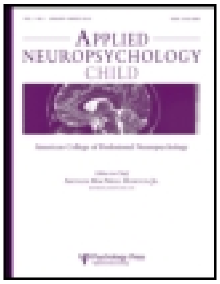

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# Attention and Executive Functions in Children With Epilepsy: What, Why, and What to Do

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# Attention and Executive Functions in Children With Epilepsy: What, Why, and What to Do

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Attention and executive function deficits are a common sequelae of many neurological conditions of childhood. Those with epilepsy frequently show such deficits, as executive dysfunction is common in all epilepsy syndromes of childhood. The purpose of this article is to review what is known about attention and executive functions, including the neurological underpinnings of these skills. Then, general cognitive function and dysfunction in childhood epilepsy is discussed with a special focus on attention and executive function impairment. Finally, treatment considerations for children and adolescents with these deficits are reviewed and future directions are discussed.

*Key words:* *ADHD, attention, epilepsy, executive functions*

## INTRODUCTION

The term "executive functions" refers to a set of higher-order cognitive processes mediated by neuroanatomical circuits of the prefrontal cortex (PFC) and its connections. Typically considered are functions such as inhibition, working memory, initiation, flexibility, and planning (Arnsten & Li, 2005; Krain & Castellanos, 2006). Executive dysfunction has been implicated in a variety of medical conditions, as well as developmental disorders and psychiatric illnesses (Barch, 2005; Borella, Carretti, & Pelegrina, 2010; Diamond, 2005; Taylor Tavares et al., 2007) and predicts functional outcomes such as academic achievement, social functioning in children, and occupational attainment later in life (Baron, 2004; Duncan et al., 2007; Miller & Hinshaw, 2010).

The development of executive functions begins in early childhood, with certain aspects of working memory and inhibition developing in early infancy and continuing to develop well into young adulthood (Anderson & Reidy, 2012; Diamond, 2013; Moffitt et al., 2011). Currently, there is no single definition of executive functioning and several models have been described. Whereas older models have discussed the concept of a central executive driven by the frontal lobes, current models view these skills as a collection of heterogeneous, higher-order cognitive processes (Diamond, 2013; Stuss, 2011). The specific functions that have been hypothesized to comprise executive functions include

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inhibition, initiation, planning, self-monitoring, self-regulation, and flexibility. For example, Diamond (2013) describes executive functions as consisting of inhibitory control, working memory, and cognitive flexibility. Inhibitory control is defined as the ability to regulate impulses and inhibit behaviors, which functionally allow individuals to resist temptations and not act impulsively (Diamond, 2013). Working memory is the ability to hold information in mind, manipulate it, and use it to solve problems, while cognitive flexibility allows one to adjust their approach to problems, adjust to task demands, and switch between tasks. Other models, such as the executive control system (Diamond, 2013), include attentional control, cognitive flexibility, goal setting, and information processing, and they note overlap and interaction between these processes. For example, working memory and attentional control are necessary for inhibiting behavior, and inhibition of irrelevant information is necessary to maintain focus on a task and a particular goal. Although there are several differing models of executive function, they generally describe the main functions as orienting and maintaining attention and regulating behavior.

Historically, the frontal lobes have been thought to be primarily responsible for executive functioning, but the neuroimaging literature demonstrates more specific involvement of the PFC and its multiple connections to other cortical and subcortical structures. PFC function is crucial for attention regulation, inhibition of distractions, and sustained effort (Arnsten & Li, 2005). Moreover, right PFC has been implicated in inhibitory control and performance on go–no go tasks (Rubia, Smith, Brammer, & Taylor, 2003). Researchers have also attempted to differentiate between the cognitive and emotional aspects of executive functioning, with cognitive executive functions being labeled as "cool" and regulated by the dorsolateral PFC, while emotional or "hot" executive functions are said to be regulated by the orbital and medial PFC. Despite the consensus on the involvement of the PFC in executive functioning, dysfunction of the PFC is neither necessary nor sufficient for executive dysfunction, and this speaks to the multiple neural networks involved, dysfunction in any of which can result in executive impairment.

