Introduction

The effects of epilepsy are felt in multiple aspects of the person’s life, including physical and mental health, cognitive function, educational achievements, vocational prospects, and family and peer relations. Cognition, which includes processes such as intelligent thinking, perceiving, remembering, reasoning, judging, expressing, and understanding, has an important role in the inception, evolution, and manifestation of many of these other aspects of function recognized to be compromised in people with epilepsy. Most cases of epilepsy have their onset in childhood, and thus seizure onset commonly occurs at a time that is essential to the development of basic cognitive, behavioral, and social skills that are crucial for long-term educational, vocational, and interpersonal adaptation. Therefore, an understanding of the cognitive deficits associated with epilepsy and of their predisposing factors is essential for appreciating the full impact of epilepsy.

Deficits in cognition are identified by people with epilepsy and their families as a significant comorbidity. For example, in a study by Arunkumar and colleagues, parents of 80 children and adolescents with epilepsy were asked to list in order of importance their concerns about living with or caring for their children with epilepsy; children who were old enough to be interviewed were asked to express (independently of their parents) their own concerns about having epilepsy. For both parents and children, the second most common item identified was that of the cognitive effects of epilepsy. Their worries included learning disabilities, academic difficulties, poor attention and concentration, and impoverished memory. In terms of impact, these issues are not specific to children; in a survey by the International Bureau of Epilepsy, 44% of patients with epilepsy complained of difficulty learning, and 45% of slowness in thinking. It has also been demonstrated that cognitive function is a significant predictor of self-evaluation of quality of life among adults with epilepsy.

Although the majority of people with epilepsy have normal intelligence, the distribution of Intelligent Quotient (IQ) scores is skewed toward lower values. A study by Smith and colleagues of 51 children with medically refractory epilepsy illustrated the wide range of cognitive functioning within this group. The
mean IQ was 84 (in the Low Average range, just over one standard deviation below the population mean of 100). The spread of IQ scores was considerable, spanning the Intellectually Deficient range (<1st percentile) to the Very Superior range (>99th percentile). In a study designed to document the occurrence of disabilities in an unselected population sample of children in Finland, 4–15 years of age, Sillanpaa\textsuperscript{13} reported that the prevalence of epilepsy in the study population was 0.68%. Among the children with epilepsy, neurological deficit was found in 39.9%, the most frequent neurological impairments being intellectual disabilities (ID) (31.4%), speech disorders (27.5%), and specific learning disorders (23.1%). Even in individuals with normal intelligence, reports of deficits in specific aspects of neuropsychological functioning are common, particularly in the areas of attention and concentration, memory, executive function, and academic achievement. Each of these areas will be briefly reviewed, as will a specific subset of developmental epilepsy syndromes that have a devastating effect on cognitive development. In addition, the effects of antiepileptic medications, and the potential effects of seizure-related variables on cognition, will be addressed.

**Attention and Concentration**

Selective attention, concentration, and the ability to sustain one’s focus are important for the efficient completion of many tasks in life. Deficits in attention are relatively common in people with epilepsy and can have far reaching consequences because attentional processes can also affect other aspects of cognition such as memory, language, and problem solving.\textsuperscript{14} Attentional deficits may be distinguished from generalized cognitive impairment. Depressed performance on tests of attention has been documented even in patients with normal IQ.\textsuperscript{15-16} Weaknesses in attentional processing were found to be disproportionate to the level of IQ in a sample of patients with ID.\textsuperscript{17}

Kalviainen and colleagues\textsuperscript{18} found that 30% of newly diagnosed adults with untreated seizures and no brain lesion had deficits in sustained attention and mental flexibility, even though attention span, speed of tracking, and psychomotor speed were intact. Patients with complex partial seizures are impaired on tasks requiring sustained concentration.\textsuperscript{19} Children with epilepsy have been shown to have slowed reaction time and impairments in selective and sustained attention.\textsuperscript{16,20-21} Not surprisingly, attentional deficits have been associated with educational problems. Teachers of children with epilepsy have reported difficulties in attention, concentration, and information processing, and they perceive these children as being less alert than their classmates.\textsuperscript{22}

