## Table of Contents

AUTHOR INFORMATION 1  
INTRODUCTION 2  
CAUSES AND MECHANISMS OF COGNITIVE DYSFUNCTION ASSOCIATED WITH EPILEPSY 2  
PATTERNS OF COGNITIVE DYSFUNCTION ASSOCIATED WITH EPILEPSY 3  
PATTERNS OF COGNITIVE DYSFUNCTION OBSERVED IN THE FOCAL EPILEPSIES 6  
EPILEPSY TREATMENTS AND COGNITION 14  
COGNITION OVER THE LIFESPAN IN EPILEPSY 14  
EVALUATING COGNITIVE FUNCTION IN EPILEPSY 15  
CONCLUSION 18  
BOARD REVIEW QUESTIONS 18  
REFERENCES 18
AUTHOR INFORMATION

EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

Note from the Publisher

This publication has been developed without involvement of or review by the American Board of Psychiatry and Neurology.

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Cognitive function in patients with epilepsy is determined by a multitude of interacting variables. These include other neurologic disease or injury that may have caused the occurrence of seizures, such as perinatal trauma, developmental abnormalities, brain tumors, stroke, systemic lupus erythematosus, and traumatic brain injury. Such conditions carry their own risk of cognitive abnormality, which must be considered. However, most cases of epilepsy are of unknown cause and lack such obvious primary sources of brain dysfunction. In all cases, regardless of epilepsy etiology, seizures can transiently disrupt neural networks leading to brief cognitive and sensorimotor dysfunction.\(^1\)\(^-\)\(^3\)

Epileptiform activity can also have chronic effects on functioning associated with permanent structural changes in the brain.\(^4\) For many with epilepsy, particularly those with well-controlled seizures on antiepileptic drugs (AEDs), the chronic cognitive effect of seizures will be mild. At the other end of the spectrum, however, there are individuals with profound impairment of cognitive abilities, ranging from isolated deficits related to the region of the seizure focus to global disability resulting from widespread changes in brain structure and function. Additionally, treatments for epilepsy carry their own associated risk of cognitive dysfunction, including the side effects of AEDs,\(^5\) neurosurgical intervention,\(^6\) and some implantable devices (eg, vagal nerve stimulator).\(^7\) Interventions for epilepsy hold the promise of improving cognition by optimizing seizure control. Overall, this review seeks to explain the interplay of variables contributing to cognitive performance in patients with epilepsy, while providing a framework for understanding the complexity of these interactions by exploring them in terms of epilepsy syndrome, etiology, and other significant disease-specific variables (eg, age of seizure onset, seizure frequency, epilepsy duration).

**CAUSES AND MECHANISMS OF COGNITIVE DYSFUNCTION ASSOCIATED WITH EPILEPSY**

Structural lesions are common in patients with epilepsy, often representing the etiology of the epilepsy (eg, tumors, dysplasia). Sometimes lesions such as hippocampal atrophy in temporal lobe epilepsy (TLE) reflect the chronic effect of epileptiform activity upon the brain.\(^8\)\(^\)\(^9\) Some patients also have structural lesions from prior surgical intervention. Structural lesions can disrupt both local and global
neural networks, generally resulting in predictable cognitive deficits.

Functional impairment of brain networks can also occur from transient chemical and electrical disruptions of brain circuitry due to interictal and ictal discharges, synaptic and ion channel abnormalities, and medication side effects. When the functional disruption of brain circuitry is potentially reversible and not from a structural lesion, effective management of such underlying processes can improve cognition (e.g., decreasing epileptiform discharges, changing an AED causing adverse effects, or altering synaptic neurotransmitter availability). Growing evidence indicates that cognitive functions are supported by large-scale, distributed neural networks of varying complexity. Less complex systems mediate basic sensory and motor processing, while higher order cognitive functions such as semantic memory and language are supported by interactions across widespread distributed neural systems. Cortical and subcortical gray matter structures function as processing nodes in these networks, which are then connected by white matter tracts. Epilepsy and its treatments produce structural and functional disruption of these networks, as do the underlying neurological processes that cause epilepsy and other associated comorbidities. Uncontrolled seizures can alter brain structure and function, as reflected by gray and white matter volumetric changes and disturbed functional connectivity demonstrated by resting state functional magnetic resonance imaging (fMRI) and diffusion tensor imaging. Disease-related variables, such as seizure duration and frequency, often determine the severity of these brain changes.

Understanding the mechanistic structure of cognitive dysfunction and its causes can help to predict the nature and magnitude of cognitive impairment experienced by a given patient and allow us to estimate their cognitive trajectory over time and anticipate the effect of different treatment interventions.

**PATTERNS OF COGNITIVE DYSFUNCTION ASSOCIATED WITH EPILEPSY**

Understanding and predicting cognitive function and change over time requires a general knowledge of the various seizure classification schemas and some key disease-related variables such as age of seizure onset. Such schemas typically group patients by seizure etiology, seizure type, and epilepsy syndrome. We will consider each schema and its relationship to cognition in turn.

**SEIZURE ETIOLOGY**

The symptomatic epilepsies most often exhibit the worst baseline cognitive functioning, although there is growing recognition that at least mild dysfunction is often present in the idiopathic "benign" epilepsies of childhood as well. Symptomatic epilepsies result from known developmental or acquired lesions, such as traumatic brain injury, tumors, developmental abnormalities (e.g., cortical dysgenesis), or mesial temporal sclerosis. Knowledge of the location and extent of the underlying lesion causing these epilepsies provides information about which cognitive functions might be compromised. Idiopathic epilepsy involves seizures occurring without a structural lesion and is believed to likely result from a genetic abnormality. Cognitive dysfunction in such patients can occur secondary to subtle abnormalities in cellular physiology, and also directly from seizures. These patients, lacking obvious structural lesions, usually experience less severe cognitive deficits than those with symptomatic epilepsy or cryptogenic epilepsy (epilepsy of unknown etiology). Patients with genetic epilepsy can have focal or generalized seizures, with dif-
different patterns of cognitive deficits. Of note, the International League Against Epilepsy has recently proposed that the terms symptomatic, idiopathic, and cryptogenic be replaced with structural-metabolic, genetic, and unknown, respectively.