Tau and Peterson (2010) described the development of neural networks that subserve executive functions in children and noted that even in infancy, children can be seen to activate frontoparietal regions during simple working-memory tasks. Notably, young children's cortex is inefficient in complex working-memory tasks and recruits ventromedial regions such as the caudate nucleus and insula (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Tsujimoto, Yamamoto, Kawaguchi, Koizumi, & Sawaguchi, 2004). Efficiency improves through adolescence, and by adulthood, more consistent recruitment of frontoparietal regions is observed during complex working-memory tasks (Tau & Peterson, 2010). Similarly, functional magnetic resonance imaging findings have demonstrated that increasing response inhibition and self-control in children is related to increased activation of the frontal and striatal networks. Hence, maturation of frontoparietal and frontostriatal networks is reflected in increased behavioral and attentional control (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002).

Deficits in the frontoparietal and frontostriatal networks have been implicated in various developmental, psychiatric, and acquired neurological disorders both in children and adults. Moreover, many of these disorders have shared executive function impairments. For example, executive function deficits have been found in children with autism, conduct disorder, Tourette syndrome, and various learning disorders (Peterson et al., 2003; Rubia et al., 2009). In addition, PFC dysfunction as well as accompanying inhibition and executive function deficits have been reported in individuals with depression, obsessive-compulsive disorder, and schizophrenia (Barch, 2005; Forbes & Dahl, 2005; Menzies et al., 2007).

Children with executive function deficits often struggle academically, socially, and functionally, as executive-functioning skills are necessary for completion of even the most basic daily tasks. For example, children with poor inhibitory control often present as hyperactive and impulsive at home and in the classroom. They may struggle with regulating their motor movements, as well as staying in their seat, waiting their turn, or waiting to be called on in the classroom. These children often require extra attention from their teachers and parents to help them manage their behavior, and they frequently get into trouble in school. They may begin to feel as if they are unable to control their behavior and that they are "bad kids," which often leads to decreased self-esteem and depressive symptoms.

In contrast to children who are behaviorally impulsive, children with working-memory problems are often calm and, at times, hypoactive. They may be slower to complete tasks and appear to daydream frequently. They have difficulties keeping track of task steps and struggle to complete tasks independently. They require much support to complete their assignments and homework and often appear inattentive. In addition, children with executive function deficits frequently struggle with planning and organizing of tasks and have difficulties in managing their time. They procrastinate on their assignments or forget to hand them in even when they have been completed. Academic deficits are also frequently observed in children with working-memory and organizational difficulties. For example, many children with working-memory problems struggle with reading comprehension due to difficulties in keeping track of what they read to fully make sense of it (Sesma, Mahone, Levine, Eason, & Cutting, 2009). Written expression is also a common area of concern given the high organizational and planning demands of this academic task. Given these symptoms, children with executive function deficits often underachieve and underperform compared with their peers without executive function deficits, despite frequently strong intellectual abilities. Besides the immediate impact executive function deficit have on children's functioning at home and at school, they frequently continue to underperform throughout life, with functional and occupational difficulties observed later in life (Miller & Hinshaw, 2010). Socially, children with executive function deficits may miss social cues or annoy children with their hyperactive and impulsive behaviors. While executive function deficits are common in a wide variety of childhood disorders, attention-deficit hyperactivity disorder (ADHD) is the most common childhood disorder that frequently presents with executive dysfunction, as well as associated academic, social, and functional difficulties (Biederman et al., 2004).

