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# Medical and Neuropsychological Predictors of Adaptive Functioning in Children with Epilepsy.

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MEDICAL AND NEUROPSYCHOLOGICAL PREDICTORS OF ADAPTIVE FUNCTIONING IN  
CHILDREN WITH EPILEPSY

by

AIMILIA PAPAZOGLU

Under the Direction of Dr. Tricia Z. King

ABSTRACT

Epilepsy is one of the most common neurological disorders in children, with both seizures and their medical treatment associated with increased risk of neuropsychological impairments. Adaptive functioning in children with epilepsy is poorly understood. This study sought to identify the neuropsychological and medical predictors of optimal adaptive functioning in pediatric epilepsy. Forty-six children with epilepsy and 16 typically developing children and their parents participated in this study at two time points. Overall, adaptive functioning was found to be in the average to low average range in children with epilepsy. A composite measure assessing cumulative seizure history was able to significantly predict Adaptive Behavior Assessment System-II (ABAS-II) scores. Whether a child had experienced one or more seizures in the last year was the only individual seizure and treatment variable able to significantly predict adaptive functioning as measured by the ABAS-II. Verbal learning, executive functioning, and internalizing and externalizing behavior problems assessed at Time 1 predicted performance on the ABAS-II at Time 2. Verbal memory and attention, however, were not significant predictors of adaptive functioning. Consistent with what was hypothesized, executive functioning was found to mediate the relationship between seizure history and adaptive functioning when

controlling for behavior problems at both Times 1 and 2. When behavior problems were the mediator and executive functioning was controlled for, mediation was not found. Executive functioning also mediated the relationship between group membership (monotherapy, polytherapy, and typically developing) and ABAS-II scores at Time 1, but not at Time 2 when a post-surgical group also was represented. Secondary analyses showed that the relationship between executive and adaptive functioning at Time 2 was moderated by whether or not a child had ever experienced seizures, such that children diagnosed with epilepsy evidenced greater correlations between these constructs than typically developing children. The results of this study suggest that a subset of children with epilepsy, those with active seizures and/or executive dysfunction, are at increased risk of adaptive deficits. These findings highlight the risk factors for suboptimal adaptive functioning in this population, and also suggest potential avenues for remediation.

INDEX WORDS: Epilepsy, Pediatric, Adaptive functioning, Epilepsy surgery, Neuropsychological functioning

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CHILDREN WITH EPILEPSY

by

AIMILIA PAPAZOGLOU

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2010

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For Mum  
With love and gratitude

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## Chapter 1

### INTRODUCTION

One percent of the population under 20 years of age will develop epilepsy and it is one of the most common neurological conditions in children (Epilepsy Foundation, n.d.). Children and young adults are particularly susceptible to epilepsy, with more than 50% of all cases beginning before the age of 25. Epilepsy is diagnosed when a person has two or more seizures, which are short bursts of electrical activity in the brain typically lasting a few seconds or minutes. Seizures have many symptoms ranging from convulsions to loss of consciousness to blank staring. Antiepileptic drugs (AEDs) are the most common treatment for epilepsy and exert their therapeutic effects by decreasing the brain's sensitivity to this electrical activity. On a single AED, 60 to 88% of children are seizure-free at 12 months with differences in the success rates due to AED and patient specific variables such as the AED used and its dose as well as patient age and genetic background (Glauser et al., 2006). The chance of obtaining freedom from seizures after one AED has failed is about 30%, and this number declines to less than 5% after failure with three AEDs (Sheth et al., 2000). In a small number of children, seizures will remit spontaneously with a rate of 4% in children with normal intelligence, and of 1.5% in children with mental retardation (Huttenlocher et al., 1990). Surgical intervention may be considered for the 20-30% of children whose seizures are not adequately controlled by medication. Of those children determined to be good surgical candidates, as many as 70% may be seizure free following surgery (Duchowny et al., 1992; Kim et al., 2000; Wyllie, 1998).

Seizures are symptoms of abnormal brain function. With the exception of very young children and the elderly, the cause of seizures is often not known. It is estimated that a cause cannot be found for approximately 70% of patients with epilepsy (Epilepsy Foundation, n.d.). These patients are labeled as having either cryptogenic (seizures presumed to be symptomatic without a genetic or other identified cause) or idiopathic (seizures presumed to be genetic in origin) epilepsy. For the 30% of cases where a cause can be identified, etiologies include lack of

oxygen during birth, head injuries, brain tumors, genetic conditions, febrile seizures, lead poisoning, cortical malformations (also known as cortical dysplasias), and infections such as meningitis or encephalitis. These patients are identified as having symptomatic epilepsy.

A diagnosis of epilepsy has not only immediate, but also lifetime, consequences for cognitive, psychological, adaptive, and social functioning. Seizures and their treatment are believed to have adverse effects on child development, with intractable seizures being especially detrimental. Children with epilepsy are frequently found to have below average cognitive performance as well as poorer academic achievement compared to typically developing peers. Impairments in memory and attention as well as mental slowing are most commonly reported. Many studies report more widespread impairments. For example, Bailet & Turk (2000) found that children with epilepsy scored significantly lower than sibling controls on measures of intelligence, psychomotor speed, memory, academic achievement, and behavior, and that these deficits persisted over time.

The presence of seizures during childhood may affect brain development. Many factors are believed to influence the functional integrity of the developing brain in children with epilepsy and these include cumulative seizure burden (e.g. seizure frequency, duration of epilepsy, incidence of status epilepticus), the underlying pathophysiologic substrate(s), comorbidities, age at onset, neuropsychological impairment, chronic AED therapy, and genetic makeup (e.g., susceptibility of seizure-induced brain injury, pharmacogenetics; Sankar & Rho, 2007). In the presence of such a multitude of factors that can affect the functional integrity of the brain and the difficulty of controlling for these potentially confounding factors, researchers have turned to animal models to better establish whether seizures negatively affect brain development (Sankar & Rho, 2007).

#### *Animal Models of Epilepsy*

Animal models of epilepsy are widely used to better understand the processes leading to epilepsy and to identify drug targets for antiepileptogenesis (Loscher, 2002b). Although more

research is needed, there is evidence that both recurrent seizures and status epilepticus may affect the developing brain. They may do so in many ways ranging from injury and altered neurogenesis to plasticity leading to epileptogenicity and behavioral and cognitive impairments even without the presence of readily discernable injury (Sankar & Rho, 2007). For example, in rat pups injected with kainic acid, an excitatory neurotoxin, short and long-term spatial memory abilities were lower than those of control rat pups, even without the presence of discernible neuronal injury (Sayin et al., 2004). Ten mg/kg of kainic acid can induce seizures in adult rats that are severe and produce hippocampal damage similar to that of mesial temporal sclerosis, while a dose of 3mg/kg of kainic acid administered to 15 day old rat pups (they cannot survive a dose of 10mg/kg), produces severe seizures, but no discernable hippocampal damage. When these same rat pups, however, were exposed to kainic acid again at 45 days they evidenced more severe brain damage and poorer performance on spatial learning tasks than rats that were only exposed to kainic acid at 45 days (Sankar & Rho, 2007). Animal models also have shown that inflammation amplifies seizure-induced injury (Sankar & Rho, 2007), which is consistent with human literature showing hippocampal signal changes on MRI in children who have experienced prolonged febrile seizures (Shinnar et al., 2005). These findings and others using animal models of epilepsy suggest that cognitive deficits may be present even in the absence of overt neuronal damage, that the genesis of neuronal damage following seizures may vary according to brain maturity, and that the experience of prior seizures may alter the impact of subsequent seizures.

