack frequency in the CBT group had declined at 6-month follow-up from 12.0 to 1.5, compared to 8.0 to 5.0 in the ST-only group ($p<0.0001$) (Goldstein, Chalder, Chigwedere, et al., 2010). There were no significant effects on secondary outcomes. In a pilot RCT, attack frequency in patients treated with CBT (with or without sertraline) declined by 50–60 % over 4 months (LaFrance Jr, Baird, Barry, et al., 2014). Some functional improvements were apparent. Neither the sertraline-only group nor the treatment as usual group showed significant benefit.

Description of the Procedure

The role of the psychologist in evaluating and managing the PNEA patient varies from center to center, depending on how closely the psychologist is integrated with the medical team. Some consult primarily on an outpatient basis after the PNEA diagnosis has been made. Others work closely with the inpatient treatment team on a daily basis. At the recent NIH symposium, participants could not agree on whether a psychologist or psychiatrist needed to be present when the diagnosis was delivered.

The process described below presumes a high degree of psychologist integration with the inpatient treatment team and engagement with family members. Our level 4, comprehensive epilepsy center supports 1.8 full-time equivalent mental health providers. A companion (typically a family member) is usually present during most of the monitoring session to identify typical events. The psychologist often interviews the patient along with the family member, almost always helps deliver the diagnosis, and may later provide outpatient treatment. Such integration and access to family may not be typical, but we believe that many features of this process can be replicated in less integrated settings with adequate support of mental health services, careful triage, and timely communication among team members.

Diagnostic Interview

The goals of the diagnostic interview are to document risk factors that would positively support the PNEA diagnosis and to identify any underlying psychiatric diagnosis in order to make appropriate treatment recommendations. It is assumed that the reader is well practiced in diagnostic interviewing and how to formulate a psychiatric diagnosis. We focus here on parts of the interview that are particularly important in identifying risk factors and facilitating the patient's understanding and acceptance of the PNEA diagnosis.

By the time patients are referred for definitive diagnosis, many have been dismissed (often by a harried first responder or emergency room physician) as having "pseudoseizures" that are "faked" or "all in their head." Encountering a psychologist often makes them even more defensive, uncooperative, and angry. The first task is to model an open-minded, non-blaming attitude that lowers defensiveness and sets the stage for exploring links between the events and risk factors that emerge in the interview. In our experience,

this is easier to accomplish when the interview precedes delivery of the PNEA diagnosis.[3] At our center, patients are flagged for psychological evaluation early in the admission if PNEA is suspected, based on a preadmission screening of history and symptoms. Patients who are wary about meeting with a psychologist are told that "seizures" (or whatever term they have been using) are known to cause significant stress and can also be provoked by stressors. The role of the psychologist is to understand how stress may be playing a role in their events so we can help them to stop or at least manage them better. Statements such as "no one thinks you are crazy," accompanied by self-deprecatory humor about "shrinks," can be effective in anticipating and defusing defensiveness. If they raise the question of a PNEA diagnosis, we ask what ideas they have about that question and what they have heard from others. We also acknowledge that PNEA is one of the diagnoses that has to be considered, but we do not yet know for sure. It remains to be determined by gold-standard, objective analysis of ictal, video-EEG data. When PNEA seems very likely or they seem particularly defensive, we may educate them about the diagnosis in the abstract, using a normalizing and non-blaming approach (see "Delivering the Diagnosis," below). This general approach lowers initial defensiveness in six ways: it normalizes and destigmatizes the mental health encounter; it models open-mindedness about the diagnostic process; it reinforces reliance on objective data; it provides a more positive view of what remains a potential (and thus less threatening) diagnosis; and it gives them time to mull over information raised in the interview while waiting to have an event.

Some PNEA risk factors (e.g., learning disability, psychiatric diagnoses, substance abuse history) can be elicited by routine history taking. Others require a more indirect approach because of their sensitive nature. Information about family dysfunction, somatizing tendencies, or personality disturbance often emerge in the course of asking about past and current medical problems and support systems, including family. Abuse history may emerge naturally from a discussion of family relationships. If not, we ask about it matter-of-factly as one of a number of routine stress-related, "exposure" questions (e.g., family history of substance abuse, psychiatric illness, significant traumatic experiences, etc.) that normally might influence how they have learned to manage stress.

When asked directly, patients will often deny any awareness of stressors around the onset of the events. However, persistent questioning with careful attention to chronology will very often reveal a temporal relationship to other important life events. Patients may not initially connect these events to the onset of the illness. They may be resistant to the idea that events could be stress related in the first place. Life events that would strike others as quite stressful have come to seem "normal" to them. They may have difficulty recognizing and articulating feelings associated with these events (alexithymia).

Including family members in the interview is extremely useful when assessing risk factors. It also can promote understanding and acceptance of a PNEA diagnosis. Family often provides critical details about the patient's history and about the circumstances surrounding the onset of the attacks and triggers that the patient may omit or may not be aware of. Seeing patients interact with family provides important insights into the patient's personality, attachment style, how the family responds to illness behavior (e.g., hypervigilant, overly solicitous, blaming/rejecting), and other predisposing or perpetuating factors. This is also a chance to develop an alliance with family that sets the stage for accepting the diagnosis when it is given. Families typically feel anxious and helpless in supporting the patient cope with terrifying symptoms, conflicting or confusing diagnoses, and ineffective treatments. Attentive listening to their observations, fears, and concerns can lower the anxiety and defensiveness of the whole family system and foster trust in the medical team.

[3] It is also more appropriate if one accepts that making the PNEA diagnosis requires positive evidence of psychogenic risk factors, not just absence of ictal epileptiform activity.

A systematic review of risk factors allows the psychologist to formulate a theory about which predisposing, precipitating, and perpetuating factors may be operating in a particular case, which has implications for treatment. However, patients and families are hardly passive participants. Most have entertained (perhaps reluctantly) the hypothesis that their events are stress related. Taking them through a systematic, stress-related "review of systems" in an open-minded, nonjudgmental manner prior to making the diagnosis allows them the time, space, and data to evaluate this hypothesis more carefully on their own. Indeed, it is not uncommon following the interview for patients to spontaneously conclude that their events are psychogenic, even before an event has been recorded.

Utility of Psychometric Testing

Unlike other areas of clinical neuropsychology, psychometric testing is less central to the diagnosis and management of PNEA. Psychometric indices of psychopathology have shown differences between PNEA and epilepsy patients (Dodrill et al., 1993). However, specificity and sensitivity are insufficient for diagnostic purposes (Hermann, 1993). In any event, psychometric diagnosis of the events is largely redundant when video-EEG data are available. Personality measures may be useful in informing management and treatment. PNEA patients have shown inconsistent effort on symptom validity testing (Drane, Williamson, Stroup, et al., 2006). Below-chance scores indicate malingered cognitive complaints and should raise the strong suspicion that the patient's PNEA may represent malingering as well.

Reporting the Findings

Making an accurate diagnosis is not useful if the patient and family do not understand and accept it sufficiently to follow the appropriate treatment plan. The following multidisciplinary approach to presenting the diagnosis and treatment recommendations is based on a published protocol (Shen, Bowman, & Markand, 1990) that has been modified to enhance understanding and acceptance (Watson & Langfitt, 2010).

After the monitoring and diagnostic interview have been completed, the neurologist and psychologist jointly present the PNEA diagnosis to the patient (and a family member, if possible), typically on the day of discharge. It may be difficult logistically to get all these people together at the same time, but it has important advantages. It ensures an unambiguous, consistent, and data-based message. It limits misunderstanding that can occur when dealing with somatoform illnesses and keeps patients, family, and providers all "on the same page" (Harden, Burgut, & Kanner, 2003). Questions requiring medical and psychological expertise can be answered together. The neurologist validates and supports the psychologist's input and vice versa. Their mutual presence literally embodies the holistic mind-body framework that is necessary to understand and treat the symptoms.

The neurologist first presents the medical data and explains that biomedical causes can be definitively ruled out. To lower anxiety and defensiveness, we present the diagnosis as the good news that it truly is (e.g., there is no evidence for brain dysfunction, no need for AEDs or emergency treatment, a low risk of injury). The attacks are a way that emotional stress is manifesting physically, but they are nevertheless "real" and not being "faked." They are a serious health problem that requires careful attention and treatment. Attacks are normalized by noting how often PNEA diagnoses are made on the monitoring unit. Patients often are reassured that they do not have a rare condition that no one has ever heard of.

At this point, patients typically ask "If it is not epilepsy, what is it?" After providing a brief overview of PNEA, the neurologist then "hands off" the presentation to the psychologist, who elaborates further on common ways that emotions normally are unconsciously and involuntarily embodied in physical responses (e.g., smiling when seeing a friend, blushing when embarrassed, nausea and palpitations before

speaking in public) (Watson, 2007). PNEAs are described as a more extreme version of this normal human tendency. Patients often express amazement or skepticism that emotions could produce such dramatic physical symptoms and confusion about why this would happen to them. If they do, we share their amazement, acknowledging our (and the field's) limited understanding of the precise cognitive and physiological mechanisms that cause the attacks. Nevertheless, we confidently fall back on the empirical data (results of the video-EEG monitoring, the risk factors elicited in the diagnostic interview) and our many years of experience in making the diagnosis. If they express confusion about why this would happen to them, we then discuss generally, and in lay terms, some of the modern etiologic theories and mechanisms that have been proposed (as discussed above). We invite them to consider whether any of these mechanisms might apply to them. We are careful not to impose our own ideas about specific predisposing, precipitating, and perpetuating factors that may be active in their case. By openly admitting the limits of our knowledge and by not imposing our own explanation, we invite them to explore collaboratively how this process may play out in their own lives. By having them actively "connect the dots" themselves rather than having a (potentially inapt) explanation imposed by the "expert," we encourage them to come to an understanding that feels more like their own. This enhances understanding and acceptance of the diagnosis and willingness to pursue psychological treatment.

Patients certainly vary in how they receive this information. While most express relief and understanding, others remain confused and resistant. They may say that they understand and accept the diagnosis, but their body language implies otherwise. We are not aware of specific empirical evidence that this approach is superior to others or affects outcome. Anecdotally, we find that patients are more confused about the diagnosis at follow-up when the psychologist was not present at the discharge discussion. In one follow-up study, only one-third of PNEA patients interviewed demonstrated an understanding of the psychological basis of their attacks (Carton, Thompson, & Duncan, 2003). Patients with persisting events were more likely to have been confused or angry about the diagnosis.

Case Vignettes

The following cases illustrate some of the different ways that predisposing, precipitating, and perpetuating factors combine to produce PNEA. They also include variations in the way the diagnosis was communicated that take these individual differences into account. Many nonessential details have been changed to obscure patients' identities.

Case 1: A 42-year-old woman with a long history of neck pain and a number of other medically unexplained symptoms was referred for daily "staring spells" lasting 6–8 min, during which she was aware but unable to respond. She had had them "off and on for years," but they had greatly increased in frequency in the past several months, prompting evaluation.

She was the oldest of nine children of a severely mentally ill, largely absent mother and an alcoholic father. The patient was effectively the primary caregiver for her siblings at an early age. A neighbor tried to rape her at age 8. She became pregnant at age 17 and married her boyfriend to escape her home. He soon became physically abusive. Her staring spells began during this marriage as did a host of vague somatic complaints that led to multiple surgeries. Spells were happening 2–3 times per week but decreased in frequency to a few times per year when her husband was deployed overseas. They recurred several years later when her teenaged daughter revealed that she had been sexually abused as a child by the patient's nephew. In the past year, her daughter had become unexpectedly pregnant and moved in with her boyfriend.

The patient worked as a pharmacy technician. She had recently been out on disability following a complicated cholecystectomy for vague abdominal symptoms. Over the past several months, she had been taking night classes toward becoming a pharmacist. Her current boyfriend, who was

present during the interview, reminded her that she had also been caring for a number of ill relatives over the past several months and sleeping and eating poorly and that her ex-husband was due to be discharged from the military soon.

During the interview, the patient acknowledged her busy, difficult life but indicated that it was "nothing I haven't handled before." Her approach was to "just deal with it." She was frustrated at her daughter's poor choices, dependence, and immaturity because the patient was doing everything for her to ensure that "she doesn't have to live the life I lived." She also reported having been diagnosed 15 years ago as "bipolar," based on a history of extreme mood lability and self-cutting. She was currently being followed by a counselor and taking an SSRI.

The patient's attacks were diagnosed as dissociative episodes. She was resistant to the diagnosis initially because she did not feel her life was any more stressful than usual. She was more accepting when it was framed more positively as a physical sign of stress that can emerge in very active, caring persons who are so focused on the needs and concerns of others that they neglect their own. She resonated with the idea that there often was no one to "take care of the caretaker." She would need to learn how to do a better job of this herself by pacing her activities and more assertively setting limits on what she allowed others to expect from her. She returned to her therapist. Three months later, episodes had decreased from daily to about once a week. She was being somewhat more assertive with her daughter, but her other somatic complaints and mood lability persisted.

Comment: Predisposing factors in this case appear to be borderline personality traits reflecting an insecure or chaotic attachment style and hypersensitivity to emotional and physical threats due to her early environment and first marriage. This may have left her prone to view vague physical symptoms as threats of illness, accounting for her many surgeries and diagnoses. Early relationships provided poor models for asserting her needs within a trusting relationship, such that physical symptoms became the safest and most reliable way to express distress and secure emotional and material support. Dissociative episodes were precipitated by being in an intolerably insecure and threatening relationship. Frequency decreased when this threat was reduced. Attacks increased when this threat reemerged symbolically with her daughter's revelation of prior sexual abuse and again in anticipation of her abusive ex-husband's discharge from the service. Episodes were perpetuated by ever-increasing emotional and physical demands, stemming from her tendency to compulsively over-function to secure relationship needs, a tendency acquired in childhood as a survival strategy. She also was unable to set appropriate boundaries around her daughter's dependence, out of a fear of replicating her own mother's failure as a parent. When her over-functioning was framed as a more positive (albeit maladaptive) attribute, she was able to experience less shame, which reduced her defensiveness around the diagnosis and the need to make changes. Although there were fewer PNEAs at follow-up, prognosis remained guarded because of the long history of other somatoform symptoms and the entrenched behaviors and social relationships that perpetuated them.

Case 2: A 41-year-old warehouse manager with a strong family history of cardiac disease had a history of cardiac symptoms that had been in remission without treatment for the past 5 years. He suffered a severe and unexpected episode of chest pain that required hospitalization. Work-up was unrevealing. Shortly after discharge, he was found by his wife, confused with intermittent left-sided weakness. Work-up was again negative. He had three similar episodes in the following week but nothing further. He reluctantly went on short-term disability and spent much time at home, ruminating about his health. He did not see a cardiologist until a month later, when a number of diagnostic possibilities were raised and invasive tests were recommended. The next day, he had episodes of left upper extremity numbness that migrated to the right side. Physicians at a local hospital gave conflicting diagnoses, so the family requested an urgent transfer. By this time, events involved all four extremities and loss of awareness and were happening multiple times per day.

The diagnostic interview revealed no history of abuse or trauma and no significant family conflicts. His wife seemed appropriately concerned and supportive. He had a history of significant cocaine abuse in his teens and early 20s but had undergone rehabilitation. He had been abstinent and functioning well at work for the past nine years. He had close, healthy relationships with his family and co-workers. He denied any psychiatric symptoms or treatment. He related well during the interview, and there was no suggestion of personality disturbance. He acknowledged being very anxious about the shaking and confusional episodes and about his general health since the episode of chest pain.

When given the diagnosis of acute conversion, he was skeptical that the events were related to stress but was relieved to hear that his neurologic work-up continued to be entirely negative. It was suggested that his events could spontaneously remit with the relief that such knowledge afforded, as we had seen happen on numerous occasions with other patients. At one-month follow-up, he had had no further events, was back at work, and had resumed all regular activities. He still wondered about the nature of the original presenting event, but he was satisfied that thorough cardiac and neurologic work-ups had been negative and that he had had no further symptoms.

Comment: Many of the typical predisposing factors (history of abuse, family conflicts, personal psychopathology) are absent in this case. Instead, the history of early cocaine abuse suggests a predisposition to manage stress maladaptively. His personal and extensive family cardiac history sensitized him to health-related threats. The timing of the events strongly suggest that they were precipitated by the unexpected chest pain and resurgent anxiety about his long-term prognosis. This was perpetuated when physicians raised the specter of additional cardiac diagnoses and openly disagreed about them, undermining his trust in the system.

Ford (1977) described a case series of action-oriented, previously healthy, medically and emotionally unsophisticated men who developed conversion symptoms in the context of an acute onset of organic symptoms that initially suggested a very dire prognosis but ultimately turned out to be more benign. They became highly anxious because they lacked adequate knowledge, experience, or coping skills to manage health crises. Anxiety was exacerbated by rumination during enforced periods of inactivity, lack of access to normal emotional outlets, and lack of confidence in providers. Referring to this as "Humpty-Dumpty syndrome," Ford emphasized these patients' fragile ability to cope with a health crisis and how difficult it can be to "put the pieces back together," once symptoms have set in. Fortunately, our patient had no psychopathology, a strong work ethic, and good family support, such that a simple, reassuring message that the events did not reflect organic disease led them to resolve, and he returned to his normal lifestyle.

Case 3: A 25-year-old woman with mild cerebral palsy had been experiencing episodes in the prior 3 months that were felt to be non-electrical by her neurologist, based on their semiology and serial negative, interictal EEGs. She was encouraged to seek mental health care. Local counselors could find no evidence of psychological disturbance and told her that something medical was being missed. She was brought to the emergency department after she presented to her neurologist's office with total amnesia for recent and remote events in her life, including the names of family members, the type of work she did, where she had grown up, and any specific facts about her early life. History was therefore obtained from her sister.

She was the younger of two daughters. Her older sister was an accomplished attorney in a high-profile, local law firm. Her parents were professionals who traveled extensively for work. Her father was described as somewhat emotionally distant. Nevertheless, the sister described the family as close, loving, and supportive. There was no personal or family history of abuse and psychiatric or behavioral issues. The patient had worked extremely hard to overcome physical and learning disabilities, but this left her little time to develop friendships. After college graduation, she moved into the city to be near her sister and found a job in retail but had difficulty making

friends and struggled to keep jobs. Her convulsive events began shortly after moving. She had not told her family about her struggles in her work or her symptoms.

During the interview, she sat passively, answered few questions, and appeared fearful and confused. When asked why she seemed so afraid, she whispered that she did not understand why she was so sick and she was afraid that she would never get better and would never be able to resume living independently. She was gently but firmly told that her body was physically healthy but that the events she was experiencing represented a severe stress response. The symptoms were very likely to respond to her making changes in the way she managed stressors, with the appropriate help. She was reassured that she would still make progress toward her goals but needed to take a more gradual and flexible approach. However, she could not go back to her apartment in her current amnesic state and needed to move in with someone until her symptoms had improved. Within an hour, the patient's amnesia had resolved. She became more alert and interactive and announced that she felt ready to be discharged.

At follow-up three weeks later, she had had no further events or memory problems. She acknowledged that she had always internalized her feelings. Because of her learning disability, she had always tried to show people that she could do more than was expected of her. She acknowledged that she needed to manage her stressors better and was willing to engage in therapy.

Comment: This patient shows many of the characteristics of the "good child" described by Kozlowska: insecure attachment to parents (due to learning problems, difficulty competing with her accomplished older sister, and father's lack of availability) that she compensated for by striving for academic achievement at the expense of developing relationships. Her events appear to have been precipitated by failure of this compulsively compliant strategy when she began to struggle with work. Having had little time growing up to learn how to develop relationships, she also struggled socially in a new environment. She felt unable to rely on her family for support, out of fear of disappointing them. Her events resolved with (a) confidently worded reassurance of her physical and mental health, (b) the suggestion that there were workable and less stressful alternatives to her compulsively compliant style, and (c) giving her an immediate incentive to get better, as she would have viewed becoming dependent as a failure.

Summary

PNEAs are commonly encountered in epilepsy practices. They are challenging for physicians to manage on their own. A large part of this challenge is communicating the diagnosis to the patient in a way that takes into account their prior experience of stigma and misunderstanding, their preconceptions about psychological explanations for physical symptoms, and our limited and still-evolving understanding of the etiology of the condition. Psychologists are well qualified to help meet this challenge, by providing a mental health encounter that is respectful and informative and invites the patient's and family's participation in the diagnostic process. We believe that the process that we have described goes a long way toward this end. We hope that providing a detailed description of this approach will lead to studies that assess its effectiveness, relative to other approaches.

References

Ainsworth, M. D. S. (1967). *Infancy in Uganda: Infant care and the growth of love*. Baltimore, MD: Johns Hopkins University Press.

Alper, K., Devinsky, O., Perrine, K., Vazquez, B., & Luciano, D. (1993). Nonepileptic seizures and childhood sexual and physical abuse. *Neurology, 43*(10), 1950–1953.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Association.

Ataoglu, A., Ozcetin, A., Icmeli, C., & Ozbulut, O. (2003). Paradoxical therapy in conversion reaction. *Journal of Korean Medical Science, 18*(4), 581–584.

Bakvis, P., Roelofs, K., Kuyk, J., Edelbroek, P.M., Sinkels, W.A., & Spinhoven, P. (2009). Trauma, stress, and preconscious threat processing in patients with psy-

chogenic nonepileptic seizures. *Epilepsia, 50*(5), 1001–1011.

Bakvis, P., Spinhoven, P., & Roelofs, K. (2009). Basal cortisol is positively correlated to threat vigilance in patients with psychogenic nonepileptic seizures. *Epilepsy & Behavior, 16*(3), 558–560.

Bartholomew, R. E. (1997). Epidemic hysteria: A dialogue with François Sirois. *Medical Principles and Practice, 6*, 38–44.

Bartholomew, K., & Horowitz, L. M. (1991). Attachment styles among young adults: A test of a four-category model. *Journal of Personality and Social Psychology, 61*(2), 226–244.

Benbadis, S. R. M. (2010). Psychogenic nonepileptic "seizures" or "attacks"?: It's not just semantics: Attacks. [Miscellaneous]. *Neurology, 75*, 84–86.

Benbadis, S. R., & Hauser, W. A. (2000). An estimate of the prevalence of psychogenic non-epileptic seizures. *Seizure, 9*(4), 280–281.

Betts, T., & Boden, S. (1992). Diagnosis, management and prognosis of a group of 128 patients with non-epileptic attack disorder. Part II. Previous childhood sexual abuse in the aetiology of these disorders. *Seizure, 1*(1), 27–32.

Bewley, J., Murphy, P. N., Mallows, J., & Baker, G.A. (2005). Does alexithymia differentiate between patients with nonepileptic seizures, patients with epilepsy, and nonpatient controls? *Epilepsy & Behavior, 7*(3), 430–437.

Binzer, M., Stone, J., & Sharpe, M. (2004). Recent onset pseudoseizures – Clues to aetiology. *Seizure, 13*(3), 146–155.

Bodde, N. M., Brooks, J. L., Baker, G. A., Boon, P.A., Hendriksen, J.G., Mulder, O.G., et al. (2009). Psychogenic non-epileptic seizures–definition, etiology, treatment and prognostic issues: A critical review. [Review] [95 refs]. *Seizure, 18*(8), 543–553.

Bowlby, J. (1969). *Attachment and loss, vol 1: Attachment*. New York, NY: Basic Books.

Bowman, E. S., & Markand, O. N. (1996). Psychodynamics and psychiatric diagnoses of pseudoseizure subjects. *American Journal of Psychiatry, 153*(1), 57–63.

Brooks, J. L., Goodfellow, L., Bodde, N. M., Aldenkamp, A., & Baker, G.A. (2007). Nondrug treatments for psychogenic nonepileptic seizures: What's the evidence. [Review] [80 refs]. *Epilepsy & Behavior, 11*(3), 367–377.

Brown, R. J. (2004). Psychological mechanisms of medically unexplained symptoms: An integrative conceptual model. [Review] [168 refs]. *Psychological Bulletin, 130*(5), 793–812.

Carton, S., Thompson, P. J., & Duncan, J. S. (2003). Non-epileptic seizures: Patients' understanding and reaction to the diagnosis and impact on outcome. *Seizure, 12*(5), 287–294.

Ciechanowski, P. S., Walker, E. A., Katon, W. J., & Russo, J.E. (2002). Attachment theory: A model for health care utilization and somatization. *Psychosomatic Medicine, 64*(4), 660–667.

Cragar, D. E., Berry, D. T., Schmitt, F. A., & Fakhoury, T.A. (2005). Cluster analysis of normal personality traits in patients with psychogenic nonepileptic seizures. *Epilepsy & Behavior, 6*(4), 593–600.

Dodrill, C. B., Wilkus, R. J., & Batzel, L. W. (1993). The MMPI as a diagnostic tool in non-epileptic seizures. In A. J. Rowan & J. R. Gates (Eds.), *Non-epileptic seizures* (1st ed.). Boston, MA: Butterworth-Heinemann.

Drane, D. L., Williamson, D. J., Stroup, E. S., Holmes, M.D., Jung, M., Koerner, E., et al. (2006). Cognitive impairment is not equal in patients with epileptic and psychogenic nonepileptic seizures. *Epilepsia, 47*(11), 1879–1886.

Escobar, J. I., Waitzkin, H., Silver, R. C., Gara, M., & Holman, A. (1998). Abridged somatization: A study in primary care. *Psychosomatic Medicine, 60*(4), 466–472.

Ettinger, A. B., Devinsky, O., Weisbrot, D. M., Ramakrishna, R.K., & Goyal, A. (1999). A comprehensive profile of clinical, psychiatric, and psychosocial characteristics of patients with psychogenic nonepileptic seizures. *Epilepsia, 40*(9), 1292–1298.

Evans, H., & Bartholomew, R. E. (2009). *Outbreak: The encyclopedia of extraordinary social behavior*. San Antonio, TX: Anomalist Books.

Farias, S. T., Thieman, C., & Alsaadi, T. M. (2003). Psychogenic nonepileptic seizures: Acute change in event frequency after presentation of the diagnosis. *Epilepsy & Behavior, 4*(4), 424–429.

Ford, C. V. (1977). A type of disability neurosis: The humpty dumpty syndrome. *International Journal of Psychiatry in Medicine, 8*, 285–294.

Galimberti, C. A., Ratti, M. T., Murelli, R., Marchioni, E., Manni, R., & Tartara, A. (2003). Patients with psychogenic nonepileptic seizures, alone or epilepsy-associated, share a psychological profile distinct from that of epilepsy patients. *Journal of Neurology, 250*(3), 338–346.

Gay, P. (1988). *Freud: A life for our time*. New York, NY: WW Norton's.

Goldstein, L. H., Chalder, T., Chigwedere, C., Kondoker, M.R., Moriarty, J., Toone, B.K., et al. (2010). Cognitive-behavioral therapy for psychogenic nonepileptic seizures: A pilot RCT. *Neurology, 74*(24), 1986–1994.

Griffith, J. L., Polles, A., & Griffith, M. E. (1998). Pseudoseizures, families, and unspeakable dilemmas. *Psychosomatics, 39*(2), 144–153.

Gumnit RJ, Walczak TS, National Association of Epilepsy Centers. (2001). Guidelines for essential services, personnel, and facilities in specialized epilepsy centers in the United States. *Epilepsia, 42*(6), 804–814.

Halligan, P. W., Athwal, B. S., Oakley, D. A., & Frackowiak, R.S. (2000). Imaging hypnotic paralysis: Implications for conversion hysteria. *Lancet, 355*(9208), 986–987.

Harden, C. L., Burgut, F. T., & Kanner, A. M. (2003). The diagnostic significance of video-EEG monitor-

ing findings on pseudoseizure patients differs between neurologists and psychiatrists. *Epilepsia, 44*(3), 453–456.

Hermann, B. P. (1993). Neuropsychological assessment in the diagnosis of non-epileptic seizures. In A. J. Rowan & J. R. Gates (Eds.), *Non-epileptic seizures* (1st ed.). Boston, MA: Butterworth-Heinemann.

Hilgard, E. R. (1977). *Divided consciousness: Multiple controls in human thought and action*. New York, NY: Wiley.

Hiller, W., Rief, W., & Brahler, E. (2006). Somatization in the population: From mild bodily misperceptions to disabling symptoms. *Social Psychiatry and Psychiatric Epidemiology, 41*(9), 704–712.

Hotopf, M. (2002). Childhood experience of illness as a risk factor for medically unexplained symptoms. [Review] [51 refs]. *Scandinavian Journal of Psychology, 43*(2), 139–146.

Janet, P. (1907). *The major symptoms of hysteria*. New York, NY: Macmillan.

Kozlowska, K. (2001). Good children presenting with conversion disorder. *Clinical Child Psychology and Psychiatry, 6*, 575–591.

Kroenke, K. (2007). Efficacy of treatment for somatoform disorders: A review of randomized controlled trials. [Review] [64 refs]. *Psychosomatic Medicine, 69*(9), 881–888.

Kroenke, K., Spitzer, R. L., deGruy, F. V., III, Hahn, S.R., Linzer, M., Williams, J.B., et al. (1997). Multisomatoform disorder. An alternative to undifferentiated somatoform disorder for the somatizing patient in primary care. *Archives of General Psychiatry, 54*(4), 352–358.

Kuyk, J., Spinhoven, P., & van Dyck, R. (1999). Hypnotic recall: A positive criterion in the differential diagnosis between epileptic and pseudoepileptic seizures. *Epilepsia, 40*(4), 485–491.

LaFrance, W. C. J. (2010). Psychogenic nonepileptic "seizures" or "attacks"?: It's not just semantics: Seizures. [Miscellaneous]. *Neurology, 75*, 87–88.

LaFrance, W. C. Jr., Baird, G. L., Barry, J. J., Blum, A.S., Webb, F., Keitner, G.I., et al. (2014) Multicenter pilot treatment trial for psychogenic nonepileptic seizures: A randomized clinical trial. *JAMA Psychiatry*, doi:10.1001/jamapsychiatry.2014.817, Published online July 2, 2014.

LaFrance, W. C., Jr., Alper, K., Babcock, D., Barry, J.J., Benbadis, S., Caplan, R., et al. (2006). Nonepileptic seizures treatment workshop summary. *Epilepsy & Behavior, 8*(3), 451–461.

LaFrance, W. C., Jr., Keitner, G. I., Papandonatos, G. D., Blum, A.S., Machan, J.T., Ryan, C.E., et al. (2010). Pilot pharmacologic randomized controlled trial for psychogenic nonepileptic seizures. *Neurology, 75*(13), 1166–1173.

Lamberty, G. J. (2008). *Understanding somatization in the practice of clinical neuropsychology*. Oxford: Oxford University Press.

Lesser, R. P. (1996). Psychogenic seizures. [Review] [84 refs]. *Neurology, 46*(6), 1499–1507.

Lieb, R., Zimmermann, P., Friis, R. H., Hofler, M., Tholen, S., & Wittchen, H.U. (2002). The natural course of DSM-IV somatoform disorders and syndromes among adolescents and young adults: A prospective-longitudinal community study. *European Psychiatry, 17*(6), 321–331.

Lilienfeld, S. O., Van, V. C., Larntz, K., & Akiskal, H.S. (1986). The relationship of histrionic personality disorder to antisocial personality and somatization disorders. *American Journal of Psychiatry, 143*(6), 718–722.

Mace, C. J., & Trimble, M. R. (1996). Ten-year prognosis of conversion disorder. *British Journal of Psychiatry, 169*(3), 282–288.

Mailis-Gagnon, A., Giannoylis, I., Downar, J., Kwan, C.L., Mikulis, D.J., Crawley, A.P., et al. (2003). Altered central somatosensory processing in chronic pain patients with "hysterical" anesthesia. *Neurology, 60*(9), 1501–1507.

Marchetti, R. L., Kurcgant, D., Neto, J. G., von Bismark, M.A., Marchetti, L.B., & Fiore, L.A. (2008). Psychiatric diagnoses of patients with psychogenic non-epileptic seizures. *Seizure, 17*(3), 247–253.

Marshall, J. C., Halligan, P. W., Fink, G. R., Wade, D.T., & Frackowiak, R.S. (1997). The functional anatomy of a hysterical paralysis. *Cognition, 64*(1), B1–B8.

Martin, R. C., Gilliam, F. G., Kilgore, M., Faught, E., & Kuzniecky, R. (1998). Improved health care resource utilization following video-EEG-confirmed diagnosis of nonepileptic psychogenic seizures. *Seizure, 7*(5), 385–390.

Moene, F. C., Spinhoven, P., Hoogduin, K. A., & van Dyck, R. (2002). A randomised controlled clinical trial on the additional effect of hypnosis in a comprehensive treatment programme for in-patients with conversion disorder of the motor type. *Psychotherapy and Psychosomatics, 71*(2), 66–76.

Moene, F. C., Spinhoven, P., Hoogduin, K. A., van Dyck, R. (2003). A randomized controlled clinical trial of a hypnosis-based treatment for patients with conversion disorder, motor type. *International Journal of Clinical and Experimental Hypnosis., 51*(1), 29–50.

Mokleby, K., Blomhoff, S., Malt, U. F., Dahlstrom, A., Tauboll, E., & Gjerstad, L. (2002). Psychiatric comorbidity and hostility in patients with psychogenic nonepileptic seizures compared with somatoform disorders and healthy controls. *Epilepsia, 43*, 193–198.

Norman, D. A., & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In R. J. Davidson, G. E. Schwartz, & D. Shapiro (Eds.), *Consciousness and self-regulation, vol 4. Advances in research and theory*. New York, NY: Plenum.

Reuber, M. (2009). The etiology of psychogenic nonepileptic seizures: Toward a biopsychosocial model. [Review] [115 refs]. *Neurologic Clinics, 27*(4), 909–924.

Reuber, M., & Elger, C. E. (2003). Psychogenic nonepileptic seizures: Review and update. [Review] [185 refs]. *Epilepsy & Behavior, 4*(3), 205–216.

Reuber, M., Fernandez, G., Bauer, J., Helmstaedter, C., & Elger, C.E. (2002). Diagnostic delay in psychogenic nonepileptic seizures. *Neurology, 58*(3), 493–495.

Reuber, M., Pukrop, R., Bauer, J., Helmstaedter, C., Tessendorf, N., & Elger, C.E. (2003). Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients. *Annals of Neurology, 53*, 305–311.

Reuber, M., Pukrop, R., Bauer, J., Derfuss, R., & Elger, C.E. (2004). Multidimensional assessment of personality in patients with psychogenic non-epileptic seizures. [See comment]. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(5), 743–748.

Roelofs, K., Hoogduin, K. A., Keijsers, G. P., Naring, G.W., Moene, F.C., & Sandijck, P. (2002). Hypnotic susceptibility in patients with conversion disorder. *Journal of Abnormal Psychology, 111*(2), 390–395.

Rosenberg, H. J., Rosenberg, S. D., Williamson, P. D., & Wolford, G.L., II (2000). A comparative study of trauma and posttraumatic stress disorder prevalence in epilepsy patients and psychogenic nonepileptic seizure patients. *Epilepsia, 41*(4), 447–452.