SEIZURE TYPE

Seizures have traditionally been classified as either focal or generalized. Focal epilepsy is characterized by seizures starting in a localized cerebral area, and typically results from symptomatic and probable symptomatic epilepsies. In some patients, focal seizures can evolve into a generalized seizure (secondary generalization). In contrast, seizures in primary generalized epilepsy begin simultaneously in both hemispheres and are frequently subcategorized into absence, myoclonic, clonic, atonic, tonic, and generalized tonic-clonic seizures. Cognitive deficits are typically greatest for patients experiencing the largest, most disruptive generalized seizures. Someone with generalized tonic-clonic seizures, for example, will likely experience greater cognitive deficits than a patient with absence or focal seizures, although the deficits associated with any seizure type can be pronounced. Knowledge of seizure type is therefore important for estimating cognitive impairment, which will typically reflect the brain regions affected by a specific seizure. Most patients experience stereotyped patterns of seizures, which means that the same cerebral networks are repeatedly disrupted. Focal seizures typically produce more circumscribed patterns of cognitive dysfunction than generalized seizures. However, recent studies demonstrate that even focal seizures often disrupt large-scale brain networks extending beyond the seizure onset zone, even without secondary generalization. Volumetric magnetic resonance imaging (MRI) demonstrates that patients with TLE have significant reduction in parietal, frontal, and temporal neocortical thickness and white matter volumes, as well as decreased thalamic volumes as compared to healthy controls. Prefrontal metabolic abnormalities have also been shown in TLE with positron emission tomography and magnetic resonance spectroscopy, although many of the metabolic abnormalities will normalize if seizures improve. For example, frontal hypometabolism in patients with TLE will frequently reverse if seizure freedom is achieved after anterior temporal lobe resection. Much of the cognitive improvement seen after seizure control likely results from the reduction of such widespread effects, allowing these broader brain regions to return to normal patterns of function.

With focal seizures, the brain region affected by structural and electrophysiological disruption will dictate the nature of any resulting cognitive deficits. In patients with focal seizures that secondarily generalize, broader dysfunction and impairment of primary attention and processing speed are more likely. The focal epilepsies have been studied in the context of presurgical planning, with most research focused on TLE due to its prevalent occurrence in adults. Current knowledge of brain-behavior relationships has been greatly informed by the study of such epilepsy surgery patients. Of note, however, classic seizure type patterns, such as TLE, are less commonly observed in children. Pediatric patients, therefore, will often present with more idiosyncratic patterns of cognitive dysfunction. Nevertheless, knowledge of brain-behavior relationships is a fundamental starting point for understanding cognitive dysfunction in any patient. Therefore, cognitive dysfunction associated with the focal epilepsies will be covered later in this review.

Primary generalized seizures are more likely to result in broader, diffuse cognitive deficits than are focal seizures. There are several different pri-
mary generalized epilepsy syndromes, which share in common the fact that seizure onset is defined as involving electrical discharges arising simultaneously throughout the brain. In actuality, a significant debate remains over whether these seizures originate in the thalamus or the cortex.\textsuperscript{31–33} Frontal lobe structures are also known to play a significant role in generating these events.\textsuperscript{34} Accordingly, patients with generalized epilepsy often exhibit impairment in a number of presumed prefrontal, executive functions, such as mental flexibility, working memory, and task shifting.\textsuperscript{35} These findings are concordant with evidence from MRI morphometry studies demonstrating frontal lobe atrophic changes.\textsuperscript{24} Otherwise, there is a tendency for the generalized epilepsies to exhibit broader, global dysfunction, which is worse in those experiencing status epilepticus or larger convulsive seizures. There are also generalized epilepsy syndromes occurring with baseline global brain dysfunction (including mental retardation), sometimes associated with progressive decline.

**EPILEPSY SYNDROMES**

Familiarity with each epilepsy syndrome is useful, as patterns of cognitive functioning are among the defining criteria for several. Such syndromes are routinely observed in children, but most epilepsy practitioners will encounter them over the course of treating patients. The following sections discuss the more commonly occurring syndromes.\textsuperscript{23}

**Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS)**

BECTS, also referred to as Rolandic epilepsy, is one of the most common epilepsy syndromes of childhood.\textsuperscript{36} Onset typically occurs between the ages of 3 and 10 years, and it is more prevalent among males.\textsuperscript{37} Patients typically experience centrottemporal spike activity followed by slow waves. Seizures usually involve brief, simple, partial hemifacial motor seizures, but sometimes include secondary generalization. Patients with this syndrome are not always treated with AEDs, as the seizures tend to occur at night, often infrequently, and the syndrome sometimes remits during the patient’s teenage years. Although this syndrome is believed to have a benign course, more recent studies have indicated that these patients will often present with neurocognitive deficits, particularly involving aspects of memory and language.\textsuperscript{38,39} Some studies have also suggested the presence of motor and executive function impairment\textsuperscript{40} and persisting verbal deficits and academic problems.\textsuperscript{41,42}