An increased risk for attention deficit hyperactivity disorder (ADHD) in children with epilepsy has been reported in many studies,\textsuperscript{23} with estimates ranging from 17% to 58%. Prevalence of ADHD does not appear to vary by seizure type or between localization-related versus generalized epilepsies.\textsuperscript{23} Children with epilepsy and ADHD differ from other samples of children with ADHD by the
higher proportion of children with ADHD predominantly inattentive type and by an equal male:female ratio.\textsuperscript{24}

There are potentially important consequences for cognition of the coexistence of ADHD and epilepsy. A comparison of groups of children with complex partial seizures with and without ADHD, children with ADHD alone, and healthy controls demonstrated that those with seizures have significant difficulty with sustained attention and maintenance of consistency of responding over time regardless of diagnosis of ADHD. However, impairments on attention tasks were greatest in the combined seizure plus ADHD group.\textsuperscript{25}

There is little consensus on the seizure variables that contribute to the behavioral and cognitive aspects of inattention in epilepsy.\textsuperscript{23} There are studies that show that seizure type, seizure history, and drug therapy do not predict performance on tests of reaction time and attention,\textsuperscript{20,26,27} whereas Aldenkamp and colleagues\textsuperscript{28} found that patients with frequent epileptiform discharges and a history of drug polytherapy were most impaired on tests of vigilance and reaction time. It has been suggested that abnormal cortical or subcortical substrates underlie the attentional deficits, irrespective of seizure type.

Memory

Memory problems are among the most common complaints of people with epilepsy. Thompson and Corcoran\textsuperscript{29} conducted a survey of 760 people with epilepsy and asked about the frequency of everyday memory failures, such as forgetting where things have been put, of losing things, going back to check if one had done something that one had intended to do, and being unable to say a word, although the word was known and “on the tip of one’s tongue.” The people with epilepsy not only endorsed a higher frequency of such events, but also rated the nuisance arising from such memory failures as higher than did people without epilepsy. Of further interest was the finding that relatives rated the frequency of forgetting among their family members with epilepsy as higher than did the persons themselves, suggesting that people with epilepsy may forget how often they do forget.

Memory deficits are most consistently observed in patients with epileptogenic foci involving the mesial temporal lobe. In most instances, the impairments seen with unilateral foci are material-specific in nature, as related to the hemisphere of the lesion (for reviews see Jones-Gotman and Smith\textsuperscript{30}; Smith and Bigel.\textsuperscript{31}) Studies have shown that, in patients with speech representation in the left hemisphere, epilepsy involving the mesial left temporal structures typically results in impairments on tasks of verbal learning and verbal memory. These individuals have difficulty with material presented in stories or text, with real or nonsense words, verbal paired-associate learning, recall of the names of actual or pictured objects, and to learning and remembering names of unfamiliar people. Right temporal lobe epilepsy has been associated with impaired performance on tasks in which the stimuli are difficult to verbalize, such as complex geometric designs, on learning across
trials of lists of designs, and on the recognition of faces, recurring nonsense figures, and unfamiliar tonal melodies.30,31 The specificity between side of focus and type of material is not always found, and more recently it has been argued that the memory requirements of the task, specifically learning over several trials, may be the critical feature in determining the specificity of a lesion effect.32-33

Bilateral damage to the mesial temporal lobe structures can result in a severe global amnesia.34 In patients with bilateral epileptogenic foci, the memory impairments are generalized in nature, involving all modalities of input and both verbal and nonverbal memoranda. However, despite having strikingly impaired memories, most patients with bitemporal epilepsy are not amnesic.30,35

The study of memory in epilepsy has also examined remote and autobiographical memory. It has been shown that people with temporal lobe epilepsy have difficulty retrieving information based on past experiences as well as information based on recent events or new learning.36-39 Despite these deficits in the personal episodic realm (specific events), memory for personal semantic information (facts about oneself) can remain intact.37,39 These remote memory deficits have been demonstrated in both left and right temporal lobe epilepsy, although in some instances they may be related to the hemisphere of seizure onset. For example, right but not left temporal lobe foci have been associated with impairments in familiarity judgments for famous faces, but foci in either temporal lobe can result in impairments in naming such faces or in providing information about famous people.39

Like adults, children with temporal lobe epilepsy experience memory deficits. For children with medically controlled seizures, findings with respect to material-specific effects have been equivocal, with some studies demonstrating verbal memory deficits in conjunction with left temporal foci, and spatial memory deficits in conjunction with right temporal foci30-41 and others not showing this pattern of specificity.44-45 Children with intractable seizures arising from the temporal lobe typically have memory disorders that have not been described as material-specific.46-51 This difference between adults and children may have to do with age of seizure onset or duration of epilepsy.