Shen, W., Bowman, E. S., & Markand, O. N. (1990). Presenting the diagnosis of pseudoseizure. [See comment]. *Neurology, 40*(5), 756–759.

Shih, J. J., LeslieMazwi, T., Falcao, G., & Van Gerpen, J. (2009). Directed aggressive behaviors in frontal lobe epilepsy: A video-EEG and ictal SPECT case study. *Neurology, 73*, 1804–1806.

Temkin, O. (1971). *The falling sickness* (2nd ed.). Baltimore, MD: Johns Hopkins Press.

Vuilleumier, P. (2005). Hysterical conversion and brain function. [Review] [123 refs]. *Progress in Brain Research, 150*, 309–329.

Waldinger, R. J., Schulz, M. S., Barsky, A. J., & Ahern, D.K. (2006). Mapping the road from childhood trauma to adult somatization: The role of attachment. *Psychosomatic Medicine, 68*(1), 129–135.

Watson, W. (2007). Bridging the mind–body split: Towards an integrative framework for thinking about somatoform symptoms. *The Family Psychologist, 23*, 30–33.

Watson, W., & Langfitt, J. T. (2010). Psychogenic nonepileptic attacks. *Family Therapy Magazine, 9*, 30–38.

Wood, B. L., McDaniel, S., Burchfiel, K., & Erba, G. (1998). Factors distinguishing families of patients with psychogenic seizures from families of patients with epilepsy. *Epilepsia, 39*(4), 432–437.

Wyler, A. R., Hermann, B. P., Blumer, D., & Richey, E.T. (1993). Pseudo-pseudoepileptic seizures. In A. J. Rowan & J. R. Gates (Eds.), *Non-epileptic seizures* (1st ed.). Boston, MA: Butterworth-Heinemann.

Wyllie, E., Friedman, D., Luders, H., Morris, H., Rothner, D., & Turnbull, J.(1991). Outcome of psychogenic seizures in children and adolescents compared with adults. *Neurology, 41*(5), 742–744.

Developmentally Delayed Children and Adults

13

Erica M. Brandling-Bennett

Introduction

Epilepsy is a disorder that can arise from a variety of etiologies, such as structural brain malformations, genetic or metabolic abnormalities, birth anoxia, cerebrovascular insults, central nervous system infections, brain tumors, or moderate to severe brain injury. It is a disorder that most often begins in childhood and adolescence but can have an onset at any point during adulthood, including older adulthood. Given the heterogeneity of epilepsy, it is not surprising that patients with epilepsy can have vastly different levels of intellectual and neurocognitive functioning. Specific factors such as the underlying pathology of seizures, age of onset, seizure type, seizure frequency, as well as antiepileptic medication regimen can have an impact on intellectual and neurocognitive functioning. Additionally, intellectual disabilities are caused by a variety of neuropathological processes, including structural brain malformations, genetic or metabolic abnormalities, birth anoxia, and cerebrovascular insults, some of which overlap with the neuropathological underpinnings of seizures. Epidemiological studies have shown that epilepsy occurs much more often in people with intellectual disability than in the general population, with estimates ranging from 10 % to over 60 % of people with intellectual disability having some form of epilepsy (Forsgren, Edvinsson, Blomquist, Heijbel, & Sidenvall, 1990; Lhatoo & Sander, 2001). In those patients with intellectual impairment and epilepsy concurrently, seizures usually present before the age of 5 years, with the severity of seizures and intellectual impairment being highly correlated (Kaufman, 2007). It is well beyond the scope of this chapter to try to characterize the intellectual functioning associated with all the different seizure types and epilepsy syndromes. However, there are several epilepsy syndromes that commonly have comorbid intellectual impairment and developmental delay, and there are several common developmental syndromes that are characterized by both intellectual impairment and seizures. This chapter will briefly outline a few syndromes that most commonly present with developmental delays and seizures. More importantly, it will attempt to provide a discussion of how neuropsychological assessment can assist in the assessment and treatment of developmentally delayed children and adults with epilepsy.

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Neurocognitive Functioning in Epilepsy Syndromes and Developmental Syndromes with Comorbid Epilepsy

There are a number of different classifications of epilepsy and specific epilepsy syndromes with which patients can be diagnosed, as designated by the International League Against Epilepsy (ILAE), many of which are diagnosed in childhood. There are also a number of different developmental syndromes in which children commonly present with intellectual impairment, developmental delays, or severe learning disorders as well as a history of seizures or a chronic epilepsy diagnosis. While the following list of classifications and syndromes is not exhaustive, it highlights several of the more common types of epilepsy syndromes and developmental syndromes that have comorbid developmental delay or intellectual impairment with concurrent seizures.

Temporal Lobe Epilepsy

It has been estimated that simple and complex focal seizures make up as many as 70 % of all the diagnosed epilepsies, and half of those originate in temporal lobe structures. Thus, approximately 30 % of all epilepsies are thought to be temporal lobe epilepsy, with two-thirds of temporal lobe epilepsies having an epileptogenic focus in mesial temporal areas and the other third having an epileptogenic focus in lateral temporal lobe regions (Crawford, 2000; Hauser, Annegers, & Kurland, 1991; Panayiotopoulos, 2002; Wiebe, 2000). For the most part, temporal lobe epilepsy is not commonly associated with developmental delay or intellectual impairment (Sauerwein, Gallagher, & Lassonde, 2005). However, cognitive functioning in patients with temporal lobe epilepsy varies from individual to individual, with the occurrence and severity of status epilepticus or a series of generalized tonic-clonic seizures presenting the greatest risk factors for amnestic syndromes and neurocognitive decline in domains other than memory (Lee, Yip, & Jones-Gotman, 2002). Furthermore, it has been demonstrated that patients with chronic, uncontrolled temporal lobe epilepsy often experience a significant decline in their overall IQ after about 30 years of uncontrolled seizure activity, although those findings are also mediated by a number of factors, including the frequency and severity of the patient's seizures and premorbid cognitive and intellectual functioning (Jokeit & Ebner, 2002). It has also been demonstrated that some proportion of patients with temporal lobe epilepsy have premorbid intellectual impairment, as lesions, areas of epileptogenesis, and seizures all interfere with the maturation and development of the brain which can lead to a global impact on cognitive development and a significant decrease in overall intellectual functioning such that even "typical" mesial temporal epilepsy with hippocampal sclerosis can be associated with impaired intellectual functioning (Sauerwein et al., 2005).

Primary Generalized Epilepsy

There are a number of primary generalized epilepsies, also known as idiopathic generalized epilepsies, most of which are presumed to have multiple genetic underpinnings that are only just beginning to be elucidated. They include syndromes such as childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalized tonic-clonic seizures upon awakening, and generalized epilepsies associated with febrile events (Shouse & Quigg, 2008). For the most part, these epilepsies respond well to antiepileptic medications, particularly valproic acid, lamotrigine, topiramate, levetiracetam, and ethosuximide. Additionally, many children with one of these primary generalized epilepsies are seizure-free within 14 years of their initial diagnosis and do not need to take medication chronically, with the exception of children with juvenile myoclonic epilepsy who often need to take antiepileptic medication throughout their lives (Shahar, Barak, Andraus, & Kramer, 2004; Williams & Sharp, 2000). Regarding the cognitive correlates of primarily

generalized epilepsy, studies have shown that children demonstrate average IQs with only mild cognitive weaknesses in the areas of attention, concentration, and impulsiveness, as well as a higher rate of diagnosed learning disorders (Bhise, Burack, & Mandelbaum, 2010; Shahar et al., 2004). In particular, juvenile myoclonic epilepsy is associated with a good intellectual prognosis, particularly if it is well controlled with medication (Williams & Sharp, 2000).

West Syndrome (Infantile Spasms)

West syndrome, also known as infantile spasms, begins between 4 and 6 months of life and generally involves clusters of myoclonic seizures. There are a variety of etiologies of infantile spasms, including CNS infection, CNS developmental abnormalities, head trauma, intrapartum asphyxia, metabolic disorders, and neurodegenerative disease (Williams & Sharp, 2000), thus many of the syndromes described in this chapter have West syndrome or infantile spasms as a presenting or core feature. The overall incidence of infantile spasms has been estimated at 2–7 per 10,000 live births and often has comorbid developmental delay (Hauser et al., 1991; Lee & Ong, 2001; Lúthvígsson, Olafsson, Sigurthardóttir, & Hauser, 1994), making it one of the most common epilepsy syndromes of childhood or presentation of childhood seizures that has comorbid intellectual impairment. Interestingly, the myoclonic seizures of infancy usually wane by the age of 4 years old. As many as 60 % of children with a history of infantile spasms then develop other types of seizures and go on to have chronic epilepsy that may or may not be treatable with antiepileptic medication (Murphy & Dehkharghani, 1994). In terms of long-term prognosis, up to 20 % of infants with infantile spasms will die in infancy, usually as a result of the underlying disease or complications from their medical condition (Jeavons, Bower, & Dimitrakoudi, 1973). Of those children who survive infantile spasms, one epidemiological study demonstrated that by the age of 10 years old, 83 % of children with a history of infantile spasms will be intellectually disabled (Trevathan, Murphy, & Yeargin-Allsopp, 1999). Additionally, that study also demonstrated that approximately 12 % of 10-year-old children with severe intellectual disability have a history of infantile spasms. Interestingly, when the etiology of infantile spasms is cryptogenic, approximately 50 % of the children have a normal cognitive outcome, particularly if the seizures are well controlled with medications or surgery (Murphy & Dehkharghani, 1994).

Tuberous Sclerosis

Tuberous sclerosis is characterized by smooth and firm nodules on the face that usually appear in adolescence. In a minority of children affected by tuberous sclerosis, they also present with seizures and intellectual disability due to cerebral tubers that correlate with the skin lesions. Additionally, children with CNS involvement of tuberous sclerosis often present with autistic-like symptoms (Hunt & Dennis, 1987; Kaufman, 2007). The severity of neuropsychiatric and intellectual impairment is correlated with the number and location of cortical tubers (Caplan, Gillberg, Dunn, & Spence, 2008). While approximately 50 % of children with tuberous sclerosis need to be institutionalized due to intractable seizures and deteriorating intellectual functioning, the other 50 % of children with tuberous sclerosis have only minimal cognitive impairment, and their epilepsy is easily controlled with antiepileptic medication. However, children with cerebral tubers often have several tubers. When children have several cortical tubers, that is often correlated with more severe seizures that are often intractable to antiepileptic medication, and their intellectual disability is often more severe. While not all cortical tubers are epileptogenic, the likelihood of intellectual impairment occurring in patients with tuberous sclerosis has been associated with a history of seizures, particularly infantile spasms (Joinson et al., 2003; Kaufman, 2007). Importantly, one study demonstrated that treatment of the infantile spasms with vigabatrin resulted in a very high rate of seizure control and

a commensurate improvement in behavioral and intellectual functioning, suggesting that seizures significantly contribute to the presentation of intellectual impairment and autistic-like behavior in children with tuberous sclerosis and not simply the presence of cortical tubers (Jambaqué, Chiron, Dumas, Mumford, & Dulac, 2000).

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is characterized by the following triad of symptoms: (1) multiple types of intractable seizures that are mainly tonic, atonic, and atypical absence seizures, (2) cognitive and behavioral abnormalities, and (3) diffuse slow spike and waves and paroxysms of fast activity on EEG (Panayiotopoulos, 2002). The syndrome usually first presents between 1 and 7 years of age, with a peak incidence occurring between 3 and 5 years of age (Rantala & Putkonen, 1999; Trevathan, Murphy, & Yeargin-Allsopp, 1997). Approximately 50 % of children with West syndrome progress to Lennox-Gastaut syndrome, and conversely up to 30 % of children with Lennox-Gastaut transition to having West syndrome (Panayiotopoulos, 2002, Rantala & Putkonen, 1999). The seizures are often difficult to control and status epilepticus is common. In about 50 % of children who are eventually diagnosed with Lennox-Gastaut syndrome, cognitive and behavioral abnormalities are evident prior to the initial diagnosis of the epileptic syndrome, but eventually intellectual disability is diagnosed in up to 96 % of children with the syndrome. Additionally, the course of intellectual impairment and developmental delay is usually progressive, and many children with the syndrome eventually require significant assistance in most aspects of daily functioning if they reach adulthood (Gastaut, 1982).

Landau-Kleffner Syndrome

Landau-Kleffner syndrome, also known as acquired epileptic aphasia, is characterized by a sudden or gradual onset of verbal deficits, particularly verbal auditory agnosia, which occurs sometime between 2 and 11 years of age following a period of normal development. It is a relatively rare epilepsy syndrome but one in which neurocognitive functioning is a hallmark feature of the syndrome. Importantly, the child should have achieved age-appropriate developmental milestones, including age-appropriate speech, at the time of the initial onset of verbal auditory agnosia (Fenichel, 2001; Panayiotopoulos, 2002). The severity of verbal deficits is highly variable between children diagnosed with the syndrome, as it can simply involve verbal auditory agnosia in which children have difficulty distinguishing speech from nonspeech sounds, or children can become totally unresponsive in oral communication and eventually demonstrate a progressive deterioration of expressive speech and vocabulary. Interestingly, the course over which verbal deficits are acquired is often fluctuating with remission and exacerbation causing a waxing and waning pattern in their behavioral and neurocognitive presentation (Paquier, Van Dongen, & Loonen, 1992). Approximately 75 % of children with Landau-Kleffner syndrome have comorbid seizures, which may have an onset before, during, or after the development of verbal deficits. Most commonly, children have generalized tonic-clonic seizures and focal motor seizures (Murphy & Dehkharghani, 1994). The seizures are usually easily treatable with antiepileptic medication, with almost all children becoming seizure-free by 15 years of age. Unfortunately, seizure remittance is not associated with an improvement in aphasia or verbal deficits, although some children do spontaneously recover all language function. To date, studies have not been able to determine what contributes to long-term recovery of language in some children, although an earlier age of onset is associated with a poorer neurocognitive outcome (Gordon, 1990). Children diagnosed with Landau-Kleffner syndrome also demonstrate a variety of behavioral problems, including hyperactivity, inattention, and impulsivity. Importantly, nonverbal abilities are generally preserved and Landau-Kleffner syndrome is not usually associated with global cognitive decline or intellectual impairment (Panayiotopoulos, 2002; Williams & Sharp, 2000).

Electrical Status Epilepticus During Sleep

Electrical status epilepticus during sleep, also known as epilepsy with continuous spike and waves during slow-wave sleep, is characterized by: (1) continuous spikes and waves during more than 85 % of non-REM sleep on EEG, (2) seizures, and (3) neurocognitive decline (Panayiotopoulos, 2002). Much like Landau-Kleffner syndrome, it is a relatively rare epilepsy syndrome in which a decline in intellectual and cognitive functioning is a hallmark feature. Usually children have a period of typical development followed by the onset of continuous spike and slow waves during sleep sometime between the ages of 4 and 14 years of age, which is accompanied by neurocognitive regression, although some children demonstrate premorbid developmental delays prior to the onset of electroencephalographic changes (Williams & Sharp, 2000). Unlike Landau-Kleffner syndrome, which is thought to be a highly related syndrome (Feekery, Parry-Fielder, & Hopkins, 1993), children with electrical status epilepticus during sleep demonstrate more global neurocognitive decline (Jayakar & Seshia, 1991). Similar to Landau-Kleffner syndrome, the seizures always remit, usually at some point during adolescence. Studies have suggested that there are some recovery of neurocognitive function and improvement in behavioral problems that occur with the remission of the continuous spike and slow waves during sleep. However, less than 25 % of children with this syndrome achieve an average level of intellectual and cognitive functioning, instead presenting with some level of cognitive and adaptive disability throughout their lives (Panayiotopoulos, 2002, Paquier et al., 1992).

Down Syndrome

Down syndrome or trisomy 21 is characterized by a range of intellectual and developmental disability, along with a number of physical and medical problems. It is the most common *genetic* cause of intellectual disability and developmental delay (Kaufman, 2007). Additionally, approximately 13–57 % of patients with Down syndrome develop seizures or an abnormal EEG at some point in their lives (Romano et al., 1990; Tangye, 1979). There is commonly a bimodal distribution of seizure onset, with the highest rate of onset occurring in childhood and another spike in onset occurring in middle age (Prasher, 1995; Tatsuno, Hayashi, Iwamoto, Suzuki, & Kuroki, 1984). Additionally, patients with Down syndrome can present with a number of different seizure types, including infantile spasms (Pollack, Golden, Schmidt, Davis, & Leeds, 1978), generalized tonic-clonic seizures, complex-partial seizures (Romano et al., 1990), and Lennox-Gastaut syndrome (Tatsuno et al., 1984).

Angelman Syndrome

Angelman syndrome is a genetic disorder in which all patients present with developmental delay that becomes apparent between 6 and 12 months of age. Behavioral and cognitive features include severely impaired expressive language, an excessively happy demeanor, very poor attention span, and autistic-like symptoms (Kaufman, 2007). Additionally, seizures, abnormal electroencephalography, and microcephaly are observed in over 80 % of patients with the syndrome. In fact, it has been estimated that about 6 % of the children who present with severe intellectual disability and epilepsy have Angelman syndrome (Guerrini, Cararozzo, Rinaldi, & Bonnani, 2003). Patients with Angelman syndrome almost always develop seizures before 3 years of age. The most frequent seizure types are myoclonic, atonic, generalized tonic-clonic, atypical absence seizures (Galván-Manso, Campistol, Conill, & Sanmartí, 2005), as well as periods of insidious myoclonic status epilepticus (Viani et al., 1995). Fortunately, there are a number of medications that have been shown to effectively treat the seizures in these patients during early childhood, including valproic acid, benzodiazepines, and ethosuximide, often in combination (Guerrini et al., 2003), with additional control of seizures also being

achieved after children are 9 years of age or older with some combination of those antiepileptic medications (Galván-Manso et al., 2005).

Fragile X Syndrome

Fragile X syndrome is a sex-linked chromosomal disorder that is characterized by intellectual impairment and distinctive non-neurological physical features. It is widely considered to be the most common cause of *inherited* intellectual disability, as it is responsible for about 10 % of all cases of intellectual disability (Kaufman, 2007). Approximately 80 % of males with fragile X syndrome are moderately or severely intellectually disabled, while 10–15 % of males with fragile X syndrome are mildly intellectually disabled or have IQs in the borderline range with significant language impairment and autistic-like symptoms. Additionally, most males with this syndrome have symptoms of attention deficit hyperactivity disorder, including distractibility and impulsivity (Fryns, Jacobs, Kleczkowska, & van den Berghe, 1984). In contrast, females carrying the fragile X gene are often asymptomatic. Approximately 30 % of females with the gene present with IQs lower than 85, and those of average intellectual functioning are at increased risk for learning disabilities (de Vries et al., 1995; Kaufman, 2007). Seizures occur in approximately 10–20 % of patients, both male and female, with fragile X syndrome, with a slightly higher prevalence of seizures in males with fragile X syndrome. The seizures that occur in fragile X syndrome most resemble those of benign focal epilepsy of childhood, including a common pattern of centrotemporal spikes, which are usually easily controlled with antiepileptic medication and often remit before 20 years of age (Berry-Kravis, 2002; Sabaratnam, Vroegop, & Gangadharan, 2001).

Rett Syndrome

Rett syndrome occurs only in females and is characterized by normal birth and typical development for the first 6–18 months of life, after which time development slows and then deteriorates with a loss of language skills, a regression of motor abilities, and a decrease in cognitive capacity. Eventually, girls with Rett syndrome are considered developmentally delayed with severe to profound intellectual disability and autistic-like symptoms (Huppke, Held, Laccone, & Hanefeld, 2003; Kaufman, 2007). It has been estimated that epilepsy occurs in 80–95 % of girls with Rett syndrome (Steffenburg, Hagberg, & Hagberg, 2001), but some studies have also argued that the incidence of seizure comorbidity in Rett syndrome is overestimated due to the frequent occurrence of autonomic dysfunction and motor symptoms that are common in the syndrome, such as twitching, jerking, head turning, falling forward, and trembling, all of which can be easily mistaken for seizures (Glaze, Schultz, & Frost, 1998). When seizures are identified in girls with Rett syndrome, they are commonly complex-partial seizures with onset occurring around 4 years of age. Most often, the occurrence of seizures is highly correlated with smaller head circumference. Additionally, girls with Rett syndrome can also present with generalized tonic-clonic, absence, myoclonic jerk, atonic, and tonic seizures. The severity and incidence of seizures decrease with increasing age, and many women with the syndrome are seizure-free (Steffenburg et al., 2001).

Dravet Syndrome (Severe Myoclonic Epilepsy in Infancy)

Dravet syndrome, also known as severe myoclonic epilepsy in infancy, is a rare form of progressive epileptic encephalopathy that is thought to have genetic underpinnings. It is estimated to affect approximately 6 % of infants diagnosed with epilepsy. It is characterized by initial febrile and afebrile, generalized and unilateral clonic or tonic-clonic seizures that occur during the first year of life in an otherwise typically developing infant (Dravet & Bureau, 2008). Over time, children will then begin to have other types of seizures, including myoclonic, atypical absences, and partial seizures, with periods of absence

status epilepticus frequently occurring between 2 and 4 years of age. One hallmark feature of the syndrome is that the seizures are often refractory to treatment with antiepileptic medication (Panayiotopoulos, 2002). As the seizures progress between 2 and 4 years of age, psychomotor delays, behavioral disturbances, and cognitive impairment become apparent. Eventually, patients with Dravet syndrome go on to have persistent refractory convulsive seizures. There has been one neuropsychological study of teenagers with Dravet syndrome that demonstrated 50 % of patients with this syndrome were severely intellectually disabled, and all teenagers had significant neurocognitive deficits in motor, verbal, and visuospatial abilities. The teenagers were described as hyperactive and psychotic-like with some autistic traits (Cassé-Perrot, Wolff, & Dravet, 2001; Wolff, Cassé-Perrot, & Dravet, 2001). Approximately 15 % of children with Dravet syndrome die as a direct or indirect result of their seizures. For those patients who survive into adulthood, their seizures always remain refractory to antiepileptic medication. Additionally, they are usually intellectual disabled and present with limited language, poor fine motor functions, generalized slowing, autistic-like behaviors, and occasionally psychiatric features, all of which are severe enough that they usually cannot work or live independently (Dravet & Bureau, 2008).

Neurocognitive Effects of Antiepileptic Drugs During Pregnancy

Epilepsy can affect not only the intellectual capacity of patients with the condition but also the intellectual functioning of children born to mothers with epilepsy. It has long been established that exposure to some antiepileptic medications in utero, particularly phenobarbital and other antiepileptic medications in high doses, can lead to fetal structural malformations (Holmes, Wysznski, & Lieberman, 2004). More recent studies have also examined the effects of fetal exposure to lower doses of antiepileptic medications and have revealed behavioral and cognitive deficits, altered neurochemistry, and reduced brain weight in the children after birth (Fisher & Vorhees, 1992; Gaily & Meador, 2007). In a groundbreaking study examining the effects of fetal exposure to four different antiepileptic medications, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group demonstrated that exposure to valproic acid in utero resulted in significantly lower IQs at 3 years of age compared with in utero exposure to carbamazepine, lamotrigine, and phenytoin (Meador et al., 2009). However, it is important to note that children exposed to valproic acid in utero had an average IQ of 92, with IQs ranging from 88 to 97. Thus, none of the children exposed to valproic acid met criteria for borderline intellectual functioning or intellectual impairment. While it is important to consider in utero exposure to antiepileptic medication as a possible factor when assessing patients born to mothers with epilepsy who took antiepileptic medication during their pregnancy, there has been little evidence to suggest that in utero exposure to antiepileptic medications is a single causative factor for developmental delay or intellectual impairment.

Neuropsychological Assessment of Patients with Developmental Delay or Intellectual Impairment and Concurrent Epilepsy

Developmentally delayed or intellectually impaired patients with epilepsy are referred for neuropsychological for a variety of reasons. Most commonly, they are referred by their neurologists for evaluation of their overall general intellectual functioning and their level of general adaptive functioning. In those cases, their degree of intellectual, neurocognitive, and developmental disability needs to be determined so that appropriate recommendations and referrals can be provided. A frequently asked additional referral question is whether or not the patient's current antiepileptic medication regimen is negatively impacting their degree of intellectual, neurocognitive, or developmental impairment or delay. It has been well

established that many antiepileptic medications can have a negative impact on neurocognition, particularly memory and verbal functioning (Aldenkamp, Baker, & Mulder, 2000; Martin et al., 1999; Loring & Meador, 2001; Meador, Loring, Hulihan, Kamin, & Karim, 2003; Motamedi & Meador, 2004), and it is important to determine whether a patient with intellectual impairment is being further negatively impacted by their antiepileptic medication regimen. Finally, developmentally delayed or intellectually impaired patients with epilepsy are also referred by neurosurgeons for neuropsychological assessment to assist with determining epileptogenic lateralization and location, as well as to predict the potential impact of surgery on cognitive, behavioral, and adaptive functioning. It is important for neuropsychologists to consider the referral source and referral question when assessing developmentally delayed or intellectually impaired patients with epilepsy so that they design their battery appropriately, with special consideration to the ability of the patient to participate in a comprehensive evaluation versus a shorter evaluation and the relative value of administering some tests over others.

Definition of Intellectual Disability

The *Diagnostic and Statistic Manual of Mental Disorders*, *Fourth Edition*, *Text Revision* (DSM-IV-TR, 2000) provides the following criteria for diagnosing mental retardation or intellectual disability:

1. A measured IQ of 70 or below on an administered test of intellectual functioning.
2. Concurrent age-related deficits in adaptive functioning in at least two of the following areas:
   (a) Communication.
   (b) Self-care.
   (c) Home living.
   (d) Social skills.
   (e) Use of community resources.
   (f) Self-direction.
   (g) Functional academic skills.
   (h) Work.
   (i) Leisure.
   (j) Health issues
   (k) Safety
3. An onset of deficits before the age of 18 years.

Additionally, the DSM-IV-TR specifies the criteria for defining the severity of a patient's level of mental retardation or intellectual disability into the following levels: borderline intellectual functioning (IQ 70–85), mild mental retardation (IQ of 50–75), moderate mental retardation (IQ of 35–55), severe mental retardation (IQ of 20–40), and profound mental retardation (IQ of less than 20). The *International Classification of Diseases*, *10th revision* (ICD-10, World Health Organization, 1993) denotes similar definitions of the four levels of mental retardation and also specifies that intellectual retardation is determined by both a low measured IQ and deficits in cognitive, language, motor, social, and other adaptive behavior skills. Approximately 85 % of people who are diagnosed with intellectual disability are mildly mentally retarded, which means they can usually attain at least a sixth grade level of academic achievement and lead somewhat independent lives (McLaren & Bryson, 1987). Adults with mild mental retardation often work or volunteer in their community and live in assisted living facilities where they are minimally supervised. Given that the severity of disability and a patient's needs increase with classifications of moderate, severe, or profound mental retardation, it is often helpful to accurately assess a patient's level of intellectual disability in order to best inform patients' caretakers of their expected quality of life.

Neurocognitive Functioning in Patients with Developmental Delays or Intellectual Disability

Patients with documented intellectual disability have, by definition, delays in several aspects of cognition and adaptive functioning. However, the nature and degree of impairment in various areas of cognition is highly variable from patient to patient. Studies have demonstrated that a diagnosis

of mild mental retardation does not always correlate with impairments in attention, memory, verbal comprehension, or visual perception. In fact, when patients with mild or moderate general intellectual disability have borderline to average functioning in attention, memory, or verbal comprehension, that is highly predictive of employment success (Su, Lin, Wu, & Chen, 2008). Thus, even though a patient may present with a measured IQ below 70, that does not necessarily mean that all other aspects of their neurocognitive profile will also be in the impaired range. A careful assessment of all aspects of the neurocognitive profile of patients with intellectual disability, particularly patients with mild or moderate intellectual disability, is warranted as that provides the most accurate evaluation of all aspects of their functioning. Additionally, a thorough neuropsychological assessment provides crucial information about the possible neurocognitive effects of antiepileptic medication or the possible neurocognitive outcome of surgery.

Intelligence Tests

Given that a patient's measured IQ is the foundation for a diagnosis of mental retardation or intellectual disability, it is often essential to at least attempt to obtain a measured IQ score for patients who are thought to be developmentally delayed or intellectually impaired. The most common measures used to assess overall intellectual and general cognitive functioning are the Wechsler scales, which allow for the assessment of children from the age of two and a half years old to adults aged 91 years old. The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III; Wechsler, 2002) is appropriate for children age 2 years, 6 months to 7 years, 3 months and provides verbal and performance indices for all children as well as a processing speed index for older children. The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) is appropriate for children aged 6–17 years old and provides subtests to assess verbal comprehension, perceptual reasoning, processing speed, and working memory. Similarly, the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008) is appropriate for adults aged 16–91 years old and provides subtests to assess verbal comprehension, perceptual reasoning, processing speed, and working memory. If the administration of a full WPPSI-III, WISC-IV, or WAIS-IV is not possible given the severity of a patient's intellectual disability, the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) is appropriate for both children and adults aged 6–90 years old, takes only 30 min to administer, and provides verbal (estimated VIQ), nonverbal (estimated PIQ), and overall (estimated FSIQ) measures of intellectual functioning. The Wechsler scales have the advantage of being the most widely used measures that have the greatest basis for empirical validity in the research literature. Additionally, the more recent versions of the Wechsler scales have been tailored to have shorter administration times, so they are more amenable to testing patients with significant cognitive limitations. However, it is not uncommon for patients who are assessed at major epilepsy centers around the United States and in other countries to be given older versions of the Wechsler scales (i.e., WPPSI-R, WISC-III, and WAIS-III), as those centers have often invested a great deal of time and effort in collecting valuable databases that incorporate older versions of the Wechsler scales, and so they continue to gather consistent data about the performance of patients with epilepsy on those older measures.

When using the Wechsler scales to obtain a measure of IQ or to estimate general overall intellectual functioning, it is important to consider the patient's level of verbal and nonverbal abilities in the context of both their level of disability and a possible lateralization of epileptogenic areas. While it is not unusual for patients with intellectual disabilities to have bilateral or diffuse pathology, both in relation to their epilepsy and with regard to other factors contributing to their cognitive limitations, it is also possible that they may have a lateralized epileptogenic focus that will result in a significant discrepancy between their verbal and perceptual reasoning abilities and thus artificially lower

their overall measured IQ. Thus, IQ alone is not a good predictor of postoperative cognition and seizure outcome, necessitating the gathering of additional neurocognitive data (Gleissner, Clusmann, Sassen, Elger, & Helmstaedter, 2006).

Nonverbal Tests of Intelligence

Many patients with intellectual disabilities have significant verbal limitations, even when the epileptogenic focus is in the nondominant hemisphere. Frequently, their verbal limitations are so severe that administration of a Wechsler scale to measure IQ results in a significant underestimate of their abilities. It is important to consider a patient's verbal abilities before administering the comprehensive but time-consuming scales. Even if it is possible to administer a comprehensive measure of intellectual functioning, such as the aforementioned Wechsler scales, it is often useful to administer a nonverbal test of intelligence that can be used to assess the validity of the measured IQ score. For children, the most widely used nonverbal measure of intelligence is the Leiter International Performance Scale, Revised Edition (Leiter-R; Roid & Miller, 1997), which can be used for children aged 2–21 years, provides a brief measure of mental age, and covers a wide range of abilities using a simple format. Another commonly administered brief nonverbal test of intellectual function is the Test of Nonverbal Intelligence, Third Edition (TONI-3; Brown, Sherbenou, & Johnson, 1997), which can be used for patients aged 6–90 years old and allows for a very brief and completely nonverbal estimate of overall intellectual functioning. In contrast to the Leiter-R, the TONI-3 does not assess a variety of different abilities, but it is much quicker to administer.

Comprehensive Neurocognitive Screening Tests

In addition to assessing overall intellectual functioning in patients with intellectual disabilities, it is also important to assess other aspects of neurocognitive functioning. If possible, again depending on the stamina of the patient being assessed, it is preferable to administer multiple measures within each neurocognitive domain in order to assure the reliability the data obtained on a given measure within a neurocognitive domain. However, there are a number of valuable screening tests that sample a variety of neurocognitive domains in a short period of time. Probably the most widely used neuropsychological screening measure is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), which can be administered to adult patients aged 20–89 years old. The RBANS provides assessments of immediate memory (immediate list learning and immediate story), visuoperceptual abilities (figure copy and line orientation), language (naming and semantic fluency), attention (digit span forward and digit-symbol coding), and delayed memory (delayed list memory with recognition, delayed story memory, and delayed figure memory). More recently, the Neuropsychological Assessment Battery (NAB; Stern & White, 2003) has provided an additional neuropsychological screening measure. The NAB can be administered to patients aged 18–97 years old. The battery is made up of six modules, each of which includes a number of different tests. The modules are (1) the Screening Module, (2) the Attention Module, (3) the Language Module, (4) the Memory Module, and (5) the Executive Functions Module. Within each module are a number of different tests that assess the designated domain. The Screening Module incorporates brief versions of several of the tests from each of the five other modules. Thus, administration of the NAB Screening Module provides a brief assessment of all global, basic aspects of neurocognitive functioning, in much the same way as the RBANS does. Furthermore, the NAB then provides the option of administering more detailed measures of a specific domain of neurocognitive functioning, if the Screening Module reveals particular weaknesses or strengths within that domain.

Language

In assessing a patient's language abilities, if a full Wechsler scale measure of intellectual functioning is administered, the individual verbal subtests from the scale may be able to provide some insight into strengths and weaknesses in the verbal profile, particularly with regard to expressive (i.e., the vocabulary and similarities subtests) versus receptive (i.e., the comprehension subtest) verbal functioning. Additionally, it may be possible to administer some of the more common measures of language functioning, such as the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001) for which there is good normative data for patients aged 5 to 90 years old (Heaton, Miller, Taylor, & Grant, 2005; Kaplan et al., 2001) and measures of phonemic and semantic verbal fluency for which there is good normative data for patients aged 8–90 years old (Heaton et al., 2005; Welsh, Pennington, & Groisser, 1991). However, it is important to recognize that the subtests of the Wechsler scales, the BNT, and verbal fluency require relatively strong verbal skills, which can be a significant limitation for patients with developmental delay or intellectual impairment. If patients perform very poorly on those measures, they provide little insight into relative strengths and weaknesses in the verbal profile. That said, it can be valuable to do a qualitative comparison of a patient's verbal output on phonemic versus semantic fluency, as that may provide insight into whether frontal or temporal language areas are more affected or involved (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 2002).