### *Seizure Types*

There are many different types of seizures; each of which may have different causes and symptoms. Patients may experience only a single type of seizure or multiple types of seizures. The 1981 classification system of the International League Against Epilepsy (ILAE) is used in many institutions around the world, and although it has its detractors it is still the most commonly used classification system (Engel, 2006; ILAE, 1981). According to this classification

system, there are two broad categories of seizures: partial seizures, which, at least initially, start in one area of the brain and generalized seizures, which involve the entire brain.

Partial seizures may also be known as focal or local seizures and can be subdivided into three groups. Simple partial seizures usually have unilateral hemispheric involvement, and consciousness is not impaired. Complex partial seizures frequently have bilateral hemispheric involvement, and consciousness is impaired. Both simple and complex partial seizures may occur with motor signs, with somatosensory symptoms, with autonomic symptoms or signs, or with psychic symptoms such as detachment, memory or time distortion, or unprovoked emotion. The third type of partial seizures are those that are secondarily generalized and may begin as either simple or complex partial seizures.

There are six types of generalized seizures. Absence seizures are characterized by brief episodes of staring, during which awareness and responsiveness are impaired. They may also involve mild clonic, tonic, or atonic components as well as automatisms. Atypical absence seizures are similar, but changes in motor tone are more pronounced, they last longer, and onset and resolution is typically more gradual. Myoclonic seizures involve the sudden jerking of extremities. Seizures with tonic and/or clonic manifestations are marked by unconsciousness, convulsions, and muscle rigidity, with clonic seizures characterized by repetitive jerking movements and tonic seizures by muscle stiffness and rigidity. Eye blinking or slight jerking movements of the mouth may occur. Atonic seizures are marked by a loss of muscle tone.

There are other types of seizures that do not fit into the above categories. Status epilepticus is defined as a single continuous seizure (or recurrent seizures between which the patient does not regain consciousness) that show no signs of stopping after a duration that encompasses the majority of seizures of that type in most patients. This duration is usually defined as 30 minutes of uninterrupted seizure activity, however, it is recommended that medical assistance be sought if a seizure continues for more than 5 minutes. It is estimated that as many as 15% of people with epilepsy will experience status epilepticus at least once



(Epilepsy Foundation, n.d.). Gelastic seizures are marked by inappropriate laughter and may be followed by eye or head movements, automatisms, and altered awareness. Although not part of the ILAE's classification system, psychogenic seizures may also occur. These events look similar to epileptic seizures, although some may appear different from typical epilepsy presentations. Psychogenic seizures are thought to be caused by subconscious mental activity rather than abnormal electrical activity. They are considered to be psychological in origin, but are typically not purposefully produced.

### *Treatments for Epilepsy*

The most common treatment for epilepsy is antiepileptic drugs (AEDs). Other treatment options include surgical removal of the epileptogenic focus, vagal nerve stimulation, and the ketogenic diet. The use of AEDs and surgical intervention are a focus of this paper and will be discussed in subsequent sections. Vagal nerve stimulation is an alternative treatment typically considered when surgical resection is not feasible or has been unsuccessful (McHugh et al., 2007). It involves electrical stimulation of the vagal nerve in the neck to reduce the frequency and severity of seizures. How it exerts its therapeutic effects is not well understood, but it is believed to prevent the hypersynchronization of neuronal activity (McHugh et al., 2007). The ketogenic diet is a strict diet of high fat, low protein, and low carbohydrate foods. Although the exact mechanism of its therapeutic benefit also is unclear, it is believed to provide seizure control by inducing a state of ketosis (Casey et al., 1999), which is a physiological state associated with chronic starvation where ketone bodies rather than glucose are the body's source of energy.

### *Antiepileptic Drugs*

The goal of treatment with AEDs is to reduce seizure frequency and enhance quality of life with as few side effects, co-medications, and long-term detrimental effects as possible. A majority of neurologists recommend waiting until after a child has had a second seizure before beginning AED therapy in order to ascertain that pharmacotherapeutic intervention is necessary

(Miller & Drislane, 2007). There are, however, times when the risk of recurrent seizures is higher (such as with a tumor or infection) and immediate AED treatment may be warranted. In children who have experienced a single unprovoked afebrile seizure, this risk of seizure recurrence has been found to range from 29% to 46% at one year and 37% to 54% at two years, with most recurrences happening within the first 6 months (Shinnar et al., 1996; Stroink et al., 1998). Once a second seizure has occurred, the risk of recurrence is greater and treatment with AEDs is typically warranted (Miller & Drislane, 2007).

AEDs are designed to reduce or remove abnormal discharges in the brain, however, the actual neurochemical bases of epileptogenic discharges are not well understood. Enhanced excitatory amino acid transmission, impaired inhibitory transmission, and abnormal electrical properties of affected neurons have all been implicated (Rang et al., 1995). AEDs act by increasing inhibition in the brain in order to prevent or reduce seizure activity. This can be done in a number of different ways. AEDs are typically grouped according to their main effect, although many are capable of multiple effects. These include sodium channel blockers, calcium current inhibitors, GABA enhancers, glutamate blockers, carbonic anhydrase inhibitors, and hormones. There are also AEDs whose mechanism of action is not currently well understood. A single AED may increase inhibition in the brain by multiple methods, and those that do so tend to be more effective against a broad range of seizure types. The two most common mechanisms of action are the enhancement of GABA and inhibition of sodium channel function (Rang et al., 1995). GABA activity may be enhanced by facilitating GABA-mediated opening of chloride channels (e.g., Phenobarbital, Benzodiazepines) or by inhibiting the enzyme that inactivates GABA (e.g. Valproate (Depakene), Vigabatrin). AEDs that block sodium channels typically do so by preventing the channels from returning to an active state following an action potential (e.g., Phenytoin (Dilantin), Carbamazepine (Tegretol)).

Over the last few decades, there have been advances in the pharmacotherapeutic treatment of epilepsy with the introduction of several new AEDs and the reformulation of several

older AEDs (Loscher, 2002a). These newer AEDs are not necessarily more efficacious, but appear to be safer, better tolerated, and have fewer interactions with other medications (Malphrus & Wilfong, 2007). Animal models of chronic epilepsy, including the kindling model of temporal lobe epilepsy and the post-status epilepticus model, are widely used to test the efficacy AEDs. Current pharmacotherapeutic research seeks to develop therapies aimed at preventing epilepsy in patients at risk, create drugs for the reversal or prevention of pharmacoresistance, and design drugs to inhibit the progression of epilepsy (Loscher, 2002a).

