ATTENTION AND LEARNING IN CHILDREN WITH EPILEPSY AND CO-MORBID SLEEP DISTURBANCE

By

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To children and families affected by epilepsy.

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Research suggests that children with epilepsy may be more susceptible to sleep disturbance, which has been associated with behavior problems and cognitive impairments in pediatric populations. However, few studies have examined the relationships among sleep disturbance, behavior, and cognition in children with epilepsy. Using a brief neuropsychology battery and parent questionnaires, we aimed to clarify the relationship between possible sleep disturbance and cognitive and behavioral problems in children with epilepsy. Our study hypothesized that children with epilepsy who had a higher frequency of sleep disturbance would perform more poorly on measures of attention and learning than children with epilepsy and a lower frequency of sleep disturbance. Parent report of sleep disturbance symptoms was also hypothesized to be directly related to impairment on neuropsychological measures of attention and learning. Finally, it was hypothesized that parents of children with epilepsy and a higher frequency of sleep disturbance would report greater attention problems and hyperactivity in their children.

Overall, results provide limited evidence for attentional impairment in children with epilepsy and co-morbid sleep disturbance. Specifically, children whose parents reported a high

frequency of sleep problems (and those who endorsed symptoms of a sleep disorder) were found to have greater difficulty sustaining attention to auditory information than children who were reported to have fewer sleep problems. Differences did not appear to be related to seizure status, seizure type, or use of antiepileptic medication, although these dissociations would need to be more directly tested in future work. Other aspects of attention and learning failed to differ between the two sleep groups, although more complex attentional control/switching approached significance. Future studies should continue to examine the relationship between sleep disturbance and cognitive performance in children with epilepsy, including research employing neuropsychological measures and objective assessments of sleep such as polysomnography and actigraphy as well as treatment-based studies in children with epilepsy and diagnosed sleep disorders.

CHAPTER 1
INTRODUCTION

Epilepsy is one of the most common neurological disorders, currently affecting approximately 2.7 million Americans (Epilepsy Foundation of America, EFA, 2008). Each year, an estimated 45,000 children under the age of 15 develop epilepsy, and current statistics suggest that 326,000 school children age 14 or younger currently have epilepsy (EFA, 2008).

Children with epilepsy are at increased risk for long-term educational, psychological, and social problems (Pellock, 2004), which necessitates a comprehensive approach to pediatric epilepsy management that goes beyond the typical goal of seizure control. More specifically, Besag (2004) suggests that after seizure control, cognition and behavior are among the most important factors in determining whether a child with epilepsy will successfully progress toward independence. Among the most commonly described neurocognitive issues for children with epilepsy are problems with attention and related daytime behaviors such as hyperactivity (CITE).

While these difficulties have previously been hypothesized to result from the effects of seizure activity on the brain or anti-epileptic medications, recent research has suggested another potential cause. Specifically, research has suggested that children with epilepsy may be more susceptible to sleep disorders, which may directly contribute to behavior problems and to attention and learning impairments. However, little to no empirical research has examined the relationships between sleep disturbance, behavior, and cognition in children with epilepsy. An established relationship would suggest proper identification and treatment of sleep disorders in children with epilepsy could be one mechanism for ameliorating daytime problems and improving cognitive performance, thereby maximizing the overall functioning of children with epilepsy. This study aims to clarify the relationship between possible sleep disturbance and cognitive and behavioral problems in children with epilepsy.

Overview of Pediatric Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Normally, the brain continuously generates tiny electrical impulses in an orderly pattern. During an epileptic seizure, a breakdown occurs in the systems that maintain the balance of electrical activity in the brain, resulting in abnormal electrical discharges. This uncontrolled surge of electrical activity in the brain results in changes in consciousness, movement, and/or sensation, the symptoms of a seizure. In most cases (60-80%), the onset of seizures in children has no apparent cause (Hauser, 2001).

Both children and adults with epilepsy may experience one or both of two primary types of seizures: generalized and partial seizures (International League Against Epilepsy, 1989). Generalized seizures emerge from cortex in both hemispheres of the brain and typically involve a disturbance of consciousness. Types of generalized seizures include absence ("petit mal") seizures, myoclonic seizures, atonic seizures, tonic seizures, clonic seizures, and the combined tonic-clonic ("grand mal") seizures (Mattson, 2003). In contrast to generalized seizures, partial seizures originate from an electrical disturbance in a specific area of cortex within one cerebral hemisphere. Because of this distinction, partial seizures are also known as focal, local, or localization-related seizures. Partial seizures are further classified based upon the impairment or preservation of consciousness, such that simple partial seizures are those in which there is no alteration in consciousness and complex partial seizures are those in which consciousness is altered or lost. Depending upon the location of the electrical disturbance, virtually any movement, sensory, or emotional symptom can occur as part of a partial seizure, including complex visual or auditory hallucinations. Finally, a partial seizure may spread to involve the entire brain, which is referred to as a secondarily generalized seizure. Convulsive generalized seizures (e.g., tonic-clonic seizures) appear to be the most prevalent seizure type during the first year of life, with partial seizures becoming the most common after the first year (Pellock, 2004).

When possible, recurrent seizures (epilepsy) are classified in epilepsy syndromes based upon the predominant seizure type and other factors such as the seizure triggers, seizure behaviors, genetic factors and specific brain wave patterns seen on electroencephalography. Examples of epilepsy syndromes diagnosed in children include benign childhoood epilepsy with centrotemporal spikes (BCECTS), absence epilepsy, juvenile myoclonic epilepsy, Lennox-Gastuat Syndrome, Landau-Kleffner syndrome, frontal lobe epilepsy, and temporal lobe epilepsy. The majority of children—approximately 59 percent—have a localized or partial seizure syndrome, such as frontal lobe epilepsy (Shinnar & Pellock, 2002). Approximately 29 percent of children with epilepsy have a generalized seizure syndrome such as absence epilepsy.

Epilepsy treatment typically involves use of anti-epileptic drugs (AEDs) aimed to reduce the frequency and severity of seizures. Specific AEDs are prescribed based on many factors, including the type of seizure, the age of patient, the side effect profile, and the patient's ability to follow the required medication regimen. Although most children with epilepsy are initially prescribed a single medication, if this medication is only partially effective, one or more medications may be added (typically after other types of monotherapy have been attempted). In cases of intractable epilepsy—those that do not respond to medication—other treatments may be considered. These include seizure surgery involving the resection of the area of the seizure focus, ketogenic diet, and vagal nerve stimulators. Prognosis for children with epilepsy has often been examined as a factor of epilepsy syndrome. For example, benign rolandic epilepsy is known to typically completely remit, whereas Lennox-Gastaut Syndrome never remits (Camfield & Camfield, 2003). With regard to prognosis more generally, most patients with epilepsy become seizure-free with appropriate antiepileptic drugs, typically within a few years of initial diagnosis (Pellock, 2004). Additionally, many are subsequently able to discontinue medication and remain free of seizures.

Pediatric Epilepsy: Cognition and Behavior

Despite the potential for effective seizure control and a positive medical prognosis, children with seizures remain at risk for long-term educational and social problems (Pellock, 2004). Accordingly, to optimally manage pediatric epilepsy it is essential to understand not only the neurological implications but also the neurocognitive effects of seizure disorders. However, the literature on cognition and behavior in children with epilepsy is relatively limited and often lacks unanimity.

In general, the pediatric epilepsy literature has tended to focus on broad intellectual functioning (i.e., IQ) and academic achievement or on the outcomes of treatments (e.g., anti-epileptic medications, epilepsy surgery) rather than on specific aspects of neurobehavioral or cognitive functioning in children with seizures. Variation across the existing studies in terms of subjects (e.g., type of seizure or epilepsy syndrome included) and methodology also makes generalizable conclusions about neurobehavioral functioning difficult. Despite these challenges, some common psychiatric, behavioral, and cognitive problems have been identified in the literature on children with epilepsy, including attention and memory problems, anxiety, and hyperactivity (e.g., Sanchez-Carpintero & Neville, 2003; Williams, 2003; Pellock, 2004)

Disruption of attentional abilities is one of the most consistently described cognitive problems in children with epilepsy (Schubert, 2005; Williams, 2003). For example, Williams, Griebel, & Dykman (1998) conducted comprehensive neuropsychological assessments including intellectual functioning, memory, attention, language, academic achievement, visual motor integration and fine motor skills with a group of children with epilepsy. Results of the assessments indicated that the children performed within the expected range given their measured intelligence on all tests except those measuring attention, on which they performed below expectations. Parents also reported attention problems within the clinically significant range on a behavior questionnaire. Consistent with this study, Mitchell, Zhou, Chavez, and Guzman (1992) found that children with epilepsy had slower reaction times and inattention on a continuous performance task.

Notably, Mitchell et al. (1992) concluded that the impaired performance of the children with epilepsy was not related to seizure severity, duration of seizure disorder, or antiepileptic drug (AED) history. Similarly, a study of Dutch children with epilepsy also found that compared to their healthy classmates, children with newly diagnosed epilepsy performed poorer on a measure of sustained attention (Oostrom, van Teesling, Smeets-Schouten, Peters, & Jennekens-Schinkel, 2005). Studies such as these suggest that attention problems are not simply a medication side effect or a hallmark of particularly complicated seizure history. With regard to medication side effects, it is also important to note that Loring and Meador (2004) reviewed the cognitive side effects of AEDs in children and concluded that although some component of cognitive deficits may be attributed to long-term use of AEDs (particularly phenobarbital), there is insufficient evidence at this time to conclude that AEDs in general have negative cognitive side effects. This is particularly true for the most recently developed AEDs, many of which have yet to be studied neuropsychologically. A very small number of studies have noted reduced attention in children taking carbamazepine and, in one study, valproic acid; however, current results are far from conclusive and much of the research has suffered from methodological flaws (Loring & Meador, 2004).

Attention problems also do not appear to be only associated with a particular epilepsy or seizure type. Attention difficulties have been reported in children with generalized seizures as well as complex partial seizures. For example, Borgatti et al. (2003) found that both children with generalized epilepsy and children with partial epilepsy demonstrated persistent attention difficulties as measured by a continuous performance task, despite control of seizures. In a study examining only children with generalized epilepsy (absence or tonic-clonic seizures), the children with epilepsy were found to have poorer verbal and non-verbal attention than a group of age- and sex-matched healthy controls, with the absence epilepsy group demonstrating the greatest impairment (Henkin,et al, 2005). In another study, children with complex partial seizures with and without a diagnosis of attention deficit disorder (ADHD) were compared to a group of children with ADHD and a healthy control group on a continuous performance task (Semrud-Clikeman & Wical, 1999). The children with partial seizures were found to have particular difficulty compared to the healthy controls, regardless of ADHD diagnosis. Interestingly, the children with epilepsy and no ADHD diagnosis performed similarly to the ADHD group, while the epilepsy with ADHD group performed the worst of all four groups. Van Rijckevorsel (2006) explains this commonality of attention problems across seizure types as resulting from the frontal lobes being a "preferential target" of both generalized and focal seizures. Specifically, he states that direct neuronal dysfunction in the frontal lobes as well as indirect effects from secondary seizure spread (e.g., "circuitry abnormalities") likely underlie attention and executive function problems in children with epilepsy.

While the majority of attention research with children with epilepsy has focused on sustained attention as measured by continuous performance tests (CPTs), most current models of attention are multifocal in nature. Research with other clinical populations suggests that different aspects of attention may be variably affected in neurological and psychiatric disorders. For the purposes of this project, we adopted the model proposed by Mirsky, Anthony, Duncan, Ahearn, and Kellam (1991). Mirsky and colleagues used principal components analysis to derive a model of attention with four essential elements that work together in a coordinated attentional system. The four components include: focus-execute, sustain, shift, and encode. Focus-execute is the ability to efficiently and quickly scan an array to select a target and to make a verbal or manual response quickly. It requires concentrating attentional resources on a particular stimulus while ignoring distracters. This aspect of attention is also referred to as "selective attention." Sustain is vigilance, or the capacity to maintain focus and alertness over time. The third attentional component is attentional shift—the ability to change attentive focus in a flexible or adaptive manner. Finally, Mirsky et al. also described a fourth element termed "encode." This component is the capacity to hold information in memory briefly in order to perform a mental operation on the information. According to Mirsky and Duncan (2001), this is equivalent to what is often termed working memory, and may reflect more complex mechanisms than attention alone.

Although CPT-based studies of sustained attention have dominated the literatures, a few studies have attempted to look at the other aspects of attention with mixed results. Hernandez et al. (2003) reported that children with frontal lobe epilepsy, but not those with temporal lobe epilepsy or generalized absence epilepsy, demonstrated impaired visual attention (i.e. selective attention) on the Coding and Symbol Search subtests of the Wechsler Intelligence Scale for Children, Third Edition (WISC-III). A study of Israeli children with generalized epilepsy found that children with generalized absence seizures and children with generalized tonic-clonic seizures both demonstrated poorer visual selective attention (Coding) than healthy controls

(Henkin et al., 2005). Children with benign childhood epilepsy with centrotemporal spikes (BECTS) with bilateral EEG discharges were reported to have impaired selective attention and divided attention as measured by the Stroop Color-Word task and the Trail Making Test respectively (D'Alessandro et al., 1990). Similar findings were reported in a French study of children with BECTS using a cancellation-type selective attention task from the Battery for Rapid Evaluation of Cognitive Functions (Pinton et al., 2006). In contrast, in another study of children with BECTS, no differences between children with seizures and healthy controls were found on the Trail Making Test, although parents reported that the children with seizures were more distractible and had poorer concentration on parent questionnaires (Croona et al., 1999). Similarly, Schoenfeld et al. (1999) used the Stroop Color Word task and the Trail Making Test to assess attention in children with complex partial seizures, and reported that they demonstrated no deficits in selective or divided attention relative to healthy sibling controls. In summary, the most consistent evidence for attention problems in children with epilepsy appears to be specifically for sustained attention difficulties, while other aspects of attention remain less understood in this population.

Children with attention difficulties may be at risk for other types of cognitive and academic problems. Pollock (2004) notes that children with epilepsy may be "predispose[d]" to attention problems, which may in turn lead to learning difficulties. For example, Oostrom et al. (2005) reported attention problems in school children with newly diagnosed epilepsy. In their discussion of their findings, the researchers noted that in their sample of children with epilepsy, poorer attentional performance was also associated with having repeated a grade in school. Oostrom and colleagues concluded that the school careers of these "repeater" children had influenced their performance on attention task. However, it seems equally—if not more—

plausible that the children with epilepsy previously did poorly in school because of their underlying attention problems and other cognitive deficits. Given its recognized association with attention and its association with academic achievement, learning is another important aspect of cognition to be considered in children with epilepsy.

However, whereas the findings on attention suggest the presence of impairment in children with epilepsy (with some inconsistencies in the exact nature of the deficits), the findings on learning are much less consistent. For example, on a location learning task, school-aged children with epilepsy performed similarly to a healthy control group, except for a trend toward being more susceptible to proactive interference (Schouten, Oostrom, Pestman, Peters, & Jennekens-Schinkel, 2002). Likewise, Williams et al. (2001) found intact new learning on a list learning task in children with epilepsy (although children with diagnosed ADHD were excluded and may represent an important sample). In contrast, Henkin et al. (2005) found that children with generalized epilepsy performed significantly poorer on a list learning task than a healthy control group (this same group also had significantly impaired verbal and non-verbal attention).

In the Dutch study described above, neuropsychological testing results also indicated that in addition to the attention problems, the children with epilepsy demonstrated poorer performance on learning tasks, with proactive interference during learning remaining an area of concern when academic history was taken into account (Oostrom, et al., 2005). In this same study, parent questionnaires also indicated that the children with epilepsy had a greater number of behavior and learning difficulties than the control group.

Finally, in addition to direct neuropsychological testing with children, parent questionnaires frequently have been employed to assess behavior in children with chronic illnesses and neurological disorders. Such studies in children with epilepsy support the cognitive findings just described, in that they frequently indicate problems with attention as well as other behavior problems (e.g., Austin et al., 2002; Keene et al., 2005; Ott et al., 2003). In a cross-sectional parent report study of children with epilepsy conducted during regularly scheduled neurology visits, approximately 16% of the children had clinically elevated total behavior problem scale scores (T-score > 70), and more than a quarter (26.9%) of the children were rated as having clinically elevated problems with attention (Keene et al., 2005). Dunn and colleagues (2003) had parents complete either the Children's Symptom Inventory or the Adolescent Symptom Inventory and determined that 38% of their sample of children with epilepsy met criteria for diagnosis of ADHD, which exceeds the prevalence rate in the general child population. It was also noted that more children with epilepsy presented with symptoms of ADHD, Inattentive type than is typically seen.