**Childhood Absence Epilepsy (CAE)**

CAE is a very common syndrome that affects approximately 10% to 15% of children with epilepsy. It is believed to represent a genetic condition that is more commonly experienced by girls than boys.\textsuperscript{43,44} Onset of CAE is typically between the ages of 4 and 10 years. This syndrome is characterized by brief staring spells and bilateral, synchronous, 3-Hz spike-wave activity. During adolescence, generalized tonic-clonic events may begin in some patients, while in others these absence events will remit or continue as the sole seizure type. Although originally considered a benign syndrome, many patients with CAE will experience ongoing cognitive and behavioral problems. This has included problems with learning and memory, attention, language, and visual-spatial functioning.\textsuperscript{43–45} Some studies have also suggested that psychosocial functioning is compromised relative to a medical control group.\textsuperscript{46}

**Dravet Syndrome**

Dravet syndrome (severe myoclonic epilepsy of infants) involves seizure onset typically occurring during the first year of life accompanied by concomitant cognitive, behavioral, and motor deficits.\textsuperscript{47} While
often starting with febrile seizures, a variety of seizure types can occur including nonconvulsive, myoclonic, absence, and generalized events. Status epilepticus is common as well. Cognitive and behavioral problems (eg, attention problems, irritability) are thought to progress for the first few years, with eventual stabilization around age 6. However, most patients exhibit mental retardation and developmental delay, and a wide range of general cognitive deficits.48,49 There appear to be subtypes of this syndrome and clear evidence of a genetic component.50,51 The extent of cognitive and behavioral abnormalities appears to be related to seizure burden and duration.52

Landau-Kleffner Syndrome

Landau-Kleffner syndrome is an epileptic syndrome with discharges in the temporoparietal regions, which is associated with acquired aphasia involving both receptive and expressive speech during the first decade of life.53,54 This syndrome is frequently accompanied by behavioral disturbance, which can include hyperactivity, attention problems, and sometimes a more pervasive developmental syndrome with autistic features.55

Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a childhood epileptic encephalopathy associated with diffuse, slow spike-and-wave electroencephalography (EEG) activity (<3 Hz) that usually begins during preschool (typically 1 to 8 years of age).23,56 Common seizure types seen in this syndrome include atonic, tonic-axial, and absence seizures, although myoclonic, generalized tonic-clonic, and focal seizures also occur. Seizure frequency is high and status epilepticus often occurs. Patients with this syndrome frequently experienced a prior encephalopathy, and mental retardation and diffuse cognitive impairment are prevalent.57

Panayiotopulos Syndrome

Panayiotopulos syndrome is a relatively common childhood seizure disorder that is typically characterized by autonomic seizures (eg, ictal vomiting) that are rare but sometimes prolonged in nature. Onset zone can be difficult to determine but is thought to typically involve the posterior cortex.58,59 Onset is between 1 and 14 years, although the majority of children with this syndrome will develop it between 3 and 6 years of age. It affects both genders about equally. Most of the seizures occur during the night. Recent studies have suggested that there may be subtle cognitive deficits associated with this syndrome, although a definitive pattern of impairment has not emerged. Mild deficits have been reported in attention, aspects of memory, reading and writing skills, and visual-spatial organization.60–62

West Syndrome

West syndrome involves a triad of features including infantile spasms, a pattern of interictal epileptiform activity referred to as hypsarrhythmia (ie, generalized, high-amplitude spike activity and delta/theta slow waves that are continuous when awake and fragmented during sleep), and mental retardation.63 Onset of West syndrome is usually during infancy (3 to 12 months), although it can occur in children through approximately 4 years of age. Autistic-like behaviors are common, and deficits in aspects of attention and visual processing have frequently been reported.64–66

PATTERNS OF COGNITIVE DYSFUNCTION OBSERVED IN THE FOCAL EPILEPSIES

Cognitive dysfunction associated with the focal epilepsies typically reflects the underlying brain regions disrupted by the focal onset zone and wider spread of the characteristic seizures experienced
by a given patient. While there are often very discrete, focal disruptions in cognitive performance,\textsuperscript{18} broader impairment can be seen as well, reflecting the obvious but often underappreciated fact that focal seizures frequently lead to disruption of widespread interconnected networks.\textsuperscript{67} As the focal epilepsies (particularly TLE) have been extensively studied in the context of epilepsy surgery, substantial research is available for review regarding these patients. A summary of the major findings follows, including a review of some of the associated surgical outcomes, which often mirror the effect of seizures on these regions. As noted, while these patterns occur more frequently in adults than children, knowledge of these brain-behavior relationships forms an essential basis for examining cognition in any patient. Pediatric findings in this area will be included when available.

**TEMPORAL LOBE EPILEPSY**

The prototypical pattern of deficit in presurgical TLE patients has been described as a material-specific pattern of episodic memory dysfunction.\textsuperscript{68} Episodic memory refers to the ability to learn and retain information related to a specific event or episode (e.g., recalling what you did today or where you parked a car), as opposed to semantic memory, which reflects knowledge of specific facts and information that tend to be unchanging and static (e.g., information about a historical figure).\textsuperscript{69,70} Auditory/verbal memory deficits are commonly observed in patients with dominant temporal lobe seizure onset, while visual memory deficits have been more associated with nondominant temporal lobe seizure onset.\textsuperscript{71–76} This pattern is supported by neuroimaging research as well, which has demonstrated that auditory/verbal and nonverbal stimuli often preferentially activate the left or right mesial temporal lobe, respectively.\textsuperscript{77,78} In contrast, not all studies have found material-specific deficits in TLE patients.\textsuperscript{79,80} Visual memory deficits associated with nondominant hemisphere dysfunction are more difficult to establish. Overall, a material-specific pattern of memory dysfunction can be observed in presurgical TLE patients, which can be helpful for confirming seizure focus in the individual patient. However, a variety of confounding factors can obscure this pattern in some individuals and can lead to divergent findings at both the individual and group level. Research suggests the material-specific pattern of memory dysfunction model may be affected by other task parameters and disease-related variables. For example, these findings may be easier to detect when examining both learning and recall patterns rather than only examining one-trial learning.\textsuperscript{81} Further, material-specific findings may be altered by side of seizure onset,\textsuperscript{82,83} and both temporal lobes may eventually be affected by a chronic duration of unilateral TLE.\textsuperscript{84}