The drugs most represented in the current study include Keppra (Levetiracetam;  $n = 12$ ), Depakote (Divalproex Sodium;  $n = 11$ ), Lamictal (Lamotrigine;  $n = 11$ ), Topamax (Topiramate,  $n = 7$ ), and Trileptal (Oxcarbazepine;  $n = 6$ ). Although each drug may be associated with distinctive side effects, generally speaking the side effects of AEDs include drowsiness, dizziness, ataxia, nausea, vomiting, and headache. In rare cases serious side effects such as liver failure may occur. AEDs have the potential to produce cognitive or behavioral impairment in any patient, but many, especially among the newer AEDs, appear to be well tolerated, though more research is needed (Bourgeois, 2004). An exception is Topamax, which will be discussed below. Additionally, toxic AED drug levels and polytherapy are more likely to be associated with cognitive and behavioral impairment (Bourgeois, 2004)

Keppra has been shown to be effective for primary generalized epilepsy, and partial, generalized tonic-clonic, and myoclonic seizures, and was approved for use in 1999. The method of action is still unclear, but may occur through the inhibition of calcium channels and/or activation of GABA and glycine receptors. Some patients experience affective side effects including emotional lability, depression, agitation. Unlike the other well-represented drugs in this study, Depakote was approved in 1978 and is not a new-generation AED, although it has recently been reformulated into extended release tablets. It has been approved for complex partial, simple partial, and absence seizures and is believed to act through the activation of GABA receptors. Lamictal was approved for use in 1994 and is effective in controlling many

seizure types including absence, atonic, myoclonic, partial, and tonic-clonic. Its therapeutic effect stems from its ability to prolong the inactivation of voltage sensitive sodium channels. Topamax has been shown to be a very efficacious AED for many seizure types and has multiple mechanisms of action including the inactivation of voltage-dependent sodium channels, activation of GABA receptors, and the blockage of the activation of the non-NMDA subtype of the glutamate inhibitors. Introduced in 1996, Topamax has been shown to be associated with a higher risk of cognitive side effects, including an overall “cognitive dulling,” compared to other AEDs and an associated decreased level of drug tolerance (Reith et al., 2003). More specifically, it has been shown to be associated with cognitive impairment and word finding difficulties, which appear to be associated with rapid titration, higher doses, and polytherapy (Aldenkamp et al., 2000; Bourgeois, 2004; Ormrod & McClellan, 2001). Trileptal was introduced in 2000 and is effective in controlling partial seizures. Its mechanism of action is believed to be through the inhibition of sodium channels.

On a single AED, 60 to 88% of children are seizure-free at 12 months (Glauser et al., 2006). Approximately 70% of children with idiopathic or cryptogenic epilepsy who are treated with AEDs will become seizure free and as many as two thirds of these children will remain in remission after discontinuing AED treatment (Berg & Shinnar, 1994). The level of seizure control achieved during the first year of therapy has been shown to be a better predictor of prognosis than clinical features at initial presentation, with the exception of developmental delay (Tang-Wei et al., 2005). In addition to affecting cognitive outcome, AEDs also may have a detrimental effect on behavioral outcome. One study reported that one third of parents felt that AEDs caused a negative change in their child’s behavior or affected their child’s alertness or ability to concentrate on the task at hand (Prahbjot & Pratibha, 2005). This study also showed that duration of treatment and polytherapy negatively impacted the child’s and family’s daily activities. More research on the impact of AEDs on children’s day to day functioning is needed.

### *Effects of Epilepsy on Neuropsychological Functioning*

Research on the effects of epilepsy on neuropsychological functioning in children is growing, and is particularly detailed with respect to intellectual functioning, academic achievement, and learning and memory. Results generally show a risk of deficits in at least a subset of this population. There remains, however, a lack of research on how epilepsy and these potential cognitive impairments may affect day to day, or adaptive, functioning in children. Studies examining neuropsychological functioning in children with epilepsy are confounded by the potential effects of AED therapy. No studies could be found that examined neuropsychological functioning in drug naïve children, rather studies on this group have been limited to examining the nature and frequency of untreated seizures to better clarify how, or if, pharmacologic treatment might alter the course of the disease (Kwam & Sandler, 2004; van Donselaar et al., 1997).

#### *Cognitive Effects*

Neurocognitive function has been asserted to be the most important measure of neuronal integrity in children with epilepsy (Sankar & Rho, 2007). There is a dearth of studies reporting results of comprehensive neuropsychological assessments of children with epilepsy. One of the few studies to do this was conducted by Williams and colleagues (1998a). The authors found that most cognitive skills were within the average to low average range and commensurate with Full Scale IQ (FSIQ; which was in the low average range overall). However, composite measures of both verbal attention (Number/Letter Memory from the Wide Range Assessment of Memory and Learning (WRAML) and Digit Span, Arithmetic, and Information from the Wechsler Tests of Intelligence) and visual attention (Finger Windows from the WRAML and Coding from the Wechsler Tests of Intelligence) were significantly below expectations based on FSIQ (Williams et al., 1998a).

The site of seizure focus may result in specific neurocognitive deficits. Specifically, partial seizures are proposed to either disrupt hemisphere-specific functions, which would result

in a relative weakness in the skills typically mediated by that hemisphere or to prompt brain reorganization, which would likely result in the preservation of verbal reasoning at the expense of nonverbal reasoning (Blackburn et al., 2007). Research has not clearly supported either of these hypotheses; however, there does appear to be some consistency in impairments according to the site of seizure focus. For example, temporal lobe focus is, in general, associated with memory impairments, behavior problems, and academic underachievement (Lassonde et al., 2000). A significant discrepancy between Verbal IQ (VIQ) and Performance IQ (PIQ), defined as  $\geq 15$  points, is often considered a sign of lateralized brain dysfunction (Blackburn et al., 2007). In children with epilepsy, significant VIQ-PIQ discrepancies were able to accurately localize seizure focus in 79% of children with typical language organization (left hemisphere) and 57% of those with atypical language organization (Blackburn et al., 2007). Furthermore, within the typical language organization group, 85% of children with a significant discrepancy, but only 63% of children without a significant discrepancy, achieved seizure control following surgical intervention. This suggests that a large discrepancy in VIQ-PIQ is not sufficient to lateralize seizure focus, but that such a discrepancy may help to identify those children who will most benefit from surgical intervention.

Within the pediatric temporal lobe epilepsy population, particular attention has been paid to assessing verbal and visual learning and memory, as these skills appear to be most adversely affected in the adult temporal lobe epilepsy population. Indeed, as children progress in school, they increasingly rely on language based skills, making measures of auditory attention, verbal learning, and verbal memory important to assess. Verbal learning and memory impairments are especially prominent in pediatric clinical populations (Delis et al., 1994), further underscoring the need to study these skills in children with epilepsy. Verbal skills, along with attention, have been shown to significantly predict academic achievement in children with epilepsy (Seidenberg et al., 1987). Deficits in attention, assessed by performance on the Wechsler Intelligence Scale for Children-Revised Digit Span and Coding subtests, have been

shown to adversely affect the retention of verbal information in children with epilepsy (Henkin et al., 2005) suggesting that attention is an important prerequisite for successful verbal memory. Additionally, parent report of attention problems on the Child Behavior Checklist has been shown to significantly predict self- and parent-ratings of everyday memory abilities in children with epilepsy (Kadis et al., 2004).

Seizure and treatment variables have been shown to affect many aspects of neuropsychological functioning. Variables such as earlier age at onset, higher lifetime total seizures, presence of multiple seizure types, and the use of multiple AEDs have been shown to correlate with academic achievement in this population (Bailet & Turk, 2000). However, Bailet & Turk (2000) did not find significant relationships between these variables and neurocognitive outcomes. Other research has shown that IQ scores as well as reaction times show a trend towards being lower in children with generalized epilepsy and with higher seizure frequency (Tromp et al., 2003). Based on a review of previous research, Lah (2004) contended that intractable seizures that start early in life and require aggressive pharmacotherapeutic intervention have a cumulative, negative impact on cognitive development. In children with complex partial seizures, seizure frequency, number of AEDs, number of seizures lasting more than 5 minutes/febrile seizures, and ethnicity were significant predictors of intellectual functioning (Caplan et al., 2004). Furthermore, expressive language skills, assessed using the Spoken Language Quotient of the Test of Language Development, have been shown to be correlated with seizure frequency, number of AEDs, and ethnicity (Caplan et al., 2004).