For patients with significant limitations in their expressive language abilities, a valuable measure of receptive language is the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-4; Dunn & Dunn, 2007), which can be administered to patients aged 2 years, 6 months to 90 years old. This test requires patients to select one picture from an array of four pictures that best represents a word that is said to them by the examiner. The test has the advantage of taking only about 15 min to administer. From the PPVT-4, it is possible to obtain an estimate of a patient's age- and grade-related receptive language abilities. Additionally, it is now possible to make direct comparisons between receptive and expressive vocabulary with the administration of the Expressive Vocabulary Test, Second Edition (EVT-2; Williams, 2007), which was normed on the same sample as the PPVT-4. The EVT-2 can also be administered to patients aged 2 years, 6 months to 90 years old and only takes about 20 min to administer. The test requires a patient to provide an acceptable one-word response when presented with a picture and a question administered by the examiner. The PPVT-4 and EVT-2 have been validated on samples with ADHD, emotional/behavioral disturbance, giftedness, hearing impairment, language/speech delay, language/speech disorder, learning disability, and intellectual impairment and thus have proven valid for assessment of both receptive and expressive language abilities in patients with developmental delay or intellectual impairment.

Finally, as mentioned before, the RBANS and the NAB also incorporate assessment of language functioning. Specifically, the RBANS has a simple naming measure, which has a low ceiling but can be sensitive in measuring naming deficits in lower functioning patients. Additionally, the RBANS has a semantic fluency measure that requires patients to name as many fruits and vegetables as they can in a 1-min period, which also has a low ceiling but can be sensitive in measuring verbal fluency deficits in lower functioning patients (Randolph, 1998). The NAB has a language module comprised of six subtests, which can be administered individually, including an oral production subtest, an auditory comprehension subtest, a naming subtest, a reading comprehension subtest, a writing subtest, and a bill payment subtest (Stern & White, 2003). These subtests, particularly the oral production and the naming subtests, have the advantage of evaluating verbal fluency and confrontation naming, respectively, with greater sensitivity for lower functioning patients than the BNT and traditional verbal fluency tests (i.e., phonemic and semantic fluency).

Visuospatial Functioning

In assessing a patient's visuospatial abilities, if a full Wechsler scale measure of intellectual functioning is administered, the individual performance subtests from the scale may be able to provide some insight into strengths and weaknesses in visuospatial abilities (i.e., the block design, matrix reasoning, visual puzzles, and picture completion subtests), particularly if both quantitative and qualitative aspects of a patient's performance can be evaluated. However, given that the subtests of the Wechsler scales are difficult, patients with intellectual impairment and developmental disability often experience floor effects on those subtests, which make meaningful interpretation of patient's performances difficult. Similarly, the administration of the Rey-Osterrieth Complex Figure Test copy trial (RCFT; Meyers & Meyers, 1995) will likely also be negatively confounded by a patient's global cognitive limitations. However, it is often still valuable to administer the copy trial of the RCFT, as a qualitative evaluation of a patient's copying of the figure may provide some information about localization or lateralization of an epileptogenic focus (Schouten, Hendriksen, & Aldenkamp, 2009).

There are several other simpler tests of visuospatial abilities that are worth administering, most of which sample a greater range of abilities and are not as susceptible to floor effects that can make their administration on patients with intellectual impairment potentially meaningless. In particular, the Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (Beery VMI; Beery, Buktenica, & Beery, 2006) can be administered to patients aged 2–100 years old. It is a simple test that involves subtests that include freehand copying of increasingly complex figures, guided motor coordination copying of tracings of the same figures, and a motor-free visuoperceptual matching of figures. The test provides both age- and grade-equivalent scores and has a relatively low floor, making it ideal for administration to patients with developmental delay and intellectual impairment. Other tests that are also simple to administer and can provide valuable information about visuospatial abilities are the Benton Judgment of Line Orientation (Benton JOLO; Benton, Sivan, Hamsher, Varney, & Spreen, 1994), which can be administered to patients aged 18–74 years old, and the Hooper Visual Orientation Test (Hooper VOT; Hooper, 1983), which can be administered to patients aged 25–69 years old.

Once again, the RBANS and the NAB also incorporate assessment of visuospatial functioning. The RBANS requires the copy of a complex figure that is much simpler than the RCFT and a judgment of line orientation subtest that is similar to but simpler than the Benton JOLO (Randolph, 1998). The NAB Spatial Module is comprised of four subtests, which can be administered individually, including a visual discrimination subtest, the design construction subtest, the figure drawing subtest, and the map reading subtest. The visual discrimination subtest has the advantage of being a motor-free test that requires matching-to-target discrimination that is relatively sensitive and has a low floor for greater sensitivity in evaluating patients with intellectual disability or developmental delay (Stern & White, 2003).

Memory

Assessment of memory functioning is particularly critical in patients with known or suspected temporal lobe epilepsy, in patients who are being considered for anterior temporal lobectomy, and in patients who self-report or whose families/caretakers report particular memory problems. If a full Wechsler intelligence scale is administered, it may also be possible to administer one of the co-normed Wechsler memory scales: the Children's Memory Scale (CMS; Cohen, 1997) for children aged 5–16 years old, the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997) for patients aged 16–89 years old and useful for comparison with the WAIS-III, or the more recently released Wechsler Memory Scale, Fourth Edition (WMS-IV; Wechsler, 2009) for patients aged 16–90 years old and useful for comparison with the WAIS-IV. In addition to the

fact that these comprehensive memory batteries can be meaningfully compared to scales of overall intellectual functioning, these inclusive batteries are made up of multiple measures of verbal and visual memory functioning, which is particularly valuable when attempting to lateralize hippocampal dysfunction. However, once again it is important to recognize that the subtests of the Wechsler scales are difficult and are designed for assessment of memory abilities in higher functioning patients, thus patients with developmental delay and intellectual impairment often experience floor effects on those measures, which makes interpretation of impaired performances on the Wechsler memory scales difficult and often meaningless. Another comprehensive memory battery that also provides comparisons of verbal and visual memory, along with some measures of general memory and attention/concentration, is the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2; Sheslow & Adams, 2003), which can be administered to patients aged 5–90 years old. While the WRAML2 does not provide data for a direct comparison between overall intellectual functioning and memory abilities, it does have a greater range of sensitivity, making it a more valuable for the assessment of memory functioning in patients with cognitive limitations.

One of the most commonly administered and researched measures of verbal learning and memory in populations of patients with epilepsy is the California Verbal Learning Test, Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), which can be administered to patients aged 16–89 years old, or the children's version of that list learning task, the California Verbal Learning Test, Children's Edition (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1986), which can be administered to children aged 5–17 years old. The standard version of the CVLT-II requires five learning trials of a 16-item word list, followed by a 20-min delay period prior to delayed memory testing. For the assessment of adult patients with developmental delay or intellectual impairment, the CVLT-II has a short-form version that involves four learning trials of a 9-item word list followed by a 15-min delay period, leading to a shorter overall administration time and lower floor effects. Another list learning measure that is shorter and easier than the CVLT-II is the Hopkins Verbal Learning Test, Revised (HVLT-R; Brandt & Benedict, 2001) for patients aged 16–92 years old. The HVLT-R involves three learning trials of a 12-item word list followed by a 20–25-min delay period. It is easy to administer and score and is well tolerated even by significantly impaired individuals. Its use has been validated with brain-disordered populations (e.g., Alzheimer's disease, Huntington's disease, amnestic disorders). Additionally, six distinct forms of the HVLT-R are available, eliminating practice effects on repeated administrations.

With regard to visual learning and memory, there are significantly fewer sensitive measures in comparison with verbal learning and memory. The most commonly cited measure of visual learning and memory is the RCFT (Meyers & Meyers, 1995), but, as stated earlier, the copy trial of the RCFT is significantly confounded by intellectual functioning, making it an insensitive measure for the quantitative assessment of visual memory in patients with developmental delay or intellectual impairment. However, there are qualitative aspects of memory for the RCFT that can be valuable to observe, so administration of delayed memory trials for qualitative if not quantitative evaluation can provide valuable information, even in patients with intellectual impairment. A simpler measure of visual learning and memory is the Brief Visuospatial Memory Test, Revised (BVMT-R; Benedict, 1997) for assessment of patients aged 18–79 years old. The test involves three learning trials of an array of six line drawings presented together on a page which the patient has 10 s to observe before attempting to reproduce the line drawings. There is also a 20-min delay trial followed by a recognition trial and an optional copy trial (which can be used to roughly assess simple visuoperceptual abilities). Much like the HVLT-R, six distinct forms of the BVMT-R are available, eliminating practice effects on repeated administrations.

Once again, the RBANS and the NAB also incorporate assessment of memory functioning.

The RBANS immediate memory component is made up of a list learning task and a brief story memory task. Similar to the CVLT-II Short Form and the HVLT-II, the RBANS list learning task is made up of four learning trials of a 10-item word list, making it more sensitive to verbal memory deficits in patients with cognitive limitations. The RBANS story memory task is also relatively simple as it is a short story that is repeated twice. Additionally, the RBANS has a delayed memory component that is made up of both a free recall and recognition trial of the word list, a free recall trial of the story, and a free recall trial of the complex figure that was copied as part of the visuospatial component. Overall, both the immediate and delayed memory components of the RBANS are relatively brief and useful in measuring immediate and delayed learning and memory deficits in patients with cognitive limitations (Randolph, 1998). The NAB has a Memory Module that is comprised of four subtests, which can be administered individually, including a list learning task, a shape learning task, a story learning task, and a daily living memory task. Much like the RBANS, the NAB list learning task is brief, involving three learning trials of a 12-item word list, followed by an interference list trial, then a short delay free recall trial, a long delay free recall trial, a long delay forced-choice trial, and a recognition trial. The NAB story memory involves two learning trials of a five-sentence story with measures of both immediate and delayed free recall of a five-sentence story. The NAB shape learning task involves three learning trials and multiple-choice immediate recognition of nine visual stimuli, followed by delayed recognition and forced-choice delayed recall of the items. Finally, the daily living task involves verbal learning as well as immediate and delayed memory of information encountered in daily living, such as medication instructions, names addresses, and phone numbers, making it a unique assessment of memory for aspects of a patients adaptive functioning. Overall, the NAB Memory Module provides measures of both verbal and visual immediate and delayed memory, much like the aforementioned memory batteries such as the WMS-IV and the WRAML2, but with much briefer administrations and a low floor for greater sensitivity in evaluating patients with intellectual disability or developmental delay (Stern & White, 2003).

Adaptive Functioning

Perhaps the most important aspect of a neuropsychological assessment of patients with intellectual disabilities is an assessment of their adaptive functioning. As highlighted earlier, age-related deficits in adaptive functioning are critical aspects of developmental delay and intellectual impairment, both for diagnosis and for the purpose of empirically evaluating everyday functioning. This aspect of a neuropsychological evaluation can often be the most meaningful for families and caretakers. The most widely used measure of adaptive functioning is the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II; Sparrow, Cicchetti, & Balla, 2005), which can be used to assess adaptive functioning in patients from birth to 90 years old. The Vineland-II includes the option of administering a survey interview of parents or caregivers that can take up to one hour to administer, an expanded interview of parents or caregivers that can take an hour and a half to administer, a parent/caregiver rating form that can take up to an hour for caregivers to complete, or a teacher rating form that takes approximately 20 min for teachers to complete. The measure assesses five different domains, including communication (receptive, expressive, and written language skills), daily living skills (personal, domestic, and community-related skills), socialization (interpersonal relationships, play and leisure time, and coping skills), motor skills (fine and gross motor skills), and an optional maladaptive behavior index (internalizing, externalizing, and other behaviors). Overall, the Vineland-II provides important information about everyday adaptive functioning that aids in the diagnosis of developmental delay and intellectual impairment. Additionally, the results of the measure can be used to determine a patient's eligibility for special services in schools or treatment facilities, to plan for rehabilitation or

intervention programs, and to track a patient's progress as it correlates with medical or surgical treatment of their epilepsy. An important aspect of the Vineland-II is that the interviews, both the survey interview and the expanded interview, must be administered by a trained and qualified licensed psychologist, which may increase the validity and reliability of the measure, particularly over repeated administrations that are designed to track a patient's progress over a number of years.

Another commonly used measure for the assessment of adaptive functioning is the Adaptive Behavior Assessment System, Second Edition (ABAS-II; Harrison & Oakland, 2003), which can be used to assess adaptive functioning from birth to 89 years. The measure is a behavior rating scale that is typically completed by parents, caregivers, and/or teachers. If the behavior rating scale is given to multiple raters, it can provide different perspectives on what a given patient can or cannot do in their everyday lives without the assistance of others. The measure assesses adaptive skills in ten different areas within three different domains, including conceptual (communication skills, functional academics, and self-direction), social (social skills and leisure skills), and practical (self-care, home or school living, community use, work, and health/safety) domains. Similar to the Vineland-II, the ABAS-II provides information about a patient's everyday adaptive functioning, aids in the diagnosis of intellectual impairment and developmental disabilities, and can assist with treatment recommendations. The ABAS-II has the advantage of being a behavior rating scale that does not need to be administered by a licensed psychologist and is therefore less time-consuming from an administration perspective. Additionally, given that the behavior rating scale can be given to multiple people, it can provide a more accurate profile of a patient's level of adaptive functioning in a variety of environments. The data available on the validity of the ABAS-II suggest that it is just as valid a measure of adaptive functioning as the Vineland-II, despite being simply a behavior rating scale that is completed by patients without the direct input of a psychologist or neuropsychologist (Harrison & Oakland, 2003).

If it is possible to directly evaluate a patient's abilities, the most commonly used measure of direct assessment of everyday abilities is the Independent Living Scales measure (ILS; Loeb, 1996). This test is an individually administered assessment of the degree to which adults are capable of caring for themselves and their property. Although the ILS is usually administered to patients aged 65 years old and older, there is normative data for patients with intellectual disabilities who are aged 17 years old and older. The ILS is composed of five scales: memory/orientation, managing money, managing home and transportation, health and safety, and social adjustment. The performance-based results from the 68 ILS items are more objective and reliable than third-party observations or examinees' self-reports (Loeb, 1996). Normative data are provided for the different scales so the various areas of competence can be identified and compared. Additionally, it is possible to administer individual subtests from the ILS in order to assess specific areas of everyday functioning.

Summary

When a patient with developmental delays or intellectual impairment and concurrent epilepsy is referred for neuropsychological evaluation, it is particularly important to consider the referral question and the capabilities of the patient when designing the neuropsychological test battery. As with all neuropsychological assessments, gathering information about all domains of neurocognitive functioning is important, if it is possible. However, patients with developmental delay or intellectual impairment often cannot tolerate a lengthy evaluation, and the traditionally administered neuropsychological tests often have high floor effects, making interpretation of impaired performances meaningless. Thus, it is often valuable to utilize screening measures (i.e., the RBANS or the NAB) or other tests with lower floor effects in order to gather more accurate information about neurocognitive functioning.

Additionally, the inclusion of measures of adaptive functioning may be essential for the accurate diagnosis of intellectual impairment, particularly if a patient is referred for an initial diagnosis of intellectual impairment or for qualification of specialized services. Finally, as is highlighted in the following case reports, it is often necessary for neuropsychologists to use both quantitative and qualitative observations of an intellectually impaired patient's performance in order to fully understand their neurocognitive strengths and weaknesses.

Case Examples

Case 1

G.L. was a 26-year-old female who began experiencing complex-partial seizures that secondarily generalized when she was 3 years old. G.L.'s developmental history was notable for intellectual disability and developmental delay. Her mother indicated that she began walking at 2 years old, spoke her first words at 8 years old (i.e., "Ma" and "Dad"), and began speaking in sentences at 13 years old. G.L. started taking formal special education classes in a mainstream school in sixth grade when she was 11 years old. She received a certificate of completion when she graduated high school at 21 years old. Her mother reported that upon leaving high school, G.L. was reading at a third grade level and was performing mathematics at a second grade level. Since graduating from high school, G.L. had been part of a day program service associated with a local regional center. Through this program, she spent weekdays volunteering in the community and participating in skills training classes. She lived with her mother and sister. G.L. said she enjoyed spending her free time with her family, liked reading books, and enjoyed singing.

Regarding a presurgical medical workup, an MRI of her brain revealed no evidence of an acute process but suggested "diffuse volume loss of white matter of the right cerebral hemisphere" as well as "Wallerian degeneration of the right pyramidal tract." The MRI also indicated that "the right hippocampus is smaller and diffusely hyperintense, suggesting mesiotemporal sclerosis." Finally, the brain MRI indicated an enlarged lateral ventricle and a small cerebellar hemisphere with the inferior portion of the cerebellum appearing asymmetric. An EEG conducted during a PET scan demonstrated, "an abnormal EEG on account of mild diffuse slowing of the background" which suggested, "diffuse cerebral dysfunction associated with a broad differential diagnosis." PET imaging demonstrated, "marked hypometabolism of the right cerebrum and right cortical gray matter, predominantly affecting the right temporal lobe. In the right clinical setting, this may function as a zone of epileptogenesis." During inpatient video EEG monitoring, six seizures were observed and recorded. Clinically, during a seizure, G.L. raised her arms above her head, repositioned herself in bed, and moved nonspecifically. She then extended her left arm and leg, followed by contraction and shaking of her left hand and fingers. She moaned and vocalized nonspecifically, sometimes followed commands, and often grabbed the rail of the bed or her oxygen mask. She had difficulty answering questions but recovered postictally in less than 15 s. Electrographically, her seizures were all stereotyped with development of an ictal rhythm over the right temporal lobe and then gradual slowing that became progressively more prominent over right frontal regions.

Given the results of the brain MRI, the PET imaging, and the inpatient video EEG monitoring, G.L. was thought to have right temporal lobe epilepsy and was being considered for a standard right anterior temporal lobectomy to neurosurgically treat her medically refractory epilepsy. G.L. was referred for a neuropsychological evaluation to assess her current level of neurocognitive functioning and to determine the extent of the neuropsychological risks (e.g., loss of memory or language function) involved in a neurosurgical intervention. Regarding general cognition, G.L. was unable to articulate and reflect on her overall level of intellectual functioning. Her mother and sister reported that she had demonstrated general improvement across all cognitive domains as she had gotten older. Although her family was not aware of any formal testing results, her mother indicated that G.L. was diagnosed with intellectual impairment at an early age.

The preoperative neuropsychological test results are given in Table 13.1. Given her

Table 13.1 Neuropsychological test results in Case 1, a 26-year-old mildly intellectually disabled female with right temporal lobe epilepsy who is being considered for a standard right anterior temporal lobectomy

General intellectual functioning	Raw score	Scaled score	Description
Peabody Picture Vocabulary Test-4	111	SS = 43	Impaired
WAIS-III			
Vocabulary	9	3	Impaired
Similarities	5	2	Impaired
Comprehension	5	3	Impaired
Digit span	14	8	Low average
Block design	12	4	Borderline
Matrix reasoning	6	5	Borderline

Attention and concentration	Raw score	T score	Description
WAIS-III digit span	14	ss = 8	Low average
Forward	7		
Backward	3		
Trails A (seconds)	53″	22	Impaired
Errors	0		

Language	Raw score	T score	Description
Phonemic fluency: F(2), A(2), S(2)	6	12	Impaired
Animal naming	9	15	Impaired
Stroop color	140	z = −6.49	Impaired
Errors/ self-corrections	1/2		
Stroop word	116	z = −10.60	Impaired
Errors/ self-corrections	0/2		
Boston Naming Test	35,0,4	25	Impaired
Language screening	13/24		
WRAT-3 reading (grade Eq = 2)	24	SS = 49	Impaired
WRAT-3 spelling (grade Eq = 2)	22	SS = 57	Impaired
WRAT-3 arithmetic (grade Eq = 2)	22	SS = 50	Impaired
WJ-III word attack (grade Eq = 1.7)	6	SS = 62	Impaired

Visuospatial skills	Raw score	T score	Description
WAIS-III block design	12	ss = 4	Borderline
WMS-III visual reproduction discrim	7/7		Average
Rey-O complex figure copy	14.5		Impaired

(continued)

Table 13.1 (continued)

Visuospatial skills	Raw score	T score	Description
Beery VMI (age Eq = 5.6)	15	<45	Impaired
Beery visual perception (age Eq = 6.2)	18	<45	Impaired
Beery motor coordination (age Eq = 5.6)	16	<45	Impaired

Verbal memory	Raw score	Z score	Description
WMS-III			
Logical memory I (5,3,8)	16	ss = 3	Impaired
Logical memory II (4,7)	11	ss = 6	Low average
Recognition (8,10)	18/30		Borderline
CVLT-II total = (6,7,8,12,11)	44	T = 38	Low average
List A Trial 1	6	−1.0	Low average
Trial 2	7	−1.5	Borderline
Trial 3	8	−2.0	Impaired
Trial 4	12	−0.5	Average
Trial 5	11	−1.5	Borderline
List B	7	0.0	Average
List A short delay free recall	10	−0.5	Average
List A short delay cued recall	7	−2.5	Impaired
List A long delay free recall	11	−0.5	Average
List A long delay cued recall	6	−3.0	Impaired
Recognition hits	16	0.0	Average
Recognition false positives	2	−0.5	Average
Total recognition discriminability	3.4	0.0	Average

Nonverbal memory	Raw score	T score	Description
WMS-III			
Visual reproduction I	57	ss = 3	Impaired
Visual reproduction II	0	ss = 1	Impaired
Recognition	38/48	ss = 4	Borderline
BVMT-R total = (2,2,4)	8	<20	Impaired
Trial 1	2	25	Impaired
Trial 2	2	<20	Impaired
Trial 3	4	<20	Impaired

(continued)

Table 13.1 (continued)

Nonverbal memory	Raw score	T score	Description
Learning	2	40	Low average
Delay	4	<20	Impaired
Percent retention	100		Average
Recognition	6, 1fp		Low average
Rey-O complex figure			
Immediate recall	3.5	<20	Impaired
Delayed recall	2.0	<20	Impaired
Recognition	18/24	28	Impaired
Whole figure recognition	no		
Executive functions	Raw score	T score	Description
WAIS-III similarities	5	ss = 2	Impaired
WAIS-III comprehension	5	ss = 3	Impaired
WAIS-III matrix reasoning	6	ss = 5	Borderline
Phonemic fluency: F(2), A(2), S(2)	6	12	Impaired
Trails B (s)	300″	2	Impaired
Errors	1		
Stroop interference	218	z = −3.68	Impaired
Errors/ self-corrections	0/14		

extremely low level of general intellectual functioning, there are a number of important aspects to her performance that should be considered. Her generally extremely low level of intellectual functioning, significantly slowed speed of information processing, and impaired motor coordination likely negatively impacted her performance on a number of measures on the evaluation. Therefore, in addition to the quantitative results of the current evaluation, it was important to consider qualitative aspects of her performance in order to more accurately characterize her strengths and weaknesses, in the context of her generally extremely low level of intellectual and information processing abilities.

Qualitatively, her verbal skills were slightly stronger than indicated by her impaired performance on formal measures of language functioning because she was able to converse with the examiner, and her comprehension of simple questions and basic task instructions was adequate. In contrast, however, she demonstrated considerable difficulty when required to appreciate the broad or abstract concepts and context of conversational speech. Generally, she demonstrated qualitatively weaker complex comprehension of the gestalt of speech, thus indicating weaknesses in right hemisphere contributions to complex language information processing. She demonstrated significant strengths on measures of simple auditory attention, indicating that she was able to attend to information at an almost age-appropriate level. On measures of verbal memory, she demonstrated poor learning and memory for contextual verbal information, which was likely negatively impacted by her inability to appreciate semantic and verbal contextual and gestalt cues, once again likely reflecting weaknesses in right hemisphere contributions to language. In contrast, she demonstrated a significant strength on a task of verbal list learning and memory, which was felt to be indicative of adequate left mesial temporal functioning. On measures of visual memory, she demonstrated impaired learning and memory for all visual information, even relatively simple visual information, which was felt to be indicative of impaired right mesial temporal functioning. Furthermore, her performances on a number of other measures of neuropsychological functioning implicated right hemisphere involvement in her seizures. Specifically, she demonstrated difficulty with visual perception and visual-motor integration. Qualitatively, she was unable to appreciate the gestalt of both verbal and visual information, which also suggested right hemisphere involvement in her seizures.

While her impaired performances on some of the neuropsychological tasks may have been negatively impacted by her extremely low level of general intellectual functioning, her relative strength in visual abstract reasoning indicated relatively adequate nonverbal reasoning skills and supported the idea that she was able to process visuospatial information at a level commensurate with her overall level of intellectual functioning. Thus, her qualitative weaknesses on

the current evaluation likely represented true neurological weaknesses in right hemisphere functioning, rather than simply impairments secondary to her extremely low level of general intellectual functioning. Overall, the results of the neuropsychological evaluation suggested a specific involvement of right mesial temporal areas along with general involvement of the right hemisphere, with relatively spared right frontal lobe functioning. These findings were felt to indicate an area of epileptogenic focus in right mesial temporal structures, consistent with findings from a brain MRI, PET imaging, and inpatient video EEG monitoring.

Although G.L.'s performance was in the extremely low range across most neuropsychological domains, her strong performance on a measure of verbal learning and memory suggested adequate left mesial temporal functioning. While her quantitative performances on measures of language functioning were also extremely low, there was some qualitative and behavioral evidence for relatively good functioning of left hemisphere language areas which were not reflected by neuropsychological measures that were insensitive to performances in the extremely low range. Furthermore, she demonstrated a relative strength (both qualitatively and quantitatively) in her visuospatial reasoning skills, which indicated that she can appreciate visuospatial information appropriately and has relatively good functioning of frontal lobe structures, bilaterally. Thus, her extremely low performances on measures of visual learning and memory, combined with dramatically disrupted processing of visual and verbal gestalt and contextual information, were felt to provide evidence for right mesial temporal and generalized right hemisphere inefficiencies, with relatively spared right frontal lobe functioning. It was recommended that if G.L. became a candidate for right anterior temporal resection, Wada testing be conducted to determine the ability of her relatively stronger left mesial temporal lobe to support memory postsurgically. However, the neuropsychological team noted that it would be important that the Wada procedure be thoroughly explained to G.L. at a developmentally appropriate level, to ensure that she understood what the procedure involved, as her cooperation would be essential to the validity of the results. Furthermore, when G.L. was asked about her understanding of the neuropsychological evaluation and the possibility of undergoing resection surgery, she indicated limited understanding of the process. Thus, an additional recommendation of the evaluation was that the surgical procedure and possible sequelae of the surgical intervention be explained to her at a developmentally appropriate level given her extremely low level of general cognitive functioning in order to ensure her cooperation and compliance with pre- and postsurgical management.

Case 2

B.R. was a 55-year-old mildly intellectually disabled female with left anterior temporal lobe epilepsy who had been seizure-free for 2 years following a standard left anterior temporal lobectomy and continued medication management on a relatively low level of lamotrigine. She was referred for a neuropsychological evaluation to assess her postoperative level of neurocognitive and behavioral functioning. In particular, her mother reported that B.R. had a tendency to talk about events that did not really happen, so she had concerns that B.R. was either lying or was experiencing medication-related hallucinations. Her mother also expressed concern that B.R.'s memory had worsened since the surgery.

B.R. had undergone two prior presurgical neuropsychological evaluations. The results of the first presurgical neuropsychological evaluation indicated, "This woman demonstrates intellectual abilities which fall within the range of mild intellectual disability overall with visual-spatial abilities just lightly stronger than those in the verbal area. Her level of academic knowledge is just slightly below her level of general intelligence, and academic achievement may never have been especially strong. The battery of neuropsychological tests which was administered resulted in the identification of moderate impairment in brain functions with findings implicating both

cerebral hemispheres about equally. This impairment is expected to have a substantial impact upon functioning in daily life…In terms of predictors for seizure relief following resection surgery for epilepsy, it was noted that only one of the four predictors of likely relief from seizures arising from this battery of tests were within a favorable range. While this is not a positive result, it should be noted that a full prognostic statement of likely relief from seizures following resection surgery must take into account other critical clinical and EEG data." The results of the second presurgical neuropsychological evaluation indicated, "The patient is a 53-year-old right-handed female with moderate intellectual disability. This is conferred on the current IQ assessment. The majority of neuropsychological measures completed are consistent with her overall level of cognitive function. Interestingly, an area of particular strength was seen for repeat trials of verbal learning and memory…The patient interacts at a higher level than would be anticipated based on her IQ…Oral and cognitive presentation is reflective of generalized cortical dysfunction with preservation of left temporal lobe capacity. These findings are consistent with her history of bilateral seizures and significant illness during critical development." It was concluded that improved seizure control would probably positively improve her life in terms of her personal safety and functional ability, with some risks to her verbal memory that would likely not be apparent in her day-to-day functional capacity.

Developmentally, B.R. and her husband lived with her parents. She was able to bathe and dress herself and do a few chores around the house, such as taking care of her cat, doing some of the cleaning, and folding the laundry, all of which she could do successfully with minimal supervision or guidance. She did not do the shopping or cooking, nor did she manage any finances. She was not able to manage her medications independently and relied on her mother to remind her to take her medication.

Postsurgically, B.R. was unable to provide subjective information about her cognitive difficulties. It had been well documented that she was mildly intellectually disabled and, per medical records, had limited insight into her cognitive limitations. Her mother reported that B.R.'s memory was poor prior to her undergoing the left anteromedial temporal resection but had seemed worse since the surgery. Additionally, she reported that B.R. had a tendency to confabulate and displayed some paranoid ideation. For example, 1 day B.R. could not find her cat and assumed someone had stolen it; in fact, the cat had simply wandered away for a short time. Another time, she found that money was gone from her husband's wallet and assumed someone had stolen it, but he had just put the money in his pocket. Of note, medical records prior to surgery indicated that B.R. had a tendency to talk about memory for events that did not really happen even back then. Thus, it appeared that her tendency to confabulate was not new since the surgery. Further consistent with presurgical reports, B.R. had always been easily confused and forgetful about upcoming appointments and had often misplaced items. However, her mother felt that those problems had worsened since surgery. Her mother also reported that B.R. had begun to make literal paraphasic errors in conversation, such as saying that she wanted to go to the "*feel good*" store instead of the *Goodwill* store. This was reportedly new since she had undergone surgery. Her mother expressed concerns that these perceived cognitive changes were being caused by her long-term medication regimen of lamotrigine.

The postoperative neuropsychological test results are given in Table 13.2. Consistent with previous presurgical evaluations, the postsurgical neuropsychological evaluation measured B.R.'s overall level of intellectual functioning to be mildly intellectually disabled. On testing, B.R. performed in the impaired range on most tests of neuropsychological functioning, consistent with her performances on two previous presurgical evaluations. She once again demonstrated a relative strength in her verbal learning and memory abilities, as her performances were largely borderline to low average across those tasks. Compared with the most recent previous presurgical neuropsychological evaluation, however, she demonstrated a very mild decline in her verbal list

Table 13.2 Neuropsychological test results in Case 2, a postsurgical evaluation of a 55-year-old mildly intellectually disabled female with left anterior temporal lobe epilepsy who is seizure-free following a standard left anterior temporal lobectomy

General intellectual functioning	Raw score	Scaled score	Description
WAIS-IV (standard norming)			
Verbal comprehension subtests			
Similarities	11	4	Impaired
Vocabulary	10	3	Impaired
Information	3	3	Impaired
Comprehension	8	3	Impaired
Perceptual reasoning subtests			
Block design	20	6	Low average
Matrix reasoning	5	4	Impaired
Visual puzzles	6	5	Borderline
Working memory subtests			
Digit span	13	3	Impaired
Arithmetic	6	3	Impaired
Processing speed subtests			
Symbol search	16	5	Borderline
Coding	20	2	Impaired
Index scores			
Full Scale IQ	38	SS = 59	Impaired
Verbal Comprehension Index	10	SS = 61	Impaired
Perceptual Reasoning Index	15	SS = 71	Borderline
Working Memory Index	6	SS = 60	Impaired
Processing Speed Index	7	SS = 65	Impaired
General Ability Index	25	SS = 63	Impaired
Index-level discrepancies	*Score 1*	*Score 2*	*Significance*
Verbal comp—perceptual reasoning	61	71	0.05
Verbal comp—working memory	61	60	NS
Verbal comp—processing speed	61	65	NS
Perceptual reason—working memory	71	60	0.05
Perceptual reason—processing speed	71	65	NS
Working memory—processing speed	60	65	NS
FSIQ—GAI	59	63	0.05

Academic abilities	Raw score	Std score	Description
WRAT-4			
Word reading (grade Eq = 3.7)	35	67	Impaired
Sentence comprehension (grade Eq = 2.8)	15	62	Impaired
Reading composite	129	63	Impaired
Spelling (grade Eq = 3.3)	26	68	Impaired
Math computation (grade Eq = 1.9)	20	61	Impaired

Attention and concentration	Raw score	Scaled score	Description
WAIS-IV			
Digit span	13	3	Impaired
Forward span	4		Cum % = 100.00
Backward span	3		Cum % = 97.00
Sequencing span	3		Cum % = 98.00
Arithmetic	6	3	Impaired
Symbol search	16	5	Borderline
Coding	20	2	Impaired
D-KEFS			
Trails: visual scanning	29″	8	Average
Errors	0		
Trails: number sequencing	44″	9	Average
Errors	0		
Trails: letter sequencing	64″	5	Borderline
Errors	0		

(continued)

Table 13.2 (continued)

Speech and language	Raw score	Scaled score	Description
WAIS-IV			
Vocabulary	10	3	Impaired
Similarities	11	4	Impaired
D-KEFS			
Verbal fluency: letter	9	2	Impaired
Verbal fluency: category	21	3	Impaired
CW Interfere: color naming	34″	8	Average
Errors/ self-corrections	0/1		
CW interfere: word reading	30″	6	Low average
Errors/ self-corrections	1/0		
Boston Naming Test	40,1,6	z = −5.63	Impaired
WRAT-4			
Word reading (grade Eq = 3.7)	35	SS = 67	Impaired
Sentence comprehension (grade Eq = 2.8)	15	SS = 62	Impaired
Reading composite	129	SS = 63	Impaired

Visuospatial skills	Raw score	Scaled score	Description
WAIS-IV			
Block design	20	6	Low average
Visual puzzles	6	5	Borderline
BVMT-R copy	8/12		
Rey-O complex figure copy	18.5		Borderline

Verbal memory	Raw score	Z score	Description
WMS-IV			
Logical memory I (10,4)	14	ss = 5	Borderline
Logical memory II (9,3)	12	ss = 6	Low average
Logical memory recognition (10,10)	20/30		Cum % = 3–9
Verbal paired associates I (2,4,5,5)	16	ss = 6	Low average
Verbal paired associates II	5	ss = 6	Low average

(continued)

Table 13.2 (continued)

Verbal memory	Raw score	Z score	Description
Verbal paired associates recognition	33/40		Cum % = 3–9
Auditory Memory Index	23	SS = 75	Borderline
CVLT-II Total = (4,5,7,8,8)	32	T = 31	Borderline
List A Trial 1	4	–1.5	Borderline
Trial 2	5	–2.0	Impaired
Trial 3	7	–1.5	Borderline
Trial 4	8	–2.0	Impaired
Trial 5	8	–2.0	Impaired
List B	4	–1.0	Low average
List A short delay free recall	6	–1.5	Borderline
List A short delay cued recall	5	–3.0	Impaired
List A long delay free recall	7	–1.5	Borderline
List A long delay cued recall	7	–2.0	Impaired
Recognition hits	14/16	–0.5	Average
Recognition false positives	1/32	(–0.5)	Average
Recognition discriminability	3.0	0.0	Average
Forced choice recognition	16/16		Cum % = 100

Nonverbal memory	Raw score	T score	Description
WMS-IV			
Visual reproduction I recall	21	ss = 4	Impaired
Visual reproduction II recall	8	ss = 6	Low average
Visual reproduction II recognition	0/7		Cum % ≤ 2
BVMT-R total = (1,2,1)	4	<20	Impaired
Trial 1	1	27	Impaired
Trial 2	2	<20	Impaired
Trial 3	1	<20	Impaired
Delay	3	22	Impaired
Percent retention	100 %		Average
Recognition	4, 1fp		Borderline

(continued)

Table 13.2 (continued)

Nonverbal memory	Raw score	T score	Description
Rey-O complex figure			
3′ immediate recall	6	23	Impaired
30′ delayed recall	1	<20	Impaired
Recognition	19/24	42	Low average
Whole figure recognition	Yes		

Executive functions	Raw score	Scaled score	Description
WAIS-IV			
Similarities	11	4	Impaired
Comprehension	8	3	Impaired
Matrix reasoning	5	4	Impaired
D-KEFS			
Trails: visual scanning	29″	8	Average
Errors	0		
Trails: number sequencing	44″	9	Average
Errors	0		
Trails: letter sequencing	64″	5	Borderline
Errors	0		
Trails: letter-number switching	131″	7	Low average
Errors	4		
Trails: motor speed	54″	7	Low average
Verbal fluency: letter	9	2	Impaired
Verbal fluency: category	21	3	Impaired
Verbal fluency: switching	7	3	Impaired
Verbal fluency: switching accuracy	6	4	Impaired
CW interfere: CW inhibition	82″	6	Low average
Errors/ self-corrections	2/4		
CW interfere: CW inhib/switching	154″	1	Impaired
Errors/ self-corrections	13/4		

Mood/personality	Raw score	Rating
BDI-II	15	Mild
BAI	3	Minimal

learning capacity and retention, which was not surprising given that left mesial temporal structures that support verbal learning and memory were resected. Once again, her visual learning and memory was not as good as her verbal learning and memory. Interestingly, she also demonstrated a mild decline in her visual learning and memory abilities compared with presurgical performances. Overall, the findings of the postsurgical neuropsychological evaluation were consistent with a woman who suffered generalized cortical dysfunction and who, as a result, had mild intellectual disability and significant developmental delays. As had been demonstrated on previous presurgical neuropsychological evaluations, B.R. had a few areas of relative cognitive strength, including her verbal learning and memory ability and some aspects of social and executive skills. Her verbal learning and memory abilities continued to be a relative strength for her, despite showing a mild decline from presurgical levels. It was concluded that she was a woman who had clearly led a life that had been meaningful to her, and she continued to have the capacity to participate in her life at a level that gave her a sense of accomplishment and kept her feeling happy. Given that she was now seizure-free, she was leading a healthier life, and it was likely that she would continue to lead a happy and productive life for the foreseeable future, with very minimal to no change in her cognitive abilities since the surgery. Overall, it was felt that the neurosurgical resection to treat her refractory epilepsy was successful. Furthermore, there was no evidence to suggest that her antiepileptic medication regimen was negatively impacting her cognitive functioning or causing a significant change in her psychiatric or cognitive functioning.