In summary, while some variation exists in the literature, the overall pattern of research findings suggests that inattention and related behavior problems pose a significant concern for children with epilepsy. Identifying the etiology of cognitive and behavior problems in children with epilepsy remains an important goal for epilepsy research, as it may improve the ability to recognize and treat these problems and accordingly improve the overall well-being of children with epilepsy in the long-term. Recently, there has been an increased interest in possible contribution of sleep disturbance to behavior and cognitive problems in children with epilepsy. To better understand this possible relationship, it is helpful to first briefly review what is known about the relationship between sleep disturbance, behavior and cognition in otherwise healthy children.

Sleep Disturbance and Neurobehavioral Problems

The effects of chronic sleep disturbance in children has primarily been examined by studying children with sleep disorders, particularly sleep disordered breathing. Sleep disorders are conditions or circumstances of a physiological and/or psychological nature that cause sleep disturbance. Mindell & Owens (2003) broadly conceptualize sleep disorders as involving one or more basic mechanisms: inadequate duration of sleep for age (insufficient sleep), disruption and fragmentation of sleep (poor sleep quality), or inappropriate timing of the sleep period (circadian rhythm disorders). The most prevalent and most researched sleep disorder diagnosis among children is sleep disordered breathing (Sadeh et al., 2002), a class of disruptive sleep disorders that involve varying severities of breathing difficulties including obstructive sleep apnea. Sleep disordered breathing (SDB) is characterized by repeated events of partial or complete upper airway obstruction during sleep that results in the disruption of normal ventilation, hypoxemia, and sleep fragmentation (O'Brien, Mervis, Holbrook, Bruner, Smith et al., 2004). Typically, a continuum of SDB is recognized, with increasing severity: primary snoring (snoring with no blood gas abnormalities), upper airway resistance syndrome (snoring with increased work of breathing), and obstructive sleep apnea (characterized by repeated episodes of prolonged partial or complete upper airway obstruction during sleep). Unlike in adults, in children SDB is commonly associated to adenotonsillar hypertrophy, or enlarged tonsils and adenoids.

SDB has been associated with a variety of neurobehavioral consequences in children, including excessive daytime sleepiness, inattentiveness, impaired executive functioning and learning, and hyperactivity (Kotagal & Pianosi, 2006). Studies with children who snore have found that snorers demonstrate poorer performance on neuropsychological tests of attention when compared with non-snorers (Blunden et al., 2000; O'Brien, Mervis, Holbrook, Bruner, Klaus, et al., 2004). In a sample that excluded snorers with diagnosed ADHD or behavior problems, attention impairment and parent-reported hyperactivity were found, which were suggested to be related to decreased REM sleep or sleep fragmentation—interruption of the normal sleep cycle by brief arousals that occur throughout the night (O'Brien, Mervis, Holbrook, Bruner, Klaus, et al., 2004). SDB, including snoring and obstructve sleep apnea, was also associated with lower attention, executive functioning, and phonological processing scores in a group of non-referred first graders, although no differences in parent report of behavior were found between the SDB and non-snoring group (O'Brien, Mervis, Holbrook, Bruner, Smith et al., 2004). In a large survey of general pediatric patients, endorsement of frequent snoring, increased sleepiness, and other symptoms of disrupted sleep was associated with inattention and hyperactivity (Chervin et al., 2002). In a similar broad sampling of children, Kaemingk et al. (2003) conducted neuropsychological testing and in-home sleep studies in a large group of school children and found that children with respiratory arousals consistent with OSA performed significantly worse (although within normal limits) on learning and delayed memory tasks compared to children with fewer or no respiratory arousals.

The relationship between attention problems and sleep disorders has also been addressed by examining sleep in children with known attention difficulties, specifically children diagnosed with ADHD. Corkum, Tannock, & Moldofsky (1998) suggested that the prevalence of sleep problems in children with ADHD is between 25% and 50%, considerably higher than the approximately 7% prevalence of sleep problems in the general pediatric population. Based upon parent report of sleep patterns, children with ADHD have been estimated to have a 2 to 3 times greater prevalence of sleep problems such as difficulty falling asleep, restless sleep, and nighttime awakenings as compared to healthy control children (Owens, 2005). Using polysomnography (i.e., overnight sleep studies) and other methodology, children with ADHD have been described as having longer sleep onset latencies, more nocturnal and early morning awakenings, shorter average sleep duration, and increased sleepiness upon awakening (Brown & Modestino, 2000). A recent study used actigraphy to compare sleep in unmedicated children with ADHD and healthy control subjects, and found that children with ADHD had shorter actual sleep time as well as more interrupted sleep (Owens et al., 2008). The children with ADHD also reported being more sleepy during the daytime. While the nature of the relationship between ADHD and sleep problems is still being investigated, research with children with ADHD certainly suggests sleep disturbance and sleep disorders should be considered as potential contributors to disrupted attentional abilities.

Finally, evidence for a direct relationship between SDB and neurobehavioral deficits such as inattention and hyperactivity has been suggested in research with children who undergo adenotonsillectomy (removal of tonsils and adenoids) for the treatment of SDB. As previously noted, enlarged tonsils and adenoids are a common cause of SDB in children, and adenotonsillectomy is often a first-line treatment. Several researchers have found that children with SDB have demonstrated neurocognitive improvement following treatment. While the children with SDB were reported to have increased cognitive problems and behavioral problems--including inattention and hyperactivity--prior to treatment, following adenotonsillectomy their cognitive performance and behaviors were tested at levels similar to healthy controls (Ali, Pitson, & Stradling, 1996; Goldstein, Post, Rosenfeld, & Campbell, 2000). Although many of the early studies were limited by fairly small sample sizes, a more recent larger scale study by Chervin et al. (2006) provided further empirical support that treating SDB can improve behavior and cognition in children. Specifically, 76 children scheduled for adenotonsillectomy (primarily for OSA) and 27 children referred to other surgical clinics were evaluated for sleep, attention performance, and behavior prior to surgery and again one year later. The children undergoing adenotonsillectomy were reported to be significantly more hyperactive per parent report and more inattentive based on a brief neuropsychological battery (including a CPT task) relative to the control group prior to surgery. They also were more likely to meet DSM-IV criteria for ADHD, based upon a child psychiatrist's assessment. One year later, the children who underwent adenotonsillectomy had improved significantly in all areas including hyperactivity and attention, eliminating the differences in performance seen prior to surgery.

While relational evidence has been reported, the exact relationship between SDB and cognitive and behavior problems has not been clearly defined. Most current theories suggest that sleep fragmentation or possibly nocturnal hypoxemia likely underlie the daytime difficulties. Sadeh et al. (2002) report that sleep fragmentation negatively impacts sleep by increasing the amount of less restorative sleep and decreasing the length of deeper, more restorative sleep stages. Additionally, Owens, Opipari, Nobile, & Spirito (1998) report that sleep fragmentation in children may not manifest as "daytime sleepiness" as seen in adults, but rather as increased activity, aggression, impulsivity, acting out, inattention, or poor concentration. Although a definitive conclusion cannot be made based on the current literature, it is clear that the presence of SDB symptoms can negatively impact children's daytime functioning. As described here and in the preceding section, there are multiple similarities in the types of cognitive and behavioral problems seen in children with epilepsy and children with sleep disorders. Given these similarities, the prevalence of sleep disorders among children with epilepsy, and the potential for relatively easy and effective intervention, it is not surprising that recent research has begun to look specifically at the impact of sleep disorders in individuals with epilepsy.

Epilepsy and Sleep Disturbance: Relationship to Cognitive-Behavioral Functioning?

There has been growing interest in the relationship of epilepsy and sleep disturbance, both in adults and children. A connection between sleep and seizures has long been recognized. For example, in the 2nd century AD, the Greek physician Galen warned his patients with epilepsy to avoid sleepiness, and Sonorus hypothesized that untreated nightmares could lead to seizures, cautioning that sleep must be "undisturbed" in individuals with epilepsy (Temkin, 1994, p. 66). In 1885, Gowers described a relationship between grand mal seizures and sleep, noting that nocturnal seizures typically occurred two hours after bedtime and from 4-5 AM while daytime seizures usually occurred in the first hour after awakening (Janz, 2000). Sleep deprivation is now well-recognized as a seizure precipitant (Janz, 1962), and may be used clinically during the diagnostic process. Despite this longstanding recognition of a sleep-seizure relationship, there is still much that is uncertain about the interrelationship of sleep and epilepsy and the impact of comorbidity on daily functioning and epilepsy management. This is particularly true in the pediatric population, in which the limited research literature has focused primarily on descriptive accounts of sleep complaints among children with epilepsy and reports of sleep architecture abnormalities in relatively small samples or subpopulations with particular epilepsy syndromes characterized by sleep involvement.

Much of the relatively limited amount of research about sleep disturbance and epilepsy has been conducted with adults. Drawing upon the adult literature, Bazil (2003) states there are multiple potential causes of sleep disturbance in patients with epilepsy, including general factors such as inadequate sleep hygiene, circadian rhythm disturbances, and coexisting sleep disorders and factors specific to the epilepsy population, including seizures themselves and anti-epileptic medication side effects. Among adults, patients with epilepsy report a greater number of sleep disorder symptoms than healthy controls (Hoeppner, Garron, & Cartwright, 1984). Sleepiness in particular has been a common complaint in adults with epilepsy relative to adults with no history of neurological disorder (Frost, Malow, & Aldrich, 1996; Hoeppner et al., 1984). Malow, Bowes, and Lin (1997) examined the predictors of excessive sleepiness in adults with epilepsy and found that participants who scored highly on the sleep apnea scale of a sleep disorders questionnaire and/or endorsed symptoms of restless leg syndrome also had an elevated score on the Epworth Sleepiness Scale (ESS). Interestingly, among this sample of adults with epilepsy, symptoms supporting the presence of a treatable sleep disorder (e.g., apnea-like arousals) were stronger predictors of sleepiness than seizure frequency or number or type of anti-epileptic medications (Malow et al., 1997). Based on these findings, the researchers suggested that before attributing sleepiness to anti-epileptic medications or uncontrolled seizures, the possibility of a co-existing sleep disorder should be considered, highlighting the importance of diagnosis of sleep disorders in patients with epilepsy (Devinsky, Ehrenberg, Barthlen, Abramson, & Luciano, 1994; Vaughn, D'Cruz, Beach, & Messenheimer, 1996). In addition, research has suggested that improving sleep by treating sleep disorders may impact seizure control. Beran, Plunkett, and Holland (1999) examined sleep disorder symptoms such as snoring in a sample of patients with epilepsy, and found that 75 percent of the sample had a diagnosable sleep disorder, including obstructive sleep apnea, periodic leg movement syndrome, and upper airway resistance syndrome. When a small sample of these patients with epilepsy and obstructive sleep apnea (OSA) began treatment for their OSA, they reported at least a 50% decrease in seizures. Finally, recent research has even suggested that OSA may contribute to worsening seizure control or the onset of seizures in the older adult population (Chihorek, Abu-Kalil, & Malow, 2007). Compared to a group of patients with resolved or improving seizures, the group with new/late onset seizures or worsening seizures had a significantly higher apnea hypopnea index (consistent with OSA) and reported greater daytime sleepiness. Similar to other studies, in a small sub-sample, treatment of OSA appeared to improve seizure control, but only for sleep-related (nocturnal) seizures (Chihorek et al., 2007)

As previously noted, relative to the adult population, less research has focused specifically on the nature of sleep disturbances in children with epilepsy. In general, child sleep patterns have been shown to be similar to those of adults, particularly as the child approaches adolescence and adulthood (Carney, Becker, & Bongiolatti, 2005; Ferber, 1996). Likewise, there are similarities in the type of sleep disorders reported in the general pediatric population (including children with epilepsy), with sleep-respiratory syndromes including obstructive sleep apnea, primary snoring, and upper airway resistance syndrome among the most commonly reported. Children with epilepsy have been reported to have higher rates of sleep problems than the general pediatric population (Zaiwalla, 1989). Parents are also more likely to report sleep problems in their children with epilepsy (Cortesi, Giannoti, & Ottaviano, 1999; Brum Batista & Lahorgue Nunes, 2007), including when they are compared to their nearest-aged sibing without epilepsy (Wirrell, Blackman, Barlow, Mah, & Hamiwka, 2005). A recent study has also found that children with epilepsy self-report greater daytime sleepiness than healthy controls (Maganti et al., 2006). In addition, polysomnography has demonstrated alterations in total sleep time, sleep latency, spontaneous awakenings, and REM latency in children with epilepsy (Becker, Fennell, & Carney, 2003; Hoeppner et al., 1984; Maganti et al., 2005; Sterman, Shouse, & Passousant, 1982). Interestingly, as has been reported in adults, Koh, Ward, Meei, and Chen (2000) found that treating a sleep disorder, specifically sleep apnea, in children with epilepsy led to decreased seizure frequency in 5 of 9 patients aged 1-6 years.

While the cognitive and behavioral effects of epilepsy and of sleep disorders have been explored separately, only a limited amount of research has examined the potential impact of sleep disorders on cognition and behavior among children with epilepsy. In children with sleep disturbance (primarily sleep-breathing disorders), hyperactivity, inattention, and opposition have been reported (Zuckerman et al., 1987; Owens et al., 1998; Blunden et al. 2000; Chervin et al. 2002). Similarly, children with epilepsy have been shown to exhibit more behavior problems such as inattention, poor concentration, and oppositionality than children with other chronic illnesses or healthy children (Austin, Risinger, & Beckett, 1992; Stores et al., 1998). In studies of children with concomitant epilepsy and sleep disturbance, a possible relationship between comorbidity and behavioral and emotional factors has been suggested. An investigation of children ages 5 to 11 years with epilepsy found an association between daytime behavior problems and sleep disturbance (Stores et al., 1998). Zaiwalla (1989) also found that behavior problems are more common in children with epilepsy and are significantly associated with their sleep problems. Further, Cortesi et al. (1999) found a strong association between sleep and behavior and/or emotional problems in children with epilepsy, particularly in the older, "overcontrolled and anxious" group. However, these studies could not conclusively state that the presence of sleep disturbance was the primary contributor to behavior problems. For example, the presence of a sleep disorder was often associated with an increase in seizure frequency, which has also associated with behavioral problems (Hoare, 1984; Austin, 1988).

Additional research has focused on behavior problems in children with epilepsy who endorse symptoms of sleep disturbance (Becker et al. 2003; Becker et al., 2004). Becker et al. (2003) employed a validated pediatric sleep questionnaire to examine parental report of sleep complaints in a sample of preadolescent children with epilepsy. Parents of children with epilepsy reported levels of daytime sleepiness, restless sleep, and snoring in their children that were comparable to parental report of symptoms in children with known obstructive sleep apnea. Overnight polysomnogram results confirmed that all 14 children with epilepsy showed signs of respiratory disturbance (apnea + hyponea index > 1). Parent report of behavior problems was also examined in the group of children with epilepsy. Based upon parent report questionnaires, sixty-four percent (64%) of the children with epilepsy were within the clinical range for attention problems and hyperactive-impulsive behavior and forty-three percent (43%) demonstrated clinical levels of externalizing and oppositional behavior. The results of this study suggested that some neurobehavioral problems reported in children with epilepsy may be related to an underlying sleep disturbance.

Becker et al. (2004) aimed to further explore the relationship between sleep disturbance and daytime behavior in children with epilepsy. Parent ratings of child behavior and child self-report of mood was examined in 30 children with epilepsy, ages 7 to 12 years. Overnight polysomngraphy was used to assess for nocturnal sleep problems, including symptoms of obstructive sleep apnea, nocturnal seizures, periodic leg movements, and sleep fragmentation. Results indicated that 80% of the children with epilepsy exhibited sleep disruption, due to either clinically significant obstructive sleep apnea, disturbance in sleep architecture, or sleep fragmentation. Further, the majority of the sample of children with epilepsy had clinical levels of inattentive/hyperactive behavior and/or problem behaviors, as reported on parent measures of behavior. Analyses indicated that increased behavior problems were associated with sleep disturbance, but not seizure severity, suggesting that sleep disturbance may play a significant role in the development of parent-reported behavior problems in children with epilepsy. Additional research with this same sample further indicated that sleep fragmentation, as measured by the number of nocturnal arousals, was associated with increased parent report of behavior problems (Bongiolatti, Fennell, & Carney, 2006). Increased sleep onset latency among the children whose parents reported significant oppositional and hyperactive behaviors, also suggests the problem behaviors may be related to increased daytime sleepiness (Bongiolatti, Fennell, & Carney, 2005). Unfortunately, direct neuropsychological testing of attention and learning was not conducted, and therefore, conclusions about potential cognitive difficulties were based solely on parent report.