There is also clear evidence that TLE patients, particularly those with dominant seizure onset, are more likely to experience deficits in naming ability (e.g., confrontational naming, naming to description) than healthy controls and patients with extratemporal seizure onset.\textsuperscript{85} Several studies have found that left TLE groups perform worse than right TLE groups on visual confrontational naming tasks,\textsuperscript{86–88} although right TLE groups often perform worse than healthy controls.\textsuperscript{87} A few studies have found both left and right TLE patients to be equally impaired preoperatively.\textsuperscript{89} Of note, patients may be impaired on these tasks for reasons other than seizure focus (e.g., patients with lower IQ show restricted scores, which likely result from their general level of impairment). Finally, patients undergoing dominant temporal lobe resection often experience significant declines on naming tasks,\textsuperscript{88,90} while those undergoing nondominant temporal lobe resection
do not,\textsuperscript{91} highlighting the critical involvement of the dominant temporal lobe in naming ability.

Recent research demonstrates that naming deficits of TLE patients may be more extensive than previously recognized. Some studies show that left (dominant) TLE patients are impaired at naming famous faces,\textsuperscript{92–95} and at least 2 of these studies suggest these deficits are worse following anterior temporal lobe resection. These findings also appear to extend to other visually complex item categories (eg, famous landmarks, nonunique animals) even when performance is completely normal on standard naming measures (eg, Boston Naming Test).\textsuperscript{92,96} These findings are also supported by functional imaging paradigms, highlighting a critical role for the anterior temporal lobes in naming certain object categories.\textsuperscript{97,98}

It is also relatively common for presurgical TLE patients to exhibit deficits on \textit{verbal fluency} tests (ie, generating items from categories, letter fluency).\textsuperscript{99} However, deficits in \textit{semantic fluency}, which involves generating items from specific categories, are often present preoperatively in patients with either dominant or nondominant temporal lobe seizure onset,\textsuperscript{100–102} and can be observed in patients with either dominant or nondominant frontal lobe seizure onset as well.\textsuperscript{103} As these findings could be affected by use of AEDs, some of which are specifically linked to deficits in these areas,\textsuperscript{104} it is important to note that other types of lesions in these regions result in semantic fluency deficits in patients without epilepsy.\textsuperscript{100,105} Semantic fluency tasks are complex in nature, requiring 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, presurgical patients with frontal lobe onset can sometimes be distinguished from those with temporal lobe onset using a semantic fluency paradigm that contrasts cued and uncued performance.\textsuperscript{103} This builds upon the idea that semantic fluency requires executive functions mediated by frontal lobe regions (ie, organization/retrieval problems making it difficult to search one’s own semantic memory stores or deficits involving initiation of action or self-monitoring)\textsuperscript{106} and a semantic memory component thought to be mediated by the temporal lobes.\textsuperscript{107}

While studies examining postoperative semantic fluency are limited in nature at present, there is evidence that performance in this domain (eg, generating types of animals) declines following dominant temporal lobe resection, and perhaps following nondominant temporal lobe resection as well,\textsuperscript{102} although the latter study had only a 1-week postoperative follow-up period. One additional study supports the idea that left and right temporal lobe resections may both affect semantic fluency performance, but found surgery effects may vary greatly between hemispheres depending upon object category.\textsuperscript{108}

Performance on \textit{letter fluency} tasks (eg, generating words that start with specific letters of the alphabet) can be impaired preoperatively due to both frontal and temporal lobe impairment,\textsuperscript{26,109} although performance on these measures typically does not decline following temporal lobe surgery. It has been proposed that deficits observed on this task in temporal lobe patients occur due to disruption of widespread neural networks secondary to epileptiform activity, and there is evidence that improvement on these measures can be seen if the temporal lobe patient becomes completely seizure free following surgery.\textsuperscript{110} A lack of decline on letter fluency tasks following temporal lobe surgery provides further evidence that the anterior temporal
lobe does not play a major role in the performance of this task.

Finally, despite the deficits mentioned in naming ability and generative fluency, presurgical TLE patients do not demonstrate a classic aphasia, unless it is caused by a separate neurological insult, such as a prior stroke. Most TLE patients do not exhibit problems with comprehension, speech fluency, or repetition of words or phrases, nor do they present with positive signs of aphasia in spontaneous speech (eg, paraphasic errors). Similarly, standard anterior temporal lobe resection does not typically lead to declines in these areas.91

With the exception of interest in visual memory, less attention has been paid to the nondominant temporal lobe in epilepsy. Most have assumed the nondominant temporal lobe 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 dominant TLE and resective surgery, can be particularly devastating, while many patients seem to be less hindered by visual memory declines. However, there is increasing evidence that we are not fully appreciating the functions of the nondominant temporal lobe, and more research is required to explore these issues. For example, little clinical work has been done exploring route learning/way finding, yet several experimental studies, often using TLE patients, suggest performance on these tasks is compromised by right anterior temporal lobe damage.111 Similarly, emerging studies indicate nondominant TLE patients often exhibit object recognition deficits. Several studies have demonstrated that postoperative right anterior temporal lobe patients exhibit recognition deficits for famous faces when compared to controls.92 One group has demonstrated that there were also recognition deficits for animals in some of these patients, and that a sense of “familiarity” was compromised as well (ie, they no longer had a sense that they had seen a famous individual previously).93,112 Patients with these deficits have greater difficulty recognizing familiar individuals, which can contribute to compromised social functioning.