## EXECUTIVE FUNCTIONING AND ADHD

ADHD is the most commonly diagnosed psychiatric disorder in children, with a worldwide prevalence of more than 5%. Currently, there are four subtypes of ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*-Fifth Edition (DSM-V): ADHD-Predominantly Inattentive Presentation (ADHD-I), ADHD-Predominantly Hyperactive/Impulsive Presentation (ADHD-H), ADHD-Combined Presentation (ADHD-C), and Other Specified ADHD for those children who present with enough symptoms to warrant attention but not enough to qualify for a full diagnosis. ADHD-I is characterized by the presence of inattention, distractibility, careless work habits, and disorganization. The ADHD-H presents with symptoms of hyperactivity and impulsivity in the absence of inattention and is the least commonly occurring subtype. The third subset of children present with symptoms of inattention, as well as overactivity and impulsivity. Given that the symptoms of ADHD relate to regulation of attention as well as behavior and impulses, it is expected that children with ADHD demonstrate deficits in executive functioning. This is an area that has received much study with regard to neuropsychological functioning, neuroimaging, and pharmacological and behavioral interventions. The most commonly observed executive deficit among individuals with ADHD has been poor inhibitory control (Diamond, 2005). However, it has been hypothesized that while inhibitory control is the main executive function deficit in ADHD-C, working memory is the underlying dysfunction in ADHD-I (Diamond, 2005). The literature has been mixed, with some studies demonstrating working-memory deficits in children with ADHD-I and others noting response inhibition as the core deficit across ADHD subtypes. Moreover, there has been increasing evidence for executive function deficits being related to the inattentive symptoms of ADHD rather than the hyperactive/impulsive symptoms (Krain & Castellanos, 2006). Another issue to consider is that although many children with ADHD demonstrate impairments in executive functioning, there are many children with ADHD who do not display such executive deficits, leading some researchers to theorize that there is a subtest of ADHD that presents with executive functions as a core deficit (Krain & Castellanos, 2006; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005).

The combination of ADHD and executive function impairment has been shown to have overall poorer outcomes, with children with ADHD and executive dysfunction fairing worse than their ADHD-only counterparts in academic achievement (Nigg et al., 2005). Although this association does not occur for all individuals with ADHD, it is not unexpected given the underlying neural networks implicated in executive dysfunction and in ADHD. Overall, children with ADHD on average have smaller brain volumes compared with control children. In addition, disruption has been demonstrated in the frontostriatal circuit, including the frontal lobes, basal ganglia, and cerebellum (Krain & Castellanos, 2006). Specifically, children with ADHD have smaller PFC volumes (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Additionally, the typical asymmetry of the frontal lobes, whereby the right frontal lobe is larger than the left, is often reduced in individuals with ADHD due to smaller right frontal regions (Castellanos et al., 1996).

Studies have also demonstrated differences in the size of the dorsolateral and orbitofrontal PFC among individuals with ADHD (Hesslinger et al., 2002; Yeo et al., 2003). Differences in basal ganglia structures, particularly the caudate nucleus and putamen, have been reported, although findings have been inconsistent (Castellanos et al., 2002; Pineda et al., 2002). Lastly, smaller cerebellar volumes have also been noted (Castellanos et al., 2002). Notably, these structural neuroanatomical findings have been associated with greater ADHD symptom severity and overall global functioning ratings (Castellanos et al., 2002). Poorer performance on executive function tasks of attention and response inhibition has also been correlated with PFC and caudate volumes (Hill et al., 2003; Semrud-Clikeman et al., 2000). Given the multiple structures involved in ADHD, as well as in executive function processes, it is not surprising that disruption of even part of that complex network can result in executive function impairment. As such, executive deficits are a common finding in various neurodevelopmental disorders such as autism and learning disorders, as well as genetic disorders, acquired brain injury, hydrocephalus, and of course epilepsy.