Similar effects have been found in adults with temporal lobe epilepsy. In one study, adverse cognitive outcomes were noted over a four year interval in approximately one quarter of participants, with lower baseline intellectual functioning, longer duration of epilepsy, and older chronological age predictive of poorer outcome (Hermann et al., 2006). This suggests that chronic seizures and the continued use of AEDs are associated with decline in neuropsychological functioning over time in a subset of adult patients. Memory, psychomotor

speed, and some aspects of executive functioning appear to be the domains most vulnerable to decline (Hermann et al., 2006).

### *Psychosocial and Behavioral Functioning*

Children with epilepsy have been shown to be at increased risk for poor psychosocial functioning (Prahbjot & Pratibha, 2005). Behavior problems may adversely impact academic performance as well as peer relationships, both of which are important for optimal outcomes both in childhood and later in life. One study found that boys with a left temporal lobe focus were more likely to be isolated, anxious, and hyperactive than boys or girls with a right temporal lobe focus (Stores, 1978). Another study showed that children with a right temporal lobe focus evidenced a trend towards greater risk of aggression and maladjustment (Elger et al., 1997). Significant elevations have been found on the Attention Problems subscale of the Child Behavior Checklist in children with epilepsy, with one study finding mean scores on this subscale to be as high as two standard deviations above the normative mean (Williams et al., 1998a). Such impaired attention has been hypothesized to have a generalized, and negative, impact on learning (Sturniolo & Galletti, 1994) which would be especially detrimental in school-age children.

Other studies have found general elevations of parent-report of internalizing problems, but these scores have not been shown to be significantly associated with seizure, demographic, or perinatal factors nor were they associated with expressive language abilities, assessed by the Spoken Language Quotient of the Test of Language Development (Caplan et al., 2004). Researchers have postulated that difficulties with school and social interaction in children with epilepsy may be more related to subtle cognitive deficits and behavior problems than to variables directly associated with a diagnosis of epilepsy (e.g., age at seizure onset; Caplan et al., 2005) further underscoring the need to establish how these factors may also affect adaptive functioning. Children with epilepsy have been found to be more socially isolated and withdrawn than children without epilepsy (Cushner-Weinstein et al., 2007). Internalizing and externalizing



behavior problems have been noted, and may be associated with reduced functioning across other domains. Behavior problems also may be associated with reduced social competence (Austin et al., 1994). Children with externalizing behavior problems may disrupt the activities of peers and adults, be more likely to be unresponsive to adult direction, and have more problematic relationships with peers. Furthermore, externalizing problems are more likely to be stable than internalizing problems, and children with externalizing problems tend to have a poorer prognosis (Robins, 1979 in Reynolds & Kamphaus, 2004). Internalizing behaviors may be harder for informants to accurately assess, but are also associated with poorer peer relationships (Kamphaus et al., 2003 in Reynolds & Kamphaus, 2004). In addition to the potential association between behavior problems and reduced social competence, lack of opportunity may also be associated with poorer social functioning (Adams et al., 2002). Reduced opportunities for social interaction in children with epilepsy may result from missing school as well as reduced inclusion in peer activities possibly as a result of stigmatization (Adams et al., 2002).

#### *Adaptive Functioning in Children with Epilepsy*

Although the adverse effects of epilepsy and its treatments have been assessed on many different aspects of functioning, their impact on adaptive functioning has not been widely researched. Assessment of neuropsychological functioning, while of undoubted importance, may not fully capture the impact of epilepsy and its treatments on functioning in the everyday world (Smith et al., 2006). Measures of adaptive functioning seek to do this by assessing the ability of people to take care of themselves and interact with and assist others at an age appropriate level. Impairments in adaptive skills can significantly impact daily life as these skills are necessary to live, work, and play in the community (Sparrow et al., 1984). It has been asserted that adaptive skills should be routinely addressed in children (as well as adults) who have impairments that interfere with daily functioning (Harrison & Boney, 2002). As people with epilepsy and their families well know, seizures themselves as well as the fear of subsequent

seizures can significantly interfere with daily functioning. More specifically, children with epilepsy, particularly those with medically intractable epilepsy, are likely to require increased supervision from adults which may interfere with the development of independence and with social functioning. Furthermore, the social stigma associated with epilepsy (Adams et al., 2002) may limit social opportunities and thereby hamper social development. Research is needed to establish how epilepsy surgery and/or AED treatment may impact the development of skills necessary for age-appropriate adaptive functioning either positively, for example, by reducing seizure frequency or negatively, for example, through adverse side effects such as fatigue.

Adaptive functioning is an important outcome variable that requires the integration of cognitive, emotional, and behavioral abilities into coherent behavior that is able to meet the demands of different environments and situations. A more precise investigation of the specific variables associated with both well and poorly developed adaptive functioning abilities is needed within the pediatric epilepsy population. Previous research has shown that children with intractable seizures, with a known brain insult or condition, or with an epileptic encephalopathy (e.g. Lennox-Gastaut syndrome) may be at particular risk of failing to acquire independent living skills at an age-appropriate rate (Berg et al., 2004). These children were shown to have below average adaptive functioning, with significant declines relative to norms over time. In children with epilepsy who have none of these risk factors, some researchers have found no deficits in adaptive functioning over time (Berg et al., 2004), while others continue to find evidence of adaptive impairments (Chapieski et al., 2005).

In a study of children all treated with monotherapy (Chapieski et al., 2005), adaptive functioning as assessed by the Vineland Adaptive Behavior Scales (VABS; 1984) within the first six months of diagnosis showed mean Communication domains scores to be within the low end of the average range ( $M = 90.55$ ,  $SD = 15.35$ ), and mean Daily Living Skills and Socialization scores to be in the low average range ( $M = 87.11$ ,  $SD = 13.89$  and  $M = 85.04$ ,  $SD = 14.89$  respectively) with 37%, 36%, and 39% of the sample of 56 children performing below one

standard deviation from the mean on each of the three domains. One year later, 42 participants and their mothers returned. Communication domain scores were comparable, with relative declines in the Daily Living Skills ( $M = 84.62$ ,  $SD = 16.10$ ) and Socialization domains ( $M = 80.04$ ,  $SD = 15.23$ ). Thirty six percent of children were below one standard deviation from the mean on the Communication domain, while 48% and 57% were impaired on the Daily Living Skills and Socialization domains respectively suggestive of notable declines in the latter two domains. Of note, all children were on a single antiepileptic medication and 66% did not experience a single seizure in the intervening year suggesting not only that adaptive impairments exist in children whose seizures are well-controlled by a single medication, but also that a failure to make age-appropriate gains in adaptive functioning may be apparent even in children with well-controlled seizures. Another study found performance to be most impaired on the Daily Living Skills domain in very young children diagnosed with epilepsy (Berg et al., 2004), with performance declining from the low average range at diagnosis to the mildly impaired range one year later. In a sample of 15 children with temporal lobe epilepsy, mean adaptive performance was in the low average (Daily Living Skills) to borderline range (Communication and Socialization; Culhane-Shelburne et al., 2002). This study also found that measures of executive functioning (Stroop Color-Word Interference and Tower of London Number of Rules Broken) and impulsivity (Impulsivity on the Test of Variables of Attention) were significantly predictive of adaptive functioning in a sample of children with either frontal or temporal lobe epilepsy (Culhane-Shelburne et al., 2002). In general, research suggests that daily living and socialization skills may be more vulnerable to decline in children with epilepsy, and that impairments in adaptive functioning may occur even in children whose seizures are well-controlled on a single AED.