References

Aldenkamp, A. P., Baker, G., & Mulder, O. G. (2000). A multicenter randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia, 41*, 1167–1178.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author. Text Revision.

Beery, K. E., Buktenica, N. A., & Beery, N. A. (2006). *BEERY VMI: The Beery-Buktenica developmental test of visual-motor integration* (Administration, scoring, and teaching manual 5th ed.). Los Angeles, CA: Western Psychological Services.

Benedict, R. H. B. (1997). *BVMT-R: Brief Visuospatial Memory Test – Revised: Professional manual*. Lutz, FL: Psychological Assessment Resources, Inc.

Benton, A. L., Sivan, A. B., Hamsher, K. D., Varney, N. R., & Spreen, O. (1994). *Contributions to neuropsychological assessment* (A clinical manual 2nd ed.). New York, NY: Oxford University Press, Inc.

Berry-Kravis, E. (2002). Epilepsy in fragile X syndrome. *Developmental Medicine and Child Neurology, 44*(11), 724–728.

Bhise, V. V., Burack, G. D., & Mandelbaum, D. E. (2010). Baseline cognition, behavior, and motor skills in children with new-onset, idiopathic epilepsy. *Developmental Medicine and Child Neurology, 52*, 22–26.

Brandt, J., & Benedict, R. H. B. (2001). *The Hopkins Verbal Learning Test – Revised*. Lutz, FL: Psychological Assessment Resources, Inc.

Brown, L., Sherbenou, R. J., & Johnson, S. K. (1997). *Test of nonverbal intelligence* (3rd ed.). Austin, TX: Pro-Ed.

Caplan, R., Gillberg, C., Dunn, D. W., & Spence, S. J. (2008). Psychiatric disorders in children. In J. Engel Jr. & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (2nd ed., pp. 1225–1233). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Cassé-Perrot, C., Wolff, M., & Dravet, C. (2001). Neuropsychological aspects of severe myoclonic epilepsy in infancy. In I. Jambaqué, M. Lassonde, & O. Dulac (Eds.), *The neuropsychology of childhood epilepsy* (pp. 131–140). New York, NY: Plenum.

Cohen, M. (1997). *Children's memory scale manual*. San Antonio, TX: The Psychological Corporation.

Crawford, P. M. (2000). Epidemiology of intractable focal epilepsy. In J. M. Oxbury, C. E. Polkey, & M. Duchowny (Eds.), *Intractable focal epilepsy* (pp. 25–40). London: WB Saunders.

de Vries, B. B., Robinson, H., Stolte-Dijkstra, I., Tjon Pian Gi, C. V., Dijkstra, P. F., van Doorn, J., et al. (1995). General overgrowth in the fragile X syndrome: Variability in the phenotypic expression of the FMR1 gene mutation. *Journal of Medical Genetics, 32*(10), 764–769.

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (1986). *The California Verbal Learning Test: Children's version*. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *CVLT-II: California Verbal Learning Test, second edition, adult version, manual*. San Antonio, TX: The Psychological Corporation.

Dravet, C., & Bureau, C. (2008). Severe myoclonic epilepsy in infancy (Dravet syndrome). In J. Engel Jr. & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (2nd ed., pp. 2337–2342). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Dunn, L. M., & Dunn, D. M. (2007). *PPVT-4: Peabody Picture Vocabulary Test* (4th ed.). San Antonio, TX: Pearson Assessments.

Feekery, C. J., Parry-Fielder, B., & Hopkins, I. J. (1993). Landau-Kleffner syndrome: Six patients including discordant monozygotic twins. *Pediatric Neurology, 9*, 49–53.

Fenichel, G. M. (2001). *Clinical pediatric neurology: A signs and symptoms approach* (4th ed.). Philadelphia, PA: WB Saunders.

Fisher, J. E., & Vorhees, C. (1992). Developmental toxicity of antiepileptic drugs: Relationship to postnatal dysfunction. *Pharmacological Research, 26*, 207–221.

Forsgren, L., Edvinsson, S. O., Blomquist, H. K., Heijbel, J., & Sidenvall, R. (1990). Epilepsy in a population of mentally retarded children and adults. *Epilepsy Research, 6*(3), 234–248.

Fryns, J. P., Jacobs, J., Kleczkowska, A., & van den Berghe, H. (1984). The psychological profile of the fragile X syndrome. *Clinical Genetics, 25*(2), 131–134.

Gaily, E., & Meador, K. J. (2007). Neurodevelopmental effects. In J. Engel Jr. & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (2nd ed., pp. 1225–1233). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Galván-Manso, M., Campistol, J., Conill, J., & Sanmartí, F. X. (2005). Analysis of the characteristics of epilepsy in 37 patients with the molecular diagnosis of Angelman syndrome. *Epileptic Disorders, 7*(1), 19–25.

Gastaut, H. (1982). The Lennox-Gastaut syndrome: Comments on the syndrome's terminology and nosological position among the secondary generalized epilepsies of childhood. *Electroencephalography and Clinical Neurophysiology, 35*, S71–S84.

Glaze, D. G., Schultz, R. J., & Frost, J. D. (1998). Rett syndrome: Characterization of seizures versus nonseizures. *Electroencephalography and Clinical Neurophysiology, 106*(1), 79–83.

Gleissner, U., Clusmann, H., Sassen, R., Elger, C., & Helmstaedter, C. (2006). Postsurgical outcome in pediatric patients with epilepsy: A comparison of patients with intellectual disabilities, subaverage intelligence, and average-range intelligence. *Epilepsia, 47*(2), 406–414.

Gordon, N. (1990). Acquired aphasia in childhood: The Landau-Kleffner syndrome. *Developmental Medicine and Child Neurology, 32*, 270–274.

Guerrini, R., Cararozzo, R., Rinaldi, R., & Bonnani, P. (2003). Angelman syndrome: Etiology, clinical features, diagnosis, and management of symptoms. *Paediatric Drugs, 5*(10), 647–661.

Harrison, P., & Oakland, T. (2003). *ABAS-II: Adaptive behavior assessment system – Second edition*. Los Angeles, CA: Western Psychological Services.

Hauser, W. A., Annegers, J. F., & Kurland, L. T. (1991). The Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. *Epilepsia, 32*(4), 429–445.

Heaton, R. K., Miller, W., Taylor, M. J., & Grant, I. (2005). *Revised comprehensive norms for an expanded*

halstead-reitan battery: Demographically adjusted neuropsychological norms for African-American and Caucasian Adults. Lutz, FL: Psychological Assessment Resources.

Holmes, L. B., Wysznski, D. F., & Lieberman, E. (2004). The AED (antiepileptic drug) pregnancy registry: A 6-year experience. *Archives of Neurology, 61*, 673–678.

Hooper, H. E. (1983). *Hooper Visual Organization Test (VOT) manual*. Los Angeles, CA: Western Psychological Services.

Hunt, A., & Dennis, J. (1987). Psychiatric disorder among children with tuberous sclerosis. *Developmental Medicine and Child Neurology, 29*, 190–198.

Huppke, P., Held, M., Laccone, F., & Hanefeld, F. (2003). The spectrum of phenotypes in females with Rett Syndrome. *Brain Development, 25*(5), 346–351.

Jambaqué, I., Chiron, C., Dumas, C., Mumford, J., & Dulac, O. (2000). Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. *Epilepsy Research, 38*(2–3), 151–160.

Jayakar, P. B., & Seshia, S. S. (1991). Electrical status epilepticus during slow-wave sleep: A review. *Journal of Clinical Neurophysiology, 8*, 299–311.

Jeavons, P. M., Bower, B. D., & Dimitrakoudi, M. (1973). Long term prognosis of 150 cases of "West syndrome. *Epilepsia, 14*(2), 153–164.

Joinson, C., O'Callaghan, F. J., Osborne, J. P., Martyn, C., Harris, T., & Bolton, P. F. (2003). Learning disability and epilepsy in an epidemiological sample of patients with tuberous sclerosis complex. *Psychological Medicine, 33*(2), 335–344.

Jokeit, H., & Ebner, A. (2002). Effects of chronic epilepsy on intellectual functions. *Progress in Brain Research, 135*, 455–463.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston Naming Test* (2nd ed.). Austin, TX: Pro-Ed.

Kaufman, D. M. (2007). *Clinical neurology for psychiatrists* (6th ed.). Philadelphia, PA: Saunders Elsevier.

Lee, W. L., & Ong, H. T. (2001). Epidemiology of West syndrome in Singapore. *Epilepsia, 23*(7), 584–585.

Lee, T. M., Yip, J. T., & Jones-Gotman, M. (2002). Memory deficits after resection from left or right anterior temporal lobe in humans: A meta-analytic review. *Epilepsia, 43*(3), 283–291.

Lhatoo, S. D., & Sander, J. W. (2001). The epidemiology of epilepsy and learning disability. *Epilepsia, 42*(Suppl 1), 6–9.

Loeb, P. A. (1996). *Independent Living Scales (ILS)*. San Antonio, TX: Pearson.

Loring, D. W., & Meador, K. J. (2001). Cognitive and behavioral effects of epilepsy treatment. *Epilepsia, 42*(Suppl 8), 24–32.

Lúthvígsson, P., Olafsson, E., Sigurthardóttir, S., & Hauser, W. A. (1994). Epidemiologic features of infantile spasms in Iceland. *Epilepsia, 35*(45), 802–805.

Martin, R., Kuzniecky, R., Ho, S., Hetherington, H., Pan, J., Sinclair, K., et al. (1999). Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology, 52*, 321–327.

McLaren, J., & Bryson, S. E. (1987). Review of recent epidemiological studies in mental retardation: Prevalence, associated disorders, and etiology. *American Journal of Mental Retardation, 92*, 243–254.

Meador, K.J., Loring, D.W., Hulihan, J.F., Kamin, M., & Karim, R. (2003). Differential cognitive and behavioral effects of topiramate and valproate. Neurology, *60*(9), 1483–1488.

Meador, K. J., Baker, G. A., Browning, N., Clayton Smith, J., Combs-Cantrell, D. T., Cohen, M., et al. (2009). Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *The New England Journal of Medicine, 360*(16), 1597–1605.

Meador, K. J., Loring, D. W., Vahle, V. J., Ray, P. G., Werz, M. A., Fessler, A. J., et al. (2005). Differential cognitive and behavioral side effects of topiramate and valproate. *Neurology, 60*, 1483–1488.

Meyers, J. E., & Meyers, K. R. (1995). *RCFT: Rey Complex Figure Test and Recognition Trial: Professional manual*. Lutz, FL: Psychological Assessment Resources, Inc.

Motamedi, G. K., & Meador, K. J. (2004). Antiepileptic drugs and memory. *Epilepsy & Behavior, 5*, 435–439.

Murphy, J. V., & Dehkharghani, F. (1994). Diagnosis of childhood seizure disorders. *Epilepsia, 35*(Suppl 2), S7–S17.

Panayiotopoulos, C. P. (2002). *A clinical guide to epileptic syndromes and their treatment*. Oxfordshire: Bladon Medical Publishing.

Paquier, P. F., Van Dongen, H. R., & Loonen, C. B. (1992). The Landau-Kleffner syndrome or acquired aphasia with convulsive disorder. *Archives of Neurology, 49*, 354–359.

Pollack, M. A., Golden, G. S., Schmidt, R., Davis, J. A., & Leeds, N. (1978). Infantile spasms in Down syndrome: A report of 5 cases and a review of the literature. *Annals of Neurology, 3*(5), 406–408.

Prasher, V. P. (1995). Epilepsy and associated effects on adaptive behaviour in adults with Down syndrome. *Seizure, 4*, 53–56.

Randolph, C. (1998). *RBANS: Repeatable battery for the assessment of neuropsychological status: Manual*. San Antonio, TX: The Psychological Corporation.

Rantala, H., & Putkonen, T. (1999). Occurrence, outcome, and prognostic factors of infantile spasms and Lennox-Gastaut syndrome. *Epilepsia, 40*(3), 286–289.

Roid, G. H., & Miller, L. J. (1997). *Leiter International Performance Scale – Revised*. Lutz, FL: Psychological Assessment Resources, Inc.

Romano, C., Tiné, A., Fazio, G., Rizzo, R., Colognola, R. M., Sorge, G., et al. (1990). Seizures in patients with trisomy 21. *American Journal of Medical Genetics. Supplement, 7*, 298–300.

Sabaratnam, M., Vroegop, P. G., & Gangadharan, S. K. (2001). Epilepsy and EEG findings in 18 males with fragile X syndrome. *Seizure, 10*(1), 60–63.

Sauerwein, H. C., Gallagher, A., & Lassonde, M. (2005). Neuropsychological deficits in children with temporal lobe epilepsy. In A. Arzimanoglou, A. Aldenkamp, H. Cross, M. Lassonde, S. Moshé, & B. Schmitz

(Eds.), *Cognitive dysfunction in children with temporal lobe epilepsy* (pp. 1–12). Paris: John Libbey Eurotext.

Schouten, D., Hendriksen, J. G., & Aldenkamp, A. P. (2009). Performance of children with epilepsy on the Rey-Osterrieth complex figure test: Is there an effect of localization or lateralization? *Epilepsy Research, 83*(2–3), 184–189.

Shahar, E., Barak, S., Andraus, J., & Kramer, U. (2004). Primary generalized epilepsy during infancy and early childhood. *Journal of Child Neurology, 19*(3), 170–174.

Sheslow, D., & Adams, W. (2003). *WRAML2: Wide range assessment of memory and learning: Administration and scoring manual*. Lutz, FL: Psychological Assessment Resources, Inc.

Shouse, M. N., & Quigg, M. S. (2008). Chronobiology. In J. Engel Jr. & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (2nd ed., pp. 1961–1974). Philadelphia, PA: Lippincott, Williams, & Wilkins.

Sparrow, S., Cicchetti, D., & Balla, D. (2005). *Vineland Adaptive Behavior Scales – Second edition*. San Antonio, TX: The Psychological Corporation.

Steffenburg, U., Hagberg, G., & Hagberg, B. (2001). Epilepsy in a representative series of Rett syndrome. *Acta Paediatrica, 90*(1), 34–39.

Stern, R. A., & White, T. (2003). *NAB: Neuropsychological assessment battery*. Lutz, FL: Psychological Assessment Resources, Inc.

Su, C. Y., Lin, Y. H., Wu, Y. Y., & Chen, C. C. (2008). The role of cognition and adaptive behavior in employment of people with mental retardation. *Research in Developmental Disabilities, 29*(1), 83–95.

Tangye, S. R. (1979). The EEG and incidence of epilepsy in Down's syndrome. *Journal of Mental Deficiency Research, 23*(1), 17–24.

Tatsuno, M., Hayashi, M., Iwamoto, H., Suzuki, Y., & Kuroki, Y. (1984). Epilepsy in childhood Down syndrome. *Brain Development, 6*(1), 37–44.

Trevathan, E., Murphy, C. C., & Yeargin-Allsopp, M. (1997). Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. *Epilepsia, 38*(12), 1283–1288.

Trevathan, E., Murphy, C. C., & Yeargin-Allsopp, M. (1999). The descriptive epidemiology of infantile spasms among Atlanta children. *Epilepsia, 40*(6), 748–751.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (2002). Clustering and switching on verbal fluency: The effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia, 40*(5), 562–566.

Viani, F., Romeo, A., Viri, M., Mastrangelo, M., Lalatta, F., Selicorni, A., et al. (1995). Seizure and EEG patterns in Angelman's syndrome. *Journal of Child Neurology, 10*(6), 467–471.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence: Administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997). *WMS-III: Wechsler Memory Scale – Third edition: Administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2002). *Wechsler Preschool and Primary Scale of Intelligence – Third edition: Administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children – Fourth edition: Administration and scoring manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale – Fourth edition: Administration and scoring manual*. San Antonio, TX: NCS Pearson, Inc.

Wechsler, D. (2009). *Wechsler Memory Scale – Fourth edition*. San Antonio, TX: NCS Pearson, Inc.

Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A normative-developmental study of executive function: A window on prefrontal function in children. *Developmental Neuropsychology, 7*(22), 131–149.

Wiebe, S. (2000). Epidemiology of temporal lobe epilepsy. *Canadian Journal of Neurological Sciences, 27*(Suppl 1), S6–S10.

Williams, K. T. (2007). *EVT-2: Expressive Vocabulary Test, second edition*. San Antonio, TX: Pearson Assessments.

Williams, J., & Sharp, G. B. (2000). Epilepsy. In K. O. Yeates, M. D. Ris, & H. G. Taylor (Eds.), *Pediatric neuropsychology: Research, theory, and practice* (pp. 47–73). New York, NY: The Guilford Press.

Wolff, M., Cassé-Perrot, C., & Dravet, C. (2001). Neuropsychological disorders in children with severe myoclonic epilepsy. *Epilepsia, 42*(Suppl 2), 61.

World Health Organization. (1993). *International Classification of Diseases: 10th revision*. Ann Arbor, MI: Commission on Professional and Hospital Activities.

The Neuropsychological Evaluation of High-Functioning Patients with Epilepsy

14

Sarah G. Schaffer

Epilepsy is a heterogeneous disorder with countless possible presentations. Knowing that someone has a diagnosis of epilepsy tells you very little about that person's experience. There are numerous factors that might moderate the impact of this diagnosis on any one person's life. Issues directly related to the occurrence of seizures might include type/severity of seizures, frequency with which they occur, predictability of occurrence (e.g., only at night, certain time of the month), presence or absence of warning signs or "aura," level of postictal debilitation, and frequency of injury (e.g., tongue biting, falls, etc.). However, there are also secondary factors to be considered that are unique to each individual. For example, not being able to drive might be more of a burden on a mother with young children living in a rural community than it would on a businesswoman living in a major metropolitan area with a well-connected public transportation system. Conversely, while that same businesswoman might not be impacted by her inability to drive, the cognitive impact of seizures and the cognitive side effects of medications might make it difficult for her to complete her work-related activities.

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Along these lines, in many professions the competition for advancement can be fierce (e.g., law, finance, academia). While any "edge" can bump a person up a rung on the ladder toward success, the inverse is also true. The legality of denying someone a job or a promotion because of factors related to medical status is not in dispute. But whether this is "legal" or not is irrelevant, as this is reality. While the stigma associated with epilepsy might result in discrimination based on faulty perceptions by employers and co-workers, the direct consequences of uncontrolled seizures, such as lost days of work and mental clouding associated with antiepileptic medications, might be just as counterproductive to employment goals. Furthermore, most people with refractory epilepsy are on high doses of antiepileptic medications and/or polytherapy (i.e., prescribed multiple medications), which increases the likelihood of such adverse medication side effects.

In light of these issues, it becomes clear that the aim of neuropsychological evaluations of patients with epilepsy is multifactorial. Presurgical evaluations do not simply boil down to lateralization of seizure focus and prediction of postsurgical cognitive decline. Rather, a holistic approach that accounts for the full spectrum of cognitive and psychosocial issues unique to each patient is required. As comprehensive neuropsychological evaluations involve examination of both cognitive and "psychological" factors that impact upon a person's overall level of

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functioning, the neuropsychologist might be more likely to consider the entire range of issues that are coming into play and as such might be in the best position to advocate on the patient's behalf. To this end, it is also helpful to know some of the issues that are common among specific subsets of patients. This chapter aims to delineate such potential issues as they pertain to high-functioning patients, that is, those who have demonstrated an ability to maintain active professional careers.

Consequences of Epilepsy

It is well established in the literature that seizures can have an adverse impact on brain functions. The extent to which patients actually experience declines in cognition due to seizure activity depends on a number of factors, including seizure type (focal vs. generalized), seizure frequency, age of onset, and number of years with seizures. There are several "secondary" factors (i.e., those not directly related to seizures) that can also impact cognition, including the presence of underlying psychopathology (which is seen at higher rates in epilepsy patients than in the general population), the presence of a lesion, and medication side effects. There is considerable evidence to suggest that these factors work in concert with each other to produce the subjective experience of cognitive decline that is so often reported in this patient population.

The most common cognitive complaint in patients with epilepsy is that of memory difficulties. Such complaints are of course validated by decades of research showing the selective impact of seizures on memory functioning. Other common complaints include mental slowing and problems with attention. While the impact of epilepsy on neuropsychological functioning is well established in the research literature, it should be noted that a number of studies have found that subjective complaints do not always correlate with objective impairments. The first part of this chapter provides a brief review of the literature related to cognitive and psychosocial functioning in patients with epilepsy, as well as a brief introduction of the various factors that are associated with magnification of subjective cognitive impairment in this population. The goal of such a review will be to delineate for the clinician the potential pitfalls to be aware of when attempting to identify the salient issues to address when rendering conclusions. The second part of this chapter focuses on specific issues related to the comprehensive neuropsychological evaluation of high-functioning epilepsy patients.

Cognitive Impact

Numerous studies have shown that cognitive impairments in people with chronic epilepsy extend beyond memory difficulties to include problems related to attention and concentration, slower information processing and psychomotor speed, language deficits, and executive dysfunction when compared to performances of normal controls on objective neuropsychological tests.

The poorest cognition is associated with early age at seizure onset and, similarly, longer duration of epilepsy, especially in the presence of a history of generalized tonic–clonic seizures, repeated episodes of status epilepticus, and increased exposure to antiepileptic drugs (AEDs). The age of seizure onset represents a particularly important variable related to degree of cognitive impairment. Childhood-onset temporal lobe epilepsy has been associated with a generalized adverse neurodevelopmental impact on brain structure and function (Hermann et al. 2002; Hermann, Seidenberg, & Bell, 2002). Late-onset patients exhibit considerably fewer volumetric and cognitive abnormalities compared with healthy controls despite a history of chronic temporal lobe epilepsy (16.2 years). Hermann and colleagues (2007) performed a cluster analysis using comprehensive neuropsychological data from 96 patients with chronic temporal lobe epilepsy and 85 healthy controls, and three distinct cognitive subgroups or phenotypes were identified: (1) minimally impaired (47 %), (2) memory impaired (24 %), and (3) memory, executive, and speed impaired (29 %). Common characteristics of patients in the most cognitively impaired group (Cluster 3) included older age at

evaluation, longest duration of epilepsy, higher number of antiepileptic medications, and more abnormal brain volumes (total, white matter and CSF). They also showed the most adverse cognitive course, especially when compared to Cluster 1. Although not significant, there were meaningful trends related to other clinical seizure variables in the Cluster 3 group, including greater number of lifetime GTCs, history of status epilepticus, and presence of initial precipitating injuries. Consistent with results from their earlier study regarding the differential impact of earlier age of onset on cognitive prognosis, Cluster 3 was characterized by earlier neurodevelopmental insult. It should be noted that although Cluster 1 exhibited the most intact cognition of the three groups, their performance on measures of language, immediate and delayed memory, executive function, and psychomotor speed was nevertheless significantly worse than that of controls.

The inverse relationship between age of onset and degree of cognitive decline can likely be attributed to that fact that there is greater opportunity for acquisition of skills in childhood prior to seizure onset in those patients who develop seizures later. It is, thus, noteworthy that later age of onset has also been associated with increased risk of postsurgical decline. This might reflect the fact that although these patients may have avoided the neurodevelopmental "hit" seen in patients with younger onset, thereby resulting in a higher level of functioning at the time of surgical intervention, this increases the likelihood that the epileptogenic zone involves functional tissue. Studies have indicated that cognitive decline is determined more by the amount of functional tissue resected than the ability for remaining tissue to support cognitive functions (Chelune, 1995).

Cognitive Prognosis Associated with Chronic TLE

When counseling patients who are in the process of deciding whether or not to undergo surgical intervention of intractable seizures, there are many issues that must be considered. However, with high-functioning patients, none is more relevant than the potential impact on cognition. Therefore, it is necessary to be able to communicate not only the risks and benefits of going forward with surgery but also the risks associated with ongoing seizure activity should they choose not to move forward. In order to do this, one must be familiar with the literature regarding the cognitive prognosis associated with chronic epilepsy.

There are some in the field who propose a neurodegenerative model when characterizing the progression of cognitive decline associated with ongoing seizures. In a large cross-sectional study specifically intended to examine this issue, Helmstaedter and Elger (2009) compared the memory profiles of patients with chronic intractable temporal lobe epilepsy at varying stages of life to those of healthy controls. They found an initial discrepancy in the acquisition of learning and memory skills during childhood and particularly during adolescence that resulted in an earlier "learning peak" in the epilepsy patients (16–17 years vs. 23–24 years). Subsequent declines in performance related to normal aging ran in parallel (i.e., there was not a steeper decline in the epilepsy group), but because of the initial distance in memory abilities between the groups, those with epilepsy reached very poor performance levels much earlier than controls. It was concluded that although there does not appear to be a progressive and/or accelerated decline related to chronic seizures in patients with TLE, the negative interaction of the initially established damage with the normal aging process results in reduced reserve capacities at an older age (Helmstaedter & Elger, 2009). These results support the notion that poor cognitive functioning is related to neurodevelopmental processes in those patients with earlier age of onset. Furthermore, they suggest that rather than benefiting from the increased plasticity that is commonly ascribed to the developing brain, the presence of recurrent seizures during development appears to be associated with an adverse effect on both brain structure and function.

In his review of the literature on cognitive progression in epilepsy, Seidenberg noted that duration of epilepsy appears to be the most reliable predictor of cognitive decline. However, he further pointed out that duration of epilepsy likely signifies the presence of a more complex

and/or severe epilepsy syndrome. At the very least, the duration of epilepsy increases the possibility of exposure to factors that result in neuronal damage (Seidenberg, Pulsipher, & Hermann, 2007). Hermann and colleagues looked at the cognitive trajectories of patients with chronic TLE and found that most patients (70–75 %) appeared to have an unproblematic prospective cognitive course. Skills that were more vulnerable to decline (i.e., decline seen in >25 % of patients) included confrontation naming, delayed visual memory, delayed verbal memory, and bilateral motor speed (Hermann, Seidenberg, Dow, & et al., 2006). In general, the patients with adverse cognitive outcomes were older, with longer duration of epilepsy, lower baseline full-scale IQ, and quantitative MRI abnormalities at baseline. Baseline volumetric abnormalities and lower IQ were the strongest predictors of abnormal trajectories in IQ, language, perception, memory, executive skills, and motor coordination over a 4-year period.

The findings that patients who exhibited significant adverse cognitive outcomes were characterized by significantly lower baseline full-scale IQ are consistent with the general notion of increased cognitive vulnerability among those with lower intellectual capacity. In a study that examined long-term outcomes in individuals who had childhood-onset epilepsy now aged 20 years and older, Wakamoto and colleagues concluded that patients who had normal intelligence had more favorable prognosis (Wakamoto, Nagao, Hayashi, & Morimoto, 2000). It stands to reason that high-functioning patients have avoided the neurodevelopmental hit that appears to characterize those patients with poorer baseline functioning, thereby allowing them to acquire the skills needed for a stronger cognitive foundation. Interestingly, and perhaps more germane to the goals of this chapter, this pattern is opposite of that observed following anterior temporal lobectomy for the treatment of intractable seizures. That is, those with the least amount of cognitive impairment going into surgery experience the greatest postsurgical declines (at least with respect to verbal memory), whereas the inverse is true of individuals with significant presurgical cognitive deficits. Stated another way, those with normal neurocognitive profiles going into surgery have more to lose. Helmstaedter pointed out in his discussion of the neuropsychological aspects of epilepsy surgery (2004) that although patients with better baseline memory show greater losses than patients with poor baseline performance, those who are better preoperatively will nevertheless be better postoperatively. That being said, for some patients the prospect of even mild memory decline might be unacceptable. Indeed, this issue might be of particular concern for the population under consideration in the current chapter, as a general assumption would be that their status as "professional/high-functioning" individuals almost by definition implies a certain degree of intact cognition (or rather precludes the presence of significant and/or widespread impairments). However, it is possible that the relative stability of cognitive functions seen in these patients can be attributed to the development and/or use of compensatory strategies that are made possible because of higher cognitive reserve seen in these patients.

Cognitive Effects of Antiepileptic Medications

Problems with learning and cognition have frequently been cited among the primary disadvantages of having epilepsy (Hayden, Penna, & Buchanan, 1992), and the majority of patients with epilepsy attribute their impairments to the side effects of their antiepileptic medication (Carpay, Aldenkamp, & van Donselaar, 2005). There are some general patterns to follow when considering the potential impact of medication side effects on cognition. Newer agents tend to produce fewer side effects than older drugs (e.g., carbamazepine and phenobarbital), with the exception of topiramate (Topamax), which is a newer medication that has consistently been shown to have an adverse impact on cognition. Patients on topiramate are more likely to discontinue this medication due to cognitive side effects. Regardless of the type of medication used, there is a dose-related effect on cognition (even at therapeutic blood serum levels), with polytherapy resulting in more adverse effects than monotherapy.

Unfortunately, given that surgery is considered for patients who are refractory to medications, these patients are more likely to be prescribed high doses and/or multiple medications, and in fact for many the desire to reduce the number of medications is a primary motivation in seeking surgery. Uijl and colleagues found that among 173 patients who were well controlled on medication, 67 % nevertheless reported moderate to severe subjective complaints. Cognitive complaints were reported most frequently, and the prevalence and severity of complaints were associated with AED polytherapy and higher scores on "psycho neuroticism" on the Dutch version of the Symptom Check List (SCL-90) (Uijl et al., 2006). The relationship of self-reported complaints and high levels of neuroticism has been reported in other studies as well (Vermeulen, Aldenkamp, & Alpherts, 1993).

Subjective Cognitive Complaints

While the potential impact of chronic epilepsy on neuropsychological status is not in dispute, patients' complaints of cognitive impairment (i.e., their subjective experience regarding the severity and functional impact of such impairments) are not always borne out via objective neuropsychological evaluation. Numerous studies have shown that self-reported cognitive complaints do not generally correlate with actual impairments. In general, research has supported an inverse relationship between subjective and objective impairment. That is, more severe cognitive complaints are associated with milder impairment on objective testing, and vise versa. One study that examined the hypothesis that more complaints might be seen in patients with higher cognitive demands in daily life found the inverse to be true (although the effect was mild; Gleissner, Helmstaedter, Quiske, & Elger, 1998). Several studies have indicated a much stronger relationship between subjective complaints and mood than is seen between either subjective and objective cognition or mood and objective cognitive performance (Hayden et al., 1992; Liik, Vahterb, Gross-Pajub, & Haldrea, 2009; Marino, Meador, Loring, Okun, Fernandez, Fessler, et al., 2009; Piazzini, Canevini, Maggiori, & Canger, 2001).

Given these findings, it is important to try to tease out the relative contributions of each factor to the overall profile, using validated neuropsychological and psychological measures, and to counsel the patient when discrepancies between objective impairment and subjective experience arise.

Psychosocial Impact

The psychosocial impact of epilepsy can be profound. Results from multiple population-based surveillance studies representing nearly half of the United States indicated that compared with healthy controls, adults with a history of active epilepsy consistently reported higher rates of unemployment, lower income (<$25 K), lower education, and being single compared with people without epilepsy. Furthermore, those patients with the most active epilepsy (i.e., seizures within the past 3 months) were most likely to report more mentally and physically unhealthy days and more limitations on activity (Kobau et al., 2004, 2007, 2008; Kobau, Gilliam, & Thurman, 2006; Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007).