## GENERAL COGNITION IN CHILDREN WITH EPILEPSY

Not surprisingly, given the spectrum of epilepsy severity with which patients may present, children with seizures have a wide range of cognitive ability. It is well known that children with epilepsy have poorer school performance than what would be predicted based on overall intelligence alone (Farwell, Dodrill, & Batzel, 1985). In children with epilepsy, there are several factors that predict neuropsychological impairments. For example, age of epilepsy onset is a robust predictor of overall cognitive dysfunction across numerous studies (Berg et al., 2008; Farwell et al., 1985; O'Leary et al., 1983; Schoenfeld et al., 1999; Sherman, Brooks, Fay-McClymont, & Macallister, 2012). Likewise, high seizure frequency (Bourgeois, Prensky, Palkes, Talent, & Busch, 1983; Farwell et al., 1985; Sherman et al., 2012), multiple seizure types (e.g., generalized seizures [generalized tonic-clonic seizures, absence seizures], partial-complex seizures), and the need for more than one antiepileptic drug (Bourgeois et al., 1983; Bulteau et al., 2000; Sherman et al., 2012) have been associated with greater cognitive dysfunction. It is also important to recognize that specific antiepileptic medications have more or less favorable side-effect profiles and may adversely impact cognition (Loring, Marino, & Meador, 2007; Loring & Meador, 2004;). With this said, newer-generation medications typically lead to fewer side effects than do older epilepsy drugs, such as phenobarbital or phenytoin. However, even newer medications like topiramate and zonisamide, can have significant cognitive side effects in sensitive children, with many showing dose-dependent side effects and greater side effects when used in combination with other medications. These effects often include attention deficits, sedation, and/or behavioral challenges such as irritability.

### Attention and Executive Functioning in Childhood Epilepsy

In assessing children and adolescents with epilepsy, careful consideration of attention and executive dysfunction is crucial given the high rate of these problems in this population, as well the fact that executive deficits predict poorer quality of life. More specifically, prior research has shown that the combination of executive function deficits, polypharamacy, and medication attenuates quality of life in children with epilepsy (Sherman, Slick, & Eyrl, 2006). Even children with very mild epilepsy (e.g., recent onset, well-controlled with medication, normal intelligence) can show executive function deficits in comparison with healthy controls (Parrish et al., 2007). As many as half of those with more severe epilepsies (i.e., presenting to tertiary care epilepsy centers) present with executive dysfunction (Slick, Lautzenhiser, Sherman, & Eyrl, 2006). As with general cognitive function, executive function deficits are associated with earlier age of epilepsy onset and higher seizure frequency (Hoie, Mykletun, Waaler, Skeidsvoll, & Sommerfelt, 2006; MacAllister, Bender et al., 2012) and can lead to academic underperformance.

There is no neuropsychological "epilepsy profile" in children, and the neuropsychological endophenotypes of children with epilepsy typically more closely reflect the underlying epilepsy syndrome as opposed to seizure or electroencephalogram (EEG) characteristics. With this acknowledged, attention and executive function impairments are a fairly universal feature in childhood epilepsy syndromes. For example, despite being characterized as a "benign" epilepsy syndrome, children with benign rolandic epilepsy often show deficits in aspects of language, memory, motor functions, and attention and executive functioning (Croona, Kihlgren, Lundberg, Eeg-Olofsson, & Eeg-Olofsson, 1999; Gunduz, Demirbilek, & Korkmaz, 1999; Neri et al., 2012; Nicolai, Aldenkamp, Arends, Weber, & Vles, 2006; Northcott et al., 2005). Cognitive deficits are also commonly seen in children and adolescents with idiopathic generalized epilepsies. For example, children with childhood absence epilepsy often show a pattern of verbal skills being stronger than visuospatial skills and visual memory being an area of deficit (Pavone et al., 2001), as well as executive dysfunction (Conant, Wilfong, Inglese, & Schwarte, 2010; D'Agati, Cerminara, Casarelli, Pitzianti, & Curatolo, 2012). Similar findings are seen in other generalized idiopathic epilepsies of childhood and adolescence, and executive dysfunction can be prominent. For example, those with juvenile myoclonic epilepsy often have deficits in executive skills such as sustained attention, inhibition, working memory, processing speed, mental flexibility, and concept formation (Devinsky et al., 1997; M. D. Holmes, Quiring, & Tucker, 2010; Pascalicchio et al., 2007; Pulsipher et al., 2009). In these children, executive function deficits should not be unexpected given that seizures begin subcortically and propagate upward through subcortical structures critical for executive functions.