Adaptive functioning capabilities influence quality of life. Intractable seizures have been shown to negatively impact quality of life in children (Sheth et al., 2000), and the use of polytherapy has been showed to be associated with reduced psychosocial and physical

functioning in children with epilepsy (Miller et al., 2003). Only two studies were found that examined adaptive functioning in children following surgery for epilepsy. In one study, patients underwent vertical parasagittal hemispherotomies (disconnection of the damaged hemisphere), and a longer pre-surgical duration of seizures was associated with lower post-surgical adaptive functioning (Delalande et al., 2007). Mean adaptive functioning was assessed using the VABS and was found to be in the profoundly impaired range across domains for the post-surgical sample of 58. In the other study, children underwent hemispherectomies (removal of the hemisphere or removal of part of the hemisphere and disconnection of the remaining part) and a longer duration of epilepsy also was found to be predictive of poorer adaptive functioning (Basheer et al., 2007). Mean adaptive functioning scores for this sample of 24 using the Scales of Independent Behavior-Revised (SIB-R; 1996) were poor, with mean Broad Independence scores in the severely impaired range. At the domain level, motor scores were in the severely impaired range, personal living, community living and support scores in the mildly impaired range, and social/communication scores in the borderline range (Basheer et al., 2007).

#### *Age at Seizure Onset*

Childhood epilepsy is marked by abnormal electrical activity in the brain, and this may adversely impact neural development. Research has not yet conclusively demonstrated the extent to which age at seizure onset may affect neuropsychological functioning and it is important to note that this variable is confounded with younger age at the start of AED therapy and may, in some studies, be further confounded by longer epilepsy duration. A number of research studies have shown that earlier age of seizure onset is associated with poorer cognitive functioning (Bulteau et al., 2000; Freitag & Tuxhorn, 2005; Shoenfeld et al., 1999). Less frequently, studies have failed to demonstrate a significant relationship between age at onset and cognitive functioning (Bailet & Turk, 2000). In adults, childhood-onset temporal lobe epilepsy appears to be associated with adverse neurodevelopmental impact on neuropsychological functioning and brain structure, with reduced total white-matter volume

compared to both healthy controls and adult-onset temporal lobe epilepsy patients (Hermann et al., 2002). In this study, childhood-onset participants (seizures beginning before 14 years of age) performed more poorly than control participants across all measures of neuropsychological functioning and significantly worse than adult-onset participants (seizures beginning after 14 years of age) on seven out of 12 measures (FSIQ, PIQ, naming, spatial orientation, verbal memory, visual memory, and problem solving) with a trend towards poorer performance on three other measures (VIQ, fluency, face perception). Childhood and adult-onset participants performed similarly in the area of speeded psychomotor processing, as measured by performance on the Trail Making Tests A and B. The late-onset group, however, differed from the controls on two out of 12 tests, performing more poorly on visual memory and speeded processing. Childhood-onset participants showed significant reductions in total cerebral tissue volume which was especially pronounced in white-matter tissue volume and was associated with poorer neuropsychological outcome. Furthermore, these reductions in brain tissue volume were not limited to the temporal lobe, and were instead found to be generalized. The results of this study by Hermann and colleagues (2002) suggest that childhood-onset temporal lobe epilepsy is associated with a generalized neurodevelopmental impact on brain structure and function that is not apparent in participants with a late onset of temporal lobe epilepsy.

Other studies also have shown age at seizure onset to be an important predictor of outcome. Children with complex partial seizures have been shown to have a broad profile of cognitive impairment, with age at seizure onset emerging as a strong predictor of cognitive functioning (Schoenfeld et al., 1999). The children in this study also were shown to have reduced social and academic competence and to display more internalizing behavior problems relative to sibling controls with seizure frequency in the last year and age at seizure onset significant predictors of these variables (Schoenfeld et al., 1999). However, in children diagnosed with epilepsy before the age of two, etiology as well as normal mental development may be the biggest predictors of seizure control (Rantala & Ingalsuom 1999).

Research by Blackburn and colleagues (2007) suggests that there may be a gradual change from a focal deficit to more generalized impairment when seizures persist over time. Furthermore, Lah (2004) asserts that longer epilepsy duration is associated with greater severity of cognitive deficits, positing that continued seizures may cause progressive cognitive decline. Blackburn and colleagues (2007) found that in children with left-hemisphere language, significant discrepancies between VIQ and PIQ were related to shorter seizure duration and longer seizure duration was marked by more generalized intellectual impairment (Blackburn et al., 2007). These findings indicate that even if children benefit from the presumed greater plasticity of the immature brain (Gleissner et al., 2005), there appear to be limits to the extent of functional reorganization and younger age at seizure onset (and, consequently, younger age at AED therapy commencement) may place children at greater risk of adverse neurodevelopmental outcome with regard to brain volume white matter integrity and neuropsychological functioning.

#### *Time Elapsed since Epilepsy Diagnosis*

Recently, more attention has been devoted to examining the degree to which neuropsychological abnormalities are present at epilepsy onset or become evident over time. The most effective way to determine whether epilepsy is a progressive disease is through the use of prospective studies that assess children prior to the onset of their seizures, however, such prospective studies are difficult, and, therefore, infrequent. A study of 72 children with seizure disorders and their seizure-free siblings suggests that epilepsy may not be a progressive disease (Bourgeois et al., 1983). Children were tested within two weeks of their first documented seizure and then tested annually for four years along with their siblings. Mean IQ of the children with epilepsy was comparable to that of their seizure-free siblings. Although group differences were not apparent, individual changes suggested that a small subset ( $n = 8$ ) evidenced a steady decline in IQ that was associated with younger age at seizure onset, greater likelihood of AED levels in the toxic range, and increased seizure frequency.

Other researchers have studied children with new-onset epilepsy to better examine trajectories (e.g., Hermann et al., 2006; Parrish et al., 2007). Children diagnosed with epilepsy in the preceding 10 months were shown to have mean IQ scores in the average range, which were nevertheless significantly lower relative to controls (Parrish et al., 2007). The children in this sample were reported to have significantly greater executive functioning impairments both according to parent report (Behavior Rating Inventory of Executive Function) and the Delis-Kaplan Executive Function System (D-KEFS) relative to control participants, suggesting that executive functioning may be a vulnerable domain in children newly diagnosed with epilepsy. Hermann and colleagues (2006) have shown that children with recent-onset epilepsy (diagnosed within the last 12 months) exhibited a pattern of mild, but diffuse, cognitive impairment irrespective of type of epilepsy relative to controls. Significantly poorer performance was noted across measures of intelligence (WASI), naming (Expressive Vocabulary Test), errors of omission (Connors' Continuous Performance Test-II), response inhibition (D-KEFS Color-Word Interference), and speeded psychomotor processing (WISC-III Digit Symbol). No significant differences were observed on measures of immediate and delayed verbal and visual memory (Children's Memory Scale Word Lists and Dot Location) or other aspects of receptive and expressive language (Peabody Picture Vocabulary Test-III, Boston Naming Test, and D-KEFS Verbal Fluency). Furthermore, in a subset of participants, academic underachievement appeared to pre-date the first recognized seizure. In this subset, there were volumetric reductions in the grey matter of the left occipital and parietal lobes relative to children with epilepsy without academic problems and relative to controls. This suggests that there might be an antecedent neurobiological abnormality in this group and that academic functioning might be particularly vulnerable to decline in at least some children with epilepsy. As prospective research has shown that a history of learning problems is a significant predictor of poor long-term psychosocial outcome (Camfield et al., 1993), this finding has potentially significant implications and warrants further exploration. Magnetic Resonance morphometric analyses