Executive Functions

A set of complex cognitive processes have been grouped under the construct “executive functions,” or those skills required to maintain an appropriate problem-solving set for the attainment of future goals. Among patients with epilepsy, as with other types of neurological compromise, impairments of executive function have been associated with frontal-lobe abnormality. In a comparison of adults with frontal lobe epilepsy and temporal lobe epilepsy, the former were found to have inferior performance on tests of memory span, visual motor speed, selective attention, visual perceptual speed, response inhibition, verbal fluency, concept formation, planning, and motor coordination.52 Factor analysis of the results identified four
frontal subfunctions: speed/attention, response maintenance and inhibition, motor coordination, and short-term memory. Both frontal and temporal lobe epilepsy were associated with deficits in the short-term memory and speed/attention domains, whereas only patients with frontal-lobe seizures were characterized by impairments in the motor coordination and/or response inhibition domains. In patients with epileptogenic foci in the frontal lobes, impairments have not been found to be related to the laterality of the focus, or to the site of localization within the frontal lobe.52-54

Case studies of children have described the onset of frontal-lobe seizures accompanied by behavioral, cognitive, and motor impairments that were reversed when seizure control was obtained with pharmacotherapy.55,56 Group studies have demonstrated that children with frontal lobe epilepsy have deficits in attention, planning, categorization, organization, memory, impulse control, verbal fluency, comprehension, and motor coordination.57-62 Prevost and colleagues63 found a significant incidence of attention deficits, behavior problems, and learning disabilities in children with nonlesional frontal lobe epilepsy. In these group studies, the appearance of abnormalities appears to be independent of seizure control.

In children with medically controlled epilepsy, some differences have been documented between the effects of frontal and temporal lobe seizures. Those with frontal lobe seizures perform more poorly on motor coordination, verbal fluency, and planning ability, whereas children with temporal lobe seizures perform more poorly on tests of verbal memory.58,59,61 In children with intractable epilepsy, differences do not appear to be as prevalent, and these two groups have been shown to have similar performance on tasks of verbal fluency, comprehension, attention, and verbal and visuospatial memory.57,60

### Academic Function

Children with epilepsy are at risk for delays in academic skills and for specific learning disabilities in the core academic areas of reading, spelling, and arithmetic.64-67 The nature of the learning difficulties is not limited to these traditional areas, and underachievement has been reported for all academic subjects.68 Prevalence rates of learning problems reported in the literature have ranged from 5–70%.69,70 While these problems may be especially prevalent in children with chronic seizures, there is a relatively high risk, even among those with relatively recent onset and with uncomplicated, well-controlled seizures.71,72 A prospective study of childhood-onset epilepsy suggested that even in individuals who eventually became medication and seizure free, academic problems persisted into adulthood.73

There are large individual differences in the incidence, nature, and severity of the academic delays, and a constellation of factors has been identified as potential determinants. Seizure severity, seizure frequency, and side effects of antiepileptic...
drugs (AEDs) have been identified as contributors.\textsuperscript{45,72,74} Child adaptive competency, (a variable that includes constructs such as degree of effort, behavior, learning, and mood) is related to achievement in both children with recent-onset and chronic epilepsy.\textsuperscript{71,72}

The academic deficits can be differentiated from more generalized impairments in intelligence and cognition, although deficits in the latter such as in attention, motor fluency, alertness, speed of information processing, and memory, can contribute to the struggles of these children in learning in the school environment.\textsuperscript{45,74} For example, in a narrative study of quality of life,\textsuperscript{69} youth with intractable epilepsy reported that they frequently felt that they were physically or mentally unavailable to learn and, therefore, were unable to count on a continuous and integrated learning experience. Fatigue and problems with memory were identified as influences that compromised their performance at school. Furthermore, children with epilepsy may differ from children with learning disabilities arising from other etiologies, in terms of the underlying cognitive correlates; for example, children with epilepsy have slower reaction times on a variety of simple and complex auditory and visual reaction time tasks than do learning disabled children without epilepsy.\textsuperscript{75}