In a large population-based study conducted in the United Kingdom, psychiatric disorders were found to occur twice as often in patients with epilepsy as in the general population (Gaitatzis, Carroll, Majeed, & W Sander, 2004). Depression is the most frequently diagnosed psychiatric disorder among people with epilepsy. The factors that have been associated with the increased risk of depression in this patient population include employment status, social support, stigma, self-management, financial strain, and activity restriction due to seizures (Reisinger & DiIorio, 2009). In a survey of 503 patients with intractable epilepsy, almost half (46 %) of those surveyed agreed that epilepsy often caused them to suffer from depression (Wheless, 2006). Patients with intractable temporal lobe epilepsy with the additional syndrome of mesial temporal sclerosis have been found to be at an even higher risk of developing psychiatric disorders, with lifetime prevalence rates up to

80 % (Gaitatzis, Trimble, & Sander, 2004; LaFrance, Kanner, & Hermann, 2008)! Not only is the lifetime prevalence of major depression in epilepsy patients far greater than that estimated for the general population (5–25 % according the DSM-IV-TR), but it is almost double the estimated prevalence rate of 20–25 % that is cited in the DSM-IV-TR as occurring in other chronic or severe general medical conditions (e.g., diabetes, myocardial infarction, carcinomas, stroke). These statistics are all the more concerning given consistent evidence implicating depression as one of the strongest predictors of reduced quality of life in patients with refractory epilepsy (Perrine et al., 1995). Despite the focus on depression in epilepsy over the past decade, studies indicate that it is woefully underdiagnosed and largely untreated (Boylan et al., 2004).

Quality of Life

While depression has been identified as an overarching factor related to poor outcome in patients with epilepsy, quality-of-life research has uncovered a variety of specific factors that are associated with patients' overall sense of well-being. Perceived stigma has emerged as one of the primary issues leading to reduced quality of life in epilepsy patients. Goffman conceptualized stigma as "a loss of status and power resulting from the separation of those stigmatized from the general population based on a characteristic that has been culturally defined as different and undesirable" (Goffman, 1963). In epilepsy patients, stigma is associated with low self-esteem, self-efficacy, and sense of mastery, perceived helplessness, increased rates of anxiety and depression, increased somatic symptomology, and reduced life satisfaction (Jacoby, Snape, & Baker, 2009). In a study out of the Netherlands, stigma accounted for twice the amount of variance in QOL scores as did clinical variables such as seizure frequency and antiepileptic drug side effects, and it was identified as the fourth most important factor in determining QOL after psychological distress, loneliness, and adjustment (Suurmeijer, Reuvekamp, & Aldenkamp, 2001). Results of a recent study showed that reported levels of stigma were associated with interactions of seizure worry and employment status, self-efficacy and social support, and quality care and age at seizure onset (Smith et al., 2009). Regarding employment status, the highest level of stigma was reported by individuals who were disabled or unemployed and reported a higher level of seizure worry, followed by those who were disabled or unemployed but reported a lower level of seizure worry; the lowest level of stigma was reported by those who were employed or "other" (not working but student, housewife, retired, etc.) and reported lower level of seizure worry. It should be noted that people with epilepsy do not universally feel stigmatized by their disorder. In an older surveillance study conducted by Ryan, Kempner, and Emlen (1980), 81 % of the 445 respondents felt that they had been treated fairly in society, and 70 % felt neither unreasonably limited nor treated differently because of their epilepsy (Ryan et al., 1980).

Researchers have also been concerned with identifying those factors that might be associated with better psychosocial adjustment in patients with epilepsy. Resilience, for example, has been found to be associated with better QOL. Sociodemographic characteristics such as gender, education, and income level have been found to be highly predictive of resilience, with poorer resilience manifested by women and individuals who had lower levels of education and lower income (Campbell-Sills, Forde, & Stein, 2009). There is a positive association between resilience and cognitive reserve (as indicated by higher educational level or occupational attainment and increased participation in mindful activities). The well-established relationship between generalized cognitive impairment and duration of epilepsy has been shown to be attenuated (to nonsignificant levels) by having more years of formal education (Oyegbile et al., 2004). The authors suggest that years of education may, in fact, be a marker "for those who, at the outset of the disorder, are on different trajectories regarding educational attainment and lifespan cognition." In fact, the role of educational level as a predictor of QOL in adults has been emphasized in a number of studies (Loring, Meador, & Lee, 2004; Pulsipher, Seidenberg, Jones, & Hermann,

2006). Socioeconomic status has also been identified as an important predictor of QOL in patients with epilepsy (Alanis-Guevara et al., 2005), and Senol and colleagues found that while income and education predict overall QOL, only income was found to significantly predict mental and physical health and cognitive function scores in a multiple regression analysis (Senol, Soyuer, Arman, & Ozturk, 2007). Therefore, in high-functioning adults, the potential for loss of income has far-reaching implications.

Impact on Employment

In a review of the literature regarding employment and epilepsy, Smeets et al. (2007) noted that employment is seen by many as an important ingredient of the quality of life of people with epilepsy. Employment is considered to be a significant predictor of well-being of people with epilepsy and a very important factor in psychosocial adjustment. In a large population-based study by Jacoby (1995), employed people with epilepsy experienced fewer psychosocial problems than unemployed people with epilepsy (Jacoby, 1995). There is little agreement in the literature on specific unemployment and underemployment rates, which vary widely between communities and countries. It is generally accepted, however, that people with epilepsy are more likely to be employed in unskilled and manual jobs. Some studies suggest a relationship between seizure type and employment status, with increased likelihood of being unemployed for patients classified as having GTC seizures (Jacoby, Baker, Steen, Potts, & Chadwick, 1996) and decreased likelihood of attributing current employment situation to epilepsy in patients who were in remission with respect to seizure activity (Chaplin, Wester, & Tomson, 1998). Although seizure frequency is an important factor determining employment status, it may not be the most important factor to consider. Other factors that can play an important role in predicting employment status include medication side effects, stigma, and psychosocial variables such as low self-esteem, passive coping style, and low self-efficacy. The impact of employment status on self-esteem and self-image has been established. Some argue that the stigma associated with having a diagnosis of epilepsy is one of the most critical barriers to employment. Stigma is associated not only with discriminatory practices, but patients often internalize the negative attitudes of others and come to view their epilepsy in a similar light. Because of this potential for discrimination, people with epilepsy are often hesitant to disclose their epilepsy status to employers. Problems at work can lead to a lack of opportunities for career advancement, and studies suggest that many people with epilepsy do not reach the employment potential corresponding to their qualifications and age.

In a study that examined the employment trajectories of individuals with single seizures or recently diagnosed epilepsy, significantly lower employment rates were seen at study entry and 2- and 4-year follow-up than were seen for the general population (Holland, Lane, Whitehead, Marson, & Jacoby, 2009). Having fair/poor self-rated health and experiencing four or more seizures predicted nonemployment at all time points. Although there was little social class mobility during follow-up, there was evidence of some downward mobility between first seizure(s) and study entry.

Wheless and colleagues reported findings from a large-scale survey that focused solely on the experiences, attitudes, and quality of life of a refractory epilepsy population (Wheless, 2006). The resulting data represented three groups of participants ($n=903$): those with epilepsy who self-reported on their condition (Group 1, $n=503$), the caregivers of those with refractory epilepsy (Group 2, $n=200$), and those with epilepsy who had their condition reported on by a caregiver (Group 3, $n=200$). The unpredictable nature of seizure occurrence was responsible for much of the fear and uncertainty associated with epilepsy in both patients and caregivers. Epilepsy was blamed for the loss of many of the everyday activities most people take for granted, such as independence, a social life, education, work, relationships, respect, and oftentimes a future. It was noted that this survey sample was surprisingly well educated compared to a prior survey conducted by Fisher and colleagues (2000), with

approximately 64 % of those with epilepsy from Group 1 having graduated from high school and 26 % having received a college undergraduate or graduate degree. Despite the high level of education in this survey, 58 % of those in Group 1 were not employed outside the home or were unable to work. They obtained an unemployment rate of 29 % when homemakers, students, or volunteer workers were excluded from the equation, which is higher than the 25 % unemployment rate reported by Fisher et al. (2000).

Sillanpaa and colleagues recently reported results from a prospective longitudinal study aimed at determining the long-term employment and predictive factors in adults with childhood-onset epilepsy living in the community (Sillanpaa & Schmidt, 2010). At the mean age of 23 years, 85 (71 %) of the 119 patients living in the community were employed. At the mean age of 48 years, only 45 (59 %) of 76 patients living in the community were employed, compared to 63 (78 %) of 81 controls (patients vs. controls, $p=0.01$). The variables that predicted employment in young adults included normal intelligence, vocational education, and age at onset of epilepsy older than 6 years, whereas those that predicted lasting employment into middle age included normal intelligence, having offspring, uninterrupted remission, and no history of status epilepticus.

There are several factors that can moderate the impact of epilepsy on employment outcomes, including personality (e.g., coping strategies and self-efficacy), social support, and intellectual abilities. Perceptions regarding self-efficacy can play a significant role in either mitigating or exacerbating the impact of epilepsy on daily functioning. How effective an individual with epilepsy perceives him- or herself to be in coping with the everyday problems of life is based on self-generated core beliefs that are central to this process (Tedman, Thornton, & Baker, 1995), yet study findings indicated that the physical effects of seizures, the unpredictable nature of epilepsy, and adverse social reactions can exhaust the coping resources of people with epilepsy. The combination of low self-efficacy seen in people with epilepsy and the tendency of this population to use of passive coping strategies to manage their disabilities can generate a vicious cycle, especially with respect to employment. High self-efficacy and an active coping strategy often result in successful psychosocial adaptation to the disorder. Thus, self-efficacy beliefs and active coping strategies might play a key role in helping people with epilepsy to enhance their employment opportunities.

Based on their literature review, Smeets et al. emphasized the important role that coping strategy, self-efficacy, and social support play in accepting and managing the psychosocial consequences or effects of having epilepsy. They note that specific attention should be focused on recent European studies that reveal that people with epilepsy who develop more active coping strategies have fewer psychosocial problems. Research findings further indicate that coping strategies play an important role in adaptation to epilepsy.

Neuropsychological Evaluation of High-Functioning Individuals with Careers

Many of the issues to be considered when conducting neuropsychological evaluations with high-functioning epilepsy patients overlap with those that come up in the general discussion of neuropsychological evaluation of epilepsy patients. Some of these issues will be addressed briefly, but for a more comprehensive discussion, the reader is referred to Chap. 2 (Neuropsychological Testing of Patients with Epilepsy) and Chap. 3 (Neuropsychological Evaluation of the Surgical Candidate).

Seizure-Related Issues

Obtaining detailed information regarding seizure-related variables should be a top priority in every epilepsy evaluation, particularly given their association with both cognitive and psychosocial status. However, some of these variables are

more relevant to high-functioning patients than others. For example, age of seizure onset and duration of epilepsy are good prognostic indicators with respect to both current and long-term cognitive status, with earlier onset and longer duration being associated with a greater likelihood of current cognitive deficits and future decline. Hence, the expectation would be that high-functioning patients might, as a general rule, present with later age of onset. Conversely, knowing that a patient's seizures started later in life might lead to an initial hypothesis regarding potential cognitive status. That being said, later age of onset does not always mean better outcome. While this relationship is more likely in patients for whom a precipitating cause cannot be identified (epilepsies of unknown cause), later age of onset might also indicate the presence of an underlying neurologic process (e.g., neoplasm) or injury (e.g., stroke or TBI) that led to the secondary development of seizures, which would obviously complicate the clinical picture quite a bit. In such cases, the clinician must consider not only the impact of current seizure activity on cognition but also the cognitive factors associated with the precipitating insult. Although the current discussion will be limited to those patients who present with "typical" epilepsy syndromes, it should be clear that there are a variety of factors that might alter the approach taken by the clinician and the importance of identifying such factors early on in an evaluation cannot be overstated.

Seizure frequency is also important to consider, particularly given its differential impact on psychosocial status and overall quality of life relative to other seizure variables. Seizure frequency is also related to seizure worry, which has been associated with reduced occupational functioning. Therefore, in addition to identifying specific data regarding seizure frequency, it is important to assess the patient's perception of their seizure frequency. Characterization of seizure semiology, including both the patient's own experience of the seizures (e.g., presence of aura/warning, awareness during the actual event, and postictal symptoms) and the behaviors observed by others, is important insofar as it can not only provide key information regarding localization of onset and general severity of events but also the potential impact that might be associated with having a seizure at work (e.g., do others notice, is there a lapse in awareness, can the patient resume normal activities?). Although not necessarily a "seizure-related" variable per se, information regarding medications, including type(s), dosage, and perceived side effects, is necessary when determining potential causes of any cognitive deficits observed on objective testing.

It is also important to understand the perceived impact that these factors have on the patient's overall quality of life. What does the patient consider to be the most impairing aspect of having epilepsy? How does having a diagnosis of epilepsy impact their day-to-day experience? In assessing the impact of epilepsy from the patient's perspective, it is important to keep in mind research findings regarding the effect that patient perceptions can have on overall well-being. For example, perceived stigma is associate with poor employment outcomes, and perceived cognitive impairment has been associated with reduced quality of life. Regarding the latter, one must also keep in mind that subjective complaints do not generally coincide with actual impairment, and in fact when reported complaints exceed actual deficits, one might suspect the presence of an underlying mood disorder that needs to be further explored.

Employment-Related Issues

Epilepsy is related to poor employment outcomes compared to the general population, and employment status is considered to be an important factor in psychosocial adjustment; employed people experience fewer psychosocial problems than unemployed people with epilepsy. Therefore, evaluations of patients with professional careers should be completed with an eye toward ensuring ongoing employment, and risks to employment status should be identified early and addressed

accordingly. The factors that might threaten employment status include impact of seizures on job attendance, frequency of seizures (at work or otherwise), unpredictability of seizures, potential for job-related injury, impact of medication on cognition, and perceived stigma associated with the diagnosis of epilepsy.

When assessing the potential impact of epilepsy on job performance, the clinician must first consider the full range of factors and associated consequences that might result from seizure activity. For example, do the seizures always occur at the same time of day (e.g., at night, when the risk of others witnessing the events would be slim), or are the unpredictable? Is the patient worried about the possibility of having a seizure at work? If they have occurred at work, what were the circumstances surrounding the event(s) and what was the outcome (both real and perceived)? Are the seizures associated with injury that might make it difficult to attend or complete work? Similarly, is the postictal period characterized by cognitive changes that might impact work performance? A more pressing and ethically challenging issue pertains to the potential for reduced work performance to result in harm to others, be it physical, legal, financial, or otherwise. This issue is complicated even further by the fact that many professionals choose not to disclose their diagnosis to employers, which should also be addressed.

The assumption when assessing patients with professional careers is that intellectual functioning is within or above the normal range. Normal intelligence and higher educational attainment are considered to be protective when it comes to overall prognosis, which is believed to be associated with resilience. Therefore, these patients might be expected to have a better prognosis than patients with lower baseline IQ. That being said, the stigma associated with epilepsy can have a negative impact on employment status, and in fact some consider this to be one of the most critical barriers to employment. Therefore, even in the absence of cognitive barriers to success, it is vital that the clinician ascertain the level of stigma that the patient perceives to be associated with his/her diagnosis, along with a more general assessment of psychosocial functioning. What is the patient's attitude about the diagnosis, and how does he or she think it has affected the ability to advance in his/her current field? Higher level of reported stigma is seen in unemployed patients with high seizure worry, whereas the lowest stigma is reported by employed patients with low seizure worry. Perceived stigma and seizure frequency might, therefore, be of particular importance when attempting to delineate the factors that might lead to a decline in employment status. Of note, this might not be as much of a concern in patients who have achieved a high level of career success given the association between occupational attainment, income level, and resilience, the latter of which has been associated with better quality of life.

Cognitive Issues

In the absence of psychosocial risk factors that might impact overall well-being in otherwise high-functioning patients, one might suspect the cognitive deficits (or at least the functional impact of such deficits) associated with epilepsy to be minimal. The status as a "professional/high-functioning" patient almost by definition implies a certain degree of intact cognition (or rather precludes the presence of significant and/or widespread impairments). When cognitive complaints do arise in such patients, it is important to keep in mind that in general such complaints may not to be associated with actual "brain dysfunction," but rather raise the question of functional changes associated with an underlying depression and/or anxiety (Liik et al., 2009, Marino et al., 2009). By the same token, it should also be kept in mind that higher-functioning individuals tend to be more sensitive to even subtle changes in cognition, which might not be detectable using standard normative data (e.g., although an "average" or even "high average" performance would be considered intact, these may represent marked declines in someone who was once functioning at a much higher level). Nevertheless, cognitive impairments are a known consequence of intractable seizures, and the importance of determining cognitive status and of preventing future cognitive

decline cannot be overemphasized in this population. This is not as much of an issue in patients who are well controlled on medication, unless such control is only achieved with the use of high doses of medication, older antiepileptic agents (or topiramate, a newer agent that is known to have cognitive side effects), and/or polytherapy. If this is the case, such patients might be considered candidates for epilepsy surgery. In general, however, the potential risk for cognitive decline is more of a concern in patients who are refractory to medication.

When considering the impact of chronic epilepsy on neuropsychological status, it is important to keep in mind that although some patients do exhibit significant impairments (memory being the most common), most patients evidence minimal deficits that tend to be confined to the areas of language (primarily naming), immediate and delayed memory, executive function, and psychomotor speed (Hermann et al., 2006). Those patients who do exhibit more pronounced and/or widespread impairments tend to be characterized by earlier age of seizure onset and lower baseline IQ. That being said, there is a risk of progressive decline in patients with chronic intractable epilepsy, which is strongly predicted by duration of epilepsy. The factors that are believed to protect against such declines include later onset of seizures (and thus shorter duration), higher educational attainment, and normal baseline IQ, all of which suggest a higher level of cognitive reserve and thus better capacity to absorb the impact of seizures in these patients. In fact, the well-established relationship between generalized cognitive impairment and duration of epilepsy has been shown to be attenuated (to nonsignificant levels) by having more years of formal education. Given the presumed demographic variables associated with higher-functioning patients, particularly those in professional careers, it would stand to reason that such patients fall into this low-risk group. However, the potential for progression of cognitive symptoms must be addressed when counseling the patient about treatment options. This will be discussed further under the section on surgical considerations.

Interpretation of Neuropsychological Results

The neuropsychological battery that is used in general epilepsy evaluations would also be appropriate for use with high-functioning patients. The interpretation of the ensuing results would also be the same in regard to lateralization/localization of seizure focus and the general factors associated with better or worse outcome (e.g., better presurgical memory predicts greater postsurgical decline). However, there are several additional interpretive considerations in higher-functioning patients. At the outset of the evaluation, the clinician should inquire about any prior evaluations. The ability to compare current results to a prior baseline can be invaluable in this population, primarily because it provides information regarding stability and/or progression of cognitive symptoms, which might impact treatment planning. Furthermore, such comparisons can reveal *focal* change in neurocognitive functioning (i.e., change confined to one specific area of functioning), which can provide valuable insight into seizure focus, particularly when EEG data is inconclusive. Regardless of whether a baseline exists or not, it is important to obtain an estimate of premorbid functioning using valid and reliable measures. This can also be used to ascertain the likelihood that there has been a decline from a prior level or relative to an expected level based on demographic variables that are known to be associated with intellectual functioning. Including demographic variables in the equation might be particularly useful in patients with onset of seizures in childhood, as this might provide clues regarding whether or not there was a developmental impact from the seizures.

The usual interpretation of the VCI–PRI split might also change with high-functioning patients, specifically those with high educational attainment. Education level is positively correlated with verbal abilities on the Wechsler intelligence scales. Therefore, a VCI > PRI split on the WAIS-IV would be expected in more highly educated patients and would not necessarily indicate right

hemisphere seizure onset (as might otherwise be the case). In contrast, the opposite might be concluded from a split in the reverse direction (i.e., a PRI > VCI discrepancy might be even more meaningful in patients with high educational attainment than it would otherwise be). The base rates of VCI–PRI discrepancies that are provided in the WAIS-IV manual are broken down by ability (IQ) level, and thus such splits should not present a problem in interpretation in cases where FSIQ is consistent with premorbid estimates. When this is not the case, however, it might be prudent to also examine the base rate using the premorbid estimate as the "ability" level. Finally, it is often the case that individuals enter into professions that are better suited to their particular strengths, and in epilepsy patients such decisions might be associated with underlying functional capacity associated with region of seizure onset in the brain. For example, someone with left TLE might find herself gravitating toward art classes in high school and computer graphics classes in college, and she might ultimately find herself in a career as a web designer. This proclivity might even hold true in the event of later seizure onset, which is more typical in higher-functioning patients, as many studies have indicated that cognitive symptoms predate the diagnosis of epilepsy. In any event, if strengths on neuropsychological assessment coincide with occupation (and weaknesses are not as important for work-related activities), this might indicate a better prognosis related to employment outcome in the event of postsurgical declines. In general it is important to consider the cognitive demands associated with the patient's line of work, as the impact of potential declines might be exacerbated or mitigated depending on work demands. For example, if the results of an evaluation of a lawyer show strong verbal memory and good expressive language, skills that are obviously necessary for a successful attorney (particularly a litigator), the risk to employment outcome associated with a left temporal lobe resection might be unacceptable. That being said, the possibility of the patient agreeing to a lateral promotion to a job that requires less litigation and more paperwork might reduce this risk to a more acceptable level.

Along these lines, there is increased likelihood that high-functioning patients would be able to utilize a wider array of compensatory strategies in the event of a cognitive "hit," and this should be considered when determining the overall risk to employment statues. In particular, high-functioning patients and those in professional careers might already use a smartphone or similar handheld device (PDA), and they might thus be in a better position to use these devices to their advantage as a way to compensate for lost ability.

Surgical Considerations

The general issues for patients considering surgical intervention have been discussed in detail in Chap. 3. Therefore, the current discussion will focus on surgical decision-making only insofar as it pertains to high-functioning patients and/or those with professional careers. The decision to proceed with surgery is made when patients are found to be refractory to pharmacologic intervention or, in some cases, when the side effects of the latter are deemed to be intolerable. As a general rule, the earlier one enters into surgery, the better the prognosis not only for seizure outcome but for cognitive outcome as well. In all cases, the risks and benefits of proceeding with surgery must be weighed against the alternative. However, this issue tends to be more complicated in patients who are functioning at a high level going into surgery. Most patients being considered for surgery are unable to work, experience increased levels of depression and other psychiatric disorders, and report generally poor quality of life. In such cases, the risks associated with cognitive decline may be weighed less heavily in the context of the potential improvement in quality of life that a reduced seizure burden might bring. Indeed, patients who have experienced seizure freedom from surgery but show postsurgical memory declines tend not to report declines in QOL associated with the latter. In the professional patient, however, the risk of cognitive decline might be much more of a factor in the decision-making process, particularly given the fact that

the risk of such cognitive declines is increased in these patients. These patients are more likely to have a later age of seizure onset and normal IQ, both of which are associated with greater cognitive declines, and it is now generally accepted that the greater the cognitive abilities going into surgery, the more there is to lose. The Wada test can assist in determining risk for decline, as good memory in the hemisphere under consideration is associated with greater risk of decline (regardless of the ability of the contralateral hemisphere's capacity to support memory functions). That being said, these patients also tend to have greater cognitive reserve and better compensatory skills, and although patients with better baseline memory show greater losses than patients with poor baseline performance, those who are better preoperatively will nevertheless be better postoperatively. It is possible that the relative stability of cognitive functions seen in these patients can be attributed to the development and/or use of compensatory strategies that are made possible because of a stronger cognitive foundation, and such strategies might be particularly beneficial in the event of postsurgical declines in cognitive abilities. That being said, for some patients the prospect of even mild memory decline might be unacceptable.

Knowing this risk, patients must determine what the functional impact of a memory hit would mean at work. If memory is found to be adequate before surgery and work is not being affected, is it better to live with seizures and continue to work at the current level, or is it more important to be seizure-free and possibly take a hit? Are job demands dependent on memory and language? Conversely, how might employment status improve in the absence of seizures and its associated factors? In the event that patients deem any memory decline to be unacceptable, there needs to be an additional discussion regarding the cognitive prognosis associated with uncontrolled seizures. Therefore, in the end, the decision for the patient boils down to: "When do I want to suffer a memory decline?" Would it be better to live with seizures and have another 10 or so years to work, or is it worth it to risk the cognitive decline for the prospect of seizure freedom, given that this is the road one might be headed down anyway? If the decision is toward the former, an additional factor to consider is that older age at surgery is associated with poorer outcome, presumably due to reduced neural plasticity. Therefore, the deficit might be even bigger if the surgery is postponed. This is further complicated by the fact that there are no guarantees of being seizure-free. Finally, the surgical decision must also be weighed in the context of the fact that continued seizures could lead to additional independent seizure foci (that may or may not be amenable to surgery or that may eliminate the potential for postoperative seizure freedom) and the small but tragic risk of SUDEP.

Postsurgical Outcome

In addition to primary issues related to surgical outcome, the neuropsychologist should also discuss goals and expectations associated with surgery. Patients sometimes set unrealistic goals that need to be reined in with the help of the surgical team, including the neuropsychologist. The potential for disappointment and reduced postsurgical adjustment needs to be circumvented by bringing the patient's goals in line with reality. For example, while seizure freedom is obviously the goal, would the possibility that seizures might only be lessened in frequency and/or severity alter the patient's decision regarding surgery? Additionally, for many patients the motivation to seek surgery stems from the intolerability of AED side effects, and the possibility of not having to take medication supersedes the prospect of being seizure-free. It is important that patients realize that medications will be tapered off slowly, if at all, and that the likelihood of not having to take medications any more is by no means guaranteed. Finally, some patients experience poor postsurgical adjustment due to a paradoxical effect associated with the dramatic positive changes that can accompany seizure freedom, a phenomenon that has been termed the "burden of normality." Conversely, some patients expect dramatic and immediate changes to ensue as a result of seizure freedom, and it is important

to evaluate such expectations and make them more realistic in order to prepare the patient for potential changes and reduce the level of disappointment that might accompany a lack of change in some areas. These issues might be tempered in higher-functioning patients, as they tend to have increased levels of self-efficacy and higher resilience going into surgery. Nevertheless, the range of potential changes that might occur as a result of surgery should be discussed thoroughly with the patient.

After patients proceed to surgery, it is important to measure postsurgical outcome. Patients should be made aware of the fact that many of the declines experienced immediately after surgery will resolve within the first year, while some will likely remain. In the event that the patient reports significant declines in the months after surgery, a brief neuropsychological follow-up exam can be conducted in order to assess the validity and nature of such complaints. Recall that most complaints are not substantiated by objective testing and in such cases complaints might better reflect poor psychosocial adjustment such as an underlying mood disorder. In the event that significant declines are noted (using reliable change indices), a referral for cognitive rehabilitation might be warranted. In the absence of significant postsurgical cognitive complaints, a more comprehensive follow-up exam can be conducted one year after surgery in order to establish a postsurgical baseline and assess the accuracy of surgical predictions. While assessment of cognitive status is important in surgical patients, ongoing follow-up to assess psychosocial well-being might be even more important, and these can be done when the patient comes in for follow-up appointments with their epileptologist, who should be reminded of the need for such appointments.

It is important to keep in mind when conducting any neuropsychological evaluation that clinical decision that are based on established research findings should be undertaken with caution. When counseling patients, it is prudent to remind them periodically that predictions are based on group data and that these general "rules" are by no means steadfast. If anything, this chapter should make it clear that there are many factors that must be considered in the evaluation of high-functioning patients, any one of which has the potential to change the outcome.

References

Alanis-Guevara, I., Pena, E., Corona, T., Lopez-Ayaa, T., Lopez-Meza, E., & Lopez-Gomez, M. (2005). Sleep disturbances, socioeconomic status, and seizure control as main predictors of quality of life in epilepsy. *Epilepsy & Behavior, 7*(3), 481–485.

Boylan, L. S., Flint, L. A., Labovitz, D. L., Jackson, S. C., Starner, K., & Devinsky, O. (2004). Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology, 62*(2), 258–261.

Campbell-Sills, L., Forde, D. R., & Stein, M. B. (2009). Demographic and childhood environmental predictors of resilience in a community sample. *Journal of Psychiatric Research, 43*(12), 1007–1012.

Carpay, J. A., Aldenkamp, A. P., & van Donselaar, C. A. (2005). Complaints associated with the use of antiepileptic drugs: Results from a community-based study. *Seizure, 14*(3), 198–206.

Chaplin, J. E., Wester, A., & Tomson, T. (1998). Factors associated with the employment problems of people with established epilepsy. *Seizure: The Journal of the British Epilepsy Association, 7*(4), 299–303.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists, 10*(5), 413–432.

Fisher, R. S., Vickrey, B. G., Gibson, P., Hermann, B., Penovich, P., Scherer, A., et al. (2000). The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions. *Epilepsy Research, 41*(1), 39–51.

Gaitatzis, A., Carroll, K., Majeed, A., & W Sander, J. (2004). The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia, 45*(12), 1613–1622.

Gaitatzis, A., Trimble, M. R., & Sander, J. W. (2004). The psychiatric comorbidity of epilepsy. *Acta Neurologica Scandinavica, 110*(4), 207–220.

Gleissner, U., Helmstaedter, C., Quiske, A., & Elger, C. E. (1998). The performance-complaint relationship in patients with epilepsy: A matter of daily demands? *Epilepsy Research, 32*(3), 401–409.

Goffman, E. (1963). *Stigma: Notes on the management of the spoiled identity*. Englewood Cliffs, NJ: Prentice-Hall.

Hayden, M., Penna, C., & Buchanan, N. (1992). Epilepsy: Patient perceptions of their condition. *Seizure: The Journal of the British Epilepsy Association, 1*(3), 191–197.

Helmstaedter, C., & Elger, C. E. (2009). Chronic temporal lobe epilepsy: A neurodevelopmental or progressively dementing disease? *Brain: A Journal of Neurology, 132*(Pt 10), 2822–2830.

Hermann, B., Seidenberg, M., Bell, B., Rutecki, P., Sheth, R., Ruggles, K., et al. (2002a). The neurodevelopmental impact of childhood-onset temporal lobe epilepsy on brain structure and function. *Epilepsia, 43*(9), 1062–1071.

Hermann, B., Seidenberg, M., Lee, E. J., Chan, F., & Rutecki, P. (2007). Cognitive phenotypes in temporal lobe epilepsy. *Journal of the International Neuropsychological Society: JINS, 13*(1), 12–20. doi:10.1017/S135561770707004X

Hermann, B. P., Seidenberg, M., Dow, C., et al. (2006). Cognitive prognosis in chronic temporal lobe epilepsy. *Annals of Neurology, 60*, 80–87.

Hermann, B. P., Seidenberg, M., & Bell, B. (2002b). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research, 135*, 429–438.

Holland, P., Lane, S., Whitehead, M., Marson, A. G., & Jacoby, A. (2009). Labor market participation following onset of seizures and early epilepsy: Findings from a UK cohort. *Epilepsia, 50*(5), 1030–1039.

Jacoby, A. (1995). Impact of epilepsy on employment status: Findings from a UK study of people with well-controlled epilepsy. *Epilepsy Research, 21*(2), 125–132.

Jacoby, A., Baker, G. A., Steen, N., Potts, P., & Chadwick, D. W. (1996). The clinical course of epilepsy and its psychosocial correlates: Findings from a U.K. community study. *Epilepsia, 37*(2), 148–161.

Jacoby, A., Snape, D., & Baker, G. A. (2009). Determinants of quality of life in people with epilepsy. *Neurologic Clinics, 27*(4), 843–863.

Kobau, R., DiIorio, C. A., Price, P. H., Thurman, D. J., Martin, L. M., Ridings, D. L., et al. (2004). Prevalence of epilepsy and health status of adults with epilepsy in Georgia and Tennessee: Behavioral risk factor surveillance system, 2002. *Epilepsy & Behavior, 5*(3), 358–366.

Kobau, R., Gilliam, F., & Thurman, D. J. (2006). Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: Results from the 2004 HealthStyles survey. *Epilepsia, 47*(11), 1915–1921.

Kobau, R., Zahran, H., Grant, D., Thurman, D. J., Price, P. H., & Zack, M. M. (2007). Prevalence of active epilepsy and health-related quality of life among adults with self-reported epilepsy in california: California health interview survey, 2003. *Epilepsia, 48*(10), 1904–1913.

Kobau, R., Zahran, H., Thurman, D. J., Zack, M. M., Henry, T. R., Schachter, S. C., et al. (2008). Epilepsy surveillance among adults–19 states, behavioral risk factor surveillance system, 2005. *MMWR. Surveillance Summaries: Morbidity and Mortality Weekly Report. Surveillance Summaries/CDC, 57*(6), 1–20.

LaFrance, W. C., Jr., Kanner, A. M., & Hermann, B. (2008). Psychiatric comorbidities in epilepsy. *International Review of Neurobiology, 83*, 347–383.

Liik, M., Vahterb, L., Gross-Pajub, K., & Haldrea, S. (2009). Subjective complaints compared to the results of neuropsychological assessment in patients with epilepsy: The influence of comorbid depression. *Epilepsy Research, 84*, 194–200.

Loring, D. W., Meador, K. J., & Lee, G. P. (2004). Determinants of quality of life in epilepsy. *Epilepsy & Behavior, 5*(6), 976–980.

Marino, S. E., Meador, K. J., Loring, D. W., Okun, M. S., Fernandez, H. H., Fessler, A. J., et al. (2009). Subjective perception of cognition is related to mood and not performance. *Epilepsy & Behavior, 14*, 459–464.

Oyegbile, T. O., Dow, C., Jones, J., Bell, B., Rutecki, P., Sheth, R., et al. (2004). The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology, 62*(10), 1736–1742.

Perrine, K., Hermann, B. P., Meador, K. J., Vickrey, B. G., Cramer, J. A., Hays, R. D., et al. (1995). The relationship of neuropsychological functioning to quality of life in epilepsy. *Archives of Neurology, 52*(10), 997–1003.

Piazzini, A., Canevini, M. P., Maggiori, G., & Canger, R. (2001). The perception of memory failures in patients with epilepsy. *European Journal of Neurology, 8*(6), 613–620.

Pulsipher, D. T., Seidenberg, M., Jones, J., & Hermann, B. (2006). Quality of life and comorbid medical and psychiatric conditions in temporal lobe epilepsy. *Epilepsy & Behavior, 9*(3), 510–514.

Reisinger, E. L., & DiIorio, C. (2009). Individual, seizure-related, and psychosocial predictors of depressive symptoms among people with epilepsy over six months. *Epilepsy & Behavior, 15*(2), 196–201.

Ryan, R., Kempner, K., & Emlen, A. C. (1980). The stigma of epilepsy as a self-concept. *Epilepsia, 21*(4), 433–444.

Seidenberg, M., Pulsipher, D. T., & Hermann, B. (2007). Cognitive progression in epilepsy. *Neuropsychology Review, 17*(4), 445–454.

Senol, V., Soyuer, F., Arman, F., & Ozturk, A. (2007). Influence of fatigue, depression, and demographic, socioeconomic, and clinical variables on quality of life of patients with epilepsy. *Epilepsy & Behavior, 10*(1), 96–104.

Sillanpaa, M., & Schmidt, D. (2010). Long-term employment of adults with childhood-onset epilepsy: A prospective population-based study. *Epilepsia, 51*, 1053–1060.

Smith, G., Ferguson, P. L., Saunders, L. L., Wagner, J. L., Wannamaker, B. B., & Selassie, A. W. (2009). Psychosocial factors associated with stigma in adults with epilepsy. *Epilepsy & Behavior, 16*(3), 484–490.