There has been very limited research attempting to objectively examine the possible relationship between sleep disturbance, epilepsy, and cognition. The only published study identified at this time compared attention performance in a small sample of children with generalized epilepsy (versus healthy controls) using a continuous performance test (Maganti et al., 2005). Children with epilepsy performed significantly worse on the attention measure, and were also found to have abnormal sleep architecture, including longer rapid-eye-movement (REM) sleep onset. However, only a trend toward an association between sleep architecture and attention performance was found. The lack of neuropsychological studies examining cognitive performance and sleep disturbance in children with epilepsy limits our understanding of this complex relationship and suggests an opportunity for additional research.

Purpose of Study

Further work is needed to objectively examine the relationship of sleep disturbance to behavioral problems and cognitive performance in children with epilepsy. The purpose of the current study was to examine the impact of sleep disturbance on attention, learning, and daytime behavior in children with epilepsy by employing neuropsychological measures, parent ratings of behavior, and a comprehensive sleep questionnaire. In addition to clarifying the nature of attention and learning problems in children with epilepsy, an established relationship would suggest treatment of sleep disorders in children with epilepsy could provide one mechanism for ameliorating neurocognitive problems. Clarification of these relationships has several potential positive implications including enhancement of seizure control, reduction of daytime behavior problems, and improvement of cognitive functioning including attention and concentration. Specific aims and hypotheses were as follows:

1. *To determine whether sleep disturbance is associated with increased attention problems in children with epilepsy.*
    a. It was predicted that children with epilepsy and elevated levels of sleep disturbance would exhibit greater impairment on neuropsychological tests of attention than those with lower levels of sleep disturbance.
    b. It was predicted that parent report of greater sleep disturbance would be directly correlated with impairment on measures of attention.
2. *To determine whether sleep disturbance is associated with increased learning difficulties in children with epilepsy.*
    a. It was predicted that children with epilepsy and greater levels of sleep disturbance would exhibit greater impairment on neuropsychological tests of learning than those with lower levels of sleep disturbance.
    b. It was predicted that parent report of greater sleep disturbance would be directly correlated with impairment on measures of learning.
3. *To further establish the association between sleep disturbance and parent reported attention and behavior problems in children with epilepsy.* It was predicted that children with epilepsy with elevated levels of sleep problems would exhibit greater levels of

attention and hyperactivity on parent report questionnaires than those with lower levels of sleep disturbance.

CHAPTER 2
METHODS

Participants

Nineteen children diagnosed with epilepsy participated in this study. Children ranged in age from 6 to 12 years old. This age range was chosen to reflect the greater prevalence of active seizure disorders among school-aged children, and in consideration of available normative data for the selected neuropsychological measures.

Children were included if they carried a diagnosis of partial or generalized epilepsy, as defined in the International League against Epilepsy (ILAE) Classification, including having previously experienced greater than one unprovoked seizure. All epilepsy diagnoses were confirmed by a University of Florida/Shands Hospital pediatric neurologist as documented in the child's neurology chart. Both partial and generalized epilepsies were included in the study as attention difficulties have been associated with both seizure types, and this allowed for maximized recruitment potential. Details regarding recruitment challenges are further discussed below. Inclusion criteria also required that a parent/caregiver was able to complete questionnaires and to provide consent for the child's participation. To reduce the impact of confounding variables such as level of cognitive functioning and medication side effects, exclusion criteria included: 1) an IQ of less than 70, as measured by the two-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI); 2) currently taking greater than 2 anti-epileptic medications or having changed medication in the past 56 days; 3) diagnosis of Lennox-Gastaut or other progressive brain disorder; 4) a significant history within the past two years of medical disease, (i.e., cardiovascular, hepatic, renal, gynecologic, musculoskeletal, gastrointestinal, metabolic, endocrine, or cancer with a metastatic potential) which might impair participation in the study; 5) multiple physical and/or cognitive disabilities or a known diagnosis of mental retardation; and 6) a history of significant psychiatric disease, which might impair participation in the study.

Measures

The full battery included brief intellectual screening, abbreviated neuropsychological testing focused on attention and learning, and parent-report behavior and sleep questionnaires (See Table 2-1). All children were administered a neuropsychological battery designed to assess attention and learning, the two primary areas of interest. Basic visuospatial/visuoconstructional ability and processing speed were also included as proposed control measures. Specifically, because visuospatial/visuoconstructional impairment has not typically been reported in children with sleep disorders nor is it strongly associated with attention performance, it was anticipated that visuospatial/visuoconstructional skills would not be strongly associated with sleep disorder symptoms in the current study (e.g., Williams, Griebel, & Dykman, 1998; O'Brien et al., 2004; Baron, 2004). In light of controversial findings regarding the impact of AEDs on children's processing speed (Loring & Meador, 2005), assessment of processing speed was also included to assess as a potential confound. Parents completed questionnaires regarding their child's behavior, mood, and sleep, as well as demographic and medical history, including seizure history.

Intellectual Screening

To screen for cognitive ability, each child was administered the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). This measure was chosen for its ability to reliably estimate intellectual functioning in a brief amount of time. The WASI has been normed for children and adults ages 6 to 89 years old. The two-subtest version of the WASI provides an estimate of general intellectual ability (Full Scale IQ), and consists of the Vocabulary and Matrix Reasoning subtests. The Vocabulary subtest required defining words and the Matrix Reasoning subtest involved correctly choosing a design to complete a visual array (Matrix Reasoning). The average reliability coefficient for the two-subtest Full Scale IQ is 0.96 and test-retest reliability is 0.88 (Wechsler, 1999). For both tasks, raw scores were converted to age-adjusted T-scores.

Attention

Test of Everyday Attention for Children

Children were administered selected subtests of the Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999). The TEA-Ch is a standardized clinical battery designed to assess attention across multiple domains, including selective attention, sustained attention, and attentional control, or switching. The TEA-Ch has been found to effectively differentiate children with Attention Deficit/Hyperactivity Disorder (ADHD) from both healthy controls and a non-ADHD clinical control population based upon patterns of performance across the three attentional domains (Manly et al., 2001; Heaton, et al., 2001). Structural equation modeling confirmed that the three factor-model of attention assumed by the TEA-Ch formed a close fit to the pattern of children's performance on the measure (Manley et al., 1999). Reliability testing of the TEA-Ch indicated moderate (.53) to high (.87) test retest correlations for all subtests (Manley et al., 1999). The complete TEA-Ch consists of nine subtests, and is normed for use with children ages 6 to 16 years based on a normative sample of 293 Australian children and adolescents. For all tasks, raw scores are converted into sex-specific, age-scaled scores, ranging from 1 through 19, with a mean of 10 (SD=3). A briefer battery was be employed for the present study, including Sky Search, Score!, and Creature Counting. First, Sky Search assesses selective attention, or the ability to filter out or ignore distracting information in order to detect relevant information. It is a brief, timed task in which the child is instructed to find and circle pairs of "target" spaceships on a sheet of multiple distracter spaceships. Sky Search includes a second part in which there are no distracters; subtracting part two from part one provides a scaled score index of the child's ability that is relatively free from the influence of motor speed (Sky Search Attention Score).

Score! measures sustained attention, or the ability to maintain attention over time, even when the given task is quite boring. Children count the number of tones they hear played on a cassette tape, as if they were keeping track of a score in a computer game. The tones are separated by long delays, which when combined with the relative simplicity of the counting task, provides little to externally maintain the child's attention. Accordingly, it requires the child to self-sustain attention in order to successfully complete the task. Outcome is the number of trials correct out of ten trials.

Creature Counting assesses attentional control/switching, which is the ability to change attentional focus flexibly and adaptively. Attentional control/switching involves efficiently stopping one task and beginning another or quickly optimizing performance after changing the way that a task is performed. In Creature Counting, the child is instructed to count aliens residing in tunnels. Occasional arrows in the tunnels direct the child to either count forward or count backward, requiring them to repeatedly switch the direction in which they are counting. Creature Counting yields two scores, accuracy and a timing score. The timing score is essentially the average amount of time required to successfully complete all of the switches in a trial (total time in seconds / total number of switches), and is calculated only for correct trials. Creature Counting Timing Score was the primary variable of interest in the current study.

Conners' Continuous Performance Test, 2nd Edition

In addition, the children were administered the Conners' Continuous Performance Test, 2nd Edition (C-CPT-II; Conners, 2000), a test of concentration and sustained attention commonly used in clinical settings. The C-CPT-II is a 14-minute computer administered task in which the respondent is required to press the space bar whenever any letter except the letter ‘X’ appears on the computer screen. The inter-stimulus intervals (ISIs) vary between stimulus presentations, with ISIs of either 1, 2, or 4 seconds. Several measures are provided by the C-CPT-II program, including overall response times and errors. The primary variable of interest for this study was Hit Reaction Time (RT) Variability (Standard Error of Reaction Time for Hits). Increased hit RT variability has been strongly associated with the presence of ADHD symptoms (Epstein et al., 2003). In addition, number of omission and commission errors were reviewed. All variables were given as T-scores. Performance is evaluated relative to a normative, non-clinical sample of 1920 participants. Split half reliability indices for all of the CPT performance measures range between .73 and .95, and test-retest reliabilities for a 3-month interval for a small sample of adults range between .55 and .84 (Conners, 2000).

Trail Making Test

Children were also administered the shortened child-version of the Trail Making Test (Reitan, 1956). This brief test evaluates visual scanning ability and the ability to switch between two tasks (components of attention), as well as sequencing and processing speed. The Trail Making Test consists of two parts. Part A requires the child draw a line connecting 15 numbered and randomly arranged circles in order (much like “connect the dots”). Part B involves a page with circles containing the numbers 1 to 8 and the letters A to G, again randomly arranged. The child must draw a line that connects the circles, alternating between a number and a letter in sequential order (i.e., 1 to A to 2 to B to 3, etc.). If the child makes a mistake on either Part A or B, the mistake is quickly corrected by the examiner and the child continues. Scoring is the time required to complete each part. Timing scores were converted to age-adjusted z-scores for each child, based on normative means and standard deviations.

Learning: Wide Range Assessment of Memory and Learning

Both verbal and nonverbal learning were assessed using subtests from the Wide Range Assessment of Memory and Learning (WRAML; Sheslow & Adams, 1990). The WRAML is a comprehensive memory and learning battery normed for children between 5 and 17 years of age. It consists of nine subtests that assess memory and learning of both visual and verbal information. For the present study, we employed the two learning subtests: verbal learning, which involves word list recall, and visual learning, which involves design location recall. On the Verbal Learning task, the child is asked to recall words from a list after each of four presentations, and following a 20-minute delay. On the Visual Learning task, the child is asked to identify the locations of designs presented on a board after each of four presentations and again following a 20-minute delay. Both the Verbal and Visual Learning tests yield a raw score that is converted to an age-adjusted scaled-score; the two scaled scores will be used in the analyses. The WRAML was normed on a group of 2,363 children on the basis of a stratified model that reflected national demographic data (Sheslow & Adams, 1990). The WRAML demonstrates high reliability based on mean coefficient alpha for Verbal Learning (.78), Visual Learning (.85) and the overall Learning Index (.91).

Processing Speed: Wechsler Intelligence Scale for Children, Fourth Edition Processing Speed Index

Processing speed was assessed using Coding and Symbol Search from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003). Together these two subtests yield a Processing Speed Index, an age-adjusted Standard Score (mean of 100, standard deviation of 15), which was used as an overall measure of processing speed. The WISC-IV was normed on a sample of 2200 children from 11 one-year age bands.

Coding is a motor speed task that is sensitive to deficits in focused or sustained attention. In this task, the child must transcribe geometric symbols that are matched with the digits 1 – 9 as quickly as possible within a two-minute limit. The score is based upon the number completed (with possible bonus points for time), and then converted to an age-scaled score (mean of 10, standard deviation of 3). Test-retest reliabity conducted with a subset of 243 children was .70.

Symbol Search is a match-to-sample test of speed of processing. Children are required to scan five geometric symbols to decide whether either one of two target symbols is present, and to then mark the appropriate "yes" or "no" box. There is a 120 second time limit, and the score is the number correct minus the number incorrect (as a correction for guessing) completed within the time limit. This score is then converted to an age-corrected scale score (mean of 10, standard deviation of 3). Symbol Search test-retest reliablity (n=243) was .76.

Visuospatial/Visuoconstructional Ability: Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition

Assessment of basic visuospatial and visuoconstructional abilities was included as a proposed control measure, as it was predicted that this aspect of functioning should not be impacted by the presence of a sleep disorder. Visuospatial/visuoconstructional ability will be assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (VMI; Beery, Buktenica & Beery, 2004). The VMI is a commonly used, standardized copy forms test with an objective scoring system. Children are required to copy a series of increasingly complex geometric shapes within a testing booklet. Scoring is based on accuracy of each copied figure, and yields an age-adjusted standard score, which was used in analyses.

Parent Questionnaires

The parent/caregiver was asked to complete a pediatric sleep questionnaire as well as two behavior questionnaires, which are described below.

Children's Sleep Questionnaire-Parent Report

An in-house questionnaire called the Children's Sleep Questionnaire-Parent Report (CSQ-PR) was employed to assess the frequency of sleep disturbance symptoms (See Appendix). The CSQ-PR is a 90-item close-ended parent report measure used to assess the presence and frequency of various sleep disorders, including sleep disordered breathing, restless leg syndrome/period leg movement disorder as well as disrupted sleep habits. It is derived in part from existing sleep questionnaires, including the Pediatric Sleep Questionnaire (Chervin, Hedger, Dillon, & Pituch, 2000) and the Children's Sleep Health Questionnaire (Owens et al., 2000). The questionnaire also includes a supplemental open-ended section for assessment of general medical history and sleep history. The CSQ-PR was used to assess for the presence of sleep disorder symptoms. For the current study, a Total Sleep Problems Score was created summing the parent report of symptoms of sleep disturbance. Individual subscales (e.g., Breathing Symptoms; Daytime Sleepiness Symptoms) were also summed. The measure had not yet been standardized. However, it was chosen for its more comprehensive assessment of symptoms of sleep disturbance.

Behavior Assessment System for Children, Second Edition

The Behavior Assessment System for Children, Second Edition (BASC-2) measures multiple aspects of observable behavior in children and adolescents. Parents completed the BASC-2 Parent Rating Scales (BASC-2 PRS), a comprehensive questionnaire designed to assess a child or adolescent's adaptive and problem behaviors both at home and in the community. The BASC-2 PRS is comprised of 14 subscales, which combine to yield four composite indices. Comparable forms are available for children age 6 to 11 years (PRS-C) and adolescents age 12 to 21 years (PRS-A). For the purposes of this study, we primarily examined the Attention Problems Subscale and Hyperactivity Subscale. Scores were converted to age-adjusted T-scores for comparison. The BASC-2 was standardized using a large, census-matched normative sample (n=3600 for PRS-C and PRS-A combined). The BASC PRS-C and PRS-A internal-consistency reliabilities are very high for the composite indices (0.90-0.95), and are also high across subscales (0.72-0.88; Attention: 0.87-0.88; Hyperactivity: 0.82-0.86).

Conners' Parent Rating Scales-Revised, Long Form

The Conners' Parent Rating Scales-Revised, Long Form (CPRS-R:L; Conners, 2001) uses parent ratings on 80 items to evaluate problem behavior in children and adolescents ages 3 to 17 years. For the purposes of this study, the CPRS-R:L was employed to assess parents' perception of ADHD-related behaviors consistent with current diagnostic criteria. The CPRS-R:L is comprised of 13 subscales. All scores are converted to age- and sex-adjusted T-scores for comparison. The CPRS-R:L was standardized using a large normative sample (n=2200). The CPRS-R:L has very good internal consistency across scales (.75 to .94) and has been shown to effectively differentiate children with and without ADHD (sensitivity of 92.3%, specificity of 94.5%; Conners, et al, 1998). The DSM-IV Symptom subscales were used in analyses to examine clinically relevant ADHD symptoms.

Demographic and medical information

The parent/caregiver completed a brief demographic/background questionnaire that included items such as age, birth date, grade level, maternal and paternal education level, maternal and paternal occupation, significant medical history aside from epilepsy, and history of academic progress and learning disabilities. Epilepsy data including epilepsy type, recent AED history, age of onset and duration of illness, and a consecutive 56-day seizure frequency count (as a gross measure of seizure severity) was also obtained. Medical and epilepsy history was supplemented and/or confirmed via medical record review as needed.

Procedure

Recruitment

Participants were recruited from the Pediatric Neurology outpatient clinics at the University of Florida/Shands Hospital in Gainesville, Florida under the supervision of three attending pediatric neurologists. Participants were initially identified via review of medical records of children scheduled for clinic visits (under a HIPAA Waiver of Authorization for Screening Subjects) or by the attending physician or nurse practitioner during routine neurological visits. Medical record review was used to determine diagnosis (e.g., does the child have epilepsy?), age, and general functional status (e.g., does child have speech?) of children presenting at clinic. Participants were recruited exclusively through direct contact by the primary investigator with the assistance of the pediatric neurologists and nurses. Based upon medical chart review or referral by the neurologist or nurse, potential parent(s) and children were approached during regularly scheduled visits and informed about the study opportunity. Recruitment fliers were also posted at Shands Hospital and the Shands Medical Plaza, but yielded no responses.