Advanced statistical methods, such as cluster analysis, have recently been applied to neuropsychological data to look for patterns or subtypes of presurgical TLE performance. While promising, such studies are often based on small sample sizes and a preponderance of patients with early seizure onset and long durations of epilepsy.113 Hermann and colleagues suggested 3 common presurgical neuropsychological profiles for patients with TLE on the basis of such analyses.113 They referred to the most common pattern (47% of their sample) as a minimally cognitively impaired group. This subset did not differ from healthy controls in regards to IQ, perception, primary attention, or immediate memory. In contrast, they scored significantly worse than controls on tasks of delayed memory, aspects of language, executive functions (eg, generative verbal fluency), and cognitive/psychomotor processing speed. Scores in all of these domains were no more than 1 standard deviation (SD) below the mean of the control sample. These patients sound fairly similar to the more prototypical findings reported over the years in many respects, with the exception that they often showed disruption of both verbal and visual memory functioning. A second sample (24%), described as a primarily memory impaired group, exhibited immediate and delayed memory scores more than 2 SDs below the mean of the control sample, and also displayed mild deficits in all remaining cognitive domains. Finally, the third cluster (almost 29% of subjects) was described as a memory, executive, and speed-impaired group, performing more than 2 SDs below
controls on all administered measures. This group, which exhibited the greatest impairment, tended to be the oldest sample and to have the longest duration of epilepsy, took the most antiepileptic medications, and showed the greatest volumetric abnormalities. They also exhibited the worst cognitive course of the 3 samples. Work of this nature is promising but still premature, and needs to be replicated across epilepsy centers and with other tests while controlling for confounding latent variables (eg, epileptiform discharges).

Researchers at the Montreal Neurological Institute noted another divergent pattern of performance in the area of memory functioning, suggesting dominant and nondominant presurgical TLE patients may differ in terms of their ability to learn and retain information.81,114 They indicate 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 finding represents a possible way in which a task paradigm may interact with material-specific findings.

A somewhat unexpected finding in presurgical TLE patients involves evidence of executive dysfunction in such patients, which is typically thought to be mediated by frontal lobe 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.115 Evidence includes impaired performances observed on neurocognitive measures thought to assess frontal lobe function, such as complex problem solving tasks (eg, Wisconsin Card Sorting Test) and generative fluency measures.25 A few studies have also reported similar findings in children.116 Preliminary research has shown that patients with successful seizure control following temporal lobe resection may show significant improvement on these tasks;26,67 suggesting distributed networks are functioning better in the absence of electrophysiological disruption. Similarly, a few functional neuroimaging studies have shown that TLE patients often show hypometabolism of the frontal lobes that correlates with aspects of executive function performance.117,118 Likewise, fMRI studies provide evidence that patterns of frontal lobe cerebral activation can show “normalization” following successful temporal lobe resections.119

FRONTAL LOBE EPILEPSY

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 reflect only 10% to 20% of all surgical referrals. This often requires researchers to collaborate across epilepsy centers or to spend many years obtaining sample sizes with adequate power to answer basic questions. Research is also hampered by limitations in our understanding of frontal lobe 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. As studies of FLE are generally lacking, the conclusions drawn in this section should be viewed as more tentative in nature, although some clear trends have emerged.

Growing evidence suggests FLE patients often exhibit problems with response inhibition (ie, the ability to stop a behavior that is elicited by en-
Environmental cues). For example, one study that compared a sizeable number of FLE and TLE patients on a variety of motor tasks and presumed frontal lobe measures found that the FLE patients performed significantly worse than the TLE group on a measure of response inhibition (Stroop Color Word Interference Test). Of note, however, these findings have not been universally observed, with some studies finding that apparent deficits in response inhibition could be explained on the basis of primary limitations in reading or processing speed. A more recent study, which added a matched control sample to the previous paradigm of comparing FLE and TLE patients, demonstrated that the FLE group was impaired on an alternative version of the Stroop task when compared to healthy controls while the TLE group was not. The left FLE group was more impaired than the right FLE group or either TLE group on the response inhibition portion of the task. These studies also highlight the need to control for potentially confounding variables and having appropriate control samples. Finally, at least 1 study suggests that response inhibition performance may decline with unilateral frontal lobe resections.

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 on these tasks will occur with some frontal lobe resections. For example, one group 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. Another group 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 frontal lobe seizure onset have demonstrated these patients have greater problems with motor coordination than do healthy controls or children with other seizure onset.

Impairment on complex problem solving tasks has been observed in some FLE patients, and this finding has been observed both pre- and postoperatively. Milner published a classic case study involving patient “K.M.,” who demonstrated severe deficits on the Wisconsin Card Sorting Test following bilateral resection of the anterior frontal lobes 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, possibly due to the spread of seizure activity to frontal lobe regions.

Verbal fluency, as noted during 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 the component skills required for successful completion.

Design fluency is often decreased in FLE patients relative to other epilepsy patients or healthy controls, with some studies suggesting lateralization to the nondominant hemisphere and others not. At least one study has reported worse performance for patients with left FLE as compared to right FLE, while another demonstrated that patients with FLE performed worse than patients with TLE regardless of seizure onset laterality. A fourth study found that patients with FLE produced a similar number of designs as did patients with TLE but made more design errors. Discrepancies across studies may in part reflect differences
in the design fluency tasks themselves, as these measures differ in regards to the structure they provide, the presence or absence of concomitant task demands (eg, shifting attention), and the aspect of performance that is emphasized (eg, design generation, self-monitoring, shifting).