Smeets, V. M., van Lierop, B. A., Vanhoutvin, J. P., Aldenkamp, A. P., & Nijhuis, F. J., (2007). Epilepsy

and employment: literature review. *Epilepsy & Behavior, 10*, 354–362.

Suurmeijer, T. P., Reuvekamp, M. F., & Aldenkamp, B. P. (2001). Social functioning, psychological functioning, and quality of life in epilepsy. *Epilepsia, 42*(9), 1160–1168.

Tedman, S., Thornton, E., & Baker, G. (1995). Development of a scale to measure core beliefs and perceived self efficacy in adults with epilepsy. *Seizure: The Journal of the British Epilepsy Association, 4*(3), 221–231.

Tellez-Zenteno, J. F., Patten, S. B., Jette, N., Williams, J., & Wiebe, S. (2007). Psychiatric comorbidity in epilepsy: A population-based analysis. *Epilepsia, 48*(12), 2336–2344.

Uijl, S. J., Uiterwaal, C. S. M. P., Aldenkamp, A. P., Carpay, J. A., Doelman, J. C., Keizer, K., et al. (2006). A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with anti-epileptic drugs. *Seizure, 15*, 242–248.

Vermeulen, J., Aldenkamp, A. P., & Alpherts, W. C. (1993). Memory complaints in epilepsy: Correlations with cognitive performance and neuroticism. *Epilepsy Research, 15*, 157–170.

Wakamoto, H., Nagao, H., Hayashi, M., & Morimoto, T. (2000). Long-term medical, educational, and social prognoses of childhood-onset epilepsy: A population-based study in a rural district of japan. *Brain & Development, 22*(4), 246–255.

Wheless, J. W. (2006). Intractable epilepsy: A survey of patients and caregivers. *Epilepsy & Behavior, 8*(4), 756–764.

The Neuropsychological Assessment of Culturally and Linguistically Diverse Epilepsy Patients

15

H. Allison Bender

According to the last US census, approximately 31.1 million immigrants currently reside in the United States, representing well over 10 % of the country's total population (US Bureau of the Census 1999, 2000). This 57 % rise in immigration over the previous decade is without parallel during any time in recent history. Hispanic immigrants comprise the most rapidly growing segment of the country's population, representing over half of all immigrants to the United States (US Bureau of the Census 1999, 2000). Recent trends also indicate that immigration from Asian countries is steadily increasing and is currently the leading region of birth of persons becoming legal permanent residents of the United States (36.9 %; Department of Homeland Security, 2009).

Much of the available literature suggests that immigrant populations are at increased risk for congenital and acquired neurological disorders (DeGiorgio et al., 2005; Gill, Lenz, & Amolat, 2003; White et al., 2005; Zahuranec et al., 2006). Epilepsy is no exception. For example, while seizures are relatively common across all ethnic groups, Hispanic adults residing in the United States have a twofold higher incidence of this disorder than non-Hispanic US residents (National Conference on Public Health and Epilepsy, 2003). Epidemiologists attribute this disproportionately high percentage to an elevated prevalence of cysticercosis (DeGiorgio et al., 2005; Medina, Rosas, Rubio-Donnadieu, & Sotelo, 1990), birth trauma, traumatic brain injury, and stroke in Hispanic populations (Santiago-Grisoli, 2000). Although large-scale investigations of seizure-related risk factors have also been limited in non-Hispanic immigrant groups, cysticercosis and other parasitic diseases have also been implicated as having a significant etiological role in the development of seizure disorders diagnosed in African nations (Preux & Druet-Cabanac, 2005).

The elevated incidence of epilepsy in ethnically and culturally diverse immigrant groups necessitates increased attention to factors which intrinsically and extrinsically limit the reliability, validity, and utility of neuropsychological assessments in these populations. In order to fully address these concerns, it is first necessary to consider the role of culture-, language-, and immigration-specific variables throughout all aspects of the testing session, data interpretation, and case formulation. Although specific procedures may vary due to the patient's individual needs (e.g., surgical candidacy, language abilities, degree of bilingualism, mental and psychiatric status), the neuropsychological assessment of epilepsy patients typically includes the following: (1) clinical interview, (2) assessment of mental status and/or (3) estimation of premorbid

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abilities, (4) evaluation of intellectual functioning and specific neuropsychological abilities, (5) examination of behavioral and psychiatric functioning, and (6) assessment of health-related quality of life. Accordingly, the focus of this chapter is to address each component of the neuropsychological assessment, as enumerated above, by providing both a framework and practical recommendations specific to the evaluation of culturally and linguistically diverse populations with epilepsy and seizure disorders. While many of the specific examples will focus on the comparatively extensive body of literature describing Hispanic immigrants residing in the United States, results could generalize to other immigrant, non-native English-speaking populations.

The Clinical Interview

Prior to initiating interview and assessment, it is first necessary to consider the patient's unique worldview and sociocultural experiences. While this is an important step for all individuals undergoing a neuropsychological evaluation, regardless of race, ethnicity, or cultural background, research in the fields of sociology, psychology, and anthropology suggests that immigrant populations are at particular risk for developing cognitive schemas which could negatively impact their performance on testing. Specifically, shifts in ethnic identity, acculturative stress, and stereotype threat may limit the individual's willingness, desire, and capacity to fully participate in the testing experience. Although one's awareness of the presence and effects of these constructs is highly variable, the clinical interview represents the first opportunity that the clinician has to ascertain the patient's perspective and experiences.

Ethnic Identity

When individuals migrate from one nation or culture to another, there is a high likelihood that cultural and ethnic identity will change. Ethnic identity is the "felt belongingness" to a specific group that can be approached, avoided, or achieved by an individual (Caltabiano, 1984). In its simplest form, ethnic identity is a multidimensional affiliative construct, whereby a person views himself or herself (and others) as belonging to a specific ethnic or cultural group (Phinney & Rotheram, 1987). As a result, immigrants may delineate boundaries between "self" and "others" or "us" and "them" altering the dynamic between examiner-patient dyads, particularly in cases of differing ethnic identities. In general, the development and subsequent shift in ethnic identification can occur as early as 4–8 years of age, necessitating careful consideration in clinical settings. Clinicians should first attempt to establish ethnic identity based on the patient's viewpoint. For example, does a recent Korean immigrant self-identify as Korean, Korean-American, Asian, Asian-American, American, or another classification? Careful questioning is essential to establishing the patient's preferences, as well as any shifts in his or her ethnic identification post-emigration, in order to facilitate a greater understanding of the individuals' psychological needs.

Acculturation and Acculturative Stress

Ethnic and cultural identity are strongly related to the theoretical construct of acculturation, the process in which an individual belonging to cultural minority changes their behaviors, beliefs, values, or customs after coming into continuous contact with a "majority" or mainstream culture (Berry, 1980; Berry, Trimble, & Olmedo, 1986; Marin, 1992). The process of acculturation in immigrant populations is generally a fluid process during which the person may identify exclusively with their "home" (native country) culture, "host" (new country) culture, or a combination of both. Sociological studies suggest that this long-term, dynamic process is shaped by each person's unique immigrant experience and occurs at differing rates, even within the same families.

It has been widely suggested that the construct of acculturation is an important culture-specific

moderator of neuropsychological test performance among non-native US populations (e.g., Arnold, Montgomery, Castaneda, & Longoria, 1994; Boone, Victor, Wen, Razani, & Ponton, 2007; Harris, Tulsky, & Schultheis, 2003; Kennepohl, Douglas, Nabors, & Hanks, 2004). In a recent study evaluating the relationship between acculturation and neuropsychological functioning in a clinical neurological sample, Boone et al. (2007) reported that acculturation is a significant predictor of neuropsychological test performance and is not attenuated by the presence of psychiatric or neurologic illness. Although these investigators did not find acculturation to be a significant performance moderator of nonverbal neuropsychological test measures, others suggest that acculturation accounts for diminished performance on nonverbal measures of tactile perception, problem solving, motor speeds, and executive functioning (e.g., Arnold et al., 1994; Coffey, Marmol, Schock, & Adams, 2005).

Given the potential impact of acculturation on neuropsychological test performance, it is necessary to gather information via real-world proxies of this construct. While much of this information can be gathered during the interview process, several self-report rating scales or "acculturation instruments" can be used to quantitatively assess the extent that individuals have adopted and assimilated in various aspects of the dominant ("host") culture, as well as how much of the person's nondominant ("home") cultural traits have been retained (see Marin & Marin, 1992). Specifically, acculturation is most frequently measured by examining several proxy variables, including: (1) language preferences, (2) behavior, (3) knowledge, (4) cultural identity, and (5) values (Cortes, Rogler, & Malgady, 1994; Marin & Gamba, 1996). One such example is the Bidimensional Acculturation Scale (BAS; Marin & Gamba, 1996), a self-report inventory that assesses acculturation among Hispanics. This scale provides an acculturation score for two major cultural dimensions (Hispanic and non-Hispanic domains) which measures three language-related areas: (1) language use, (2) linguistic proficiency, and (3) electronic media. The BAS evaluates bidirectional changes in behavior that are central to the individual in both of these domains. Another instrument, the Short Acculturation Scale for Hispanics (SASH; Marin, Sabogal, Marin, Otero-Sabogal, & Perez-Stable, 1987), evaluates a broader range of acculturation-related constructs, including sociocultural relations. One advantage of the SASH is that its questions are presented in both English and Spanish, allowing for use with either bilingual or monolingual Spanish-speaking populations.

The process of acculturation can be the source of significant psychological turmoil for many immigrants, termed "acculturative stress." Berry (1980) proposes a model of acculturation which serves to explain the sources of stress based upon the individual's degree of participation in home (e.g., cultural maintenance) and host (contact participation) culture. In this two-dimensional model, individuals who subscribe to neither their home nor host culture are described as undergoing "marginalization" and are therefore at considerable risk for psychological and emotional distress. Similarly, those who maintain contact with their native culture and forgo participation in majority culture are considered "separated" or "segregated" and are also at increased risk for economic stressors (e.g., difficulty finding suitable employment, adequate housing, or sufficient income) and coping difficulties. Even individuals who assimilate with the host culture often do so at the expense of the long-standing cultural identity and beliefs. As a result, assimilation can be associated with guilt and unstable support systems within one's ethnic or cultural group. Optimized long-term outcomes (e.g., economic, social, psychological, and physical) are most often achieved with "integration," whereas cultural attitudes and mores are accepted from both home and host cultures. Although the direct relationship between acculturative stress and neuropsychological test performance has yet to be clearly established, clinicians are encouraged to consider its role in cases where their patients report feelings of isolation or in those who lack a support system of culturally similar peers. The Social, Attitudinal, Familial, and Environmental Acculturation Stress Scale (SAFE; Mena, Padilla, & Maldonado, 1987) is a useful tool for evaluat-

ing an individual's feelings of stress and perceived discrimination within Hispanic populations.

Stereotype Threat

Stereotype threat is another powerful psychological process with the potential to limit the validity and reliability of neuropsychological assessment with minority populations. Most often studied in the context of racial and gender differences, stereotype threat is a situational feeling or awareness of alleged intellectual inferiority, thereby creating anxiety and fear of confirming the possibility (Aronson et al., 1999; Aronson, Steele, Salinas, & Lustina, 1998; Steele, 1997; Steele & Aronson, 1995). Such increased anxiety may interfere with, and decreases performance on, tasks to which the stereotype applies. In their seminal study, Steele and colleagues (1997) assessed the performance of well-educated African-American young adults on difficult verbal items from the Graduate Record Exam; half of the sample was told that the task measured intellectual ability, and the others were informed that it was a laboratory problem-solving task. African-American students performed below their Caucasian peers with matched SAT scores when told that their scores were being used to measure intellectual ability, while African-American students in the non-ability condition performed equally to Caucasian students. In these cases, the salience of racial stereotypes to African-Americans depressed their score on measures of cognitive functioning. Similar findings have been reported in a sample of West Indian immigrants, who are typically perceived as Black in the United States (Deaux et al., 2007). Interestingly, while first-generation immigrants do not exhibit a decrease in performance on testing conditions which activate stereotype threat, US-born second-generation immigrants exhibited stereotype threat effects and a concomitant decrease in performance. Although it is difficult to gauge a patient's feelings of stereotype threat during the testing session, it is certainly a potential performance moderator that should be thoroughly guarded against, and its effects fully considered.

Cultural Competence and Respect for Cross-Cultural Differences

Beyond the impact of factors stemming from the patient's worldview and immigrant experiences, several variables *within* the testing room must also be considered prior to testing and interpretation. In an effort to provide optimum care to non-native US populations, neuropsychologists should strive to broaden their cultural competence through peer supervision, independent research, participation in continuing education, and/or journal clubs and by remaining abreast of current world events. Although a daunting and, at times, overwhelming prospect, the first step in raising a clinician's own level of awareness can be achieved by obtaining a basic understanding about the culture and history of the country from which each patient originates. In doing so, themes salient to a patient's degree of openness and willingness to provide an honest, complete history may emerge. For example, immigrants from countries recently engaged in warfare may hesitate to fully participate in the evaluation process due to concerns of retribution, stigmatism, and/or deportation.

The aforementioned research and study should, at a minimum, include a basic understanding of culturally based communication practices, interactional style, family structure, and taboos. Failure to consider the presence and impact of such social mores can lead to unintentional offenses which may interfere with fluid rapport. For example, in several cultures, being addressed by one's given name, rather than his/her surname, is indicative of disrespect. The use of titles (e.g., Mr., Mrs., Miss, Ms.), last name (*apellido*), hyphenated surnames (*apellidos* in Hispanic culture, e.g., Señora Rodriguez-Rivera, indicating the patient's mother's last name, Rivera, and father's last name, Rodriguez), and patronymics (e.g., Svetlana Grigorievna Lermontov, denoting that Svetlana is the daughter of Grigory) is unique to individual cultures and should be carefully studied and considered prior to assessment. Similarly, pronoun usage can be highly culture specific and reflective of status, rank, formality, and/or familiarity of a relationship;

the pronoun "you" in Spanish can differ to indicate the informality of a relationship, "*tú*" [used with children, family, and friends by most groups], or great respect, rank, and courtesy, "*usted*" [used with older adults and with professionals, such as teachers].

A patient's communication style is also largely governed by cultural practices and expectations. For example, individuals from Latino culture may often engage in *plática* or *platicar* (loosely translated as "small talk" in Spanish) upon introduction with a health-care provider (Ríos & Fernández Torres, 2004). In such scenarios, patients may initially discuss themes unrelated to their illness, such as the weather or traffic. Although many Western or European countries value communication efficiency, many areas in Latin America or Mexico would consider it rude or offensive to begin an interaction without such preliminaries. According to Davila and colleagues (2011), *plática* was shown to be instrumental when establishing empathetic relationships and facilitating cooperation in a focus group designed to evaluate the health behaviors of Spanish-speaking Hispanics. Anecdotal evidence further suggests that beginning clinical interviews with similar, non-health-related themes is useful for establishing rapport and a therapeutic alliance (M. Rodriguez-Rivera, personal communication).

Knowledge and awareness of cultural taboos are often important and necessary considerations in the assessment of culturally and ethnically diverse immigrant patients. Beyond the need to demonstrate respect of the patients' belief systems, understanding cultural taboos is also instrumental in gathering and contextualizing the historical information provided by the patient (and his or her family) during the clinical interview. Specifically, direct discussion of death, dying, or accidents can be considered "bad luck" in many Asian cultures (Wong, Strickland, Fletcher-Janzen, Ardila, & Reynolds, 2000). In such cases, an Asian patient's reluctance to discuss the history of present illness or his/her vague responses to health-based questions should not be potentially misinterpreted as the result of memory difficulties, emotional disturbance, or psychological resistance. To this end, a review of available medical records and/or a discussion with a family member, community elder, or patient representative may be a particularly important source of medically relevant information (e.g., seizure semiology and postictal sequelae) and seizure-related risk factors (e.g., traumatic brain injury and central nervous system infection). Similarly, non-verbal behaviors which a European-American clinician may view as his/her own expressions of keen interest, warmth, and sincerity (e.g., direct eye contact, body contact, hand shaking) can be construed as inappropriate by culturally dissimilar patients. For example, individuals from China may consider extended direct eye contact from a male examiner to be rude or sexual in nature towards females (Ivey & Ivey, 2003).

Consideration of the Patient's Family Structure

Family structure and hierarchy varies considerably across cultures and can reflect societies which are matriarchal, patriarchal, individualistic, or collectivistic. For example, Hispanic populations are largely collectivistic, valuing group needs and goals above one's own (Marin & Marin, 1991a, 1991b). *Familismo*, or the care and concern for a multigenerational, extended family network is frequently noted, whereas family members often take a high degree of responsibility in the day-to-day care and long-term planning of individuals with epilepsy. Neuropsychologists should be particularly mindful of the potential consequences of collectivistic culture or *familismo* during the clinical interview, as patients may rely heavily on family members for assistance and can often rely on them as behavioral and attitudinal referents (Marin & Marin, 1991a, 1991b). Accordingly, clinicians should take care as to not misinterpret diminished independence as reduced adaptive functioning or health-related decline. Moreover, family members, including those outside the "nuclear family," should be involved in the assessment process (where possible and with the patient's consent) and may be excellent collateral sources of information.

Selecting the Primary Language of Assessment

In large part because of its changing cultural landscape, America is also experiencing a collective shift away from the previously held assumption of English as the nation's primary "mother tongue." According to a recent US Census Bureau report, the number of people aged five and older who primarily speak a language other than English at home has doubled from 1980 to 2007 (US Bureau of the Census, 2007 American Community Survey). In that time frame, the percentage of non-English speakers has reportedly risen by 140 %; a dramatic increase compared to an overall population growth of 34 %. Spanish-speakers represent the largest numeric increase (23.4 million more speakers in 2007, as compared to 1980), whereas the Vietnamese-speaking population accounts for the largest percentage increase (an approximate 511 % rise in the same time frame).

While compelling, these statistics do not fully capture the degree of English-language proficiency or bilingualism in non-native US populations. Notably, it is relatively rare to encounter patients who are capable of functioning equally well in either language in each domain or activity (ambilingualism; Halliday, McKintosh, & Strevens, 1970) or who use both languages equivalent to monoglot speakers in their respective languages (balanced bilinguals). Rather, it is much more common for non-native English-speaking, particularly newly arrived immigrants, to demonstrate either monolingualism for their primary language (L1) or functional bilingualism. To this end, ascertaining an individual's degree of bilingualism is a critical aspect of the clinical interview of non-native English-speaking populations undergoing assessment in an epilepsy setting. Such information has important implications for the patient's obtained neuropsychological profile, and, by extension, the lateralizing value of the data and post-operative outcome. Direct questioning of the patient is necessary to establish the following information: (1) age of primary and secondary language acquisition, (2) setting in which secondary language was learned, (3) language spoken at home and in social settings, (4) primary language of education, (5) primary language spoken at current job, (6) language-related media preferences (e.g., television, radio, newspaper), (7) frequency that primary and/or secondary languages were spoken in recent months, (8) and patient's subjective sense of impairment in primary vs. secondary language (e.g., word-finding difficulties are more prominent in French (L1) than English (secondary language; L2). Only after obtaining such information can neuropsychologists plan an appropriate assessment strategy, including performing the evaluation in the patient's native language, in English only, or obtaining language-related measures in both languages. Should the latter option be selected, it is important to evaluate the patient's comparative level of abilities across languages by assessing functioning in all aspects of this construct, including word reading, reading comprehension, verbal fluency, confrontation naming.

The Neuropsychological Evaluation

While there is well-documented evidence for test bias in neuropsychological testing with culturally diverse, immigrant populations (Ardila, Rosselli, & Puente, 1994; Artiola i Fortuny & Mullaney, 1997; Gasquoine, 1999), further investigation is necessary to determine the presence of bias both at the level of test instrument (i.e., test construction and data interpretation) (Anastasi, 1988) and at the level of the individual (Arnold et al., 1994). Test bias, in this case, refers to any measure upon which non-native US-born individuals achieve lower scores than English-speaking Caucasians due to reasons other than neurological differences (Anastasi, 1988). From the former perspective, the overwhelming majority of neuropsychological tests used in the United States were designed by Americans, Canadians, or Europeans and may have a Eurocentric worldview and derivative psychometric technology (Trimble, Lonner, & Boucher, 1983). Although language-specific testing instruments obviate some of these concerns, test measures available in languages other than English are few in num-

ber and have relatively untested psychometric properties in clinical populations (Wong et al., 2000). It is important to recognize that in any assessment context, it is unwise to examine the validity, reliability, and sensitivity of data in isolation, that is, without considering the medical and experiential history of the individual. Interpretation and application of test data taken out of context may result in increased error variance.

The Use of Translated Test Materials

In cases where clinicians opt to use test measures which were translated from English (source text) into another language (target text), careful attention must be paid to the specific translation practices and procedures. The process of translatorship is a socially defined role, involving at least two languages and two cultural traditions, each of which is being governed by its own set of culture-bound standards of behavior (e.g., "norms") (Toury, 1980, as cited in Bender, García, & Barr, 2010). Inasmuch, translators can choose to subscribe to the norms of either the source or the target culture, thereby indicating the overall sociocultural relevance of the translation for the target audience. If the source culture is selected, as in the case of most neuropsychological test measures and practices, cultural and linguistic incompatibilities may occur, thus favoring *adequacy* of the source text. However, if the translator follows the target text, he/she will deviate from the source and will consequentially foster target-culture *acceptability.*

When selecting translated test materials, clinicians should attempt to evaluate the balance between acceptability and adequacy. For example, concern has been raised regarding linguistic equivalence of the phrase "no ifs, ands, or buts," across multiple languages. When translated from English into another language, this Folstein Mini-Mental Status Exam (Folstein, Folstein, & McHugh, 1975) item must possess an equivalent number of function words, a comparable mixture of vowels and consonants (e.g., the word "gymnasium" in English is "*гимнастический зал*" in Russian, pronounced "geem-nas-ti-che-skii-zall," a much longer, consonant-dense word which is more difficult to pronounce than the English version) and a similar idiomatic meaning in order to evaluate the underlying abilities in the same manner the original does. Although several alternative Spanish-language phrases have been suggested, including "*No hay pero que valga*" (There is nothing that is not of worth; as cited in Valle, 1990), "*Si no bajo, entonces me subo*" (If I do not go down then I will go up; as cited in Valle, 1990), and "*Él quiere irse a casa*" (He wants to go home; Teng et al., 1994), they lack comparable frequency and pragmatic ease.

To obviate similar problems, a French translation of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) battery substituted "no ifs, ands, or buts" with the phrase, "*pas de si ni de mais*" (literally translated as "neither yes, nor but" or, more loosely as "no ifs or buts"), as this phrase preserves the overall meaning and the grammatical categories of its constituents, and it also serves to evaluate the same cognitive and articulatory functions as Geschwind's original phrase (e.g., articulatory agility, comprehension, and presence of paraphasias in repetition; Demers et al., 1994).

Neuropsychological test translation is further complicated by transliterated words (e.g., "laundromat" or "launderette" are referred to as "*washatería*" by Mexican populations residing in Texas or "*el londri*" for Hispanic individuals residing in Los Angeles; Pontón & Ardila, 1999) or those that are region- or country-specific (e.g., the word "bus" is most commonly referred to as "*autobús*" in Spain, "*camión*" in Mexico, and "*guagua*" in Cuba, Canarias, and Antillas). When translating the Boston Naming Test (CERAD version) into French, test translators acknowledged differences in intracultural salience of a picture of a canoe to French-speaking Canadians, as compared to the French population residing in France (Demers et al., 1994). To this ENP, test makers should consult multiple translators from a variety of communities speaking derivatives of the same official language (e.g., French text translated by professionals in French-speaking Canada, Haiti, France, Belgium, and the Republic of the Congo)

to resolve such sociocultural disparities (American Psychiatric Association, 2000). Information detailing translation procedures, including those used to minimize region-specific dialectical differences and colloquialisms, should be provided in the test manual. Prior to using such test measures, neuropsychologists should critically evaluate these processes in relation to the needs and abilities of their individual patients.

Assessment of Mental Status and Estimated Premorbid Abilities

The following subsection will provide brief descriptions of measures of mental status and general intellectual functioning appropriate for culturally and linguistically diverse epilepsy patients. Of note, many of the tests described herein are appropriate for Hispanic populations, as multiple instruments have been developed or translated for use with Spanish-speakers.

The Cognitive Abilities Screening Instrument

The Cognitive Abilities Screening Instrument (CASI) is a brief measure of mental status developed for use with geriatric populations of varying levels of education and literacy (Teng et al., 1994). Scored out of a possible 100 points, this instrument includes items assessing orientation, attention, concentration, abstraction, repetition, visuospatial reproduction, naming, verbal fluency, handwriting abilities, judgment, remote memory, new learning, and delayed recall. The CASI has been translated into multiple languages, including Japanese, Chinese, Vietnamese, and Spanish. Test authors have reportedly modified standard mental status items (e.g., the repetition item, "no ifs, ands, or buts," was substituted for the more linguistically salient Spanish-language item "*Él quiere irse a casa*," which means "he wants to go home;" Teng et al., 1994). The clinical utility of the CASI has been well validated throughout dementia literature among international studies of community-based samples (Graves et al., 1996; Liu et al., 1994; Tsai, Lin, Wang, & Liu, 2007). In addition to its broad appeal, another advantage of the CASI is that it can be used to estimate scores on other more commonly administered clinical measures (i.e., the Mini-Mental State Examination, Modified Mini-Mental State Test, and Hasegawa Dementia Screening Scale).

Neuropsi

The NEUROPSI (Ostrosky-Solís, Ardila, & Rosselli, 1997, 1999) is an extended mini-mental evaluation which was developed for and normalized in Spanish-speaking adults. Among one of the only assessment measures created directly in Spanish rather than translated from another source language, the NEUROPSI includes measures of orientation, attention, concentration, executive functioning (e.g., categorization and abstraction), visuomotor skills, language skills (e.g., naming, repletion, fluency, and comprehension), memory (e.g., immediate and delayed recall and visual-nonverbal functioning), reading, writing, and calculation. Task items on the NEUROPSI were designed to be completed by individuals with a broad range of literacy, socioeconomic status, and educational attainment. In this vein, language-based items include high-, medium-, and low-frequency Spanish-language words. Also of note, the authors of the NEUROPSI sought to maximize the cultural salience of concepts underlying task items. For example, unlike other available mental status examinations or dementia-rating scales, the NEUROPSI does not include an item asking for the season of the year in order to assess the patient's orientation; the concept of a "season" may be less clearly defined in tropical areas or may refer to a wet season or a dry season. The NEUROPSI was normalized on a sample of 800 Mexican individuals aged 16–85 years (i.e., 16–30 years, 31–50 years, 51–65 years, and 66–85 years).

Developed by the same team of investigators, the NEUROPSI Attention and Memory test (Ostrosky-Solís et al., 2003, 2007) is a Spanish-language instrument which assesses attentional, executive, and memory abilities. Specific items tapping attention and executive abilities include

assessment of alertness, orientation, supraspan, vigilance, selective attention, mental flexibility, concept formation, and inhibitory control. Immediate memory and delayed recall are also assessed in visual and verbal modalities.

Word Accentuation Test

The initial Spanish version of the National Adult Reading Test (NART; Nelson, 1982), the Word Accentuation Test, can be used as an estimate of premorbid intelligence (Del Ser, Gonzalez-Montalvo, Martinez-Espinosa, Delgado-Villapalos, & Bermejo, 1997).

First validated in Spain, more recent versions were adapted and normalized for Spanish-speaking individuals residing in Argentina (Burin, Jorge, Arizaga, & Paulsen, 2000) and the United States (Schrauf, Weintraub, & Navarro, 2006). This measure consists of a list of 30 low-frequency words printed without their corresponding accent (e.g., "moare" is written without the accented "é." It means a type of silk material) and requires examinees to add the accent by verbally placing the stress on the correct phoneme. To do so, individuals must possess both word-specific knowledge and awareness of the rules of accentuation (e.g., which syllable requires a lexical stress, which necessitates an accent). Del Ser and colleagues (1997) reported that the WAT has strong correlations with the Spanish (Spain) version of the WAIS (e.g., Vocabulary subtest *r*, 0.842 and Picture Completion *r*, 0.722). Regression equations are provided for estimating Batería Woodcock-Muñoz Revisada (BWM-R) and Ravens Progressive Matrices scores from WAT scores (Schrauf et al., 2006).

Measures of Nonverbal Intelligence

Ravens Standard Progressive Matrices (SPM; Raven, Raven, & Court, 1993) is one of the most widely administered measures of nonverbal reasoning and estimated premorbid intelligence in the world. For each of the 60 test items, examinees are required to correctly select one of the multiple-choice options in order to complete a pattern within an organized matrix. This measure assesses one's ability to form perceptual relations and to reason by analogy independent of language and education. Despite being widely identified as a "culture-fair" test measure, multiple studies have demonstrated differences on RSPM performance based on race and ethnicity (Lynn, Backhoff, & Contreras, 2005; Rushton & Jensen, 2005).

Like the RSPM, the Comprehensive Test of Nonverbal Intelligence (CTONI; Hammill, Pearson, & Wiederhold, 1997) is a measure of nonverbal reasoning (i.e., analogical reasoning, categorical classifications, and sequential reasoning) which requires limited spoken language or motor skills. Appropriate for individuals aged 6 through 90, the CTONI consists of six subtests: pictorial analogies, pictorial categories, pictorial sequences, geometric analogies, geometric categories, and geometric sequences. The resultant data yield three composite indices, Nonverbal Intelligence Quotient (NIQ), Pictorial Nonverbal Intelligence Quotient (PNIQ), and Geometric Nonverbal Intelligence Quotient (GNIQ). The Test of Nonverbal Intelligence-3 (TONI-3; Brown, Sherbenou, & Johnsen, 1997), a 50-item test which takes approximately 15 min to administer, can be similarly used as an estimate of premorbid intellectual abilities. Raw scores of are then converted to Deviation Quotients with a mean of 100 and an SD of 15; the TONI-3 manual indicates that non-native English speakers (i.e., English as a second language), African-American individuals, and Hispanic persons obtained average scores of 93, 95, and 96, respectively.

Evaluation of Intellectual Abilities

More comprehensive assessments of intellectual functioning are often warranted when performing neuropsychological evaluations with epilepsy patients. Notably, such measures can be used to more accurately assess premorbid intelligence, identify areas of strengths and weaknesses, track performance from a neurocognitive baseline, and as a prognostic indicator of post-surgical outcomes.

Escala de Inteligencia de Wechsler para Adultos

The *Escala de Inteligencia de Wechsler para Adultos* (EIWA; Wechsler, Green, & Martinez, 1968) is an adaptation of the original version of the Wechsler Adult Intelligence Scale (WAIS) which was normed on 616 Puerto Ricans, ranging in age from 16 to 54 years. Although the development of the original EIWA represented an important first step in the assessment of Spanish-speaking persons, it has been widely criticized for having questionable psychometric properties and a restricted standardization sample (e.g., Lopez & Taussig, 1991; Melendez, 1994). Of note, significant performance disparities emerged among bilingual individuals (Spanish/English) administered both the WAIS and the EIWA (Melendez, 1994). Perhaps most strikingly, cognitive functioning in non-English-speaking Hispanics was shown to be underestimated by the WAIS-R but overestimated using the EIWA, whereas WAIS-R subtests indicated cognitive impairment in neurologically healthy Spanish speakers, and the EIWA subtests suggested less cognitive impairment in participants with Alzheimer's disease (Lopez & Taussig, 1991). Attempts were made to develop a "short form" of the EIWA, similar to the English-language Wechsler Abbreviated Intelligence Scale (WASI), by using derivations of 2–5 of the existing subtests; however, many of these combinations lacked the ability to calculate verbal and performance IQs (Demsky, Gass, Edwards, & Golden, 1998). Moreover, none of the brief forms with strong reliabilities and validities (0.95–0.98) included Object Assembly, Digit Span, and Digit Symbol Coding; the latter two subtests are known to be potential areas of weakness in epilepsy patients.

More recently, several revisions and updates of the EIWA have been published to address many of the aforementioned concerns. The *Escala de Inteligencia de Wechsler para Adultos—Tercera edición* (EIWA-III; Wechsler, 2004, 2008) was published with specific considerations and modifications appropriate for Puerto Ricans. Developed in collaboration with the Ponce School of Medicine in Puerto Rico, the EIWA-III possesses improved psychometric properties, extended "floors" for lower functioning patients, and a reduced administration time. A version of the WAIS-III has also been developed for individuals from Spain (TEA Ediciones, 2001); this version of the EIWA-III was normed on 1,369 subjects representative of the adult population of Spain in the late 1990s.

Assessment of Neurocognitive Domains

The goals of evaluations aimed solely at characterizing seizure focus have considerable overlap with those conducted in preoperative contexts, as test data are interpreted to assess functional brain status in populations with epilepsy and, by extension, lateralize a resectable region of cortex responsible for seizure onset (Loring, 1997). Inasmuch, neuropsychologists administer domain-specific tests with relevance to hemispheric lateralization and functional postoperative outcome (e.g., language, visuospatial processing new learning, and delayed recall) (Jones-Gotman, 1991). Briefly, it is believed that when the left hemisphere is dominant, left-sided seizure focus is identified by a relatively consistent material-specific deficit in verbal abilities (e.g., naming, verbal fluency) and verbal declarative memory (Jones-Gotman, 1991). Right-sided lesions (again, in patients with left hemisphere dominance) typically correlate with poor visuospatial skills (e.g., visuospatial construction, visual abstract reasoning) and nonverbal memory deficits. At times, a clear pattern of material-specific deficits in language or memory-related abilities emerge during preoperative assessments, thereby suggesting the side of epileptogenesis (Buelow & McNelis, 2002; Loring & Meador, 2001; Milner, 1975).

While there is a considerable, albeit inconsistent, body of literature evaluating the predictive power of material-specific patterns of neuropsychological deficit in lateralizing seizure focus in English speakers, comparably few investigations have studied the efficacy of neuropsychologically predicted lateralization in non-US-born, non-native English-speaking individuals with

epilepsy. Yet, it is well known that a variety of methodological and ecological factors place ethnic minorities at an inherent disadvantage on testing, when compared to monolingual Anglo-Americans, resulting in considerable performance disparities (Ardila et al., 1994; Rosselli, Ardila, & Rosas, 1990). Clinically, consistently low scores, which may or may not reflect the patient's true level of cognitive functioning, can result in an overestimation of cognitive impairment in non-native English-speaking minorities. Therefore, the risk of misdiagnosis is great. The subsequent subheadings will introduce three linguistically appropriate test batteries (e.g., NeSBHIS, RBANS-SRE, and the CCNB) and several domain-specific measures with the potential to yield the breadth and quality of neuropsychological test data necessary for the diagnostic decision-making and treatment planning of epilepsy patients.