Level of intelligence influences the likelihood of learning disability. In a population-based cohort of adults with childhood-onset epilepsy,\textsuperscript{76} 76\% had a history of learning disability. The occurrence of learning disability was closely linked to IQ. Half of the patients (51\%) with learning disability had ID. Among those with IQs in the normal range or above, the prevalence was 57\%, in the mentally near-normal (IQ=71–85) it was 67\%, and in those with ID (IQ >71), all had learning disabilities by self-definition. Intellectual disabilities and subsequent learning disability were predicted by presence of cerebral palsy, onset of epilepsy before the age of six years, and poor early response to AEDs. Among intellectually normal or near-normal subjects, a symptomatic etiology of epilepsy was the only predictor of a learning disability. The degree of learning disability significantly affected medical, social, and educational long-term outcomes.

One approach to understanding the relationship between epilepsy and academic achievement might be in the comparison of epilepsy syndromes.\textsuperscript{77} Children with idiopathic generalized or with localization-related epilepsy have been found to have a higher probability of mainstream schooling than those with symptomatic or cryptogenic generalized epilepsy or undetermined epilepsy syndromes.\textsuperscript{78} Vanasse and colleagues\textsuperscript{79} examined reading skills in children with temporal lobe epilepsy, frontal lobe epilepsy, or absence epilepsy. All groups were reading at levels approximately two years behind expectations. Children in the frontal lobe group, and to a lesser extent, those in the absence group, had deficits on tasks related to phonological processing, whereas those with temporal lobe epilepsy did not differ from controls. An epileptogenic focus in the frontal lobe apparently affects the phonological underpinnings of reading. This finding suggests that the syndrome approach may reveal a relationship between specific epileptogenic features and other component processes underlying the academic skills.
Other Cognitive Functions

In patients with foci in the left lateral temporal cortex, mild impairments have been documented in the areas of verbal perception, object naming, and language processing. Impairments in span of attention or working memory have also been noted in patients with temporal neocortical epilepsy. An association between impaired discourse ability and working memory has been found in patients with temporal lobe epilepsy. Mild visual perceptual deficits have been reported in association with foci in the right temporal lobe.

Intractable Epilepsy Syndromes of Childhood

Intractable epilepsy syndromes of childhood onset are associated with a high risk for cognitive impairment and frequently for global developmental delays. To illustrate this association, a brief review of four syndromes follows.

Infantile Spasms.

The syndrome of infantile spasms begins in the middle of the first year of life with the onset of characteristic flexor spasms. Development of cognitive and motor function may be normal or abnormal prior to onset, and deterioration in development commonly, although not inevitably, accompanies the onset of seizures. The developmental outcome is likely related to the underlying etiology; many of the symptomatic cases are seen in association with genetic disorders or cortical malformations that in themselves carry risk for generalized developmental delays.

Lennox-Gastaut Syndrome.

Lennox-Gastaut syndrome is characterized by three features: multiple seizure types, slow spike and wave disturbance with bursts of fast rhythms on EEG, and psychological disturbances, including psychomotor delay, personality disorders, or both. In some children with no identifiable etiology, psychomotor retardation may be evident before the onset of seizures, but the psychological abnormalities typically appear in conjunction with the first seizure or evolve shortly thereafter. The level of IQ deteriorates progressively over time, either as a consequence of developmental arrest or loss of previously acquired skills. The vast majority of cases have marked ID, which may be most pronounced in children who previously had infantile spasms.
Landau-Kleffner Syndrome

The syndrome of “acquired aphasia with convulsive disorder in children” was first described by Landau and Kleffner in six children with normal early language development who suddenly developed aphasia in relation to an epileptic disorder. The language disturbance typically first involves verbal comprehension (classically a verbal auditory agnosia) that may be mistaken for an acquired deafness. The usually gradual deterioration in verbal production follows the loss of comprehension, occurs together with it, or even precedes it. Several variables can influence the severity and the duration of the language disorder: frequency of the epileptic discharges in the language zones, the duration of the epileptic disorder, the spread of the epileptic discharges to the homologous contralateral cortex, and the efficacy of the AED therapy.