Some evidence exists that FLE patients may perform worse than TLE patients on measures of attention, working memory, and psychomotor speed. For example, one group demonstrated that a small sample of FLE patients \((n = 23)\) performed worse than a set of TLE patients on measures of attention and psychomotor speed. In the FLE group, no differences were observed on the basis of side of seizure lateralization or depending on whether or not there was a structural lesion. Another study also 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 several published studies with small numbers of FLE patients demonstrating deficits on a variety of tasks presumed to be sensitive to frontal lobe dysfunction, although most of these represent isolated findings that no one has attempted to replicate. Areas of dysfunction have included deficient cost estimation, an elevated rate of questions required to identify objects on the Twenty Questions Test, problems with determining temporal order, and aspects of social cognition (eg humor appreciation, recognition of facial emotion, perception of eye gaze expression). A few studies have reported that FLE patients have more behavioral problems than do other epilepsy patients and controls, but these appear to be mild as compared to findings obtained in other neurological patients with structural frontal lobe lesions.

Memory performance has not been studied extensively in patients with frontal lobe 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 studies have failed to demonstrate differences between FLE and controls on memory measures, others have reported worse functioning for FLE, at least on some types of tasks. FLE patients tend to perform worse on the more complex learning paradigms (eg, list learning tasks), with their limitations attributed to problems with encoding and/or retrieval.

A few studies suggest that certain aspects of learning and memory are perhaps more impaired in FLE than in other epilepsy groups. For example, Pigott and Milner demonstrated that preoperative FLE patients exhibit problems with release from proactive interference (ie, earlier memories interfere with learning new information). Milner attributed this deficit to problems with encoding and retrieval mechanisms. Another group more recently demonstrated this pattern in postoperative FLE patients, and provided further evidence that encoding/retrieval deficits may underlie this pattern. In this 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 (ie, they showed similar rates of retention over trials). Milner has also shown that FLE patients have difficulty structuring and segregating events in memory, 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. These findings applied to a wide range of stimuli, and may be material-specific in nature.

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 pre/post-surgical decline and most seeming to be underpowered. There are also numerous cognitive functions attributed to the frontal lobes that 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 and vice versa, presumably due to seizure spread across large interconnected neural networks. However, there also appear to be some distinct patterns between patients with FLE and TLE, which may yet be useful for confirming the region of seizure onset.

POSTERIOR CORTEXAL EPILEPSY

Some have argued that seizures arising from the parietal lobe, the occipital lobe, the occipital border of the temporal lobe, or a combination of these regions should be referred to as posterior cortical epilepsies (PCEs), as it is difficult to find clear anatomic or pathophysiological differences in these regions. The occurrence of posterior cortical epilepsies tends to be much rarer, and such conditions have been less well studied. Therefore, for the purposes of this review we have decided to consider all of the work related to neurocognitive profiles related to parietal or occipital lobe seizure onset together. One group reported that just over 5% of their total referrals for long-term video-EEG monitoring experienced PCE, and of these less than half were actually considered surgical candidates. Overall, this group probably 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 frontal lobe seizures.

Cognitive studies of PCE patients tend to be 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 study examined retrospective pre- and postoperative clinical data collected on 28 PCE patients between 1991 and 2000. These investigators reported that mild declines occurred in Performance IQ from the WAIS-R regardless of hemisphere being resected, and also reported declines in some measures of visual-spatial processing. They also reported that gains were made in some tasks thought to be mediated by frontal lobe regions and noted that there was no decline in WAIS-R Verbal IQ. However, not only was the sample size very small, but this resulted in a pool of subjects with potentially very different lesions (eg, left temporo-occipital vs 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 visuoperceptual abilities.

One very small, retrospective study examining the neurocognitive status of children with occipital lobe seizure onset suggested that such patients experience an elevated rate of scholastic difficulty, psychiatric disorders (ie, primarily depression), and cognitive dysfunction involving problems with face processing and making spatial judgments.

A recent study completed in Germany with a small series of occipital lobe epilepsy surgery patients prospectively examined visual-field integrity, demonstrating that a significant proportion of these
patients experienced visual-field defects postoperatively (ie, 42% of occipital lobe patients experienced new or increased visual-field defects). This study and others have shown that preoperative patients with seizure onset involving the mesial occipital lobe are more likely to exhibit baseline visual-field defects (eg, reports suggest approximately 40% to 50%) than those with lateral occipital lobe onset (eg, ranging from 0 to 18%). 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 PCEs 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 occipital lobe could cause problems with face recognition, object localization, color processing, or object recognition, and that lesions in the parietal region could cause deficits involving visual-spatial processing, object recognition, sensory discrimination, arithmetic skills, and aspects of reading and language functioning. Case studies and functional neuroimaging, for example, have suggested that there is a visual word form area in the area of the left lateral occipitotemporal sulcus that may be critical to reading, and have pointed to the left precuneus as a hub of the “default mode network” and potentially important for aspects of episodic memory and language.

Cognitive deficits observed in the focal and generalized epilepsies are summarized in the Table.