Multiple challenges were faced during the recruitment phase of this project. The initial study design required that children be scheduled for an overnight sleep study and excluded children with a diagnosis of or symptoms consistent with ADHD (as assessed by a screening measure). These criteria proved to be overly restrictive for our sample of children, as recruitment over several months yielded only five potential subjects of which one consented and completed participation. Weekly screening of referrals to the University of Florida Sleep Center yielded no children with epilepsy within the study age range over a six month period. Removal of the sleep study inclusion criterion and the ADHD exclusion criterion increased participant eligibility, although overall recruitment numbers remained lower than anticipated at the initial proposal of the project. Specifically, an estimated 45 families were approached regarding the study, and of these, approximately 35 parents of eligible children expressed interest in participating. After initial expression of interest, several families were unable to participate for extraneous reasons, including the inability to return to Gainesville for testing due to the expense of travel. Approximately five families failed to return telephone calls regarding scheduling a testing session or did not show for scheduled testing appointments. Twenty-four child/parent diads were consented/assented and enrolled in the study, and 19 children completed all study requirements. Following initial enrollment, three children were excluded based upon IQ score or the lack of basic skills required for the neuropsychological testing (e.g., counting, letter recognition). Two children who were successfully screened were unable to complete testing, one due to illness and the other due to the death of the parent.

Screening and Assessment

Prior to initiating testing, consent of parents of children meeting inclusion/exclusion criteria and assent of children age 7 and older were obtained per University of Florida and Shands Hospital IRB protocol. Participants were either tested following their regularly scheduled Pediatric Neurology clinic visit at the Shands Medical Plaza or at a later date in the UF/Shands Hospital Psychology Clinic. Two participants were tested in private study rooms at the public library in their hometown.

Participants were first screened for general cognitive ability using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). When possible, the screening was completed at the Pediatric Neurology Clinic visit in order to confirm eligibility prior to additional scheduling for testing. Children who met the eligibility criteria of a Full-Scale IQ of $\geq$70 were administered the remainder of the neuropsychological test battery as described above while the parent/guardian completed the demographic/medical questionnaires and behavior questionnaires.

The full neuropsychological test battery required approximately two hours to complete (including the screener). Breaks were provided as needed to prevent fatigue. Test administration followed a fixed order that did not vary between participants. Children were given a small gift (valued at less than or equal to $5) to thank them for their participation, and parents were provided with a brief written summary of the neuropsychological findings.

Table 2-1. Study measures.

Respondent	Domain	Measure
Child	Intellectual Screening	Wechsler Abbreviated Scale of Intelligence (WASI)
	Attention	Test of Everyday Attention in Children (TEA-Ch) Sky Search
		TEA-Ch Score!
		TEA-Ch Creature Counting
		Trail Making Test
		Conners' Continuous Performance Test, 2^{nd} Edition (C-CPT-II)
	Learning	Wide Range Assessment of Learning and Memory (WRAML) Verbal Learning
		WRAML Visual Learning
	Processing Speed	Wechsler Intelligence Scale for Children, 4^{th} edition (WISC-IV) Coding
		WISC-IV Symbol Search
	Visuospatial/Visuoconstructional	Beery-Buktenica Test of Visual-Motor Integration, 5^{th} edition (VMI)
Parent	Sleep	Children's Sleep Questionnaire—Parent Report (CSQ-PR)
	Attention/Behavior	Behavior Assessment System for Children, 2^{nd} Edition (BASC-2)
		Conners' Parent Rating Scale-Revised:Long Version (CPRS-R:L)

CHAPTER 3
RESULTS

Preliminary Analyses

All statistical tests were performed using the SPSS 16.0 statistical analysis package. Raw scores were converted to Standard Scores (M = 100, SD = 10), T-scores (M = 50, SD = 5) or Scaled Scores (M = 10, SD = 3) for statistical analysis, per standardized administration and scoring procedures. For all statistical tests, the level of significance was set at $\alpha = 0.05$. All dependent variables were evaluated for skewness as a measure of distribution symmetry. Using a cut-off of ± 2.0 as an indication of normality, all dependent variables were determined to be within acceptable limits of normal distribution. No formal normalization corrections were necessary. Data was missing for three variables: the C-CPT-II (one case), Trail Making Test Part B (one case), and the Creature Counting Timing Score (seven cases). Missing data was attributed to functional limitations, and therefore it was excluded casewise from statistical analyses. In addition, one case was excluded from the C-CPT-II variable based upon its questionable validity (per standardized administration guidelines), which was noted to be related to the child's poor cooperation with the task.

Group Assignment

The primary aims of this study involve assessing differences in attention and learning performance in children with epilepsy with and without sleep disturbance. For the purpose of data analysis, participants were assigned to one of two groups based upon parent report of sleep problems on the Children's Sleep Questionnaire-Parent Report (CSQ-PR). Based upon a median split of the total sleep problems score on the CSQ-PR, ten children were assigned to the Higher Frequency Sleep Problems group and nine to the Lower Frequency Sleep Problems group. The median total score on the CSQ-PR was 99.00 (range 31 to 202).

Demographics

Demographic variables between groups were compared using independent sample t-tests and Chi-square or Fisher's exact test analyses. A summary of demographic information for both groups is presented in Table 3-1. The mean age of the Higher Frequency Sleep Problems group was 9 years, 4 months (range 6 years, 3 months to 12 years, 6 months). The mean age of the Lower Frequency Sleep Problems group was 10 years, 5 months (range 6 years, 4 months to 12 years, 9 months). T-tests indicated that there were no significant differences between groups in age. The Higher Frequency Sleep Problems group consisted of five females, and five males, while the Lower Frequency Sleep Problems group consisted of six females, and three males. Among the Higher Frequency Sleep Problems group, nine of the children were reported by their parent to be Caucasian and one was reported to be African-American/Hispanic (mixed ethnicity). The Lower Frequency Sleep Problems group was composed of seven Caucasian children, one Hispanic child, and one African-American/Caucasian (mixed ethnicity) child. Initial Chi-square analyses indicated that Fisher's Exact test should be employed, which revealed no significant differences in the male:female ratio or the ratio of various racial/ethnic classifications between the two groups. Maternal education was used as a marker for socioeconomic status. Mothers of children in the Higher Frequency Sleep Problems group had an average of 14 years of education, and the mothers of the children in the Lower Frequency Sleep Problems group had an average of 12 years of education. T-tests indicated that there were no differences in maternal education.

Children were screened for eligibility using the Wechsler Abbreviated Scale of Intelligence (WASI) 2-Subtest Form. In one case the child was administered the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV). Results of an independent samples t-test comparing the two groups on intellectual functioning revealed that there was no significant difference in mean Full Scale IQ between the two groups (See Table 3-1).

Medical and epilepsy information was also collected from the parents and the medical record. In total, twelve children with generalized epilepsy and seven children with partial epilepsy participated in the study. Among the children with generalized epilepsy, six were diagnosed with absence epilepsy, five had primary generalized epilepsy, and one child had myoclonic epilepsy. In the Higher Frequency Sleep Problems group, eight children had generalized epilepsy and two children had partial epilepsy. In the Lower Frequency Sleep Problems group, four children had generalized epilepsy and five children had partial epilepsy. Fisher's Exact test indicated that the ratio of generalized epilepsy to partial epilepsy did not differ significantly between the two groups (see Table 3-2). Seizure status was also recorded, and categorized based upon whether the child has had a seizure in the past two months. The result of Fisher's Exact analysis revealed that the ratio of children who had seizures in the past two months and those who had no seizures in the past two months did not differ between the two sleep groups.

Finally, anti-epileptic medication information was also collected for all children. Children were predominantly on monotherapy for the treatment of epilepsy (57.9% of total sample). Three children were treated with two anti-epileptic medications (15.8% of total sample), while five children were not currently taking any anti-epileptic medication (26.3% of total sample). Anti-epileptic medications were also compared in the two groups (See Table 3-2). In the Lower Frequency Sleep Problems group, four children were taking no AEDs, four children were taking one AED, and one child was taking two AEDs. In the Higher Frequency Sleep Problem group, one child was taking no AEDs, seven children were taking one AED, and two children were taking two AEDs. Because of the small sample size, AED status was reduced to a two-factor variable (on or off AEDs). Fisher Exact test analysis revealed that there were no differences between groups.

Aim 1: Comparison of Attention Performance in Lower Frequency Sleep Problem and Higher Frequency Sleep Problem Groups

Means, standard deviations, and statistical results for the attentional tasks are presented in Table 3-3. Independent samples t-tests were employed to test whether children with epilepsy with a higher frequency of sleep problems performed more poorly on attentional tests than children with epilepsy and a lower frequency of sleep problems. Initial dependent variables for selective attention included the TEA-Ch Sky Search Attention score (time per target) and Trail Making Test Part A. For sustained attention, the dependent variables included the TEA-Ch Score! number correct and the C-CPT-II Hit Rate Variability score. Dependent variables for attentional control/switching were the TEA-Ch Creature Counting Accuracy score and Trail Making Test Part B.

Selective Attention

The Higher Frequency Sleep Problems group and the Lower Frequency Sleep Problems group did not differ on either measure of selective attention. On the TEA-Ch Sky Search test, the mean performance of both groups fell within the low average range relative to age-based norms, but did not differ significantly from one another, (See Table 3-3). On the secondary measure of selective attention, Trail Making Test Part A, the two groups also did not differ from each other. The mean of both groups fell within the average range relative to age-based normative data. Cohen's *d* effect sizes (Cohen, 1977) were calculated using pooled standard deviations (Rosnow & Rosenthal, 1996). Effect sizes for both Sky Search and Trails A were very small.

Sustained Attention

Two measures were used to assess sustained attention, TEA-Ch Score! auditory sustained attention test and the C-CPT-II visual sustained attention test. Results are presented in Table 3-3. The Higher Frequency Sleep Problems Group performed significantly worse than the Lower Frequency Sleep Problems group on the auditory sustained attention test (TEA-Ch Score!). Notably, the Higher Frequency Sleep Problems group also performed within the clinically significant range (scaled score < 7) on this task, whereas the Lower Frequency Sleep Problems group was within normal limits. Cohen's *d* effect size was in the very large range. It should be acknowledged that given the total number of t-tests employed in this study, there is a high experiment-wise error rate. If the *p*-value for the t-tests examining all attention variables were Bonferroni-corrected (.05/9), the critical value of alpha would be adjusted to $p < .00556$, and this finding would no longer be significant.

In contrast to the auditory sustained attention findings, the two groups did not differ on the visual sustained attention task, the C-CPT-II. Hit Reaction Time (RT) Variability was similar in both the Higher Frequency Sleep Problems group and the Lower Frequency Problems group. In addition, the number of Omissions—which is strongly and specifically associated with poor vigilance—did not differ between the groups. The performance of both groups on both C-CPT-II measures were within normal limits. Effect sizes were in the small to medium range.

Attentional Control/Switching

Finally, the groups were compared on two measures of attentional control and switching (See Table 3-3). The first proposed measure of attentional control/switching was the Timing score from the TEA-Ch Creature Counting subtest. The Timing score takes into account both speed, accuracy, and the number of switches made during the task, and can be calculated when greater than 2 of the 7 test items are correct. However, only 12 of the 19 children in the study were able to correctly complete 3 or more items. Because these missing cases were due to limitations in task performance, it was determined that standardized methods for replacing missing data would not be appropriate. Among this smaller sample (6 children per group), the Creature Counting Timing Score did not differ between the Higher Frequency Sleep Problems group and the Lower Frequency Sleep Problems group. A medium effect size was calculated. Both groups performed within broad normal limits, although the mean score of the Higher Frequency Sleep Problems group was lower than the Lower Frequency Sleep Problems group. In light of the apparent difficulty that several children had on this task, the Creature Counting Accuracy score was also examined. Again, there was no significant difference in the number of items correct between the two Sleep Problem groups, and the effect size was small. Both groups performed generally in the low average range (mean scaled scores of 7 to 8).

Trail Making Test Part B was included as a second measure of attentional control/switching. There was no significant difference in performance between the two groups. Both groups performed within normal limits relative to age-based normative data, although it should be noted that the Higher Frequency Sleep Problems group performed somewhat better than the Lower Frequency Sleep Problems group. The effect size was small.

Correlation between Parent Report of Sleep Disturbance and Attention Performance

Pearson's correlations using the Total Sleep Problems Score from the CSQ-PR and the attention variables from the TEA-Ch, C-CPT-II, and the Trail Making Test were conducted to examine the relationship between parent report of child sleep disturbance and attention performance. TEA-Ch Score! and the CSQ-PR were moderately negatively correlated, although the correlation did not quite reach statistical significance (See Table 3-4 and Figure 3-1). Otherwise, results indicated that there were no significant relationships between the Total Score on the CSQ-PR and the attention variables in this sample of children with epilepsy. The correlations between the CSQ-PR and each of the attention variables are graphically presented in Figures 3-1, 3-2, and 3-3. Employing scatterplots enabled closer review of the data correlations, and suggested that some correlations, such as that between the Creature Counting scaled score and the CSQ-PR, may have been adversely skewed by outliers (See Figure 3-3).

Aim 2: Comparison of Learning Performance in Lower Frequency Sleep Problem and Higher Frequency Sleep Problem Groups

Group Comparison

Independent sample t-tests were conducted to compare verbal and visual learning performance in children with epilepsy and a higher frequency of sleep problems and children with epilepsy and a lower frequency of sleep problems. Means, standard deviations, and statistical results for the learning variables are presented in Table 3-5. The dependent variables for learning included the Verbal Learning score and the Visual Learning score from the Wide Range Assessment of Memory and Learning (WRAML).

The Lower Frequency Sleep Problems group did not perform significantly better than the Higher Frequency Sleep Problem group on the WRAML Verbal Learning test. The mean scores for both groups also fell solidly within the average range relative to age-adjusted norms. A similar result was found for Visual Learning. The Lower Frequency Sleep Problems group performed only slightly better (not significantly) than the Higher Frequency Sleep Problems group on the Visual Learning test, and scores for both remained within normal limits. Effect sizes for both Verbal Learning and Visual Learning were in the small to medium range.

Correlation Between Parent Report of Sleep Disturbance and Learning Performance

As were done for the attention scores, Pearson's correlations using the Total Sleep Problems Score from the CSQ-PR and the WRAML Verbal and Visual learning scores were conducted to examine the relationship between parent report of child sleep disturbance and learning performance (See Figure 3-4). There was no significant correlation between sleep problems and verbal learning ($r = -0.30$, $N = 19$, $p = 0.10$, one-tailed) or visual learning ($r = 0.00$, $N = 19$, $p = 0.49$, one-tailed). Although the relationship was not significant, it was noted that there was a trend towards verbal learning and sleep problems being negatively correlated, which could bear out with a larger sample size (See Figure 3-4).

Aim 3: Comparison of Parent Report of Attention and Behavior Problems in Lower Frequency Sleep Problem and Higher Frequency Sleep Problem Groups

The final study aim was to replicate prior findings of an association between parent report of sleep problems and parent report of inattention and behavior problems in children with epilepsy. For the purpose of this study, hyperactivity was chosen as the primary behavior of interest because of its frequent association with inattention. Independent sample t-tests were again employed to test whether the children with epilepsy reported to have Higher Frequency Sleep Problems and the children with epilepsy reported to have Lower Frequency Sleep Problems differed on parent report measures of attention and hyperactivity. Dependent variables included the Attention subscale score and Hyperactivity subscale score from the Behavior Assessment System for Children, Second Edition, Parent Rating Scales (BASC-2:PRS). In addition, to more specifically look at diagnostic symptoms associated with Attention Deficit Hyperactivity Disorder (ADHD), the DSM-IV: Inattentive subscale, the DSM-IV: Hyperactive-Impulsive subscale, and the DSM-IV: Total subscale from the Conners' Parent Rating Scales-Revised, Long Form (CPRS-R:L) were included as dependent variables.

Means, standard deviations, and statistical results for the parent report questionnaires are presented in Table 3-6. Parents reported a greater degree of attention problems in the Higher Frequency Sleep Problems group than the Lower Frequency Sleep Problems group on the BASC-2 Attention subscale; however, this difference was not significant. Cohen's *d* effect size was medium to large in size. Although the Higher Frequency Sleep Problems group was relatively elevated on this scale, neither group fell within the clinically elevated range on the measure (T-score > 65). The Higher Frequency Sleep Problems group also did not differ significantly from the Lower Frequency Sleep Problems group on the BASC-2 Hyperactivity scale. Cohen's *d* was of medium size. The means for both groups were solidly within the average range for this scale and not indicative of clinical concern.