Severe Myoclonic Epilepsy in Infancy

Severe myoclonic epilepsy in infancy typically has its onset in the middle of the first year of life and begins with tonic or tonic-clonic seizures, with later occurrence of myoclonic jerks, atypical absence seizures, and partial seizures. Development prior to the onset of seizures is usually normal, but later development is slow, behavioral problems are frequent, and motor skills become compromised. The cognitive impairments are usually generalized, and the behavioral features include hyperactivity, autistic traits, and impaired interpersonal relations.

Antiepileptic Drugs

Antiepileptic drugs reduce the propensity for seizures by decreasing neuronal excitability or by enhancing inhibitory neurotransmission, and by these same mechanisms can produce cognitive side effects. A number of physical side effects, such as sedation, somnolence, insomnia, or dizziness, may affect multiple aspects of cognition. Other effects may more directly impact specific aspects of cognition, such as psychomotor slowing, reduced vigilance, distractibility, language impairment, and memory impairment. These side effects can significantly impact on daily functions in multiple domains. It has been shown that there is a strong negative relationship between self-reported adverse effects of AEDs and perception of quality of life.

Many reviews of side effects of AEDs distinguish between “traditional” and “newer” drugs. The traditional category – drugs available prior to the 1990s – includes phenobarbital, phenytoin, valproate, primidone, ethosuximide, and carbamazepine. These drugs have been associated with clinically significant side effects.
effects. Of these, phenobarbital has been most frequently associated with adverse cognitive and behavioral consequences, including attentional deficits, hyperactivity, decreased short-term memory, and conduct disturbances. Phenytoin has been associated with declines in intellectual function. These effects appear to be most pronounced in patients with more severe epilepsy, coexisting neurobehavioral disorders, and drug toxicity. Many of the studies on these traditional AEDs have been confounded by methodological limitations, and it is not always possible to disentangle potential side effects from effects due to ongoing seizures, preexisting disorders, or other factors.

Studies that have attempted to control for such confounds have not always found effects of AEDs. For example, Williams and colleagues followed up with 37 children with newly diagnosed epilepsy for six months. A baseline assessment was conducted prior to the initiation of AED treatment, and performance was compared with a control group of children with newly diagnosed epilepsy. Children were treated with monotherapy, and blood serum levels were in the therapeutic range throughout the six-month follow-up period. At baseline, significant group differences were not present, although the children with epilepsy performed more poorly than the controls on all cognitive measures and were rated as having more problematic behavior. However, changes in performance over the six months did not differ between the children with epilepsy and the control group.

In healthy adult volunteers, in whom the effects of the drugs can be assessed without the confounds of seizures, neuropathology, genetic vulnerabilities, and psychosocial factors, the effects of the traditional AEDs have been modest and similar across carbamazepine, phenytoin, and valproate, whereas phenobarbital has a more adverse effect than the latter two. However, all of phenobarbital, phenytoin, valproate, and carbamazepine result in impairments of cognitive function and/or motor speed when compared with a no-drug control condition. The newer AEDs, including gabapentin, levetiracetam, lamotrigine, oxcarbazepine, and tiagabine, tend to be associated with fewer side effects than the traditional ones.

Topiramate has documented effects in both healthy controls and patients with epilepsy, adversely affecting concentration, processing speed, and aspects of verbal function, including intelligence, fluency, learning, and short-term memory. The effects of topiramate are accentuated when administered at higher doses, with rapid titration, and in combination therapy.

Many of these findings are based on trials and clinical experience with adults, and the results may not generalize to all ages. There may be some age-specific side effects of AEDs that can reduce cognitive efficiency, such as depression in adults and aggression and hyperactivity in children. There is a pressing need for well-designed AED drug trials in both the elderly and in children. The elderly may have different absorption and metabolic rates than younger adults, there are age-related physiological changes that influence the metabolism of AEDs, and the elderly tend to have a greater number of other medical conditions. The effects of AEDs may be different in the developing than in the adult brain. Long-term consequences of AEDs can be particularly devastating in children, as even modest cognitive impairments may have cumulative consequences if they affect learning and limit
the acquisition of academic skills. Children with ID may be more susceptible to cognitive loss after AED treatment. Children with pre-existing behavior disorders such as attention deficit disorder may be more vulnerable to an exacerbation of behavioral difficulties.