**Epilepsy Treatments and Cognition**

Many treatments such as AEDs and neurosurgery can also worsen cognitive function, regardless of epilepsy type. It has long been known that AEDs can have a negative effect on cognitive function, although this effect is generally considered to be small when recommended dosages and therapeutic blood levels are not exceeded and when polypharmacy is avoided. However, certain AEDs can affect cognition more severely in a subset of patients. In addition, some AEDs such as sodium valproate can adversely impact neurodevelopment. Questions remain as to whether AED treatment can result in chronic changes in brain structure and function. Epilepsy surgery can also lead to deficits when resected regions were relatively healthy and functional, or when destruction of fiber pathways decreases network connectivity. Post-surgical changes tend to mirror the findings related to the focal epilepsy that is being treated (eg, left temporal lobe patients are at risk for further decline in verbal memory, naming, and verbal fluency).

**Cognition Over the Lifespan in Epilepsy**

Research has recently demonstrated that cognitive, behavioral and psychiatric deficits often precede seizure onset in both children and adults. Deficits at onset may include attention, executive function, memory, processing speed, and visual spatial and constructional ability. In addition, nearly half of children with new-onset, idiopathic, or generalized epilepsy experienced more psychiatric problems prior to their first recognized seizures than did age-matched controls. These problems included depression, anxiety, and attention deficit/hyperactivity disorders. Although MRI structural abnormalities, outside of those causing symptomatic epilepsy, have been less consistently observed in new-onset patients, there is evidence of
restricted white matter development, compared to controls, 2 years after seizure onset.\textsuperscript{158}

Neurodevelopmental factors can affect cognition. For example, early life seizures originating in the language dominant cerebral hemisphere can lead to reorganization of function within the same hemisphere, or to the contralateral one, leading to compensated cognitive performance.\textsuperscript{159,160} Some patients with poorly controlled epilepsy experience progressive decline in function. Patients with an earlier age of seizure onset and a longer duration of seizures tend to show worse cognitive functioning than those with briefer seizure durations.\textsuperscript{161} While early studies were usually cross-sectional and lacked adequate control groups, more recent studies demonstrate that patients with uncontrolled epilepsy often show declines in memory. In addition, aging also affects patients with epilepsy, with some indication that refractory epilepsy is associated with higher risk for developing dementia.\textsuperscript{162} As noted above, some epilepsy syndromes show progressive changes in neuroimaging in addition to cognitive decline over time.\textsuperscript{163}

One longitudinal study demonstrated that at least 20\% to 25\% of patients with poorly controlled TLE experienced significant cognitive decline over 3 to 7 years. This group with the worst outcome was older, had the longest duration of epilepsy, took more medications, and had more abnormal brain volumes.\textsuperscript{113} Of note, a lack of practice effects upon repeat testing was also observed for nearly the entire sample of TLE patients (ie, the vast majority failed to show the expected gains typically observed in healthy controls undergoing repeat testing).

**EFFECT OF INTERICTAL AND SUBCLINICAL EPILEPTIFORM ACTIVITY ON COGNITIVE FUNCTION**

In addition to the effects of actual seizures, emerging research over the past decade offers strong support that interictal epileptiform discharges can have a pronounced, albeit transient, influence on cognitive function.\textsuperscript{2,3} Once again, focal discharges tend to produce restricted cognitive impairment, while more widespread discharges can affect wider regions of brain function, potentially leading to significant deficits that are not present to the same degree in the absence of these discharges. Assessment of function during these events can help characterize the patient’s seizure focus, and failure to recognize the influence of such activity can lead to erroneous conclusions about cognitive functioning.

**EVALUATING COGNITIVE FUNCTION IN EPILEPSY**

All patients with refractory epilepsy should be screened annually for cognitive and behavioral problems as part of their follow-up care with their treating neurologist.\textsuperscript{164} This can be as simple as just regularly inquiring about cognitive functioning during a yearly examination. For those with cognitive complaints, neuropsychological evaluation can be a useful tool for exploring the nature and veracity of their symptoms. Often there are reversible causes of cognitive dysfunction that are amenable to treatment (eg, modification of an AED regimen, management of depression). Obtaining a baseline assessment of cognitive function can be a valuable method to monitor for change in function over time, particularly when changes in treatment occur. This is quite important for children, as it can be used to identify those at increased risk of academic difficulty, and assist in formulating plans to offset further cognitive and functional deficits. It can also be useful for assessing the effects of AEDs on cognition and behavior, recognizing psychiatric comorbidities (including psychogenic

(continued on page 18)
Table. Summary of Cognitive Deficits Typically Observed in the Focal and Generalized Epilepsies

**Temporal Lobe Epilepsy (TLE)**

### Memory
Material-specific episodic memory deficits are frequently observed:71–73
- TLE patients with language-dominant (typically left) hemisphere seizure onset frequently exhibit deficits in auditory/verbal learning and memory.
- TLE patients with nondominant (right) hemisphere seizure onset often exhibit deficits in visual learning and memory.

More global memory deficits may be observed in bilateral epilepsy.

Left and right TLE patients may differ in terms of their ability to learn and retain information;81,114
- Left TLE patients may learn verbal information better than they retain it.
- Right TLE patients may exhibit significant problems learning novel visual information, but show less impairment involving its retention.

Semantic memory does not appear to be affected in TLE or by its treatments, but this area has not been thoroughly studied.

Deficits in route learning have been observed in TLE patients, but this has not been widely assessed.111

### Language
Both left and right TLE patients will perform worse than controls on both visual naming and naming to description tasks (left worse than right), but only the left TLE patients will decline following surgery.87,88

Significant naming deficits are more associated with dominant TLE dysfunction (algorithms exist for predicting side of seizure onset).170

Classic aphasia patterns are not typically observed (except in cases where aphasia occurs secondary to a structural lesion or injury).91

Verbal fluency deficits are common, including semantic (proper noun worse than common noun) and letter generation.99,103

Although research remains scant, it appears that verbal fluency deficits may occur as a result of left or right TLE dysfunction.102,103

Semantic fluency may decline after TLE surgery, but letter and verb fluency are more likely to improve (particularly following good seizure outcome).28

Reading deficits (although not as common) can occur depending on the location of seizure onset and potential surgery site, and have been observed in children.171

### Visuo-Perception/Visual-Spatial Processing
Visuo-perceptual and visual-spatial deficits are rare occurrences in TLE and its treatments.