Endorsement of symptoms of attention and hyperactivity/impulsivity consistent with a DSM-IV diagnosis of ADHD were compared in the two groups using the CPRS-R:L. The Higher Frequency Sleep Problems group scored higher than the Lower Frequency Sleep Problems group across all three DSM-IV subscales, but the difference between the two sleep problems groups was not statistically significant (See Table 3-6). Cohen's *d* estimates of effect were small to medium in size. Although neither group exceeded clinical cutoff scores on the measure (T-score > 65), the mean of the Higher Frequency Sleep Problems group was at least one standard deviation above the normative mean (T-score = 50) on all three subscales.

Additional Analyses

Supplementary Neuropsychological Measures: Processing Speed and Visuospatial/ Visuoconstructional Ability

In addition to the primary study battery, supplementary neuropsychological measures were included as potential control measures. Specifically, the Processing Speed Index composed of Coding and Symbol Search from the Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV) was included to assess for potential deficits in processing speed that might underlie performance on attention tasks. The Beery-Buktenica Test of Visual Motor Integration (VMI) was included as a proposed dissociation control, as it was anticipated that the children with epilepsy would perform similarly on this visuospatial/visuoconstructional measure regardless of the presence or absence of sleep problems.

In order to test whether the Higher Frequency Sleep Problems group and the Lower Frequency Sleep Problems group demonstrated similar processing speed skills, an Independent Samples t-test was conducted using the Processing Speed Index score as the dependent variable. Although the difference was not statistically significant, the Higher Frequency Sleep Problems group (M = 80.80, SD = 21.81) performed worse on the processing speed measures than the Lower Frequency Problem Sleep group (M = 92.67, SD = 13.26), $t(17) = 1.45$, n.s.

An independent samples t-test was also conducted to assess whether the two groups differed in visuospatial/visuoconstructional skills. The ability to reproduce line drawings did not significantly differ between the children in the Lower Frequency Sleep Problems (M = 87.33, SD = 10.55) group and the Higher Frequency Sleep Problems group (M = 79.80, SD = 9.88), $t(17) = 1.61$, n.s. Clinically, the Lower Frequency Sleep Problem group performed within broad normal limits; however, the Higher Frequency Sleep Problems group performed below average.

Comparison of Diagnostic Groups: Sleep Disorder Symptoms

As described above, the two group of interest in this study were created using a median split employing the parent responses to a comprehensive sleep questionnaire (Total Sleep Problem Score), the CSQ-PR. This method was adopted in part because the small sample size precluded the use of other anticipated statistical approaches, including regression analyses. Subsequently, a more qualitative, diagnostic method was employed to better ensure that the two groups represented clinically—and not just statistically—different groups of children with regard to sleep disorder symptoms. Specifically, review of the CSQ-PR was conducted to select specific items from the Breathing Subscale, Movement Subscale, and Daytime Sleepiness Subscale that were representative of key diagnostic signs or symptoms of the more common pediatric sleep disorders. A list of these items is available in Appendix A. Children who were described as "often" or "very often" experiencing the majority of symptoms from either the Breathing Subscale or the Movement Subscale and the Daytime Sleepiness Subscale were assigned to the Sleep Disorder Symptoms group (n = 8), while the children described as predominantly "sometimes," "rarely", or "never" experiencing the symptoms were assigned to the Non-symptomatic group (n = 11). The performance of these two groups on the neuropsychological measures of attention and learning were then compared as described above for the Higher Frequency and Lower Frequency Sleep Problems groups. Specifically, independent samples t-tests comparing the Sleep Disorder Symptoms group and Non-symptomatic group were conducted using the following dependent variables: TEA-Ch Sky Search Attention score, TEA-Ch Score!, TEA-Ch Creature Counting Accuracy, C-CPT-II Hit RT Variability, C-CPT-II Omissions, C-CPT-Commissions, WRAML Verbal Learning, and WRAML Visual Learning. Results are presented in Table 3-7. Consistent with the prior analyses, the Sleep Disorder Symptoms group demonstrated poorer auditory sustained attention on the TEA-Ch Score! test, relative to the Non-symptomatic group. The two diagnostic groups did not differ significantly on any other measures of attention and learning.

Clinical Inattention Symptoms among the Two Sleep Disorder Symptom Groups

To reduce the multiple attention variables to a single variable that could be examined across the two diagnostic sleep groups (Sleep Disorder Symptoms group and Non-symptomatic group), a similar approach was used to assign children to either a clinical or non-clinical attention group. TEA-Ch scaled scores and C-CPT-II HIT RT Variability were examined to identify children who demonstrated impairment on at least two of the measures (TEA-Ch scaled score < 7, C-CPT-II T-score > 65). Based upon these criteria, five children were assigned to the Clinical Inattention group and the remaining 14 were assigned to the Non-Clinical group.

The frequency of clinical inattention in the two sleep disorder symptoms groups was then examined. Only one of the 11 children (9.1%) in the Non-symptomatic Sleep group had signs of clinically significant attention problems. In contrast four of the eight children (50%) in the Sleep Disorder Symptoms group had clinically significant attention problems. A Fisher's Exact test was employed to examine the association between symptoms of sleep disorder and attention impairment. There was no statistically significant relationship between sleep disorder symptoms and tendency toward attention impairment ($p = .07$).

Effect of Seizure Type

In order to determine whether there were unique effects of seizure type on neuropsychological performance or sleep disturbance, independent samples t-tests were employed comparing children with generalized seizures ($n = 12$) and children with partial seizures ($n = 7$). The dependent variables included the attention and learning variables used in the primary analyses as well as the CSQ-PR Total Sleep score, Breathing subscale score, Movement Related subscale score, and Daytime Sleepiness subscale score. Means, standard deviations, and statistical results are presented in Table 3-9. The children with partial seizures performed significantly worse than the children with generalized seizures on the TEA-Ch Sky Search measure of selective attention. The two groups did not differ on any other measure of attention or learning.

Effect of Seizure Status

The final sample for the study included both children who have recently been seizure-free and children who are currently experiencing seizures on a more frequent basis. To determine whether there were differences in neuropsychological performance or sleep problems based upon current/recent seizure activity, independent samples t-tests employing two levels of the independent variable—children with recent seizures ($n = 8$) and without recent seizures (n =

11)—were employed. Neuropsychological dependent variables were the attention and learning variables included in the primary analyses. Sleep complaint variables included the CSQ-PR Total Sleep score, Breathing subscale, Movement Related subscale, and Daytime Sleepiness Subscale. Means, standard deviations, and statistical results are presented in Table 3-10. The children who have had seizures in the past two months did not differ significantly from the children who have not had seizures on any of the measures.

Table 3-1. Demographic characteristics of higher and lower frequency sleep problem groups

Variable	Higher Frequency (n = 10)	Lower Frequency (n = 9)	Test Statistic	*p*-value
Age (months)	112.20 (30.69)	125.00 (22.34)	1.03[1]	NS
Sex (# males)	5	3	NA[2]	NS
Race/ethnicity (# Caucasian)	9	7	NA[2]	NS
Maternal Education (years)	14.2 (3.0)	12.2 (2.4)	-1.38s[1]	NS
Full Scale IQ	92.10 (10.27)	93.67 (16.87)	0.26[1]	NS

Note: Values presented as Mean (*SD*) unless otherwise noted; [1] *t*-value; [2]Fisher's Exact test was used, which yields no test statistic.

Table 3-2. Epilepsy/seizure characteristics of higher and lower frequency sleep problem groups

Variable	Higher Frequency (n = 10)	Lower Frequency (n = 9)	*p*-value
Seizure type (# generalized)	8	4	NS
Seizure status (# seizure-free)	5	3	NS
AED Status (# medication-free)	1	4	NS

Note: Analyses conducted using Fisher's Exact test which yields no test statistic; AED = Anti-epileptic drug.

Table 3-3. Mean comparison of attention performance between sleep problem frequency groups

Domain	Variable	Higher Frequency (N = 10)	Lower Frequency (N = 9)	One-tailed *p*-value	Effect size (Cohen's *d*)
Selective Attention	Sky Search Time per Target	7.80 (2.15)	7.56 (3.40)	0.42	0.08
	Trails A	0.04 (0.92)	0.09 (1.07)	0.47	0.05
Sustained Attention	Score!	6.80 (2.30)	9.56 (2.51)	0.01*	1.15
	C-CPT-II Hit RT Variability	53.56 (9.98)[1]	50.78 (8.79)	0.28	0.30
	C-CPT-II Omissions	53.00 (8.40)[1]	49.54 (5.25)	0.16	0.49
	C-CPT-II Commissions	54.78 (2.34)[1]	53.14 (9.12)	0.31	0.25
Attentional Control/Switching	Creature Counting Accuracy	7.50 (2.99)	8.44 (3.54)	0.27	0.29
	Creature Counting Timing	8.83 (1.72)[2]	10.00 (1.90)[2]	0.15	0.65
	Trails B	0.10 (0.86)[3]	-0.27 (1.18)	0.23	0.05

Note: Mean (*SD*); *p<.05; [1]*n* = 8, [2]*n* = 6, [3]*n* = 9

Table 3-4. Correlation of sleep disorder symptoms on the CSQ-PR and attention problems

Domain	Variable	Pearson's *r*	*p*-value
Selective Attention	Sky Search Time per Target	0.10	0.35
	Trails A	0.03	0.46
Sustained Attention	Score!	-0.38	0.05
	C-CPT-II Hit RT Variability	0.08	0.38
	C-CPT-II Omissions	0.04	0.45
	C-CPT-II Commissions	0.23	0.18
Attentional Control/Switching	Creature Counting Accuracy	-0.08	0.38
	Creature Counting Timing	-0.24	0.23
	Trails B	0.20	0.22

Table 3-5. Mean comparison of learning performance between sleep problem frequency groups

Variable	Higher Frequency (N = 10)	Lower Frequency (N = 9)	One-tailed *p*-value	Effect size (Cohen's *d*)
WRAML Verbal Learning	9.60 (1.96)	10.44 (3.40)	0.22	0.36
WRAML Visual Learning	8.30 (3.02)	9.89 (3.79)	0.16	0.46

Note: Mean (*SD*)

Table 3-6. Mean comparison of parent report of attention and behavior problems between sleep problem frequency groups

Measure	Variable	Higher Frequency (N = 10)	Lower Frequency (N = 9)	One-tailed *p*-value	Effect size (Cohen's *d*)
BASC-2	Attention	58.60 (6.59)	50.89 (12.96)	0.07	0.75
	Hyperactivity	55.00 (5.16)	48.67 (12.04)	0.06	0.68
CPRS-R:L	DSM-IV Inattentive	60.90 (11.82)	55.56 (15.22)	0.20	0.39
	DSM-IV Hyperactive/Impulsive	60.60 (8.11)	55.67 (10.65)	0.13	0.52
	DSM-IV Total	62.40 (11.26)	56.56 (13.69)	0.07	0.55

Note: Mean (*SD*); BASC-2 = Behavior Assessment System for Children, 2nd Edition; CPRS-R:L = Conners' Parent Rating Scale-Revised, Long Form; DSM-IV = Diagnostic and Statistical Manual, 4th Edition

Table 3-7. Comparison of attention and learning performance between sleep disorder diagnostic groups

Domain	Variable	Sleep Disorder Symptoms (N = 8)	Non-symptomatic (N = 11)	One-tailed *p*-value	Effect size (Cohen's *d*)
Selective Attention	Sky Search Time per Target	8.00 (2.33)	7.45 (3.08)	0.34	0.20
	Trails A	-0.04 (0.77)	0.14 (1.12)	0.35	0.19
Sustained Attention	Score!	6.25 (1.98)	9.45 (2.42)	0.01*	1.45
	C-CPT-II Hit RT Variability	50.48 (9.26)[1]	52.97 (9.49)	0.30	0.27
	C-CPT-II Omissions	50.64 (6.36)[1]	51.45 (7.48)	0.41	0.12
	C-CPT-II Commissions[a]	54.27 (2.45)[1]	53.71 (8.27)	0.42	0.09
Attentional Control/Switching	Creature Counting Accuracy	7.88 (3.14)	8.09 (3.33)	0.44	0.06
	Creature Counting Timing	8.40 (1.52)[2]	10.14 (1.77)[3]	0.05*	1.05
	Trails B	0.10 (0.76)[3]	-0.21 (1.17)	0.27	0.31
Learning	WRAML Verbal Learning	9.12 (1.89)	10.64 (2.46)	0.08	0.69
	WRAML Visual Learning	9.00 (2.98)	9.09 (3.83)	0.48	0.03

Note: Mean (*SD*); [a]Unequal variances for this measure; *p<.05; [1]*n* = 6, [2]*n* = 5, [3]*n* = 7

Table 3-8. Comparison of attention, learning, and sleep disorder symptoms between partial and generalized seizure groups

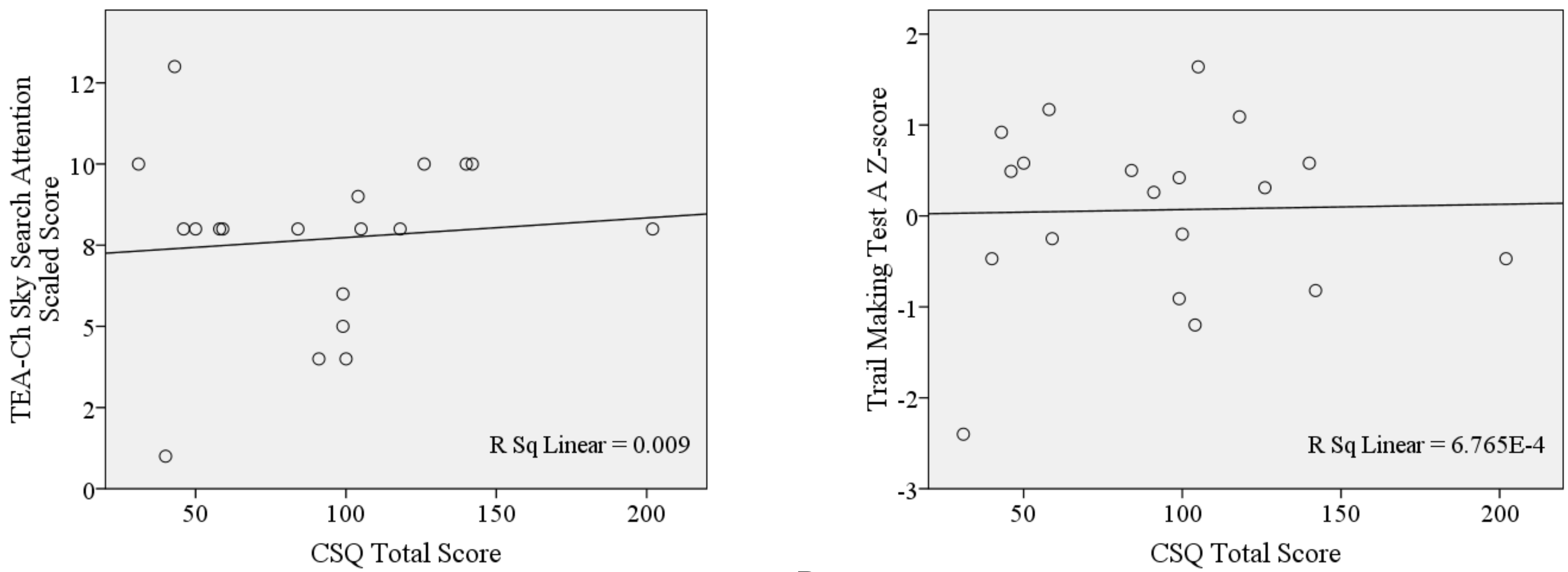
Domain	Variable	Partial (N = 7)	Generalized (N = 12)	*p*-value	Effect size (Cohen's *d*)
Selective Attention	Sky Search Time per Target	6.00 (2.77)	8.67 (2.27)	0.04*	1.05
	Trails A	0.39 (0.62)	-0.12 (1.10)	0.28	0.57
Sustained Attention	Score!	9.00 (3.00)	7.58 (2.54)	0.29	0.51
	C-CPT-II Hit RT Variability	51.53 (10.62)[1]	52.39 (8.84)[2]	0.86	0.09
	C-CPT-II Omissions	48.42 (4.51)[1]	52.66 (7.70)[2]	0.24	0.67
	C-CPT-II Commissions	56.95 (7.95)[1]	52.25 (5.60)[2]	0.17	0.68
Attentional Control/Switching	Creature Counting Accuracy	9.43 (3.10)	7.17 (3.01)	0.17	0.74
	Creature Counting Timing	10.20 (1.79)[3]	8.86 (1.77)[4]	0.23	0.75
	Trails B	0.20 (1.15)[1]	-0.23 (0.97)	0.42	0.40
Learning	WRAML Verbal Learning	11.00 (2.31)	9.42 (2.19)	0.16	0.70
	WRAML Visual Learning	10.00 (4.08)	8.50 (3.00)	0.37	0.42
Sleep Disorder Symptoms	CSQ-PR Total Score	78.43 (27.23)	99.00 (50.36)	0.34	0.51
	CSQ-PR Breathing	7.86 (4.45)	8.83 (6.65)	0.73	0.17
	CSQ-PR Movement Related	9.86 (7.43)	13.33 (8.48)	0.38	0.44
	CSQ-PR Daytime Sleepiness[a]	10.86 (7.65)	21.42 (15.38)	0.06	0.87