suggest that volumetric abnormalities are not yet apparent in children newly diagnosed with epilepsy (within the preceding 12 months), however, there are indications of an altered structure-function relationship (Hermann et al., 2006). More specifically, control participants showed a strong association between cognitive development and increasing cerebral tissue volume (especially in white matter volume), whereas this relationship was absent in children with epilepsy. There were no significant differences between the two groups with respect to white matter volume, however, white matter integrity was not assessed. Although there is not yet a definitive answer to the question of whether epilepsy is a progressive disorder, at the very least there appears to be a subset of children with epilepsy whose cognitive functioning does decline over time.

### *Surgical Intervention for Epilepsy*

Children whose seizures are not adequately controlled by medication may undergo surgical resection to improve seizure control, with as many as 70% seizure free following surgery (van Empelen et al., 2005). Surgical intervention is typically considered once three appropriate medications at therapeutic doses have failed to provide seizure control (Malphrus & Wilfong, 2007). Candidacy for surgery is determined by a number of factors including whether a focal onset of epileptogenic activity can be determined, surgical accessibility of the seizure focus, proximity to areas necessary for critical skills such as speech, and the integrity of the contralateral hemisphere (Chelune, 1995). The goal of surgery is to stop or at least significantly reduce the frequency of intractable seizures, thereby improving quality of life. Surgical resection is most common with a seizure focus in the temporal lobe, and is known as a temporal lobectomy.

Many studies have focused primarily on seizure control when defining successful post-surgical outcomes (Kim et al., 2000). As the primary goal of surgical intervention is to reduce seizure frequency, it is important to ensure that seizure control improves for the majority of patients. This is, however, only one component of successful outcome and focusing primarily on



it may not address the full picture of post-surgical outcome. An underlying reason for this may be the assumption that successful seizure control will result in improvements in neuropsychological, behavioral, and social functioning. However whether this is indeed the case has not been fully examined (Smith et al., 2004). More recently, clinicians have begun to assess the effects of surgical intervention on intellectual, memory, and language abilities, however, its influence on adaptive functioning is not well researched. The key questions when evaluating surgical outcome are whether and how surgery has altered the course of development across domains (cognitive, adaptive, behavioral functioning and the like) from what it would have been had the child continued to have intractable seizures (Smith et al., 2004).

Children who undergo surgical resection typically have a presurgical neuropsychological assessment in order to quantify cognitive, behavioral, and emotional functioning at baseline. This assessment can provide information about a child's deficits and strengths, as well as assist with patient selection by predicting who is at risk for significant cognitive impairments from surgery, and aid in language lateralization (Lassonde et al., 2000). Wada testing is also typically used as part of the presurgical work-up. In this procedure, sodium amobarbital is injected into the internal carotid artery to temporarily incapacitate one hemisphere of the brain and determine lateralization of memory and language abilities (Westerveld et al., 1994). Patients typically undergo both left and right hemisphere injections. Injection ipsilateral to the seizure focus can be used to "model" the effect of surgery and assesses the capacity for the contralateral hemisphere to support memory and language function should the patient and family choose to undergo surgery. Injection contralateral to the seizure focus assesses the functional adequacy of the diseased hemisphere.

### *Cognitive Functioning*

With respect to post-surgical intellectual functioning, many studies have shown that IQ does not change significantly in children who have undergone temporal lobectomies (e.g., Williams et al., 1998b), however, some studies suggest that IQ may actually increase following

surgery with Gilliam and colleagues (1997) reporting that 29% of their sample had a 10 point or greater increase in VIQ or PIQ following surgery. Some of the inconsistencies across studies with respect to post-surgical intellectual functioning might be due to different study methodologies. For example, Westerveld and colleagues (2000) found no significant changes in IQ across their whole sample, but when they divided the sample according to side of temporal lobectomy they found that children who underwent a left temporal lobectomy had no significant changes on VIQ, but improved significantly on PIQ. Children who underwent a right temporal lobectomy did not evidence significant changes in VIQ or PIQ. Furthermore, when Westerveld and colleagues (2000) examined individual changes, they found that 10% of their sample experienced a significant decline and 9% experienced a significant improvement in verbal functioning. With respect to PIQ, 16% of the sample improved significantly, and only 2% showed significant declines.

Westerveld and colleagues (2000) examined the predictors of significant gains in intellectual functioning following surgery. They found that younger age at surgery predicted significant gains in verbal functioning, while higher pre-surgical VIQ was associated with a decline in verbal functioning post-surgery. There was a trend towards males making more gains in VIQ than females post-surgery. The authors also found evidence suggesting that structural lesions may be a risk factor for declines in VIQ, possibly because children with such lesions may have larger resections or get follow-up treatment (radiation, chemotherapy) which may adversely impact cognitive functioning. Significant post-surgical increases in PIQ were best predicted by higher pre-surgical VIQ and longer duration of follow-up (Westerveld et al., 2000). Overall, it appears that the risk of significant decline in intellectual functioning is low, and that there is a general trend towards improvement in intellectual functioning following surgery.

Although no significant mean changes in intellectual functioning were reported, the above studies may be misleading as they do not account for the possible presence of practice effects, test-retest reliability issues, and regression to the mean. Studies assessing post-

operative change frequently do not have a comparison group nor do the researchers statistically correct for these potentially confounding factors. All of the aforementioned studies do acknowledge these limitations (Gilliam et al., 1997; Westerveld et al., 2000; Williams et al., 1998b). It has been argued that looking only at absolute change, as these studies do, may be misleading and result in high numbers of false positives or false negatives (Chelune et al., 1996).

Although empirical methods to assess meaningful change in neuropsychological measures, such as calculating reliable change index scores and change norms through the use of regression have been reported, they have not been widely utilized (Chelune et al., 1996). Westerveld and colleagues (2000) make a compelling proposal about why they do not believe any changes in cognitive functioning in their study represent practice effects. They argue that research has demonstrated stability in IQ over long periods of time in participants with seizures, suggesting that practice effects cannot be assumed in this population. They also put forward that children with intractable seizures are commonly reported to demonstrate decline rather than improvement in cognitive functioning and that those children undergoing surgical intervention are likely at the greatest risk for cognitive decline without intervention. Finally, they re-tested children at an average follow-up interval of 14 months, and point out that children must demonstrate better performance over time in order to maintain the same IQ, and that children who fail to progress at the expected developmental rate may actually show a decline in IQ.