Executive dysfunction is also seen in focal epilepsy syndromes. Of course, frontal-lobe epilepsy has been associated with such deficits; these children often show problems with planning, impulse control, temporal orientation, sequencing, categorization, mental flexibility, and verbal reasoning (Auclair, Jambaque, Dulac, LaBerge,

& Sieroff, 2005; Braakman et al., 2011; Culhane-Shelburne, Chapieski, Hiscock, & Glaze, 2002; Hernandez et al., 2002; Luton, Burns, & DeFilippis, 2010; Patrikelis, Angelakis, & Gatzonis, 2009; Riva, Saletti, Nichelli, & Bulgheroni, 2002; Upton & Thompson, 1997). However, even children with focal seizures that do not originate in the frontal regions can show attention and executive dysfunction. For example, children with temporal-lobe epilepsy often show executive function deficits (Guimaraes et al., 2007; Rzezak et al., 2007, 2009) and attention impairments on formal testing (Dunn & Kronenberger, 2005; Schubert, 2005). This likely reflects that fact that although seizures may begin in mesial temporal structures, they spread rapidly to nontemporal regions. Given the dense interconnectivity between the temporal lobes, subcortical structures, and the frontal regions, damage caused by seizures is not delimited to the site of epilepsy onset and more widespread cognitive deficits are expected.

In assessing executive dysfunction, fairly standard neuropsychological instruments have been employed successfully in children and adolescents with epilepsy. For example, in a 2009 study (Rzezak et al., 2009), the Wisconsin Card-Sorting Task emerged as the most sensitive executive measure in children with temporal-lobe epilepsy. Tasks such as the Tower of London are useful in assessing not only planning skills, but also impulsivity and processing speed (MacAllister, Bender et al., 2012). Impairment on generative fluency tasks is also common in children with epilepsy (Rzezak et al., 2009). Further, continuous performance tasks, which classically measure sustained attention but also assess processing speed and response inhibition, are also commonly used in the assessment of attention and executive functioning in children with epilepsy; impairments on such measures are common (MacAllister, Vasserman, et al., 2012; Semrud-Clikeman & Wical, 1999).

Rating forms of attention and executive functions is also helpful in the assessment of children and adolescents, given that performance-based tests do not always detect dysfunction even in those who display prominent "real-world" problems. In those with epilepsy, broad-band scales such as the Child Behavior Checklist (Achenbach, 1991) and the Behavior Assessment System for Children-II (Reynolds & Kamphaus, 2004) have shown utility (Bender, Auciello, Morrison, MacAllister, & Zaroff, 2008). Considering executive functions more specifically, the Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000) has shown utility in this population (MacAllister, Bender et al., 2012; Parrish et al., 2007; Slick et al., 2006), with parents reporting significant deficits in working memory, planning and organization, etc.

As attention and executive function deficits are common cognitive concerns in childhood epilepsy, recent work has examined the comorbidity of ADHD in these individuals. In a study of 175 children and adolescents with various seizure types, 11.4% had ADHD-C, 44% had ADHD-I, and 2.3% had ADHD-H; interestingly, ADHD-I was more common in those with epilepsy, whereas the ADHD-C is more common in those without seizures. Moreover, girls with epilepsy showed slightly more attention problems than did boys, but epilepsy variables such as seizure type and seizure focus were unrelated to inattention and hyperactivity (Dunn, Austin, Harezlak, & Ambrosius, 2003). In 2007, Hermann et al. characterized the rate, subtype, and correlates of ADHD in children with idiopathic epilepsy. In this study, 31.5% of children with recent-onset epilepsy met formal diagnostic criteria for ADHD in comparison with only 6.4% of matched controls (Hermann et al., 2007). Consistent with the findings of the Dunn et al. (2003) study, ADHD-I was the most common subtype in these children with epilepsy. Also, consistent with prior work, epilepsy variables (e.g., seizure type, location of onset) were unrelated to ADHD diagnosis. An interesting finding in this study was that symptoms of ADHD predated onset of epilepsy in the majority (82%) of cases (Hermann et al., 2007).