Note: Mean (*SD*); [a]Unequal variances for this measure; *p<.05; [1]*n* = 6, [2]*n* = 11, [3]*n* = 5; [4]*n* = 7

Table 3-9. Comparison of attention, learning, and sleep disorder symptoms between seizure status groups

Domain	Variable	Seizure Free (N = 8)	Recent Seizures (N = 11)	*p*-value	Effect size (Cohen's *d*)
Selective Attention	Sky Search Time per Target[a]	8.25 (1.28)	7.27 (3.44)	0.40	0.38
	Trails A	0.00 (1.18)	0.11 (0.83)	0.81	0.11
Sustained Attention	Score!	8.25 (3.58)	8.00 (2.10)	0.85	0.09
	C-CPT-II Hit RT Variability	52.04 (11.12)	52.13 (7.76)[1]	0.98	0.01
	C-CPT-II Omissions	53.22 (8.14)	49.34 (5.45) [1]	0.26	0.56
	C-CPT-II Commissions	53.41 (8.67)	54.36 (4.82)[1]	0.78	0.14
Attentional Control/Switching	Creature Counting Accuracy	9.62 (3.20)	6.82 (2.68)	0.05	0.95
	Creature Counting Timing	9.71 (1.98)[2]	9.00 (1.73)[3]	0.53	0.38
	Trails B	-0.47 (1.06)	0.22 (0.92)[4]	0.16	0.70
Learning	WRAML Verbal Learning	9.88 (2.03)	10.09 (2.59)	0.85	0.09
	WRAML Visual Learning	9.12 (4.29)	9.00 (2.83)	0.95	0.03
Sleep Disorder Symptoms	CSQ-PR Total Score	77.62 (34.59)	101.45 (48.18)	0.25	0.57
	CSQ-PR Breathing	8.38 (5.40)	8.55 (6.27)	0.95	0.03
	CSQ-PR Movement Related	9.38 (5.78)	14.00 (9.18)	0.23	0.60
	CSQ-PR Daytime Sleepiness	12.12 (10.44)	21.45 (15.10)	0.15	0.72

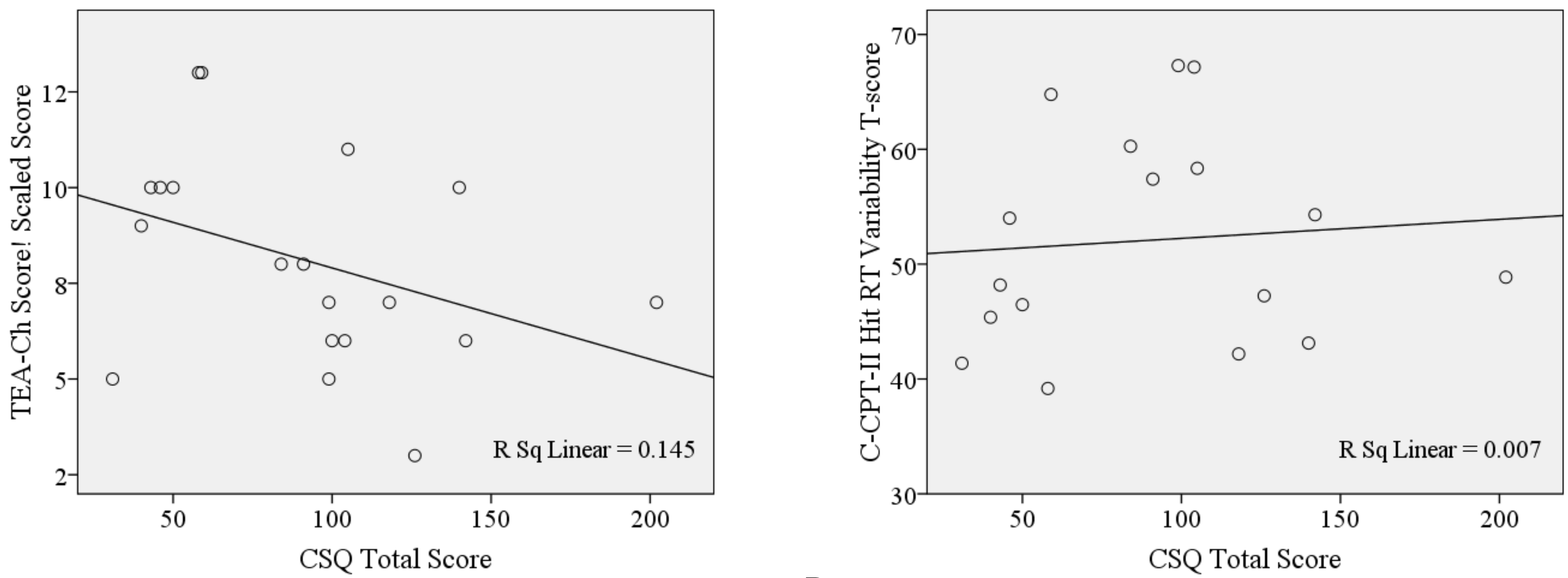
Note: Mean (*SD*); [a]Unequal variances for this measure; [1]$n = 9$, [2]$n = 7$, [3]$n = 5$; [4]$n = 10$



A

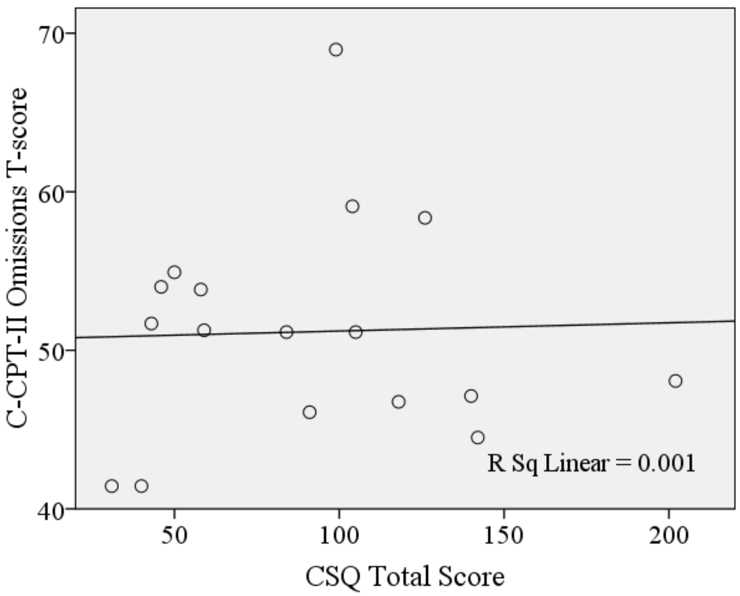
B

Figure 3-1. Scatterplots of correlation between selective attention measures and Children's Sleep Questionnaire-Parent Report (CSQ-PR). A) Sky Search Attention score from Test of Everyday Attention for Children and CSQ-PR. B) Trail Making Test Part A and CSQ-PR.

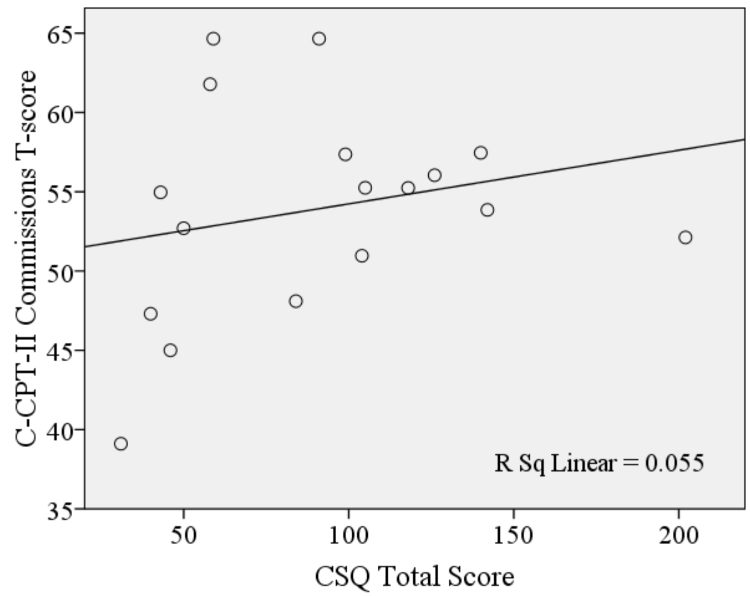


A B

Figure 3-2. Scatterplots of correlation between sustained attention measures and Children's Sleep Questionnaire-Parent Report (CSQ-PR). A) Score! from Test of Everyday Attention for Children and CSQ-PR. B) Conners' Continuous Performance Test, 2nd Edition (C-CPT-II) Hit Reaction Time Variability CSQ-PR. C) C-CPT-II Omissons and CSQ-PR. D) C-CPT-II Comissions and CSQ-PR.

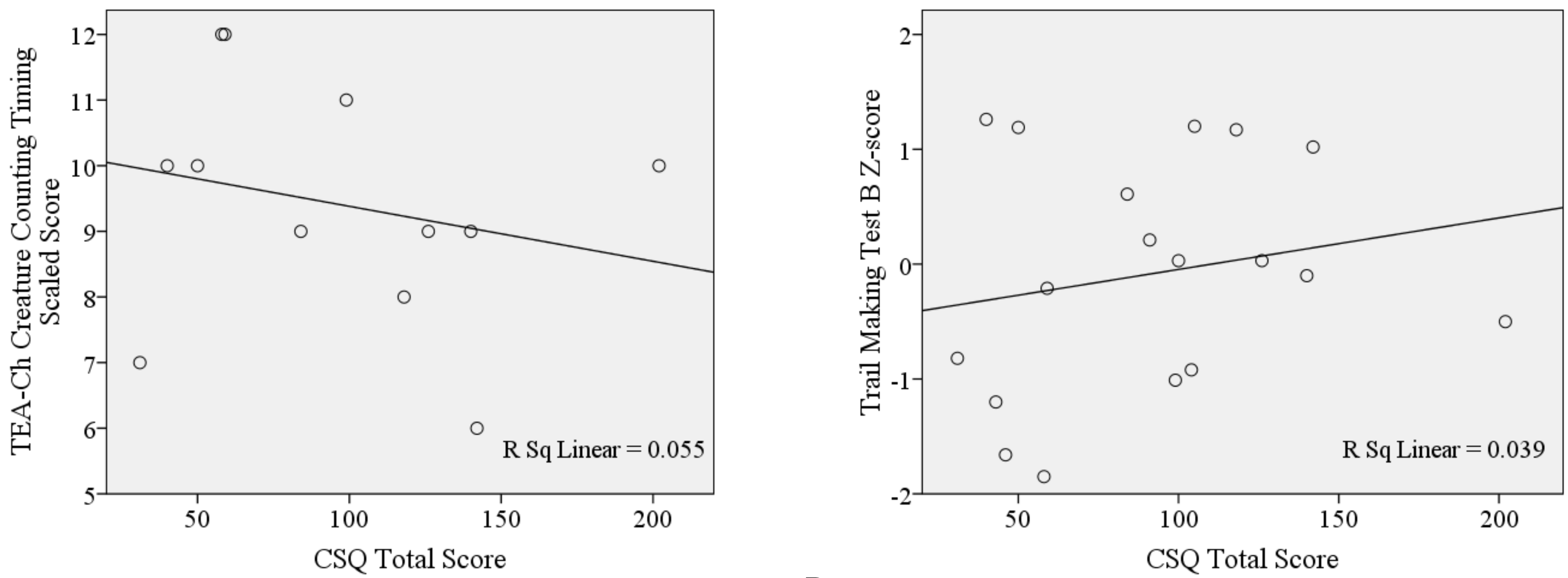


C



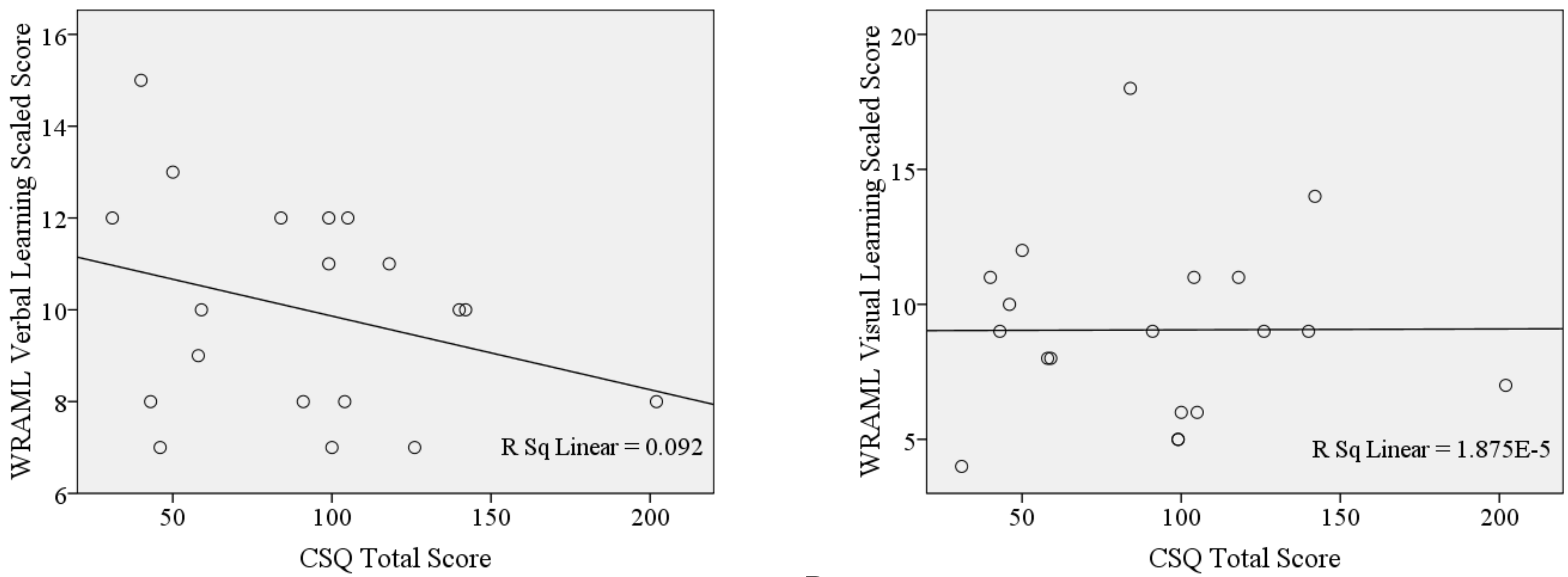
D

Figure 3-2 Continued.



A B

Figure 3-3. Scatterplots of correlation between attentional control/switching measures and Children's Sleep Questionnaire-Parent Report (CSQ-PR). A) Creature Counting Timing score from Test of Everyday Attention for Children and CSQ-PR. B) Trail Making Test Part B and CSQ-PR.



A B

Figure 3-4. Scatterplots of correlation between learning measures and Children’s Sleep Questionnaire-Parent Report (CSQ-PR). A) WRAML Verbal Learning and CSQ-PR. B) WRAML Visual Learning and CSQ-PR.

CHAPTER 4
DISCUSSION

Overview

The current study examined the relationship between sleep disturbance and attention and learning in children with epilepsy. Prior research has suggested that children with epilepsy may be at greater risk for sleep disturbance (Becker, Fennell, & Carney, 2003), and that sleep disturbance can negatively impact attention and learning performance (e.g., Stores, Wiggs, & Campling, 1998; Kotagal & Pianosi, 2006). This study aimed to determine whether children with epilepsy and co-morbid sleep disturbance demonstrate attention and learning impairment relative to children with epilepsy with few or no sleep complaints.

Children with epilepsy and co-morbid sleep disorders have been reported to have increased attention problems and other behavior problems in questionnaire-based studies. However, to date only one other study has been published looking specifically at sleep disturbance and attention performance on a neuropsychological measure in children with seizures. In addition to expanding the neuropsychological understanding of attention in this population, this study was unique in that it examined multiple domains of attention and assessed performance in the related domain of learning. The study also attempted to replicate earlier research associating increased sleep disturbance with parent report of hyperactivity and inattention.