The Neuropsychological Screening Battery for Hispanics

The Neuropsychological Screening Battery for Hispanics (NeSBHIS; Pontón et al., 1996) was specifically developed to address the fundamental lack of resources available for use with Spanish-speaking Hispanics. Based on a battery of tests first used by the World Health Organization (Maj et al., 1993, 1994), the NeSBHIS assesses several neurocognitive domains, including language, memory, mental control, psychomotor speed, visuospatial functioning, and nonverbal reasoning. The principal advantage of the NeSBHIS is that it is one of the limited few to provide normative data stratified by age, gender, and education using a moderately large (N = 300) standardization sample of community-referred, Spanish-speaking Hispanics. According to the findings of Pontón, Gonzalez, Hernandez, Herrera, and Higareda (2000), the NeSBHIS has a stable factor structure, indicating that this battery adequately measures the putative neuropsychological domains that it was designed to assess. The following five distinct factors emerged: (a) language (as measured by the *Escala de Inteligencia Wechsler para Adultos* [EIWA] Digit Span subtest, Pontón-Satz Boston Naming Test, and the Controlled Oral Word Association Test), (b) verbal learning (World Health Organization—UCLA Auditory Verbal Learning Test final learning, short-delay free recall following a distracter, and 20-min delayed recall trials), (c) attention-mental control (EIWA Digit Symbol and Block Design subtests, as well as Color Trails 1 and 2), (d) visuospatial (Rey-Osterrieth Complex Figure Test—Copy and Delayed Recall scores, as well as the Ravens Standard Progressive Matrices), and (e) psychomotor (Pin Test) (Osterrieth, 1944).

The construct validity of the NeSBHIS was recently evaluated in a sample of Spanish-speaking epilepsy patients with Grooved Pegboard substituted for the Pin Test. (Bender et al., 2009a, 2009b). Specifically, data were analyzed using confirmatory factor analysis with the a priori assumption that variables would load according to the theoretical expectations enumerated above (Pontón et al., 2000). Findings indicated that overall model fit indices were in the desired range: Comparative Fit Index = 0.936, Tucker Lewis Index = 0.915, RMSEA = 0.090, and SRMR = 0.069. Furthermore, all NeSBHIS subtests were found to load significantly ($p < 0.001$) on their respective factors; the standardized loadings were high, ranging from 0.562 to 0.995, with the exception of Block Design (−0.308). These findings suggest that the NeSBHIS has robust construct validity in a sample of Spanish-speaking epilepsy patients; all participants were evaluated at New York University Medical Center's Comprehensive Epilepsy Center, a tertiary care setting in the Northeastern United States. The diagnostic utility of the NeSBHIS for use with Spanish-speaking epilepsy patients was also evaluated by Barr et al. (2009). Overall, over 40 % of participants exhibited impairment (as defined as scores >2 standard deviations below the normative mean) on measures of naming and processing speed. Similar deficits were observed in 29 and 26 % of the sample on measures of verbal and visual recall, respectively. The obtained profile of impairment suggests that the NeSBHIS is sensitive to identifying cognitive impairments commonly seen in patients with epilepsy. However, there may be some limitations to this battery's sensitivity to identifying deficits in

patients with lateralized temporal lobe seizures, whereas no significant differences in test performance were observed between patients with video-EEG evidence of left ($N = 48$) versus right ($N = 24$) temporal lobe epilepsy.

Although the NeSBHIS represents a significant advancement in Spanish-language neuropsychological assessment, stringent inclusionary criteria were applied to the sample of healthy volunteers (e.g., participants were free of neurological or psychiatric disorder, head trauma, and/or substance use), thereby potentially limiting its generalizability to clinically and psychiatrically referred patient populations. Furthermore, future studies are necessary before utilizing this battery with a geographically heterogeneous sample of Spanish speakers. According to Pontón et al. (1996), participants included in the NeSBHIS reference group originated from the following Spanish-speaking world regions: Mexico—62 %, Central America—15 %, and "Other"—23 %. Though the composition of the NeSBHIS normative sample was representative of the Hispanic population (by place of origin) in 1992, these data are not indicative of the current cultural characteristics of the Hispanic population across the United States today. For example, the percentage of Hispanic individuals from Mexico and Puerto Rico differs greatly between New York (Mexico, 9.1 % and Puerto Rico, 36.63 %) and California (Mexico, 77.11 % and Puerto Rico, 1.28 %). More broadly, the proportion of Mexican and Puerto Rican immigrants residing in the Northeastern states (e.g., Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont) varies considerably from the other geographic regions of the contiguous United States. Accordingly, while the NeSBHIS reference groups are, and continue to be, representative of Hispanic population residing in much of the United States, the normative data provided by Pontón et al. (1996) may not accurately reflect the "standard" performance of a Northeastern, predominantly Puerto Rican sample of Spanish speakers. Accordingly, caution should be used when administering the NeSBHIS to Hispanic epilepsy patients who immigrated from countries other than Mexico.

Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998a, 1998b) is a 35–50-min neuropsychological test battery often administered in inpatient settings due to its brief administration time. Furthermore, It is a useful tool in hospitals and clinics because it has parallel forms, allowing NP functioning to be tracked serially over time. IT was designed to evaluate the domains of attention, language, visuospatial/visuoconstructional abilities, learning, and delayed memory. The twelve subtests of this battery generate five index scores, as well as an overall total score.

The RBANS has been translated into Spanish by the test developers (Repeatable Battery for the Assessment of Neuropsychological Status—Spanish Research Edition; RBANS—SRE; Randolph, 1998b), and back translation has been independently verified by multiple native Spanish speakers with extensive neuropsychology training (Barr, personal communication). Preliminary evaluation the Spanish-language RBANS suggests that this battery is useful in identifying impairments that are frequently observed in populations with epilepsy, such as reduced confrontation naming, new learning, delayed verbally and visually mediated recall. However, these observed findings may be an artifact of test bias. In an investigation evaluating 42 Spanish speakers with epilepsy administered the RBANS-SRE and 45 age- and education-matched English-speaking epilepsy patients administered the RBANS, (Bender et al., 2009b) significant performance differences were observed on the Language Index ($p \leq 0.05$), Picture Naming ($p \leq 0.01$), and Digit Span ($p \leq 0.05$); linear trends were also noted on the line orientation and list recall subtests (both $p \leq 0.10$). Although diminished performances obtained using the RBANS-SRE may be attributed to the lexical dialectical issues discussed throughout this chapter, such factors cannot explain the disparities on Digit Span or line orientation subtests. Rather, it is important to note that the RBANS-SRE lacks unique norms for Spanish speakers; the English-language

standardization sample is used to normalize this measure regardless of the language of administration. Until a Spanish-language normative sample can be collected, the results of the RBANS-SRE should be interpreted with extreme caution. In the interim, raw scores should be used in situations where neuropsychological testing is needed to track changes from baseline or to compare pre- and postoperative functioning.

Cross-Cultural Neuropsychological Test Battery

The Cross-Cultural Neuropsychological Test Battery (CCNB, as discussed in Dick, Teng, Kempler, Davis, & Taussig, 2002) was developed to assess a broad range of cognitive functioning in five racially, culturally, and/or linguistically diverse populations (i.e., African-American, Caucasian, Hispanic, Vietnamese, and Chinese individuals). Taking 90 min to administer, the CCNB is comprised of 11 subtests, assessing functioning in six domains, including: attention (i.e., WAIS-R Digit Span), reasoning ability (i.e., Modified Picture Completion), language (i.e., Body Part Naming, CERAD category fluency for animal naming, and Auditory Comprehension), visuospatial skills (i.e., Read & Set Time, CERAD Drawing, WAIS-R Block Design), psychomotor speed (i.e., Trail Making Test, Part A), and recent memory (Common Objects Memory Test, including 3 learning trials, 3–5-min recall, 30-min recall, 5-min recognition, and 30-min recognition). Of note, the CASI (see the *Assessment of Mental Status and Estimated Premorbid Abilities* subheading) is a component of the CCNB.

Although the CCNB represents an admirable effort to design a battery of "culture-fair" test measures, both education and ethnicity were shown to significantly effect performance on several of the subtests. According to Dick and colleagues (2002), education accounted for approximately 15 % of the variance among scores. While ethnicity was not found to account for as much variance, it was still shown to significantly impact performance on animal fluency, the CERAD drawing task, and the WAIS-R Digit Span. As a whole, Hispanics included in the normative sample obtained lower scores on the Digit Span and animal fluency subtests than all other groups. Moreover, scores on the Body Part Naming, WAIS-R Digit Span, and Trail Making Test did not accurately distinguish neurologically healthy Hispanic older adults from those with cognitive impairment. Also, as a stand-alone measure, the CCNB is not appropriate for the comprehensive assessments typically administered in an epilepsy setting, as this battery does not assess verbal learning, verbal delayed recall, and confrontation naming, each of which is a potential area of impairment in individuals with seizure disorders, regardless of language and/or country of origin (e.g., Campos-Castelló & Campos-Soler, 2004; Elger, Helmstaedter, & Kurthen, 2004; Jones-Gotman, 1991; Lippé & Lassonde, 2004; Loring, 1997).

Tests of Language Abilities

Measures evaluating expressive language are particularly susceptible to sociocultural bias. While confrontation naming tasks have been widely recognized as being among the most sensitive for identifying and quantifying language impairment, they are also some of the most difficult to maintain equivalence between the elicited verbal responses in the source language versus the target language. Thus, it is important for clinicians to maintain awareness of potential effects of these dialectal lexical differences, as different terms may be culturally salient to specific world regions. For instance, the terms "*cometa*," "*papalote*," "*chiringa*," and "*barrilete*" are all technically correct Spanish-language responses to a line drawing of a kite presented on a confrontation naming test (as presented on the Repeatable Battery for the Assessment of Neuropsychological Status—Spanish Research Edition; RBANS—SRE; Randolph, 1998b). While extant Spanish-language confrontation naming subtests (e.g., the Pontón-Satz BNT; Pontón et al., 1992) provide multiple responses to each test item, it would be nearly impossible to provide every potentially correct response in

all regional dialects of Spanish (e.g., with most notable differences occurring between Peninsular Spanish and Spanish of the Americas). In such cases, phonemic cueing provided to patients after an obvious failure (e.g., when the response for "*latch*" is supplied by the patient as "diving board") becomes nothing more than a culturally based "guessing game" when judging which initial phoneme to provide. It is highly unlikely that even fully bilingual neuropsychologists have the knowledge and language ability required to consider all existing correct synonymous options for each test item administered. Although standardized administration practices dictate that points can only be awarded for correct responses provided in the manual, clinicians should factor in the role of dialectical differences when interpreting the obtained test data.

The role of dialectal lexical differences should also be considered when evaluating the appropriateness and applicability of test instructions and their meaning for each individual patient. For example, subtest instructions provided for the RBANS—SRE (Form A) Semantic Fluency subtest have the potential to affect test performance and interpretation of derivative test data. The instructions for this test are as follows: "*Ahora quiero que me diga todos los nombres de los diferentes tipos de frutas y verduras que pueda recordar.*" Although the comparable instructions provided with the English version of the RBANS (Harcourt Assessment, 1998) require examinees to "…tell [me] all the names of all different kinds of fruits and vegetables that you can think of," the Spanish-language text, provided above, is not semantically equivalent. Rather, the Spanish word "*verduras*" indicates to examinees that they should provide semantic exemplars from a specific subset of comestible plant life, rather than the more general, all encompassing category of "vegetables." According to the Real Academia Española's *Diccionario de la lengua Española—Vigésima segunda edición* (2003), "*verduras*" is defined as "vegetables, especially leafy greens." The difference between instructions may result in reduced semantic fluency among Spanish speakers, stemming from the additional cognitive burden as compared to English speakers who are able to provide exemplars from a broader semantic category. Although region-specific standardization samples and base rates would obviate much of these concerns (i.e., reduced verbal fluency produced by Puerto Ricans given instructions "*verduras*" would not confer as great a disadvantage if the normative sample and base rates of impairment reflected the additional difficulty of this subtest), most translated subtests do not possess local normative samples which are unique to world regions or country of origin.

Test de Vocabulario en Imágenes Peabody

Test de Vocabulario en Imágenes Peabody: Adaptación Hispanoamericana (TVIP; Dunn, Padilla, Lugo, & Dunn, 1986) is a Spanish-language version of the Peabody Picture Vocabulary Test, a widely administered measure of receptive vocabulary. For each of the 125 items, participants are shown four line-drawn pictures and are asked to select the picture which best describes the word provided by the examiner. According to test developers, all TVIP items were selected through careful item analysis to maximize their universality and cultural appropriateness for Spanish-speaking populations. The TVIP possesses two major advantages over other tests of language abilities, as this measure does not require spoken language from the participant, and it possesses normative samples that are specific to Mexican and Puerto Rican examinees, as well as to Hispanics who originate from, or reside in, other world regions (e.g., *Compuestas*) While this "compuestas" normative group is a thoughtful attempt at improving linguistic appropriateness, it is akin to developing one unified set of norms for individuals residing in the U.S., Belize, Nigeria, New Zealand, Singapore, and Ireland, as English is considered to be the primary language spoken in each of these countries.

Pontón-Satz BNT

Although naming is one of the most fundamental functions of language, confrontation naming has long been recognized as one of the most sensitive

tasks for identifying and quantifying language impairment (Neils et al., 1995). In a well-designed study, a moderate-sized sample of young, well-educated bilingual adults were administered the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) in both English (L2) and their native language, Spanish (L1) (Kohnert, Hernandez, & Bates, 1998). Surprisingly, higher scores were obtained in the English-language administration, rather than the Spanish-language administration. Khonert and colleagues (Kohnert et al., 1998) posited that the difference in word frequency across languages was one possible explanation for their findings (i.e., the word "funnel" is a higher-frequency word in English than the Spanish word "*embudo*"). Methodologically, it is important to note that the aforementioned sample was comprised of well-educated subjects who were educated almost entirely in English. The results may have been strikingly different had the authors chosen to study a less-educated and less-acculturated sample. These data underscore the need to obtain detailed cultural-linguistic information (e.g., onset and trajectory of L1 development and L2 acquisition, acquisition setting, proficiency level of each language, and language of education) and acculturation during the clinical interview.

As stated elsewhere, bilingual individuals with epilepsy undergoing neuropsychological assessment, particularly surgical candidates, often require language testing in both their primary and secondary languages. Gomez-Tortosa, Martin, Gaviria, Charbel, and Asuman (1995) report a case study of a 25-year-old bilingual woman undergoing testing prior to surgical resection of an arteriovenous malformation (AVM) in the left presylvian region. The patient immigrated from a Spanish-speaking country at the age of 10, receiving the majority of her education in English, her second language. As a graduate of a US high school, the patient was believed to be a "proficient bilingual" preoperatively. An abbreviated, 30-item BNT was administered in Spanish prior to surgery; the English-language BNT was not administered. Both Spanish and English administrations of the BNT were administered postoperatively. These data revealed that the patient's performance on the English-language BNT (44 out of 60 pictures were correctly identified) was superior to her Spanish-language naming abilities (32 out of 60 pictures were correctly identified); an additional four responses were considered to be phonemic paraphasias. Although the patient's diminished Spanish-language naming abilities were assumed to be the direct result of the resection of the AVM (presumably leaving substrates underlying English naming abilities intact), it is difficult, if not impossible, to draw such conclusions without an adequate baseline in both languages.

Administered as part of the NeSBHIS battery, the Pontón-Satz Boston Naming Test (P-S BNT; Pontón et al., 1992) is the 30-item Spanish-language equivalent of the 60-item English-language BNT; the Spanish-language adaptation also differs in presentation order from the standard BNT. Culturally loaded items for Hispanics (e.g., "pretzel" and "beaver") and stimuli with ambiguous or multiple dialectical variations were also excluded to promote cultural and linguistic relevance.

Measures of Verbal Fluency

Measures of verbal fluency are typically key components to the evaluation of epilepsy patients and are frequently shown to be an area of weakness in this poplication. That said, assessment of verbal fluency is susceptible to test bias due to several linguistically, demographically, and culturally mediated variables, including lexical or dialectical differences, age, level of education, bilinguality, and gender (Bender et al., 2009a, 2010; Bethlehem, de Picciotto, & Watt, 2003; da Silva, Petersson, Faisca, Ingvar, & Reis, 2004; Ostrosky-Solís, Gutierrez, Flores, & Ardila, 2007). In a recent study, Ostrosky-Solís, Gutierrez, et al. (2007) conducted an investigation to determine the contribution of age, education, and Spanish-speaking country of origin (e.g.., Mexico, Spain, Argentina) on semantic verbal fluency. Although significant performance differences reportedly emerged between countries, much of the disparity was attenuated when age and education were considered. Beyond the

variability in age and education, Ostrosky-Solís, Gómez, et al. (2007); Ostrosky-Solís, Gutierrez, et al. (2007) suggested that the observed differences may be the result of administration and scoring differences. They recommended utilizing a standardized set of instructions (e.g., "I am going to ask you to mention all the names of animals that come to mind, you have 1 min, and I am going to tell you when to stop"). Furthermore, items should receive full, one-point credit if the following criteria are met: (1) the name provided is one of an animal (e.g., actual, extinct, imaginary, or mythical animals); (2) the animal does not belong to a supraordinate category (e.g., fish); (3) the animal(s) is not a different breed of the same species (e.g., beagle, Chihuahua, fox terrier); or (4) animals do not belong to an interspecies variation (e.g., horse/mare).

Language-related bias on a verbal fluency measures may also arise secondary to cross-cultural variations in the phonological structure of words and the amount of effort necessary to produce a single word (i.e., the *word length effect*). Speakers of languages with more multisyllabic words may be at a disadvantage, due to the longer amount of time it takes to produce each word (e.g., Escandell, 2002; Kempler, Teng, Dick, Taussig, & Davis, 1998). To illustrate, the word "orange" in Russian is *Оранжевый*, pronounced *a-ran-zhi-viy*, which is a 4-syllable word. The Spanish the word for "orange" is *naranja,* a 3-syllable word, as compared to the 2-syllable word in English. Based on this example, when asked to rapidly produce exemplars to the category of "fruit," neurologically healthy Russian speakers would ostensibly be able to provide fewer words than their Spanish-speaking counterpart, who, in turn, would be able to generate less words than their English-speaking peer in a 1-min period of time, due solely to the longer length of each word and the amount of time each word requires to produce. Moreover, the impact of the word length effect on Digit Span subtests should also be carefully considered; although English requires the working memory abilities to hold single-digit, single-syllable number in mind (with the exception of the two-syllable number "seven"), administration of this subtest in other languages necessitates single-digit, multisyllable words (e.g., the number "4" is three syllables in Russian). Although language-specific normative sampling would obviate much of these concerns, such data is unavailable for most culturally and linguistically diverse populations.

Tests of Visuospatial Functioning

Assessment of visuospatial functioning is of particular importance when assessing non-native English-speaking epilepsy patients. Specifically, a profile of lateralized deficit whereas visuospatial skills are more impaired than verbally mediated skills (e.g., ideally indicating right hemisphere pathology), in cultural and linguistic minorities may be is presumably more reliable and valid than data indicating a left hemisphere lateralization (i.e., language problems > visuospatial problems), due to the widespread test biases confounding performance on language-based tasks. However, multiple anthropological and psychological investigations have demonstrated that culture can affect the development of non-verbal skills, such as perceptual and constructional abilities (cf. Ardila, 2005; Ardila & Moreno, 2001; Berry, 1979). Yet, in neuropsychology, our understanding of the cognitive disturbances that are pathognomonic for underlying neuropathology is largely based on a very limited and heterogeneous subgroup of world cultures, namely, Western, urbanized, middle-class, literate, brain-damaged individuals (Ardila & Moreno, 2001). To this end, clinicians should contextualize their patient's performance on visuospatial skills, just as they would on tests of verbal materials—on a *case-by-base* basis by considering previous exposure and cultural relevance.

Among the first studies implicating cultural differences in visuospatial abilities is the landmark study by Gay and Cole (1967) in which Kpelle farmers were compared to working-class Americans on a cognitive estimations task; farmers were considerably more accurate in visually estimating the amount of rice presented on bowls

of different sizes containing varying amounts of rice. A similar, much more recent evaluation of the Aruaco Indians, an indigenous population residing in Colombia (Ardila & Moreno, 2001), further underscores performance disparities on visual tasks, such as the Wechsler Intelligence Scale for Children-Revised (WISC-R) Block Design subtest (Spanish-language administration), the Rey-Osterreith Complex Figure Test (ROCFT), Recognition of Overlapped Figures, and the Ideomotor Praxis Test. Specifically, 15 % of the participants studied, those with no formal education and very low levels of Western acculturation, were "virtually unable" to draw a cube or copy the ROCFT, as they had never used a pencil before or had they engaged in any drawing or copying activity. Although considerable difficulties were also noted on the WISC-R Block Design subtest (i.e., each of these participants received a score of zero), performance on the Overlapped Figures and Ideomotor Praxis tests were nearly perfect. Ardila and Moreno (2001) posit that the pencil-based tasks, and those reliant on time, lacked meaningfulness to the less-acculturated Aruacos, whereas tasks evaluating the functions which underlie their activities of daily living (e.g., visual discrimination and motor coordination which are required to hunt) were much more successful.

Both the NeSBHIS and the RBANS include measures of visuospatial construction and perception (i.e., Ravens Standard Progressive Matrices (RSPM), ROCFT, RBANS Figure Copy and RBANS Line Orientation); however, the extent to which these tasks are affected by cultural factors is largely unclear, particularly in clinical populations. A recent study by Saez et al. (2008) examined the relationship between acculturation and visuospatial/visuomotor performance in a Spanish-speaking epilepsy sample; participants were administered the ROCFT, Ravens Standard Progressive Matrices (RSPM), Grooved Pegboard (GP), and Brief Visual Memory Test-Revised (BVMT-R). The English domain of the Bidimensional Acculturation Scale (BAS) was used to determine participants' degree of acculturation to English-speaking, U.S. culture. Findings revealed that level of acculturation was positively correlated with performance on the RSPM (Spearman r, 0.411, $p = 0.006$), BVMT-R total recall (Spearman r, 0.344, $p = 0.018$), RCFT Copy (Spearman r, .386, $p = 0.007$), and delayed recall (Spearman r, 0.338, $p = 0.022$). However, degree of acculturation was inversely correlated with visuomotor dexterity bilaterally (Spearman r, −0.361, −0.318, $p \leq 0.05$). These preliminary findings demonstrate that the impact of acculturation is not attenuated by neurological illness and suggest that acculturation should be considered when administering tests of visuospatial and visuomotor abilities to an epilepsy sample.

Tests of Learning and Memory

As stated above, subtests of the NeSBHIS, RBANS, CCNB, and NEUROPSI Attention and Memory test include multiple measures of new learning and delayed recall in both verbal and non-verbal modalities (e.g., WHO-UCLA Auditory Verbal Learning Test, ROCFT RBANS List Learning, Story Memory, and Figure Recall, Common Objects Memory Test) (Osterrieth, 1944). While the NeSBHIS and RBANS have demonstrated clinical utility and adequate psychometric properties for use with epilepsy patients, the CCNB, NEUROPSI Attention and Memory test, and other Spanish-language measures of learning and memory (i.e., the Story Memory Test and Spanish Verbal Learning Test) would require similar empirical study and revalidation in a neurological sample.

The Story Memory Test (SMT; Artiola i Fortuny, Heaton, & Hermosillo, 1998) is a 29-item measure of verbal learning which generates learning efficiency (based on learning trials 1–5), delayed retention (based on a 1-h delayed recall), and recognition indices (36 items presented in a "yes/no" response paradigm presented after the 1-h delayed recall assessment). The SMT is modeled after English-language Story Memory Test adapted by Heaton, Grant, and Matthews (1991); however, the English-language version has a memory evaluation after a 4-h period. The Spanish Verbal Learning Test (SVLT;

Artiola i Fortuny et al., 1998) is a serially presented list learning task modeled after the format of the English-language California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The SVLT includes two distinct 16-item lists (Lists A and B) which share semantic categories. According to Artiola i Fortuny and coauthors (1998), words were selected by asking 45 Spanish speakers from ten different Spanish-speaking countries to generate words belonging to several semantic categories; categories which did not share regional commonalities were discarded. Six of the remaining categories were selected for inclusion on lists A and B if they shared words that possessed the same meaning in the Spanish-speaking regions of the world that were sampled. Both the SMT (*Aprendizaje de Prosa)* and SVLT (*Aprendizaje de Palabras*) are presented in the Appendix A of Artiola i Fortuny, Heaton & Hermansillo (1998).

Tests of Attention and Executive Abilities

As described above, the NeSBHIS contains an Attention-Mental Control Factor, which includes the EIWA Digit Symbol and Block Design subtests and Color Trails 1 and 2. Of note, the EIWA Block Design subtest is not a strong indicator of Attention and Mental Control, as it failed to meet the criteria for factor loading in Pontón and coauthors' (2000) original factor analytic study of the NeSBHIS (it was included on this factor based on historical data). Although EIWA Block Design loaded onto this factor in a more recent confirmatory analysis evaluating the construct validity of the NeSBHIS in a Hispanic epilepsy population (Bender et al., 2009a, 2009b), 91 % of subtest variance was explained by other constructs. This finding is not entirely surprising, as Block Design may not accurately measure the putative cognitive domain that it was developed to assess in non-native English-speaking, non-Western cultures, because it requires specific cognitive processes that may not be taught and cultivated across cultures (Ardila, 1995; Cohen, 1969). Similarly, the original theoretical model of the NeSBHIS (Pontón et al., 2000) indicated that the EIWA Digit Span subtest would load on the Language Factor, not on the Attention-Mental Control Factor. While findings from an epilepsy sample (Bender et al., 2009a) were consistent with these a priori assumptions, the obtained factor structure was unexpected, as the Digit Span subtest is typically a robust measure of sustained auditory attention and executive functioning in English-speakers with epilepsy (e.g., Bornstein, Drake, & Pakalnis, 1988). The above findings obtained in a Spanish-speaking epilepsy sample suggest that the measures subsumed by the NeSBHIS Attention—Mental Control Factor (i.e., EIWA Digit Span, EIWA Block Design, and Color Trails A and B) require multiple cognitive processes (e.g., cognitive flexibility, speed of processing, response suppression), rather than a single unitary function. Accordingly, assessing specific qualitative and quantitative variables, including Color Trails 2 set loss errors, COWAT number of produced words, perseverances, and errors, as well as maximum span on Digits Backward, may provide further explanations of the NeSBHIS component structure and, by extension, executive abilities in Spanish-speaking Hispanic populations. Similar attempts to define specific factors from frontally mediated tasks have been successfully undertaken throughout the extant literature (American Psychiatric Association, 2000; Burgess & Wood, 1990; Nagahama et al., 2003; Rodriguez-Aranda & Sundet, 2006).

Clinicians should also consider the moderating role of measurable culture-specific variables on attention and executive functioning, as task performance in this domain has been shown to be strongly influenced by acculturation (Coffey et al., 2005). Results of the aforementioned study suggested that higher levels of acculturation were associated with significantly improved Wisconsin Card Sorting Test performance. Future studies are needed to assess the role of acculturation on performance on other measures of attention and executive abilities in epilepsy samples, as well as the effects of other culture-specific factors (e.g., degree of bilinguality) on this neurocognitive domain. Although a series of studies by Bialystock (1987) suggest that bilinguals are superior to monolinguals on tasks requiring high levels of selective attention, these observations

should be further evaluated in adult, non-English-speaking clinical samples.

Motor Speed

Time, as a construct, is strongly culture driven and is a known moderator of neuropsychological test performance (Perez-Arce & Puente, 1996). For example, while the concept of a "fast performance" needed by a patient to perform well on measures of motor speed, is believed to be an important cultural value in the United States, it is not necessarily valued in many other cultural groups (Ardila, 2005). Specifically, in Western, industrialized nations, the concept of time holds elevated importance, and therefore the culture emphasizes punctuality and adherence to a schedule (e.g., Rojas-Méndez, Davies, Omer, Chetthamrongchai, & Madran, 2002). In contrast, the ethos in developing countries, as well as several others in Eastern Europe, Latin America, and the Mediterranean, emphasizes the "quality" of the interaction, rather than the time spent engaging in it. In this vein, individuals may take a more relaxed, flexible attitude towards scheduling and spending increased lengths of time with people and on tasks that are interesting, enjoyable, or mentally challenging (Perez-Arce & Puente, 1996). Thus, a patient who is not a native of the United States or another country which upholds a "clock time" orientation may be at a distinct disadvantage upon speed-dependant tasks.

Assessment of Psychological and Behavioral Functioning

Patients with epilepsy have a high prevalence of comorbid psychiatric disorders.

Depression is among the most common, particularly in patients with temporal lobe epilepsy, with estimates ranging from 13 to 18 % or higher (Patten et al., 2005; Tellez-Zenteno, Patten, Jetté, Williams, & Wiebe, 2007). Anxiety disorders are also frequently noted affecting approximately one third of epilepsy patients (Barry, Lembke, Gisbert, & Gilliam, 2007; Kobau, Gilliam, & Thurman, 2006). The etiology of affective disorders in this population is multifactorial in nature and includes neurobiological and clinical substrates (e.g., seizure foci), presence of psychosocial stressors (e.g., ability to maintain employment, financial concerns, marital status), and diminished health-related quality of life (e.g., unpredictable nature of seizures, medication-related side effects) (see Barry et al., 2007, for review). Specific culture-related factors which may contribute to increased affective distress in non-US-born, immigrant populations with epilepsy may include feelings of stigmatization, real or perceived community-based discrimination, misconceptions regarding disease symptoms, and its etiology, and/or poor access to health care.

Personality Inventories

Currently, there is no "gold standard" for the mental health assessment of non-native English-speaking and/or immigrant populations. Many well-standardized objective measures of personality generate concerns regarding their appropriateness and applicability cross-culturally. Although translated into 150 languages for use in 50 countries, many of the translations of the Minnesota Multiphasic Personality Inventory (MMPI or MMPI-2; Hathaway & McKinley, 1989) have been reported to be inaccurate and lacking in linguistic equivalence (Butcher, 1985). For example, in an English-to-Spanish translation of the MMPI-2, the item "dirt frightens or disgusts me" is translated as "the concept of dirtiness/being dirty bothers me" (Butcher, 1985). As a result of this difference in linguistic connotation, the statement was endorsed 58–68 % more frequently by Mexican adolescents and young adults than in the standardization sample. Butcher (1985) attributes this high rate of item endorsement as being the result of the alteration in meaning; in Mexican cultures the concept of dirtiness is commonly associated with disease, poverty, and infection.

Multiple investigators have also demonstrated that elevations on MMPI/MMPI-2 scores can be attributed to a Hispanic immigrant's traditionality or retention of "home culture" (see Dana,

1995). The importance of acculturation as a significant moderating variable again underscores the need to address this construct during both the clinical interview and via self-report ratings. Such data provides clinicians with the ability to "correct" elevated MMPI/MMPI-2 profiles which may otherwise falsely indicate the presence of psychopathology.

Diagnostic Interviews

Given the paucity of well-standardized, valid, and reliable psychometric instruments, the use of informal, unstructured, or semi-structured interviews may be a valuable tool in obtaining clinically relevant psychological information. Rather than relying on confusing, misleading, or culturally charged questionnaires and personality inventories, contextual information, such as acculturation level, can also be discussed. Diagnostic interviews may also be beneficial because many of the traditional, Western behavior rating scales cannot fully capture the "culture-bound syndromes" discussed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; 2013). For example, commonly administered symptom rating scales would likely misdiagnose an individual suffering from an "*ataque de nervios*," a culture-bound idiom of distress consisting of a dramatic display of emotion with an acute onset principally reported in Latino and Caribbean populations. It is not very highly uncommon for individuals of Latino heritage to suffer from an *ataque de nervios* upon receiving bad news, such as the death of a loved one. Although varying in presentation, sufferers may fall to the ground and lie there motionless or violently convulse as if having a seizure (Guarnaccia, Lewis-Fernandez, & Marano, 2003). Although these episodes are typically brief, a period of post *ataque* exhaustion, similar to postictal fatigue exhibited in epilepsy patients, is not unusual. Although experiencing an *ataque de nervios* is strongly associated with meeting criteria for a range of anxiety and depression-related diagnoses, (Guarnaccia et al., 2003), there are typically subtle factors that distinguish it from panic disorder and dissociative disorder. Symptom clarification in patients with *ataque de nervios* is also particularly challenging due to its similar presentation to epilepsy.

Projective Testing

Although projective testing is not typically included in standard assessments of patients with seizure disorders they may be used as a supplemental measure of psychological status, social-emotional functioning, and personality. Such measures are also useful for individuals with limited levels of formal education and literacy or those who may not possess the level of language proficiency needed to complete written self-report inventories or audiotaped versions of personality inventories. To this end, the TEMAS ("*temas*" corresponds to the Spanish word "themes") or Tell-Me-A-Story test is a culturally sensitive version of the Thematic Apperception Test (TAT) initially developed for urban Hispanic children and adolescents. Created by Costantino, Malgady, and Rogler (1988), the TEMAS is particularly effective for use with Hispanics and other children of non-Anglo backgrounds. This measure is comprised of brightly colored pictures of Hispanic and African-American characters engaged in different situations within an urban setting and presents a conflict that provides the basis for a child-driven narrative. While viewing each picture, the child is asked to create a story about the character and the scene he/she is engaged in. Responses are transcribed verbatim and scored for its cognitive style, affective state, and personality functioning. Multiple cognitive dimensions are evaluated by the TEMAS, each with varying degrees of reliability and validity, including 18 "cognitive" areas (e.g., fluency, imagination, reaction time, and sequencing), affective state (e.g., "ambivalent," "angry," "inappropriate," "neutral," or "sad") and personality functions (e.g., aggression, anxiety/depression, interpersonal relations, reality testing, and sexual identity). Normative data are available for Puerto Rican and non-Puerto Rican respondents; the latter group is further partitioned by country of origin

or region, including the Dominican Republic, Mexico, and South America. Although the structure and psychometric properties of the TEMAS have been a target of criticism in recent years, this measure may yield important insights onto the patient's worldview, affective state, and personality traits which may be untapped by other measures.

Health-related Quality of Life

Limited studies have empirically assessed the attitudes and beliefs of culturally and linguistically diverse patients towards epilepsy or other chronic neurological conditions. In 2005, Sirven and collaborators conducted a survey examining knowledge and perceptions about epilepsy in a sample of 760 Spanish-speaking adults living in the seven metropolitan areas of the U.S. with the highest concentrations of Hispanics. Several interesting themes emerged regarding the general terminology and connotations of the disorder in this population. Although *convulsiones* or *ataque* were the most common terms to describe seizure-related phenomena, the third most frequently provided term was "*sobredosis*," which is translated as "overdose," suggesting a connection with drug or alcohol abuse. In a similar vein, seizures were more likely to be perceived by Hispanics to be the result of bad behavior (e.g., "sins," "lack of spiritual faith," or "evil spirits"), severe medical condition (e.g., brain tumors, anoxia at birth, head injury during infancy, neurocysticercosis), or contagious illness (e.g., meningitis), as compared to non-Hispanic controls. Moreover, a person with epilepsy was perceived as "dangerous to others" in 31 % of Hispanic respondents, as compared to 17 % on non-Hispanic interviewees.