Object recognition deficits appear to occur in right (nondominant) TLE patients, with significant evidence of problems with famous person recognition. There is also evidence of object recognition deficits involving animals and landmarks.13,92,93

Sense of familiarity/feeling of knowing also appears to be more impaired in right TLE patients (emerging research).13

### Executive Function
Deficits in this domain are common in TLE, although research suggests that such deficits may resolve if seizure freedom is obtained.

Specific areas of deficit have included complex problem solving, generative fluency, and response inhibition.25,26

### Other
Attention/working memory may be restricted in TLE patients, and studies have related this to mesial temporal lobe dysfunction as well as potential side effects of antiepileptic drugs.

Motor speed and strength deficits can be observed in TLE patients, which also may be related to seizure spread to frontal lobe networks.

This represents another area that has not been well studied.

Deficits in theory of mind, social cognition, and other aspects of emotional processing (eg, recognizing affect from facial expression or voice) have been observed in TLE patients (with some evidence of greater involvement of right temporal lobe regions in these functions).172

IQ scores are frequently lower than healthy controls.173

(continued on page 17)
Table. Summary of Cognitive Deficits Typically Observed in the Focal and Generalized Epilepsies (continued)

<table>
<thead>
<tr>
<th>Frontal Lobe Epilepsy (FLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
</tr>
<tr>
<td>Memory functioning in FLE has not been extensively studied.</td>
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<tr>
<td>FLE patients tend to perform worse on the more complex learning paradigms (eg, list learning tasks), with their limitations attributed to problems with encoding and/or retrieval. Some evidence that preoperative FLE patients exhibit problems with release from proactive interference (ie, earlier memories interfere with learning new information), and this impairment has been attributed to problems with encoding and retrieval mechanisms. FLE patients have difficulty structuring and segregating events in memory, and may exhibit problems with organization of materials to be learned and having difficulty recalling the temporal order of information. These findings applied to a wide range of stimuli, and may be material-specific in nature.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td>No significant naming deficits. Classic aphasia patterns are not typically observed (except in cases where aphasia occurs secondary to a structural lesion or injury). May exhibit verbal fluency deficits, which can involve a variety of generative tasks (eg, letter, semantic, verb). Not associated with reading deficits.</td>
</tr>
<tr>
<td><strong>Executive Functions</strong></td>
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<tr>
<td>A wide range of executive function deficits have been identified in FLE patients, although formal research is still in its infancy. Some areas in this domain that appear to be affected include complex problem solving, generative fluency (verbal and design), response inhibition, determining temporal order and sequence, and organization/planning.</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
</tr>
<tr>
<td>FLE patients appear to exhibit greater motor dysfunction across a wide range of tasks, including measures of motor speed and coordination, and bimanual hand sequencing.</td>
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<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Isolated studies have suggested that FLE patients are worse in a variety of areas, such as time estimation, cognitive estimation, and aspects of social cognition (eg, humor appreciation, recognition of facial emotion, perception of eye gaze expression) as compared to controls or other patient groups. Attention and working memory deficits appear to be common in FLE patients. Behavioral problems appear to be greater in FLE patients than in other focal epilepsy groups, although milder than observed in other neurologic syndromes involving the frontal lobe regions.</td>
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<tr>
<td><strong>Posterior Cortical Epilepsy (PCE)</strong></td>
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<tr>
<td>Less research has been completed in this area, making this a more tentative domain of knowledge. Visual functioning deficits (eg, visual-field loss) often occur in epilepsy patients with occipital lobe onset. Visual-spatial and visuo-perceptual deficits appear to be greater in patients with PCE, particularly those with parietal lobe onset. Face processing and object recognition deficits are possible. Some evidence of elevated rates of scholastic activity and restricted Performance IQ.</td>
</tr>
<tr>
<td><strong>Generalized Epilepsy</strong></td>
</tr>
<tr>
<td>General dysfunction, such as attention, working memory, and speed of motor and cognitive processing are often decreased in the generalized epilepsies. Executive functions are often compromised in generalized epilepsy. IQ scores and general function are often restricted as well. All of these deficits tend to be worse for patients experiencing greater seizure burden.</td>
</tr>
</tbody>
</table>
non-epileptic seizures in a small subset of patients), and for making appropriate referrals for neurologic rehabilitation when needed. In the neurosurgical context, neuropsychological testing is also useful for assessing risk/benefits of potential cognitive change with treatment, confirming the lateralization or localization of seizures, informing surgical planning in an attempt to protect eloquent functions, and measuring objective post-surgical change. The Wada procedure, fMRI, and stimulation language mapping can be useful tools for assessing and protecting cognitive function in the neurosurgical context as well.\(^{165-169}\)

CONCLUSION

The severity, pattern, and progression of cognitive dysfunction in patients with epilepsy is determined by many factors, including underlying disease pathology, duration and type of seizures, chronic AED exposure and other treatment effects, psychosocial variables, and neurodevelopmental and aging effects. Measuring cognitive functions, and understanding these modulating factors, allows appropriate interventions and provides understanding of their potential for change with treatment, and the likely trajectory of cognitive function over time. Reducing seizures, particularly achieving a seizure-free state, may reduce cognitive impairment and decline.

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