Sleep Disturbance and Attention and Learning Performance

Consistent with most current models, a multi-modal approach to attention assessment was taken in this study. Drawing from the model by Mirsky et al. (1991), selective attention, sustained attention, and attentional control/switching were all examined. It was predicted that children with epilepsy who had a greater report of sleep problems would demonstrate greater impairment than children with fewer sleep problems across the measures of attention. However, the Higher Frequency Sleep Problem group only performed significantly worse on one measure of auditory sustained attention. Although this finding no longer met significance with Bonferroni correction, it offers at least trend support for the study hypothesis. On the other measures of attention, the children with epilepsy who had a greater frequency of sleep disturbance performed statistically similar to the children with epilepsy who had few or no complaints of sleep disturbance.

Sustained attention deficits have been described in children with epilepsy and children with sleep disorders in prior studies, including in children with generalized epilepsy and identified abnormal sleep architecture (Maganti et al., 2005). While it was predicted that the epilepsy group with higher frequency sleep problems would demonstrate greater sustained attention impairment, it was not anticipated that this difference would be found only for the auditory sustained attention task (TEA-Ch Score!) and not the visual sustained attention task (C-CPT-II). Given the magnitude of the difference between the two groups on C-CPT-II Omissions (approximately 0.5 standard deviation), it is possible that the failure to find significant results was due to a lack of power resulting from the small sample size. In a larger sample both auditory and visual sustained attention differences would likely be found. It should also be acknowledged that in the present study the scores for both groups on the visual sustained attention task were largely within normal limits for their age, particularly on Omissions, the more specific measure of inattention. In contrast, other studies of sustained attention in children with epilepsy have reported clinically impaired performance (e.g., Hernandez et al., 2003; Williams, Griebel, & Dykman, 1998; Mitchell et al., 1992). This suggests that the sample of children with epilepsy in the current study might be atypical in their overall performance (i.e., have relatively better attention skills). Alternatively, it could reflect differences in the continuous performance task parameters and outcome variables, which have been cited as a source of inconsistent findings between studies of attention (Fletcher, 1998). Given the dearth of research in this particular area, further study is necessary to better characterize sustained attention performance in children with epilepsy and co-morbid sleep disturbance.

As previously noted, neither selective attention performance nor attentional control/switching performance differed significantly between the two sleep frequency groups. Although previous research has suggested that children with sleep disorders, particularly sleep disordered breathing, tend to demonstrate greater impairment on selective attention tasks, (Owens et al., 2000; Beebe et al., 2004), this did not bear out in this sample of children with seizures. In fact, both sleep problem groups performed below average relative to the normative sample on the TEA-Ch Sky Search task (but within normal limits on Trailmaking Part A). While selective attention deficits have been described in some studies of children with epilepsy, the literature as a whole has been inconsistent, making conclusive interpretations difficult. One possible interpretation is that epilepsy alone is a risk factor for poorer performance on the more complex selective attention task and sleep disruption in the higher frequency group did not additionally contribute to the children's performance. Additional research, particularly involving control groups such as children only diagnosed with sleep disorders is needed to further clarify this relationship.

While not statistically significant, the Higher Frequency Sleep Problems group did tend to perform worse on the TEA-Ch measure of attentional control/switching, Creature Counting. As indicated by the effect size analysis, the children with more frequent sleep problems performed over a half a standard deviation below the children with few or no sleep complaints as assessed by the Creature Counting timing score, a comprehensive score that takes into account accuracy, time, and the number of times the child had to switch between sets. A larger sample size would likely provide sufficient power to detect the differences between these groups. Notably, across both groups, several cases had to be excluded from the analysis because low accuracy precluded the calculation of the timing score (four from the Higher Frequency group, and three from the Lower Frequency group). Although the excluded cases could not be statistically compared given the small samples, review of potential contributing features such as seizure type, seizure status, and medication did not suggest any clear patterns. Qualitatively, these children were the most impaired on the task but could not be included in statistical analyses due to test validity limitations. The exclusion of these lower performers limited the comprehensive assessment and comparison of attentional control between the two groups. In contrast, children from both groups performed within normal limits on the less cognitively demanding Trailmaking Part B switching task. The contrast in the performance patterns of the two sleep problem groups on Creature Counting and Trailmaking Part B might reflect the involvement of abilities better described as "executive function" and working memory than attention. Trailmaking Part B is a fairly straightforward task and easily instructed task, involving switching back and forth between two sequential sets (numbers and alphabet) in a repetitive manner (1-A, 2-B, etc.). Creature Counting, however, involves what are arguably more complex cognitive skills including inhibiting the pre-potent response in order to switch counting direction mid-sequence and maintaining the last number spoken while identifying the new direction for counting. Manly et al. (2001) recognized this complexity in describing the Creature Counting task as reflecting a "broad 'executive' or 'attentional control' factor" in their initial description of the TEA-Ch normative sample (p. 1074).   Although beyond the scope of the present study, executive functioning is an aspect of cognition that may merit further research in children with epilepsy and co-morbid sleep disorders.

Both the Behavior Assessment System for Children, 2nd Edition (BASC-2) and the Conners Parent Rating Scales-Revised: Long Edition (CPRS) were employed to look at parent report of varying aspects of attentional performance. For example, items on the BASC-2 Attention scale are more narrowly targeted to attention problems, such as "is easily distracted", "has a short attention span", and "listens carefully." In contrast, the DSM-IV Inattention scale looks more broadly at the signs and symptoms of ADHD, Inattentive type, including poor sustained attention as well as including items such as avoiding mental effort, making careless errors, being poorly organized, and losing things. Contrary to the study hypothesis, parent report of attention problems did not differ significantly between the two groups on either measure. As was found for the neuropsychological measures of visual sustained attention and attentional control, review of analyses suggested that low power may have contributed to the lack of findings. In a larger sample, we predict that a significant difference would be found supporting our hypothesis that children with epilepsy with increased sleep problems would demonstrate higher levels of parent reported attention problems. Clinically significant levels of hyperactivity were also not endorsed on either measure, and no differences in hyperactive behavior were found between the higher frequency and lower frequency sleep problem groups.

Notably, not only were scores in the present study below clinical levels, scores on the CPRS-R:L fell well below those reported in prior research examining children with epilepsy and sleep disruption. Specifically, Becker, Fennell, and Carney (2004) reported that their sample of children with epilepsy and sleep complaints had a mean score on the Total DSM-IV scale of the CPRS-R:L nearly one full standard deviation above what was reported in the present study.

Additionally, over 70 percent of the children in the Becker sample had individual scores within the clinical range (T-score > 65). In contrast, only 5 of 19 (26%) children in the total sample of this study had DSM-IV Total scores exceeding this clinical cutoff score. This finding raises interesting questions about the nature of the current study sample. Specifically the children in the Becker, Fennell and Carney (2004) study differed from those in the present study in that they were recruited on the basis of being referred for sleep studies, and 80 percent ultimately demonstrated signs of disordered sleep during polysomnography. In contrast, the current study recruited children via their regularly scheduled neurology appointments, without regard to sleep complaints or concerns. The results of the Becker, Fennell, and Carney (2004) study suggest that clinical attention problems may be most strongly associated with more significant sleep disorder symptoms. Particularly given the relatively small sample size, it is possible the current study under-sampled children with epilepsy with more severe sleep disturbance and more profound attention problems.

Attempts were made in post-hoc analyses to more stringently define the two sleep problems groups to ensure that the “higher frequency” sleep problem group captured children with significant sleep concerns (more similar to those that would have presented for sleep studies in the Becker, Fennell, and Carney study). Using questionnaire items consistent with clinical screening for sleep disordered breathing and movement-related sleep disorders, children were reassigned to the Sleep Disorder Symptoms group and the Non-symptomatic group. Group assignments remained largely the same, with only two children being reassigned to the Non-symptomatic group. Similarly, the pattern of findings remained the same in the new groups, with the Sleep Disorder Symptoms group demonstrating statistically significant impairment for sustained attention and a trend toward greater impairment for attentional control. Finally, a greater percentage of the children with in the Sleep Disorder Symptoms group also presented with symptoms of clinical attention problems than in the Non-symptomatic group (50% versus 9%). Although this difference did not meet significance, the finding is promising in that it reflects the pattern seen in earlier research.

In addition to attention, the present study aimed to examine learning performance in children with epilepsy and co-morbid sleep disturbance. Results did not support the hypothesis that children with epilepsy and sleep disturbance would perform worse on measures of verbal and visual learning. Further, the mean scores of both groups fell within the average range for both verbal learning and visual learning, suggesting that there were no clinically relevant performance problems. In light of the differences found for auditory sustained attention, it was somewhat surprising that similar findings were not found for verbal learning. Learning was chosen as a variable of interest because of its frequently described connection to attention, and sustained attention in particular. Specifically, in order to successfully encode information on a supraspan learning task like those used in this study, the child must be able to sustain his or her attention to the task, both within a trial and over the successive presentation trials. While certainly other cognitive processes are involved in learning, it was suspected that if children with sleep problems exhibited poor sustained attention, they would also exhibit poor learning. The small sample size precluded any statistical examination of the direct relationship between attention performance and learning performance; however, it is possible to speculate why the hypothesis was not supported. One hypothesis is that the learning tasks—especially the visual learning test—were experienced as more engaging or fun by the children, and thus they allocated more attention to the task at hand. In fact, during testing, many of the children commented that the visual memory task reminded them of a game, and several children demonstrated eagerness to improve their performance over trials of both tasks (e.g., asking “did I get more?”, or stating “I’m getting better”). In addition, the verbal learning task involves calculating a total score across four trials. While a child might miss encoding informing during a transient moment of inattention on a single trial, he or she has the opportunity to recuperate the information on a following trial. Subtle difficulties in encoding across the trials might be missed in a measure that uses only a summation score like that of the WRAM Verbal and Visual Learning tests.

Additional Results

Subsequent to addressing the primary analyses, additional analyses were undertaken to examine potential study confounds. Learning performance and sleep problems were found not to differ based upon seizure type (generalized versus partial) or seizure status (seizure-free or not in past 56 days). Among the attention variables, only selective attention differed between the two seizure types. While more direct regressional analyses were not feasible given the sample size, these results suggest that the modest findings in the study are not likely attributable to epilepsy characteristics. Additionally, the children with more frequent sleep problems tended to perform more slowly on measures of processing speed than the children with less frequent sleep problems, although the difference was not statistically significant. It should be acknowledged that while Symbol Search and Coding were chosen as measures of processing speed, both tasks also involve attentional abilities, particularly visual scanning and selective attention. However, the processing speed differences did not translate to differences on the primary measures of selective attention, and would not be expected to influence the differences on the motor-free, auditory sustained attention task.

Limitations

This study has several limitations that are important to consider with regards to the present outcomes and planning for future endeavors. First and foremost, the current study is best conceptualized as an exploratory pilot study due to the small sample of participants. Multiple barriers to recruitment and study completion negatively impacted the final sample size, which in turn limited the options for statistical analysis of the original study aims and hindered interpretation of findings. Ideally, a larger sample would have enabled planned regressional analyses to more directly examine the relationship between sleep problems and attention and learning performance. Instead, a suboptimal approach employing a median-split (with subsequent symptom-based classification in follow-up analyses), was necessitated in order to create groups for comparison. Although there was sufficient power to find group differences on auditory sustained attention, the small sample size limited the ability to make conclusions regarding other aspects of performance including visual sustained attention and attentional control/switching. Importantly, effect size calculations indicated that with a larger sample, significant difference would have been found for one measure of attentional control as well as for parent report of attention problems.

The results of the study may have been affected by outliers, which can be particularly influential when using central tendency-based statistics with small samples. As noted in the review of correlations, auditory sustained attention (Score!) and the sleep measure demonstrated a fairly clear, albeit not significant, negative linear relationship (See Figure 3-1). However, other correlations (e.g., Creature Counting) appeared to be skewed by suspected outliers that distorted the results by pulling the mean in their direction. Reviewing scatterplots also suggested that there were atypical, non-linear relationships between the sleep questionnaire and some variables such as Sky Search that would not have been detected by t-tests. It is possible that such atypical relationships might have become more “normalized” in a larger sample.

The present study was also hindered by the lack of a well-defined control group. Although the implementation of a two-group design was a post-hoc decision, it contributed to the diminished statistical power and the challenge of interpretation of findings. Unfortunately, it is difficult to establish a control group consisting of children who have epilepsy but no sleep disorder without using objective measures of sleep quality. Similarly, the lack of objective sleep measures and the reliance on parent report of sleep problems on a newly developed measure is another study limitation. As is true of other such measures, the parent's report on the CSQ-PR may be confounded by the subjectivity of the informant. Without established normative data or diagnostic guidelines, it was necessary to adopt a more qualitative approach to using the measure. The gold standard for sleep disorder diagnosis is the polysomnogram (PSG), or overnight sleep study, which allows a more precise examination of sleep disorder symptoms. Inclusion of PSGs in the present study was not possible due to the significant cost involved and the low rates of children eligible for the study who were being evaluated for sleep problems as part of their standard care. In fact, while access to the data from existing PSGs was allowed under the study IRB, none of the children enrolled in the study underwent an overnight sleep study during the project timeframe. In addition to their diagnostic utility, PSGs would also have been valuable because sleep studies can capture sources of disruption that would not be detected by parents, including microarousals that can occur in children throughout the night. Frequent arousals during sleep can cause sleep fragmentation, or disruption of the sleep cycle, which has been hypothesized to underlie neurobehavioral problems in children with sleep disorders (O'Brien and Gozal, 2004). While not studied extensively, sleep fragmentation has been associated with increased daytime behavior problems in children with epilepsy (Bongiolatti, Fennell, & Carney, 2006). It is possible that some children assigned to the "Lower Frequency" sleep problems group currently experience these more subtly presenting, yet impactful, types of sleep disturbance or have a sleep disorder that has not been recognized by the parent. Unfortunately, without the aid of PSG this could not be determined.

Finally, epilepsy is a diverse diagnosis, and children with epilepsy differ in terms of seizure presentation, severity, course of illness, and medication regimen. For the primary analyses, the current study did not separate children with epilepsy on the basis of any disorder-related factors such as partial versus generalized seizures. While we tried to account for potential differences between the two groups, including the number of AEDs and seizure status, it would be advantageous to limit the potential contribution of these additional variables by focusing on more narrow subgroups and thereby increasing interpretability of findings. Unfortunately, recruiting this type of selective sample requires a greater timeframe than was available for this study.

Future Directions

The relationship between sleep disorders and neurobehavioral functioning in children with epilepsy has only recently become a topic of research interest. Accordingly, there are multiple avenues for future research. Although the findings in the current study were limited, they provide support for continued investigation. Combined with the existing literature associating parent report of inattention and sleep problems in children with epilepsy, as well as the growing research associating sleep disorders such as sleep apnea and periodic leg movement disorder to daytime attention problems, it seems likely that future studies will find further support for a connection between sleep problems and attention impairment in children with seizures. A large sample study examining attention performance in children with epilepsy and co-morbid sleep disorders is needed in order to further elucidate this relationship. A large sample should allow for comparisons across seizure types, as well as more appropriate controls for seizure severity and medications. Additionally, because so little is known about the relationship between sleep and cognition in children with epilepsy and other neurological disorders, it would be advantageous to employ more comprehensive neuropsychological assessments to create a profile of performance across domains.

It will be vital to employ polysomnography (PSG) in future studies to objectively characterize sleep disturbance in children with epilepsy. Use of PSGs would allow for more diagnosis and classification of children into sleep disorder groups for comparison, and examination of sleep architecture. Ideally, future studies should use PSG and parent-report measures (as well as self-report measures when age appropriate) in conjunction to thoroughly examine sleep in children with epilepsy. Use of standardized sleep measures may facilitate interpretation of findings in future studies, and when used in collaboration with PSG will begin to inform the development of screening measures that can be used in clinical settings. Research to develop an effective screener for use in pediatric medical and psychological settings would aid health care providers in identifying children who are most at risk for a sleep disorder and co-morbid neurobehavioral problems.

Finally, future studies should examine the effects of treating sleep disorders in children with epilepsy. Unlike adults, children with obstructive sleep apnea (OSA) most frequently present with enlarged tonsils and adenoids, and first line treatment tends to be adenotonsillectomy. This treatment protocol provides an opportune structure for testing children with epilepsy before and after intervention that would help to clarify the specific relationship between sleep and seizures. Recent studies in adults with epilepsy and OSA have focused primarily on the seizure control benefits associated with treating OSA (e.g., Malow et al., 2008). However, based upon the pediatric sleep apnea literature, it appears likely that treating sleep apnea in children with epilepsy would not only improve seizure control (Koh et al., 2000), but also improve daytime attention and behavior.