Despite landing in the same "diagnostic box" as outlined by the DSM, the neuropsychological endophenotypes in children with developmental ADHD versus ADHD in the context of epilepsy appear to differ slightly; in both the ADHD-I and ADHD-C groups, those with comorbid epilepsy have lower IQ estimates and show poorer performances on digit span tasks. Differences were also seen on other attention/executive tasks; of individuals with ADHD-I, those with epilepsy had slower reaction times on a continuous performance task than did those with ADHD and no seizures. Moreover, those with epilepsy and ADHD-I were less variable in their response times than were those with ADHD-I without epilepsy, showing slow but less erratic responding. In comparing the ADHD-C groups, those with epilepsy were slightly more impulsive on the continuous performance test and made more anticipatory responses (MacAllister, Vasserman, et al., 2012).

In this group of children with epilepsy who meet formal diagnostic criteria for ADHD, intelligence and perceptual reasoning skills were lower in those with higher seizure frequencies, while polypharmacy attenuates verbal comprehension and working memory in the overall group, as well as inattention in the ADHD-I group. For those with ADHD-C, higher seizure frequency and number of medications were related to poorer working memory as was number of Antiepileptic Drugs (AEDs; MacAllister, Vasserman, et al., 2012). The authors highlighted that in those with seizures, attentional impairment is secondary to many factors, including not only the underlying brain pathology that causes both the cognitive deficits and epilepsy, but also the seizures themselves, which cause ictal and postictal symptoms. Further, interictal epileptiform EEG phenomena (i.e., ‘‘spike and wave’’ activity) can disrupt attention (Binnie, 1993), and many epilepsy medications can result in slowed processing speed and inattention as side effects (Loring et al., 2007; Loring & Meador, 2004).

## TREATMENT

### Behavioral Approaches

Of course, given the high rate of attention and executive function deficits in children with epilepsy, standard behaviorally based treatments for children with developmental ADHD may be promising. Interventions such as behavioral parent training at home and behavioral contingency management in the classroom are evidence-based behavioral treatments (Pelham & Fabiano, 2008). At its core, behavioral parent training is a program to teach behavior modification techniques to parents. Likewise, behavioral contingency management utilizes a system of rewards and punishments to reinforce positive behaviors and punish misbehavior. Typically, these interventions are most useful in high-intensity and long-duration models, such that numerous learning trials and opportunities for acquiring and practicing new (positive) behaviors can be given. This should include practice in multiple settings and situations to provide the most generalization of treatment. Manualized treatment guides are available for such approaches (Barkley, 1997; Eyberg, Boggs, & Algina, 1995; Webster-Stratton, 1992). In addition, it is standard practice in school-based interventions for teachers to track behavior via daily report cards (Power et al., 2012) wherein teachers provide feedback about a child’s in-class behavior through written reports to the parent. Parents, in turn, provide positive reinforcement for good behaviors and punishment for negative ones. The American Academy of Pediatrics provides guidelines for developing a daily report card (American Academy of Pediatrics, 2003). The added benefit of a daily report card is that it provides a closed feedback loop between behavior at home and school and facilitates teacher–parent communication. Further, studies have shown summer treatment programs for ADHD can be effective (Pelham & Fabiano, 2008), with large effect sizes for improving compliance, classroom productivity, self-esteem, and parent ratings of behavior.