Other Influences on Cognition

A multitude of studies have addressed questions about the specific features of the seizure disorder in their implications for the appearance and severity of cognitive deficits. Some of these features have been covered in more depth (such as the localization and laterality of seizures) or have merely been touched on in the preceding sections. In this final section, a discussion of epileptiform discharges, duration of epilepsy, frequency of seizures, and age is presented.

Attention, language, and memory may be disrupted by subclinical epileptiform discharges, a phenomenon known as transient cognitive impairment. Transient cognitive impairment apparently results from the effects of these subclinical discharges on brain function, rather than from the underlying brain pathology.

Two interrelated variables have received considerable attention for their impact on cognitive function: duration of epilepsy and age of seizure onset. Hermann and colleagues found an association between age at seizure onset, neuropsychological function, and brain structure. Adults with onset of temporal lobe epilepsy earlier in childhood (mean of 7.8 years) had a more diffuse pattern of cognitive deficits (i.e., greater degree of impairment and evident across a greater number of cognitive domains), and showed more magnetic resonance imaging structural abnormalities (particularly a reduction in white matter volume) that extended into the extratemporal regions, beyond the site of epileptogenic focus, than did adults with later-onset temporal lobe epilepsy (mean of 23.3 years). This study is important in that it demonstrated an association between age of onset, cognitive dysfunction, and extent of brain abnormality. The authors concluded that childhood-onset temporal lobe epilepsy is associated with an adverse neurodevelopmental impact on brain structure and cognition.

Thompson and Duncan reported on 136 patients with a median duration of epilepsy of 35 years who had undergone cognitive testing on two occasions with a median retest interval of 13 years. They found decline in all areas assessed (intelligence, memory, naming, verbal fluency, and mental flexibility). This finding is consistent with earlier studies. For example, a review of longitudinal studies of intelligence in children with epilepsy identified several studies in which patients with a four-year or longer duration of seizures showed a decline in intelligence, suggesting the conclusion that seizures had a causative role in this decline. Declines in intelligence over time have been reported among patients with poor seizure control, whereas patients who had experienced improvements in seizure control have shown gains in intellectual performance. Among patients with temporal lobe epilepsy followed over a four-year interval, cognitive prognosis was
poor for a subset (20–25%) characterized by chronicity of epilepsy, older age, lower intellectual ability at baseline, and more baseline abnormalities in quantitative magnetic resonance volumetrics.\textsuperscript{121}

Other studies have failed to identify changes related to the duration of epilepsy or changes in seizure control.\textsuperscript{122,123} In attempting to reconcile these differences across studies, it has been suggested that seizure frequency and type rather than duration may be of importance. For example, it has been found that the frequency of generalized tonic clonic seizures predicts decline in cognitive function among chronic epilepsy patients.\textsuperscript{116,124} A history of status epilepticus has been associated with decline in memory.\textsuperscript{116,124}

The majority of studies that have investigated age as a factor in cognitive impairment focused on age at seizure onset or duration. More recently, attention has been given to the elderly, a group at risk for developing epilepsy and for cognitive impairment associated with aging.\textsuperscript{116} Elderly patients with focal epilepsy have been found to differ from demographically matched controls in diverse areas of cognition, including attention, perseveration, memory, construction, conceptualization, and verbal fluency.\textsuperscript{125–127} Age of seizure onset and seizure duration were not associated with neurocognitive function,\textsuperscript{125} but performance was related to AED polytherapy.\textsuperscript{125–127} Seniors with epilepsy were found to have more pronounced deficits in aspects of executive function than older adults diagnosed with mild cognitive impairment.\textsuperscript{126}

**Conclusion**

This review has identified the increased risk for impairment in multiple aspects of cognitive function in persons with epilepsy. The precise factors determining the appearance or severity of these deficits are not completely understood. Nonetheless, individuals with epilepsy, families, social support networks, and health care providers need to be aware of these issues in order to understand the full impact of epilepsy. Proper and early identification is necessary to provide early developmental interventions, appropriate school programming, vocational counseling, supportive work settings, and a safe environment for promotion of independence across the life span.

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