Given the health attitudes surrounding epilepsy, it is not surprising that many Hispanic individuals with epilepsy consult with traditional faith healers, such as *santeros*, *curanderos*, or *yerberos,* in addition to or instead of, Westernized health-care providers. In addition to being more accessible to historically underserved populations, "spiritual practitioners" often address the cause of seizures in a more culturally acceptable manner, encouraging prayer, rituals, and offerings to rid the individual of demonic influence. A national survey conducted for the Epilepsy Foundation of America (2005) reported that 30 % of Hispanic individuals with epilepsy believe that seizures can be successfully treated by herbal, holistic remedies, a spiritual healer, or an exorcism (6 %).

Related investigations sought to develop a reliable and valid rating scale, the Epilepsy Beliefs and Attitudes Scale (EBAS), to assess the beliefs and attitudes about epilepsy in a culturally diverse sample residing in North America (e.g., Caucasians, East Asians, and South Asians) (Gajjar, Geva, Humphries, Peterson-Badali, & Ostubo, 2000). The revised version of the scale, which was refined from pilot testing, consisted of 51 items pertaining to a vignette about a child with complex partial seizures, 18 items examining the medical beliefs of the individuals' biological, psychological, and neurological constitution, 16 items describing non-medical beliefs influencing individuals to have seizures, and 13 items indicating positive and negative attitudes towards people with epilepsy. Overall, Caucasians, as a group, were more likely to select neurological explanations as the root causes of epilepsy than South or East Asians, who endorsed more enviro-psycho-physical and metaphysical causes. The differences in attitudes and beliefs about epilepsy and its potential impact on psychological and psychosocial functioning reflect the need to formally address these constructs during the clinical intake, assessment (via the EBAS or similar scale), or feedback session(s) with the patients and/or their family.

Given the broad range of attitudes and beliefs surrounding an epilepsy diagnosis, it is not unexpected that the concept of health-related quality of life would also vary greatly across cultures. Although multiple instruments assessing quality of life (QOL) in epilepsy have been developed (e.g., the QOLIE-89 and Liverpool QOL Battery), scales appropriate for multi-national cohorts are difficult to develop due to translation issues and differing conceptualizations of "health" across cultures (Cramer et al., 1998). A 31-item measure of QOL, the Quality of Life in Epilepsy

Inventory (QOLIE-31), was derived from the QOLIE-89 and professionally translated into Chinese, Danish, Dutch, German, Canadian French, French, Italian, Spanish, Swedish, and UK English. QOLIE-31 items were shown to cluster into two distinct factors: emotional/psychological effects (i.e., overall QOL, seizure worry, emotional well-being, and energy/fatigue) and medical/social effects (i.e., medication effects, work-driving-social limitations, and cognitive functioning subscales) (Cramer et al., 1998). Although validation of the QOLIE-31 is still needed for most languages and related cultural group, this instrument possesses the strong psychometric properties (e.g., reliability and validity) needed to comprehensively address epilepsy-specific QOL across a range of cultural groups.

Feedback of Neuropsychological Evaluation Findings

The informational and therapeutic benefits of feedback sessions have been well described throughout the extant literature (e.g., Finn & Tonsager, 1992; Quirk, Strosahl, Kreilkamp, & Erdberg, 1995). During such sessions clinicians have the opportunity to not only explain the neuropsychological test findings and their "real-world" implications through face-to-face or telephone meetings. However, the goals of such sessions often widen further in breadth and scope with culturally and linguistically diverse populations. Rather, it may be necessary to provide psychoeducation regarding the causes, manifestations, and comorbidities of epilepsy to the patient and their family members. Providing this type of information is of particular importance when treating newly arrived immigrant populations and/or individuals who are predominantly monolingual speakers of a language other than English, such patients are likely to have limited access to other health-care providers. Like all other aspects of neuropsychological assessment, the presentation of assessment findings is largely governed by culture-specific factors, such as interactional style, expectations, and health attitudes. For example, it is not unusual for patients to defer their decision-making or transfer their power to another family member, community elder, or advocate. In such cases, clinicians need to balance their adherence to privacy practice regulations with their respect of the patient's wishes. Although eager to learn and share the results of testing with their family and/or community members, patients may wish to disclose certain aspects of test findings but not others (e.g., having the clinician divulge the cognitive sequelae of a disorder but not the psychiatric and behavioral symptoms). These requests should be explicitly discussed with the patients prior to the start of the group feedback session.

Neuropsychologists should also recognize that a patient's view of the doctor-patient relationship can vary greatly based on their culture/ethnicity. Specifically, individuals raised in cultures which emphasize adherence to a hierarchy of power or authority may be reluctant to challenge or contradict the clinician and his or her recommendations. To illustrate, Streltzer (2004) presented an anecdote of a middle-aged Filipino-American patient with dangerously high blood pressure who refused to tell the prescribing physician that he had stopped taking anti-hypertensives several weeks prior (due to intolerable side effects) in deference to the physician's perceived "authority." Similarly deferential attitudes has been described in middle-class Argentine culture (Madinaveitia, personal communication). To facilitate open, honest communication, neuropsychologists should explicitly encourage patients and their families to utilize a collaborative team approach to treatment planning. Rather than dictating a treatment plan and potentially fostering an "us" (patient/family) versus "them" (neuropsychologist and medical treatment team) mentality, it is important to actively engage the patients in the decision-making process via an "us" (the neuropsychologist, medical treatment team, patient, and their family) versus "disease" approach. Once these parameters are established, neuropsychologists should be encouraged to taking a directive, problem-focused approach to treatment. Recommendations should be made explicit and presented in a "cause and effect" format, for example, "if your Mother attends psychotherapy, we not only expect for her

symptoms of depression to lessen, but also for an improvement in any mood-related memory problems."

Summary

Careful consideration of the psychometric and culture-specific factors with the potential for causing test bias is particularly critical in the neuropsychological evaluation of epilepsy patients. Failure to do so may obscure the true pattern of the patient's neuropsychological deficit, resulting in potentially incorrect test administration, scoring, data interpretation, case formulation, and treatment recommendations. Rather, clinicians should critically evaluate the sources of information prior to drawing definitive conclusions about the causal factors of the patient's neuropsychological and behavioral performance and functioning (which, at times, can differ considerably). To this end, several key pieces of information should be considered. First, the test measures should be professionally translated, back translated, and critically assessed for dialectal and/or cultural artifacts. Second, selected assessment measures should have strong psychometric properties when evaluating a clinical sample (e.g., populations with known cerebral dysfunction). More specifically, it should be statistically determined whether or not test data correctly measures what it was intended to measure (e.g., construct validity), reliably evaluates the desired constructs, and is stable over time (E.G. Test Retest Reliability). Third, the battery selected should assess a broad range of functions, and these abilities should be differentially compared across the patient's primary and secondary languages. Fourth, the normative sample selected to normalize patient data should be as closely matched to the sample characteristics of the standardization sample as possible. When such comparisons are unavailable (e.g., the English-language standardization sample was used to "norm" test data produced by a Spanish speaker), these discrepancies should be clearly noted throughout the patient's report and carefully considered during all aspects of the case conceptualization. Lastly, the potentially moderating effects of culture-specific experiences (e.g., years of education, level of acculturation, degree of bilinguality) should also be thoroughly considered and objectively measured, prior to, during, and after engaging in testing procedures.

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References

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders – Text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.

Anastasi, A. (1988). *Psychological testing* (6th ed.). New York, NY: Macmillan.

Ardila, A. (1995). Directions of research in cross-cultural neuropsychology. *Journal of Clinical and Experimental Neuropsychology, 17*, 143–150.

Ardila, A. (2005). Cultural values underlying psychometric cognitive testing. *Neuropsychology Review, 15*, 185–195.

Ardila, A., & Moreno, S. (2001). Neuropsychological test performance in Aruaco Indians: An exploratory study. *Journal of the International Neuropsychological Society, 7*, 510–515.

Ardila, A., Rosselli, M., & Puente, A. E. (1994). *Neuropsychological evaluation of the Spanish speaker*. New York, NY: Plenum.

Arnold, B. R., Montgomery, G. T., Castaneda, I., & Longoria, R. (1994). Acculturation and performance of Hispanics on selected Halstead–Reitan neuropsychological tests. *Assessment, 1*, 239–248.

Aronson, J., Lustina, M. J., Good, C., Keough, K., Steele, C. M., & Brown, J. (1999). When white men can't do math: Necessary and sufficient factors in stereotype threat. *Journal of Experimental Social Psychology, 35*, 29–46.

Aronson, J., Steele, C. M., Salinas, M. F., & Lustina, M. J. (1998). The effects of stereotype threat on the standardized test performance of college students. In E. Aronson (Ed.), *Readings about the social animal* (8th ed., pp. 415–430). New York, NY: Freeman.

Artiola i Fortuny, L., Heaton, R. K., & Hermosillo, D. (1998). Neuropsychological comparisons of Spanish-speaking participants from the US-Mexico border region versus Spain. *Journal of the International Neuropsychological Society, 4*, 363–379.

Artiola i Fortuny, L., & Mullaney, H. A. (1997). Neuropsychology with Spanish speakers: Language use and proficiency issues for test development. *Journal of Clinical and Experimental Neuropsychology, 19*, 615–622.

Barr, W. B., Bender, H. A., Morrison, C., Cruz-Laureano, D., Vazquez, B., & Kuzniecky, R. (2009). Diagnostic validity of a neuropsychological test battery for Hispanic patients with epilepsy. *Epilepsy and Behavior, 16*, 479–483.

Barry, J. J., Lembke, A., Gisbert, P. A., & Gilliam, F. (2007). Affective disorders in epilepsy. In A. Ettinger & I. Kanner (Eds.), *Psychiatric issues in epilepsy: A practical guide to diagnosis and treatment* (pp. 203–247). Philadelphia, PA: Lippincott Williams & Williams.

Bender, H. A., Cole, J. R., Aponte, M., Cruz-Laureano, D., Myers, L., Vazquez, B., et al. (2009a). Construct validity of the NeSBHIS in a neurological sample. *Journal of the International Neuropsychological Society, 15*, 217–224.

Bender, H. A., García, A. M., & Barr, W. B. (2010). An interdisciplinary approach to neuropsychological test construction: Perspectives from translation studies. *Journal of the International Neuropsychological Society, 16*, 227–232.

Bender, H. A., Rivera-Rodriguez, M., Aponte-Samalot, M., MacAllister, W. S., Murphy, K., Karantzoulis, S., et al. (2009b). *The clinical utility of the RBANS-Spanish Language Edition in a neurological sample*. San Diego, CA: 7th Annual Conference of the American Academy of Clinical Neuropsychology.

Berry, J. W. (1979). Culture and cognition style. In A. Mrsella, R. G. Tharp, & T. J. Ciborowski (Eds.), *Perspectives in cross-cultural psychology* (pp. 117–135). New York, NY: Academic.

Berry, J. W. (1980). Acculturation as varieties of adaptation. In A. Padilla (Ed.), *Acculturation: Theory, models and some new findings* (pp. 9–26). Boulder, CO: Westview Press.

Berry, J. W., Trimble, J. E., & Olmedo, E. L. (1986). Assessment of acculturation. In W. J. Lonner & J. W. Berry (Eds.), *Field methods in cross-cultural research* (pp. 291–325). Beverly Hills, CA: Sage.

Bethlehem, D., de Picciotto, J., & Watt, N. (2003). Assessment of verbal fluency in bilingual Zulu-English speakers. *South African Journal of Psychology, 33*, 236–240.

Bialystock, E. (1987). Words as things: Development of word concept by bilingual children. *Studies in Second Language Learning, 9*, 133–140.

Boone, K. B., Victor, T. L., Wen, J., Razani, J., & Ponton, M. (2007). The association between neuropsychological scores and ethnicity, language, and acculturation variables in a large patient population. *Archives of Clinical Neuropsychology, 22*, 355–365.

Bornstein, R. A., Drake, M. E., Jr., & Pakalnis, A. (1988). WAIS-R factor structure in epileptic patients. *Epilepsia, 29*, 14–18.

Brown, L., Sherbenou, R., & Johnsen, S. (1997). *Test of nonverbal intelligence: A language-free measure of cognitive ability*. Austin, TX: Pro-ed.

Buelow, J. M., & McNelis, A. (2002). Should every child with epilepsy undergo a neuropsychological evaluation? *Epilepsy & Behavior, 3*, 210–213.

Burgess, P. W., & Wood, R. L. (1990). Neuropsychology of behaviour disorders following brain injury. In R. L. Wood (Ed.), *Neurobehavioural sequelae of traumatic brain injury* (pp. 110–132). London: Taylor & Francis.

Burin, D. I., Jorge, R. E., Arizaga, R. A., & Paulsen, J. S. (2000). Estimation of premorbid intelligence: The Word Accentuation Test – Buenos Aires version. *Journal of Clinical and Experimental Psychology, 22*, 677–685.

Butcher, J. N. (1985). Current developments in MMPI use: An international perspective. In J. N. Butcher & C. D. Spielberger (Eds.), *Advances in personality assessment* (Vol. 4, pp. 83–94). Hillsdale, NJ: Lawrence Erlbaum Associates Inc.

Caltabiano, N. (1984). Perceived differences in ethnic behavior: A pilot study of Italo-Australian Canberra residents. *Psychological Reports, 55*, 867–873.

Campos-Castelló, J., & Campos-Soler, S. (2004). Neuropsychology and epilepsy. *Revista de Neurologia, 39*, 166–177.

Coffey, D. M., Marmol, L., Schock, L., & Adams, W. (2005). The influence of acculturation on the Wisconsin card sorting test by Mexican Americans. *Archives for Clinical Neuropsychology, 20*, 795–803.

Cohen, R. A. (1969). Conceptual styles, culture conflict, and nonverbal tests. *American Anthropologist, 71*, 828–856.

Cortes, D. E., Rogler, L. H., & Malgady, R. G. (1994). Biculturality among Puerto Rican adults in the United States. *American Journal of Community Psychology, 22*, 707–721.

Costantino, G., Malgady, R. G., & Rogler, L. H. (1988). *Manual for the TEMAS thematic apperception tests*. Los Angeles, CA: Western Psychological Services.

Cramer, J. A., Perrine, K., Devinsky, O., Bryant-Comstock, L., Meador, K., & Hermann, B. (1998). Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia, 39*, 81–88.

Cultural Competence in Clinical Psychiatry (Core Competencies in Psychotherapy S) by Wen-Shing Tseng and Jon, M.D. Streltzer (Aug 2004).

da Silva, C. G., Petersson, K. M., Faisca, L., Ingvar, M., & Reis, A. (2004). The effects of literacy and education on the quantitative and qualitative aspects of semantic verbal fluency. *Journal of Clinical and Experimental Neuropsychology, 26*, 266–277.

Dana, R. H. (1995). Culturally competent MMPI assessment of Hispanic populations. *Hispanic Journal of Behavioral Sciences, 17*, 305–319.

Davila, Y. R., Reifsnider, E., & Pecina, I. (2011). Familismo: influence on Hispanic health behaviors. *Applied Nursing Research, 24*, 67–72.

Deaux, K., Bikmen, N., Gilkes, A., Ventuneac, A., Joseph, Y., Payne, R., et al. (2007). Becoming American: Stereotype threat effects in Black immigrant groups. *Social Psychology Quarterly, 70*, 384–404.

DeGiorgio, C., Pietsch-Escueta, S., Tsang, V., Corral-Leyva, G., Ng, L., Medina, M. T., et al. (2005). Sero-

prevalence of Taenia solium cysticercosis and Taenia solium taeniasis in California, USA. *Acta Neurologica Scandinavica, 111*, 84–88.

Del Ser, T., Gonzalez-Montalvo, J. I., Martinez-Espinosa, S., Delgado-Villapalos, C., & Bermejo, F. (1997). Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia. *Brain and Cognition, 33*, 343–356.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *California verbal learning test*. San Antonio, TX: The Psychological Corporation.

Demers, P., Robillard, A., LaFleche, G., Nash, F., Heyman, A., & Fillenbaum, G. (1994). Translation of clinical and neuropsychological instruments into French: The CERAD experience. *Age and Ageing, 23*, 449–451.

Demsky, Y., Gass, C., Edwards, W. T., & Golden, C. J. (1998). Optional short forms of the Spanish WAIS (EIWA). *Assessment, 5*, 361–364.

Department of Homeland Security. (2009). *2009 Yearbook of immigration statistics*. Washington, DC: Office of Immigration Statistics. http://www.dhs.gov/xlibrary/assets/statistics/yearbook/2009/ois_yb_2009.pdf.

Dick, M. B., Teng, E. L., Kempler, D., Davis, D. S., & Taussig, I. M. (2002). The cross-cultural neuropsychological test battery. In F. R. Ferraro (Ed.), *Minority and cross-cultural aspects of neuropsychological assessment* (pp. 17–41). Lisse: Swets and Zeitlinger.

Dunn, L., Padilla, E., Lugo, D., & Dunn, L. (1986). *Test de vocabulario en imagenes peabody: Adaptacion Hispano-Americana (peabody picture vocabulary test-Latin american adaptation)*. Circle Pines, MN: American Guidance Services.

Ediciones, T. E. A. (2001). *WAIS-III, Escala de Inteligencia Wechsler para Adultos – III*. Madrid: TEA Ediciones.

Elger, C. E., Helmstaedter, C., & Kurthen, M. (2004). Epilepsy and cognition. *Lancet Neurology, 3*, 663–672.

Epilepsy Foundation of America. (2003). *Report of the 2003 National Conference on Public Health and Epilepsy*. Landover, MD: Epilepsy Foundation of America.

Epilepsy Foundation of America. (2005). *Survey: Beliefs about epilepsy among Hispanics a significant national health issue*. Landover, MD: Epilepsy Foundation of America.

Escandell, V. A. (2002). Cross-cultural neuropsychology in Saudi Arabia. The cross-cultural neuropsychological test battery. In F. R. Ferraro (Ed.), *Minority and cross-cultural aspects of neuropsychological assessment* (pp. 299–325). Lisse: Swets and Zeitlinger.

Finn, S. E., & Tonsager, M. E. (1992). Therapeutic effects of providing MMPI-2 test feedback to college students awaiting therapy. *Psychological Assessment, 4*, 278–287.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini mental state: A practical guide for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.

Gajjar, M., Geva, E., Humphries, T., Peterson-Badali, M., & Ostubo, H. (2000). A new scale to assess culture-specific beliefs and attitudes about epilepsy. *Epilepsy and Behavior, 1*, 235–255.

Gasquoine, P. G. (1999). Variables moderating cultural and ethnic differences in neuropsychological assessment: The case of Hispanic Americans. *Clinical Neuropsychology, 13*, 376–383.

Gay, J., & Cole, M. (1967). *The new mathematics and an old culture: A study of learning among the Kpelle of Liberia*. New York, NY: Holt, Rinehart, & Winston.

Gill, J. R., Lenz, K. A., & Amolat, M. J. (2003). Gunshot fatalities in children and adolescents in New York City. *Journal of Forensic Science, 48*, 832–835.

Gomez-Tortosa, E., Martin, E. M., Gaviria, M., Charbel, F., & Asuman, J. I. (1995). Selective deficit of one language in a bilingual patient following surgery in the left perisylvian area. *Brain and Language, 48*, 320–325.

Graves, A. B., Larson, E. B., Edland, S. D., Bowen, J. D., McCormick, W. C., McCurry, S. M., et al. (1996). Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington State: The *Kame* Project. *American Journal of Epidemiology, 144*, 760–771.

Guarnaccia, P. J., Lewis-Fernandez, R., & Marano, M. R. (2003). Toward a Puerto Rican popular nosology: Nervios and ataque de nervios. *Cultural Medical Psychiatry, 27*, 339–366.

Halliday, M. A. K., McKintosh, A., & Strevens, P. (1970). The users and the uses of language. In J. A. Fishman (Ed.), *Readings in the sociology of language* (pp. 139–169). The Hague: Mouton.

Hammill, D. D., Pearson, N. A., & Wiederhold, J. L. (1997). *Comprehensive Test of Nonverbal Intelligence (CTONI)*. Austin, TX: Pro-Ed.

Harris, J. G., Tulsky, D. S., & Schultheis, M. T. (2003). Assessment of non-native English speaker: Assimilating history and research to guide clinical practice. In D. S. Tulsky & D. H. Saklofske (Eds.), *Clinical interpretation of the WAIS-III and WMS-III* (pp. 343–390). San Diego, CA: Academic.

Hathaway, S. R., & McKinley, J. C. (1989). *MMPI-2*. Minneapolis, MN: University of Minnesota Press.

Heaton, R. K., Grant, I., & Matthews, C. (1991). *Comprehensive norms for an expanded Halstead–Reitan Battery: Demographic corrections, research findings, and clinical applications*. Odessa, FL: Psychological Assessment Resources, Inc.

Ivey, A., & Ivey, M. (2003). *Intentional interviewing and counseling: Facilitating client development in a multicultural society*. Pacific Grove, CA: Brooks/Cole.

Jones-Gotman, M. (1991). Localization of lesions by neuropsychological testing. *Epilepsia, 82*, S41–S52.

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test* (2nd ed.). Philadelphia, PA: Lea & Febinger.

Kempler, D., Teng, E. L., Dick, M., Taussig, I. M., & Davis, S. (1998). The effects of age, education, and ethnicity on verbal fluency. *Journal of the International Neuropsychological Society, 4*, 531–538.

Kennepohl, K., Douglas, S., Nabors, N., & Hanks, R. (2004). African American acculturation and neuropsychological test performance following traumatic brain injury. *Journal of the International Neuropsychological Society, 10*, 566–577.

Kobau, R., Gilliam, F., & Thurman, D. J. (2006). Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 HealthStyles Survey. *Epilepsia, 47*, 1915–1921.

Kohnert, K. J., Hernandez, A. E., & Bates, E. (1998). Bilingual performance on the Boston Naming Test: Preliminary norms in Spanish and English. *Brain and Language, 65*, 422–440.

Lippé, S., & Lassonde, M. (2004). Neuropsychological profile of intractable partial epilepsies. *Revue Neurologique (Paris), 160*, S144–S153.

Liu, H. C., Chou, P., Lin, K. N., Wang, S. J., Fuh, J. L., Lin, H. C., et al. (1994). Assessing cognitive abilities and dementia in a predominantly illiterate population of older individuals in Kinmen. *Psychological Medicine, 24*, 763–770.

Lopez, S. R., & Taussig, I. M. (1991). Cognitive–intellectual functioning of Spanish-speaking impaired and non-impaired elderly: Implications for culturally sensitive assessment. *Psychological Assessment, 3*, 448–454.

Loring, D. W. (1997). Neuropsychological evaluation in epilepsy surgery. *Epilepsia, 38*, S18–S23.

Loring, D. W., & Meador, K. J. (2001). Cognitive and behavioral effects of epilepsy treatment. *Epilepsia, 42*, 24–32.

Lynn, R., Backhoff, E., & Contreras, L. A. (2005). Ethnic and racial differences on the Standard Progressive Matrices in Mexico. *Journal of Biosocial Science, 37*, 107–113.

Maj, M., D'Elia, L., Satz, P., Janssen, R., Zaudig, M., Uchiyama, C., et al. (1993). Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: A WHO study. *Archives of Clinical Neuropsychology, 8*, 123–135.

Maj, M., Satz, P., Janssen, R., Zaudig, M., Starace, F., D'Elia, L., et al. (1994). WHO Neuropsychiatric AIDS study, cross-sectional phase II: Neuropsychological and neurological findings. *Archives of General Psychiatry, 51*, 51–61.

Marin, G. (1992). Issues in the measurement of acculturation among Hispanics. In K. Geisinger (Ed.), *Psychological testing of Hispanic* (pp. 235–251). Washington, DC: American Psychological Association.

Marin, G., & Gamba, R. J. (1996). A new measurement of acculturation for Hispanics: The Bidimensional Acculturation Scale for Hispanics (BAS). *Hispanic Journal of Behavioral Sciences, 18*, 297–316.

Marin, G., & Marin, B. V. (1991a). *Research with Hispanic populations*. Thousand Oaks, CA: Sage.

Marin, G., & Marin, B. V. (1991b). *Applied social science research methods series: vol 23. Research with Hispanic populations*. Newbury Park, CA: Sage.

Marin, G., Sabogal, F., Marin, B. V., Otero-Sabogal, R., & Perez-Stable, E. J. (1987). Development of a short acculturation scale for Hispanics. *Hispanic Journal of Behavioral Sciences, 9*, 183–205.

Medina, M. T., Rosas, E., Rubio-Donnadieu, F., & Sotelo, J. (1990). Neurocysticercosis as the main cause of late-onset epilepsy in Mexico. *Archives of Internal Medicine, 150*, 325–327.

Melendez, F. (1994). The Spanish version of the WAIS: Some ethical considerations. *The Clinical Neuropsychologist, 8*, 388–393.

Mena, F. J., Padilla, A. M., & Maldonado, M. (1987). Acculturative stress and specific coping strategies among immigrant and later generation college students. *Hispanic Journal of Behavioral Sciences, 9*, 207–225.

Milner, B. (1975). Psychological aspects of focal epilepsy and its neurosurgical management. *Advances in Neurology, 8*, 299–321.

Nagahama, Y., Okina, T., Suzuki, N., Matsuzaki, S., Yamauchi, H., Nabatame, H., et al. (2003). Factor structure of a modified version of the Wisconsin card sorting test: An analysis of executive deficit in Alzheimer's disease and mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 16*, 103–112.

Neils, J., Baris, J. M., Carter, C., Dell'aira, A. L., Nordloh, S. J., Weiler, E., et al. (1995). Effects of age, education, and living environment on Boston Naming Test performance. *Journal of Speech and Hearing Research, 38*, 1143–1149.

Nelson, H. E. (1982). *National adult reading test: Test manual. Windsor, Berks: NFER-Nelson. Office of Population Censuses and Surveys (OPCS) (1980). Classification of occupations*. London: HMSO.

Osterrieth, P. A. (1944). Le test de copie d'une figure complex. Contribution a l'etude de la perception et de la memoire. *Archives de Psychologie, 30*, 286–356.

Ostrosky-Solís, F., Ardila, A., & Rosselli, M. (1997). *Manual, instructivo y protocolo de aplicación. Neuropsi: Evaluación neuropsicológica breve en Español.*. México: Bayer de México.

Ostrosky-Solís, F., Ardila, A., & Rosselli, M. (1999). Neuropsi: A brief neuropsychological test battery in Spanish with norms by age and educational level. *Journal of the International Neuropsychological Society, 5*, 413–433.

Ostrosky-Solís, F., Gómez, M. E., Ardila, A., Rosselli, M., Pineda, D., & Matute, E. (2003). *NEUROPSI: Atención y memoria. Manual, perfiles y material*. México: American Bookstore & Teletón.

Ostrosky-Solís, F., Gómez, E., Matute, E., Rosselli, M., Ardila, A., & Pineda, D. (2007). NEUROPSI attention and memory: A neuropsychological test battery in Spanish with norms by age and educational level. *Applied Neuropsychology, 14*, 156–170.

Ostrosky-Solís, F., Gutierrez, A. L., Flores, M. R., & Ardila, A. (2007). Same or different? Semantic verbal fluency across Spanish-speakers from different countries. *Archives of Clinical Neuropsychology, 22*, 367–377.

Patten, S. B., Beck, C. A., Kassam, A., Williams, J. V., Barbui, C., & Metz, L. M. (2005). Long-term medical conditions and major depression: strength of association for specific conditions in the general population. *Canadian Journal of Psychiatry, 50*, 195–202.

Perez-Arce, P., & Puente, A. (1996). Neuropsychological assessment of ethnic minorities. In R. J. Sbordone & C. J. Long (Eds.), *Ecological validity of neuropsychological tests* (pp. 283–300). Delray Beach, FL: GR Press.

Phinney, J. S., & Rotheram, M. J. (1987). *Children's ethnic socialization: pluralism and development*. London: Sage Publications.

Pontón, M. O., & Ardila, A. (1999). The future of neuropsychology with Hispanic populations in the United States. *Archives of Clinical Neuropsychology, 17*, 565–580.

Pontón, M. O., Gonzalez, J. J., Hernandez, I., Herrera, L., & Higareda, I. (2000). Factor analysis of the neuropsychological screening battery for Hispanics (NeSBHIS). *Applied Neuropsychology, 7*, 32–39.

Pontón, M. O., Satz, P., Herrera, L., Ortiz, F., Urrutia, C. P., Young, R., et al. (1996). Normative data stratified by age and education for the Neuropsychological Screening Battery for Hispanics (NeSBHIS): Initial report. *Journal of the International Neuropsychological Society, 2*, 96–104.

Pontón, M. O., Satz, P., Herrera, L., Young, R., Ortiz, F., D'Elia, L., et al. (1992). Modified Spanish version of the Boston Naming Test. *The Clinical Neuropsychologist, 3*, 334.

Preux, P., & Druet-Cabanac, M. (2005). Epidemiology and aetiology of epilepsy in sub-Saharan Africa. *The Lancet Neurology, 1*, 21–31.

Quirk, M. P., Strosahl, K., Kreilkamp, T., & Erdberg, P. (1995). Personality feedback consultation to families in a managed mental health care practice. *Professional Psychology: Research and Practice, 26*, 27–32.

Randolph, C. (1998a). *RBANS manual*. San Antonio, TX: The Psychological Corporation.

Randolph, C. (1998b). *RBANS manual (US Spanish research)*. San Antonio, TX: The Psychological Corporation.

Raven, J., Raven, J. C., & Court, J. H. (1993). *Manual for the Raven's progressive matrices and vocabulary scales*. Oxford: Oxford Psychologists Press.

Real Academia Española. (2003). *Diccionario de la lengua española, vigésima segunda edición*. Madrid: Espasa Calpe.

Ríos, J., & Fernández Torres, J. (2004). *McGraw-Hill's Spanish for healthcare providers*. New York, NY: McGraw-Hill.

Rodriguez-Aranda, C., & Sundet, K. (2006). The frontal hypothesis of cognitive aging: Factor structure and age effects on four frontal tests among healthy individuals. *The Journal of Genetic Psychology, 167*, 269–287.

Rojas-Méndez, J. I., Davies, G., Omer, O., Chetthamrongchai, P., & Madran, C. (2002). A time attitude scale for cross cultural research. *Journal of Global Marketing, 15*, 117–147.

Rosselli, M., Ardila, A., & Rosas, P. (1990). Neuropsychological assessment in illiterates. II. Language and praxic abilities. *Brain and Cognition, 12*, 281–296.

Rushton, J. P., & Jensen, A. R. (2005). Thirty years of research on race differences in cognitive ability. *Psychology, Public Policy, and Law, 11*, 235–294.

Saez, P., Bender, H. A., Barr, W. B., Morrison, C., Vazquez, B., & Rivera-Mindt, M. (2008). *The relationship between acculturation and non-verbal neuropsychological test performance among Hispanic epilepsy patients*. Atlanta, GA: 37th Annual Meeting of the International Neuropsychological Society.

Santiago-Grisoli, J. S. (2000). Epilepsy of the borderlands: seizure disorders in US Latinos. *Epilepsy and Behavior, 1*, 150–152.

Schrauf, R. W., Weintraub, S., & Navarro, E. (2006). Is adaptation of the Word Accentuation Test of premorbid intelligence necessary for use among older, Spanish-speaking immigrants in the United States? *Journal of the International Neuropsychological Society, 12*, 391–399.

Steele, C. M. (1997). A threat in the air: How stereotypes shape the intellectual identities and performance of women and African Americans. *American Psychologist, 52*, 613–629.

Steele, C. M., & Aronson, J. (1995). Stereotype threat and the intellectual test performance of African-Americans. *Journal of Personality and Social Psychology, 69*, 797–811.

Tellez-Zenteno, J. F., Patten, S. B., Jetté, N., Williams, J., & Wiebe, S. (2007). Psychiatric comorbidity in epilepsy: A population-based analysis. *Epilepsia, 48*, 2336–2344.

Teng, E. L., Hasegawa, K., Homma, A., Imai, Y., Larson, E., Graves, A., et al. (1994). The cognitive abilities screening instrument (CASI): A practical test for cross-cultural epidemiological studies of dementia. *International Psychogeriatrics, 6*, 45–58.

Toury, G. (1980). *In search of a theory of translation*. Tel Aviv: The Porter Institute for Poetics and Semiotics.

Trimble, J., Lonner, W., & Boucher, J. D. (1983). Stalking the Wily Emic: Alternatives to cross-cultural measurement. In S. H. Irvine & J. W. Berry (Eds.), *Human assessment and cultural factors*. New York, NY: Plenum.

Tsai, R. C., Lin, K. N., Wang, H. J., & Liu, H. C. (2007). Evaluating the uses of the total score and the domain scores in the Cognitive Abilities Screening Instrument, Chinese version (CASI C-2.0): Results of confirmatory factor analysis. *International Psychogeriatrics, 19*, 1051–1063.

U.S. Bureau of the Census. (1999). *United States Census, race, Hispanic origin, and ancestry: Why, what and how*. Washington, DC: U.S. Department of Commerce.

U.S. Bureau of the Census. (2000). *Statistical abstract of the United States: 2000 Washington, DC*. Suitland, MD: U.S. Bureau of the Census.

Valle, R. (1990). Cultural and ethnic issues in Alzheimer's disease family research. In E. Light & B. Lebowitz (Eds.), *Alzheimer's disease treatment and family stress* (pp. 122–154). London: Taylor & Francis.

Wechsler, D. (2004). *Escala de Memoria de Wechsler III. Manual Tecnico*. Madrid: TEA Ediciones.

Wechsler, D. (2008). *Manual de administración y puntuación. Escala de Inteligencia Wechsler para Adultos – III*. San Antonio, TX: Pearson.

Wechsler, D., Green, R. F., & Martinez, J. N. (1968). *Manual para la Escala de Inteligencia Wechsler para Adultos (EIWA)*. Cleveland, OH: Psychological Corporation.

White, H., Boden-Albala, B., Wang, C., Elkind, M. S., Rundek, T., Wright, C. B., et al. (2005). Ischemic stroke subtype incidence among whites, blacks, and Hispanics: The Northern Manhattan Study. *Circulation, 111*, 1327–1331.

Wong, T. M., Strickland, T. L., Fletcher-Janzen, E., Ardila, A., & Reynolds, C. R. (2000). Theoretical and practical issues in the neuropsychological assessment and treatment of culturally dissimilar patients. In E. Fletcher-Janzen, T. L. Strickland, & C. R. Reynolds (Eds.), *Handbook of cross-cultural neuropsychology* (pp. 3–18). New York, NY: Academia.

Zahuranec, D. B., Brown, D. L., Lisabeth, L. D., Gonzales, N. R., Longwell, P. J., Eden, S. V., et al. (2006). Differences in intracerebral hemorrhage between Mexican Americans and non-Hispanic whites. *Neurology, 66*, 30–34.

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