These arguments are thought provoking, however, they still do not appear to address the issue of whether the reported presence or lack of change over time represents a real effect or an artifact of re-administering the same measure. More research is needed to determine if findings in this population are truly confounded by practice effects, test-retest reliability issues, and regression to the mean. If children with epilepsy do not show the expected practice effects researchers should examine why and consider the potential implications particularly for academic functioning where practice-based learning is widely used. The possible influence of

practice effects, test-retest reliability issues, and regression to the mean, which might mask decline or simulate improvement in certain cognitive skills, should be kept in mind while reading the subsequent paragraphs on post-surgical functioning. A number of the subsequent research studies, however, have matched participants undergoing left temporal lobectomies with those undergoing right temporal lobectomies, which, while not as ideal as a non-surgical comparison group, does help to highlight results which may be less likely to be due to these potential confounds.

With respect to the adult temporal lobectomy literature, deficits in verbal learning and memory have consistently been found following left temporal lobectomy, while visual learning and memory deficits are associated with right temporal lobectomy (e.g., Hermann et al., 1992). Although this material-specific learning and memory deficit is considered by many to be a key feature of temporal lobe epilepsy in adults (Lah, 2004), there are some who challenge a strict adherence to this material-specific model contending that both right and left adult temporal lobectomy patients are at risk of deficits in verbal memory (Baxendale & Thompson, 2005). The picture is even less consistent in children who have undergone a temporal lobectomy. Many aspects of neuropsychological functioning including academic skills, executive functioning, and fine motor speed have not been shown to change significantly following surgery (Williams et al., 1998b).

Some studies have found hemisphere specific cognitive impairments which are a hallmark of the adult literature, with children with left temporal lobe epilepsy at greater risk of poorer verbal memory performance, and children with right temporal lobe epilepsy at greater risk of disrupted visual memory abilities (Adams et al., 1990; Szabo et al., 1998), but other studies have not shown seizure focus differences (Camfield et al., 1984; Lendt et al., 1999). Gleissner and colleagues (2002) found evidence for similar lateralization effects to adults at short-term follow-up in children, but these effects appear to be transient as they were not present one year following surgery. In another study Gleissner and colleagues (2005)

demonstrated that there appears to be greater plasticity and compensational capacity in childhood. In this study they matched children with adults also undergoing temporal lobectomy. At 3 months post-surgery both children and adults who had undergone left temporal lobectomy displayed a significant decline in verbal memory, but only the children recovered to their pre-operative level at 1 year post-surgery. With respect to those undergoing right temporal lobectomy, the children's visual memory showed a transient decline at 3 months post-surgery followed by improvement at 1 year post-surgery. Adult right temporal lobectomy patients experienced a decline in visual memory that persisted over time. These findings suggest that some of the inconsistencies in past studies regarding lateralization effects in children following surgery might be the result of different periods of follow-up. Adams and colleagues (1990) assessed functioning at 6 months post-surgery and Szabo and colleagues (1998) at 6-9 months following surgery with both finding lateralization effects. Thus, it seems that children may be at increased risk of a relative decline in performance within the first year following surgery, but that these deficits on average appear to resolve one year post-surgery (Gleissner et al., 2005). This is consistent with research which has shown that developmental gains may accrue over a longer period of time following surgery and may not necessarily be apparent in the early months following surgery (Freitag & Tuxhorn, 2005).

#### *Adaptive Functioning*

No studies could be identified that examined changes in adaptive functioning in children following surgical intervention, however, adults who have undergone temporal lobectomies have been shown to make significant improvements in psychosocial functioning as well as independent living skills, and perform significantly better than pharmacologically managed controls (Jones et al., 2002). Nevertheless, in this study, a quarter to a third of the surgical group continued to experience significant psychosocial difficulties. Being seizure-free following surgery was not a necessary prerequisite for improvements in psychosocial outcome, though the seizure-free group did self-report significantly higher quality of life. Adults who underwent a

temporal lobectomy were significantly more likely to live independently (85%) than adults whose seizures were pharmacologically managed (48%) suggesting substantial relative differences in adaptive abilities in adults treated with surgery (Jones et al., 2002). Although children with epilepsy appear to be at risk of reduced adaptive functioning, little research has been published assessing these deficits, their correlates, and means by which to ameliorate suboptimal adaptive functioning. Furthermore, as surgical intervention becomes increasingly more common to treat pharmacologically intractable pediatric epilepsy, a greater understanding of how surgery may affect adaptive functioning is warranted.

#### *Time Dependent Effects of Epilepsy Surgery*

Gleissner and colleagues (2002) sought to better understand the time-dependent deficits that may occur following surgery. In this study, children identified for right or left temporal lobectomies did not differ significantly with respect to verbal memory prior to surgery, and performance was not significantly related to duration of epilepsy, attention, or the number of AEDs. Three months following surgery, however, the left temporal resection group showed declines in verbal learning and delayed memory, performing significantly more poorly than the right temporal resection group. At one year post-surgery, the left temporal resection group's verbal memory skills recovered such that they were no longer performing significantly more poorly than the right temporal resection group. Interestingly, at 3 months post-surgery, both groups evidenced a decline in verbal recognition, with recovery at 1 year post-surgery. The degree of recovery in verbal recognition scores was only significant, however, in the right temporal lobectomy group. Longer duration of epilepsy was a predictor for poorer post-operative verbal learning, and similarly to the findings of Szabo and colleagues (1998) higher preoperative verbal learning and memory performance were significant predictors of post-operative loss. This finding might represent an actual loss of verbal learning and memory skills, regression to the mean, reduced functional integrity of the side contralateral to surgery, or greater functional adequacy of the resected tissue (Chelune et al., 1995).

Surgery may cause new deficits or exacerbate those already present, but it may also result in the restoration of cognitive processes and behavioral functioning. For example, significant improvements following temporal resection (left or right) have been noted in language performance and attention (Gleissner et al., 2005; Lendt et al., 1999), psychomotor speed (Gleissner et al., 2002), and problem solving abilities (Hermann & Wyler, 1988). Duchowny and colleagues (1992) contacted families following their children's surgery and found reported increases in the children's self-esteem and self-confidence, as well as improved mood. Child-report of post-surgical gains in competence and self-worth also were noted by van Empelen and colleagues (2005). Parents also have reported significant improvements in their child's social relationships and activities, an increase in independence, increased mood, more energy, decreased fatigue, and reductions in internalizing behavior problems following surgery (Elliot et al., 2000; Smith et al., 2004; van Empelen et al., 2005; Williams et al., 1998b). Children who are younger at time of surgery may show a greater improvement in behavior problems following surgery (Smith et al., 2004). Many of cited improvements in neuropsychological functioning appear to be linked to the degree of seizure control (Smith et al., 2004).

Early surgical intervention is becoming increasingly popular for children with epilepsy, because it might not only lead to improved seizure control, but also help to normalize brain development and because more immature brains may be more plastic allowing for greater post-surgical recovery (Holmes 1996; Rossi, 1995; Wyllie, 1998). Early surgical intervention also could halt the detrimental effects of seizures on the brain, help facilitate academic achievement, and aid in the development of social and adaptive skills (Lah, 2004). Indeed, continual seizures are thought to slow the rate of cognitive and psychological development (Hirsch et al., 2000). Nevertheless, the optimal time for surgical intervention in childhood remains controversial, with surgery currently offered most often as a last-resort treatment (Sheth et al., 2000). More longitudinal studies are needed to help shed light on this issue.