One of the most common complaints and presenting symptoms in children with executive dysfunction is that of disorganization, poor time management, and weak planning abilities that have significant functional impacts. The manifestation of such difficulties often includes children forgetting to write down assignments, misplacing necessary items, forgetting to hand in homework, etc. Additionally, parents often report time management challenges and poor skills in planning large tasks and long-term assignments. To target these specific deficits, organizational skills-training programs have shown promising results. The approach is based on the premise that children with executive function problems have a skill deficit rather than a performance deficit. The organizational skills-training program, therefore, includes skills training, as well as a parent training in the use of behavior management strategies. Children are taught a variety of organizational skills through direct instruction, practice, and positive reinforcement. Skills include tracking of assignments, using calendars and schedules, time estimation, and task planning. Overall, children who completed the 20-session organizational skills-training program demonstrated significant improvements in their organizational skills as rated by parents and teachers. In addition, they demonstrated improvements in their academic performance, as well as in homework and family functioning (Abikoff et al., 2013).

It is important to note, however, that these programs are validated for use in children with developmental ADHD and executive skill deficits and have not specifically been tested in children with epilepsy. Moreover, behavioral parent training and behavioral contingency management are largely geared toward reducing disruptive behaviors most often associated with impulsivity seen in ADHD-H or ADHD-C. As such, they may be less applicable to, and perhaps less successful with, children with epilepsy and ADHD, as ADHD-I is more common in these children. With that said, one study recently showed some promising results with children with ADHD-I (Pfiffner et al., 2007).

### Pharmacological Approaches

For many years, the use of stimulant medications was thought to be contraindicated in the treatment of attentional deficits in children with epilepsy, with many clinicians erroneously believing these medications would lower the seizure threshold. Though one still may find a physician here and there that clings to this mistaken belief, those intimately familiar with epilepsy in children, and the cognitive concerns with which they present, are now well versed in the use of psychostimulants in this population. Although a comprehensive review of the pharmacology is beyond the scope of this article, several points should be made.

Currently, there are numerous medications used to treat ADHD; these include methylphenidates, amphetamines, and some nonstimulant formulations. Presently, we have the most safety data for the use of methylphenidate in individuals with epilepsy. For example, several case series have documented the safety, tolerability, and efficacy of methylphenidate in this population (see Torres, Whitney, & Gonzalez-Heydrich, 2008, for review), and improvements on cognitive testing have been documented (Semrud-Clikeman & Wical, 1999). Moreover, several prospective trials have been conducted. For example, one showed that not only was the medication well tolerated (i.e., did not produce problematic effects, did not change epilepsy medication plasma levels, and did not cause seizures), but behavioral improvement was reported by teachers in 70% of the sample. Further, significant improvement on neuropsychological tests of attention and executive function were found. Several subsequent studies have also documented the safety and utility of various formulations of methylphenidate in children with seizures (Baptista-Neto et al., 2008; Feldman, Crumrine, Handen, Alvin, & Teodori, 1989; Gross-Tsur, Manor, van der Meere, Joseph, & Shalev, 1997; Gucuyener et al., 2003; Santos et al., 2013; Shalev, 2013; Yoo et al., 2009).

Far less data are available for the safety and efficacy on amphetamines to treat attention deficits in those with epilepsy. However, in their review of the limited data available, Torres et al. (2008) concluded that while amphetamines may cause seizures if abused, for some, they may be anticonvulsant. Unfortunately, case series have shown that response rates to amphetamines are disappointing (Torres et al, 2008).

Although it is fairly well established that seizure risk is low for those taking atomoxetine (Torres et al., 2011; Wernicke et al., 2007), only very limited data are available for the effectiveness of this medication in children with epilepsy. One retrospective study reviewed the medical records of children with epilepsy treated in a tertiary care center. The majority of those who had been tried on atomoxetine had previously shown a poor response to stimulant medications. Though there was no apparent effect on epilepsy characteristics, of those prescribed atomoxetine, more than half showed an inadequate response, whereas more than a quarter discontinued the medication due to a worsening of irritability or other side effects (Torres et al., 2011). In short, there is little evidence that children with epilepsy and attention problems benefit from atomoxetine, but data are lacking and methodological limitations of Wernicke et al. (2007) make it difficult to interpret.