APPENDIX
CHILDREN'S SLEEP QUESTIONNAIRE—PARENT REPORT

Child's Name: ______________________________________ Today's Date: ___________________
Child's Date of Birth: ______________________ Child's Age: ___________ Child's Grade: ________

Child's Ethnicity: ☐ Caucasian ☐ African American ☐ Hispanic ☐ Asian American/Pacific Islander
☐ Native American ☐ Other (please specify _______________________________)

Name of Person Completing Form: ____________________ Relationship to Child: _______________

Directions for Caregivers:
The following statements are about your child's sleep habits and possible difficulties with sleep. Think about a **<u>typical week</u> during the past month** in your child's life when answering these questions. If there were no typical weeks in the past month for your child or the family (e.g., child was sick, visitors in the home, family vacation, etc.), please base your responses on the **most recent typical week**.

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Also, at the end of each section, we will ask you about how sure you were about your answers in that section.
Please answer every question. If you are not sure of an answer, provide your best guess.

General Sleep Section

<u>Your child…..</u>	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
1. Sleeps too little	☐	☐	☐	☐	☐
2. Sleeps the right amount	☐	☐	☐	☐	☐
3. Sleeps too much	☐	☐	☐	☐	☐
4. Sleeps about the same amount each day (combining nighttime and naps)	☐	☐	☐	☐	☐
5. Has a regular bedtime routine	☐	☐	☐	☐	☐
6. Goes to bed at the same time at night	☐	☐	☐	☐	☐
7. Falls asleep within 20 minutes after going to bed?	☐	☐	☐	☐	☐
8. Has difficulty falling asleep	☐	☐	☐	☐	☐

9. **On this page, how sure are you about your answers?** ☐ **very sure** ☐ **somewhat sure** ☐ **very unsure (guessing)**

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Breathing Section **While sleeping**, your child:	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
10. Snores	☐	☐	☐	☐	☐
11. Snores loudly	☐	☐	☐	☐	☐
12. Sleeps with the mouth open	☐	☐	☐	☐	☐
13. Has "heavy" or loud breathing	☐	☐	☐	☐	☐
14. Snorts and/or gasps during sleep	☐	☐	☐	☐	☐
15. Has trouble breathing, or struggles to breathe	☐	☐	☐	☐	☐
16. Seems to stop breathing during sleep	☐	☐	☐	☐	☐
17. Needs shaking to get him/her to breathe or wake up and breathe	☐	☐	☐	☐	☐
In the morning, your child:					
18. Wakes up with a snorting sound	☐	☐	☐	☐	☐
19. Has a dry mouth upon waking up in the morning	☐	☐	☐	☐	☐
20. **On this page, how sure are you about your answers?**	☐ **very sure**		☐ **somewhat sure**	☐ **very unsure (guessing)**	

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Movement Related Section **At night time**, your child…..	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
21. Is restless and moves a lot during sleep	☐	☐	☐	☐	☐
22. Has twitches or jerks while sleeping	☐	☐	☐	☐	☐
23. Has brief kicks of one leg or both legs while sleeping	☐	☐	☐	☐	☐
24. Becomes sweaty at night or pajamas become wet with perspiration	☐	☐	☐	☐	☐
25. Has trouble sleeping because he/she feels too hot	☐	☐	☐	☐	☐
26. Has trouble sleeping because he/she feels too cold	☐	☐	☐	☐	☐
27. Has leg pains that are worst in bed	☐	☐	☐	☐	☐
28. Describes funny feelings in his/her legs when lying down or sitting (e.g., creeping, crawling, tingling, or tickling sensations)	☐	☐	☐	☐	☐
29. If your child sleeps with you, he/she kicks you hard enough that it disrupts your sleep or wakes you (If child does not sleep with you, check here:________)	☐	☐	☐	☐	☐
During the day, your child….					
30. Complains of leg pains that are relieved by moving	☐	☐	☐	☐	☐
31. Becomes weak in the legs, or anywhere else, after laughing or being surprised by something	☐	☐	☐	☐	☐
32. **On this page, how sure are you about your answers?**	☐ **very sure**	☐ **somewhat sure**	☐ **very unsure (guessing)**		

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Night Time Waking Section **At night time**, your child…..	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
33. Awakes once during the night	☐	☐	☐	☐	☐
34. Awakes more than once during the night	☐	☐	☐	☐	☐
35. Awakens during the first 2 hours after falling asleep	☐	☐	☐	☐	☐
36. Wakes up saying he/she is scared	☐	☐	☐	☐	☐
37. Wakes up complaining of an upset stomach	☐	☐	☐	☐	☐
38. Awakens during night screaming, sweating and inconsolable	☐	☐	☐	☐	☐
39. Awakens alarmed by a frightening dream	☐	☐	☐	☐	☐
40. Awakens, but appears confused or disorientated (e.g., does not respond to you, talks about things that don't make sense)	☐	☐	☐	☐	☐
41. Has trouble falling back asleep if wakes up during the night	☐	☐	☐	☐	☐
42. Moves to someone else's bed during the night (parent, brother, sister, etc.)	☐	☐	☐	☐	☐
43. Reports feeling unable to move for a short period of time, although he/she is awake and can look around	☐	☐	☐	☐	☐
44. Describes dreaming while still awake at night (i.e., sees images or hears sounds)	☐	☐	☐	☐	☐
45. Talks during sleep	☐	☐	☐	☐	☐
46. Grinds teeth during sleep (your dentist may have told you this)	☐	☐	☐	☐	☐
47. Sleepwalks during the night	☐	☐	☐	☐	☐
48. Gets out of bed night (for any reason)	☐	☐	☐	☐	☐
49. Gets out of bed to use the bathroom	☐	☐	☐	☐	☐
50. Wets the bed at night	☐	☐	☐	☐	☐

51. **On this page, how sure are you about your answers?** ☐ **very sure** ☐ **somewhat sure** ☐ **very unsure (guessing)**

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Morning Time Waking Section **In the morning,** your child….	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
52. Wakes up very early in the morning and has difficulty going back to sleep	☐	☐	☐	☐	☐
53. Has difficulty getting out of bed in the morning	☐	☐	☐	☐	☐
54. Falls back to sleep after being awakened in the morning	☐	☐	☐	☐	☐
55. Wakes up by him/herself in the morning	☐	☐	☐	☐	☐
56. Adults or siblings wake up child	☐	☐	☐	☐	☐
57. Wakes up in the morning tangled up in the sheets	☐	☐	☐	☐	☐
58. Wakes up with headaches in the morning	☐	☐	☐	☐	☐
59. Wakes up in a negative mood (e.g., cranky, irritable)	☐	☐	☐	☐	☐
60. Complains of still being tired	☐	☐	☐	☐	☐
61. Takes a long time to become alert in the morning	☐	☐	☐	☐	☐
62. Takes a long time to get ready in the morning	☐	☐	☐	☐	☐
63. **On this page, how sure are you about your answers?**	☐ **very sure**	☐ **somewhat sure**	☐ **very unsure (guessing)**		

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Daytime Sleepiness Section **<u>During the daytime,</u>** <u>your child…..</u>	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
64. Has a problem with sleepiness during the day	☐	☐	☐	☐	☐
65. Seems tired	☐	☐	☐	☐	☐
66. Teachers or other supervisor comment that he/she appears sleepy during the day	☐	☐	☐	☐	☐
67. Feels an irresistible urge to take a nap during the day	☐	☐	☐	☐	☐
68. When awake, disrupts family activities because of sleepiness	☐	☐	☐	☐	☐
69. Yawns a lot during the day	☐	☐	☐	☐	☐
70. Takes a nap during the day	☐	☐	☐	☐	☐
71. Falls asleep if sent to room for misbehaving	☐	☐	☐	☐	☐
72. Is very sleepy while watching TV	☐	☐	☐	☐	☐
73. Falls asleep while watching TV	☐	☐	☐	☐	☐
74. Is very sleepy while riding in a car	☐	☐	☐	☐	☐
75. Falls asleep while riding in a car	☐	☐	☐	☐	☐

76. **On this page, how sure are you about your answers?** ☐ **very sure** ☐ **somewhat sure** ☐ **very unsure (guessing)**

Answer **Very Often** if something occurs **5-7 days or nights** during a week
Answer **Often** if something occurs **2-4 days or nights** during a week
Answer **Sometimes** if something occurs **1 day or night** during a week
Answer **Rarely** if something occurs **less than 1 day or night** a week but **at least once in a month**
Answer **Never** if something **never** occurs during a typical week or month **(i.e., does not happen)**

Sleep Habits Section

Your child…..	Very Often (5-7)	Often (2-4)	Sometimes (1)	Rarely (< 1)	Never (0)
77. Falls asleep alone in own bed	☐	☐	☐	☐	☐
78. Falls asleep in parent's or sibling's bed	☐	☐	☐	☐	☐
79. Needs parent in the room to fall sleep	☐	☐	☐	☐	☐
80. Is afraid of sleeping alone	☐	☐	☐	☐	☐
81. Is afraid of sleeping in the dark	☐	☐	☐	☐	☐
82. Sleeps with a light or night-light on	☐	☐	☐	☐	☐
83. Has trouble sleeping away from home (visiting relatives or friends, on vacation)	☐	☐	☐	☐	☐
84. Falls asleep with rocking, rhythmic or head banging movements	☐	☐	☐	☐	☐
85. Struggles at bedtime (e.g., cries, refuses to stay in bed, etc.)	☐	☐	☐	☐	☐
86. Has temper tantrums at bedtime	☐	☐	☐	☐	☐
87. Eats, drinks, or exercises within 2 hours of going to bed	☐	☐	☐	☐	☐
88. Watches TV or plays video or computer games within 1 hour of going to bed	☐	☐	☐	☐	☐
89. Is punished by "going to bed" or being placed in his/her bed	☐	☐	☐	☐	☐

90. **On this page, how sure are you about your answers?** ☐ **very sure** ☐ **somewhat sure** ☐ **very unsure (guessing)**

CHILD'S GENERAL MEDICAL HISTORY	
Child's Height: _____feet _____inches	Child's Weight: _______pounds
Does your child still have his/her tonsils and/or adenoids? ☐ Yes ☐ No	
Has your child ever sustained a head injury where they were knocked out? ☐ Yes ☐ No If yes, describe what happened & how long unconscious:	
Does your child have any problems with their hearing or eyesight? ☐ Yes ☐ No If yes, describe:	
Does your child have any medical or neurological conditions, such as seizures, sickle cell anemia, diabetes, cancer, or autism? ☐ Yes ☐ No If yes, describe:	
Has your child been diagnosed with or treated for problems with attention or hyperactivity, such as ADHD or ADD? ☐ Yes ☐ No **If yes**, please answer the following questions: At what age was he/she diagnosed? _____________ Are they diagnosed as ☐ Primarily Inattentive Subtype, ☐ Primarily Hyperactive/Impulsive Subtype, ☐ Combined Subtype, or ☐ do not know subtype? Does your child currently take medication(s) for ADHD? ☐ Yes ☐ No Do you think your child's medication ☐ helps, ☐ hurts, or ☐ not have an effect on his/her sleep?	
Has your child ever been enrolled in classes where they get special assistance? ☐ Yes ☐ No If yes, describe:	
Has your child been diagnosed with or treated for a learning disability? ☐ Yes ☐ No If yes, describe:	
Have you ever been told that your child had a low IQ or was mentally handicapped? ☐ Yes ☐ No If yes, describe:	
Is your child currently taking any medications? ☐ Yes ☐ No If yes, please list names and what they are treating (e.g., asthma, sleep problems, ADHD): _______________________ _______________________ _______________________ _______________________ _______________________ _______________________	

CHILD'S SLEEP RELATED MEDICAL HISTORY
Has your child ever been diagnosed or treated for a sleep disorder? ☐ Yes ☐ No If yes, describe:
Does your child have respiratory or breathing-related allergies? ☐ Yes ☐ No If yes, do these allergies affect your child's ability to breathe through the nose? ☐ Yes ☐ No
For the **most recent typical week**, how many nights did your child have a congested or "stuffed" nose? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
For the **most recent typical week**, did your child tend to breathe through his/her mouth? ☐ Yes ☐ No
CHILD'S SLEEP HISTORY
Weekday Sleep Schedule
Your child's usual **bedtime** on weekday nights is between _____ : _____PM and _____ : _____PM Your child usually **falls asleep** on weekday nights between _____ : _____PM and _____ : _____PM/AM Your child's usual **waketime** on weekday mornings is between _____ : _____AM and _____ : _____AM
Weekend/Vacation Sleep Schedule
Your child's usual **bedtime** on weekend/vacation nights is between _____ : ____PM and ____ : ____PM Your child usually **falls asleep** on weekend/vacation nights between ___ : ___PM and ___ :_____PM/AM Your child's usual **waketime** on weekend/vacation mornings is between ____ : ___AM and ___ : ____AM
Naps
How many naps does your child take in a **typical day**? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐other:______
If your child naps, how long is a typical nap? _______hour(s) ________minutes
General Sleep
Child is usually put to bed by: ☐ Mother ☐ Father ☐ Both Parents ☐ Self ☐ Others
Write in the amount of time the child spends in his/her bedroom before going to sleep: ___ hours ____ minutes
What time does your child's school typically start in the morning? _____ : _____AM
How many days each week is your child late to school because of difficulty getting going in the morning? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
Write the number of times that you think your child wakes up each night: ________
If your child wakes up at night, on average, how long does it take him/her to fall back to sleep? _____ hours ______ minutes
On a typical day, how long does it usually take for your child to become fully alert and oriented after waking up in the morning: _______hour(s) _________minutes

On a typical day, how many cups or cans (12 ounces) of caffeinated beverages (e.g., soda, tea, coffee) does your child drink? __________

If it is easier to estimate based on ounces (because some beverages are sold in 16, 20, and 32 ounce sizes), please write in the number of ounces here: _____________

FAMILY'S SLEEP HISTORY

Does anyone in the family have a sleep disorder? ☐ Yes ☐ No

If yes, mark the disorder(s):

Insomnia	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Snoring	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Sleep apnea	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Restless legs syndrome	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Periodic limb movement disorder	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Sleepwalking/sleep terrors	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Sleep talking	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Narcolepsy	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent
Other:	☐ Mother	☐ Father	☐ Brother/sister	☐ Grandparent

OTHER FAMILY INFORMATION

Do any of the family members smoke in the house? ☐ Yes ☐ No

Do any of the family members smoke in the car? ☐ Yes ☐ No

Highest level of education completed by Female caregiver: (check one)

Grade School: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Junior High: ☐ 6 ☐ 7 ☐ 8

High School: ☐ 9 ☐ 10 ☐ 11 ☐ 12

College: ☐ 13 ☐ 14 ☐ 15 ☐ 16

Graduate School: ☐ 17 ☐ 18 ☐ 19 ☐ 20 ☐ 21 ☐ 22

Other: ____________

Highest level of education completed by Male caregiver: (check one)

Grade School: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Junior High: ☐ 6 ☐ 7 ☐ 8

High School: ☐ 9 ☐ 10 ☐ 11 ☐ 12

College: ☐ 13 ☐ 14 ☐ 15 ☐ 16

Graduate School: ☐ 17 ☐ 18 ☐ 19 ☐ 20 ☐ 21 ☐ 22 Other: ____________

Some questions have been adapted from the PSQ (Chervin et al., 2000), CSHQ (Owens et al., 2000), ESS (Johns MW, 1991), OSAS (Franco et al., 2000), PDSS (Drake et al., 2003), PRSP (Marcotte et al., 1998), OSA-QOL (Cohen et al., 1998), PSQI (Buysse et al., 1989), & PSS (Owens, 2001).

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BIOGRAPHICAL SKETCH

Susan R. Bongiolatti was born in Springfield, Missouri. She spent her childhood years in Fairfield, Iowa, and later moved to Paducah, Kentucky, where she graduated valedictorian from Lone Oak High School in 1995. Susan attended Washington University in St. Louis, Missouri. She completed an honors thesis examining working memory in children with Attention Deficit/ Hyperactivity Disorder (ADHD) with Sandra Hale, Ph.D., and graduated summa cum laude with a bachelor's degree in psychology. Susan remained at Washington University for two years as a cognitive neuroscience research assistant, working with Todd Braver, Ph.D. She entered the University of Florida's doctoral program in Clinical and Health Psychology in 2001, and earned her M.S. in clinical psychology in May 2003. Her primary area of study is neuropsychology, with a focus on pediatric populations including children with epilepsy. In June 2008, Susan completed a pre-doctoral clinical psychology internship at the Children's Hospital of Philadelphia. She will earn her Ph.D. in clinical psychology in December 2008 with a concentration in neuropsychology. Upon completion of her dissertation, Susan will begin a postdoctoral fellowship in clinical neuropsychology at the Cleveland Clinic, with a continued focus on pediatric populations.