### Novel Approaches

Cognitive neuroscientists in Sweden have recently developed a computer-based working-memory remediation program (Cogmed), which is now commercially available. To date, several controlled, randomized trials conducted by the developers documented some effectiveness of this program in treating working-memory deficits in children and adolescents with developmental ADHD (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002). More recently, independent researchers documented the utility of this program in children with developmental ADHD (J. Holmes, Gathercole, & Dunning, 2009; J. Holmes, Gathercole, Place, et al., 2009). Further, the program has shown promise in neurological populations, such as in adults with cerebrovascular accidents (Westerberg et al., 2007). Functional neuroimaging studies have shown that the Cogmed program can increase activity in cortical regions associated with working memory as well as executive functions more generally, including the middle frontal gyrus and parietal cortex (Klingberg & McNab, 2009; McNab et al., 2009; Olesen, Westerberg, & Klingberg, 2004; Westerberg & Klingberg, 2007). Although the program is showing promise in some populations, the effectiveness of Cogmed in children and adolescents with working-memory deficits in epilepsy remains largely unexamined. However, some preliminary work has been conducted.

For example, our own group demonstrated the feasibility of using Cogmed in children with epilepsy, with some promising results (Whitman, Marsh, Vasserman, Vaurio, & MacAllister, 2012), though the effectiveness of the intervention in this case was confounded by antiepilepsy medication titration during the course of the trial. In another small sample, 17 children and adolescents with epilepsy were randomly assigned to treatment or placebo Cogmed groups. The results of the intervention demonstrated that the working-memory training group evidenced improvement from baseline to post-training assessment on working memory and reaction time tests. Unfortunately, group differences were no longer evident at the 3-month follow-up (Westerberg et al., 2006). As such, currently, it cannot be stated with any certainty that interventions such as Cogmed show much utility in improving working memory in those with epilepsy. It should also be noted that recent critical reviews of this intervention have suggested the early claims may be somewhat overstated. For example, Shipstead, Hicks, and Engle (2012) reviewed the literature and cited several methodological problems with prior research as well as problems in replicating the findings that led them to conclude that the claims of Cogmed are largely unsubstantiated. Likewise, a 2013 review of the Cogmed literature revealed that findings across studies were mixed and that, given the methodological issues in the studies, the effectiveness of Cogmed in the treatment of ADHD is best considered "possibly efficacious" (Chacko et al., 2013). This is an applicable description of Cogmed for working-memory deficits in epilepsy as well.

## CONCLUSIONS AND FUTURE DIRECTIONS

It is clear that attention and executive function deficits are a major concern for many children and adolescents with epilepsy. Such deficits can be seen in all seizures types and in all of the epilepsy syndromes of childhood. Further, the severity of such deficits is predicted by variables such as age of epilepsy onset, seizure frequency, and the number of antiepilepsy medications needed to adequately control seizures. The high rate of attention deficits and executive dysfunction are responsible for the increased incidence of ADHD in children and adolescents with epilepsy, though the underlying neuropsychological endophenotype of ADHD in those with epilepsy appears to differ from those with ADHD and no seizures. Importantly, poor executive function and attention are a major determinant in school performance and overall quality of life.

Given this, it is unfortunate that effective interventions for treating these deficits are lacking; presently, the only interventions that have been shown to have a positive impact on children and adolescents with epilepsy are pharmacological in nature. Though there are effective organizational skills-training programs for those with ADHD, these have not specifically been studied in children with epilepsy. Likewise, behavior management via behavioral parent training at home and behavioral contingency management has not been studied in epilepsy, though clinicians generally assume that the principles should apply. It is hoped that the ensuing years witness a surge in empirically validated treatments for attention and executive dysfunction in children with epilepsy. Presently, studies are under way on programs such as Cogmed, but other effective interventions must be sought.

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