Children with below average intellectual functioning are less likely to attain post-surgical seizure control than children with average intellectual ability (Chelune et al., 1998; Lee et al., 2004 in Blackburn et al., 2007). This is consistent with research on adults with epilepsy. It has been postulated that below average intellectual functioning in this population is a marker of diffuse neuronal damage, which cannot be addressed through a focal resection (Blackburn et al., 2007). Nevertheless, the effect sizes are small when using baseline IQ scores to predict pediatric seizure outcome suggesting that IQ scores alone may be of little utility in identifying surgical candidacy. Due to the linear relationship between IQ and later seizure freedom, however, IQ may be of more utility in estimating the chance of becoming seizure free post-surgery (Chelune et al., 1998).

Surgical intervention results in improved seizure control for many children, with approximately 70% seizure-free in the first year following surgery (Gilliam et al., 1997; Gleissner et al., 2002). Positive post-surgical seizure and AED outcomes appear to decline over time, with a higher percentage of children being seizure free and off of AEDs within the first five years of surgery, as compared to more than five years following surgery (Tellez-Zenteno et al., 2007). Children have, however, been shown to have better post-surgery seizure outcomes than adults with epilepsy, with 27% of children off of AEDs and seizure-free at 5 year follow-up as compared to 19% of adults (Tellez-Zenteno et al., 2007). This may reflect surgery during childhood having an increased probability of curing epilepsy or differences in the extent of surgical resection in children as compared to adults. Temporal lobectomies are the most prevalent type of seizure surgery in children and appear to have the highest rate of success with respect to seizure control (Kim et al., 2000). Other neuroanatomical variables also may influence surgical outcome. For example, children with symptomatic epilepsy as evidenced by the presence of discrete lesions on MRI show improved seizure control compared to children with no lesion or non-specific MRI findings (Kim et al., 2000).



Surgical intervention in children does not seem to be associated with a substantial risk of greater neuropsychological impairments, and some children may even make cognitive gains following temporal lobectomy. Research conducted thus far suggests that the risk of cognitive impairment following temporal lobectomy is small, with learning and memory abilities appearing to be the most vulnerable, and any deleterious effects in these domains may be transient. The minimal risk of adverse outcome that many studies report is important to note because children who undergo temporal lobectomies are those in whom seizures are most difficult to control and who are at the greatest risk of delays in cognitive and psychological development without surgical intervention (Gleissner et al., 2005; Westerveld et al., 2000). Nevertheless, more research is needed to examine the effects of surgery on other outcomes, such as adaptive functioning, and to provide more information on the variables that correlate with optimal and suboptimal seizure control and cognitive functioning. More studies that control for the effects of practice, test-retest reliability issues, and regression to the mean also are needed.

#### *Infrequent Use of Comparison Groups*

In addition to a poor understanding of adaptive functioning in this population, past research also has been limited by the infrequent use of comparison groups. Comparison groups are important in neuropsychological research because they help to clarify how people with neurological impairments are functioning differently from their peers without neurological impairments. Comparison groups also are beneficial in studies where the same measures are administered multiple times, as they can help control for practice effects. The use of comparison groups in pediatric neuropsychological research is particularly important to ensure that any findings in a neurological sample are not due to developmental trends, but rather reflect meaningful deviations from the norm with respect to brain development and function. The use of comparison groups in studies of epilepsy, particularly those assessing post-surgical outcome has been infrequent, with Lendt and colleagues (1997) emphasizing the need for controlled comparisons in order to accurately characterize the benefits of surgery. An informal search of

PubMed in Spring 2009 using the search terms “pediatric, epilepsy, comparison group” and “pediatric, epilepsy, control group” revealed 59 studies that have used comparison groups when conducting research in this population. This is in stark contrast to the 3,094 studies that were listed using the search terms “pediatric, epilepsy.” Adding the word “cognitive” to the above search terms revealed 8 studies with comparison groups and 206 studies without comparison groups.

Comparison groups are of particular importance when trying to assess change over time. For example, Hermann and colleagues (2006) assessed the neuropsychological functioning of adults with chronic epilepsy at one time point and again four years later. They also tested healthy controls at these same intervals. When examining only the epilepsy patients, the course of epilepsy might erroneously have been concluded to be benign as mean performance on only one out of 16 measures changed significantly. However, the inclusion of a healthy control group painted a dramatically different picture as 57% of the control group showed significant improvements on the tests, while only 6% of the epilepsy group improved significantly. This suggests that test-retest trajectories are very different for the two groups and that the majority of participants with chronic epilepsy failed to make the expected gains from learning associated with practice effects. When assessing children after a temporal lobectomy, a non-surgical comparison group with epilepsy is of particular importance in order to better understand how surgery may alter the relationship being examined. This is because without a comparison group, it is impossible to know whether a relationship has been affected by surgical intervention, ongoing development, the course of the seizure disorder, or some combination of the above (Smith et al., 2004).

The use of a typically developing comparison group can be beneficial as it allows for commentary on how the course of development may deviate from the norm in clinical samples. One study examined the prevalence of parent-report of behavior problems in children with seizures, children with heart conditions, and typically developing children (McDermott et al.,

1995). They found that behavior problems were 3 times more likely in children with heart conditions and 4.7 times more likely in children with epilepsy compared to control participants. Furthermore, children with epilepsy were noted to be at greater risk of hyperactive and dependent behaviors (McDermott et al., 1995). This suggests that epilepsy itself or factors associated with epilepsy such as compromised developmental status or higher rates of learning disabilities, attention deficit disorders, and behavioral disorders (Adams et al., 2002) are associated with a notably greater increase in the number of parent-reported behavior problems compared not only to children with a different chronic medical condition, but also to children who are developing typically.

### *The Current Study*

Understanding the influence of epilepsy and its treatments on adaptive functioning will help researchers quantify the effects of these variables on neurodevelopment and to fine-tune neuropsychological interventions. In order to better understand how these variables affect adaptive functioning, children with epilepsy and a typically developing, seizure free (comparison) group were recruited for this study. This study was conducted at two time points with Time 1 representing when children underwent a neuropsychological evaluation and Time 2 when parents completed follow-up questionnaires on their child's functioning. This study examined the relationship between individual and cumulative measures of seizure severity and adaptive functioning. Additionally, the relationship between neuropsychological functioning at Time 1 and adaptive functioning at Time 2 was studied in order to establish the best neuropsychological predictors of later adaptive functioning. As intact language based skills, such as auditory attention, verbal learning, and verbal memory, are especially critical for school-age children and because impairments in these areas may be especially prominent in pediatric clinical populations (Delis et al., 1994) and associated with academic underachievement (Seidenberg et al., 1987), measures of these constructs were the focus.

The relationship between behavior problems, executive functioning, and adaptive functioning also was assessed. Children with epilepsy are known to be at risk of behavior problems (Caplan et al., 04; Elger et al., 1997; Stores 1978), which are associated with reduced psychosocial functioning (Adams et al., 2002; Austin et al., 1994). Executive functioning, which refers to cognitive abilities that are necessary for goal-directed behavior, has been shown to be a particularly vulnerable domain in children with epilepsy (Hermann et al., 2006; Parrish et al., 2007), and is associated with adaptive outcome (Culhane-Shelburne et al., 2002). Neuropsychological functioning was examined as a mediator of the relationship between seizure severity/group membership and adaptive functioning. This model was proposed to better understand the causal relationship between variables, and to establish whether seizure and treatment variables directly affect adaptive functioning or indirectly affect it through altering cognitive or behavioral functioning.

With the ultimate goal of improving the lives of children with epilepsy, more research is needed in order to increase our understanding of the variables associated with positive adaptive outcome, suggest means by which to assist children in achieving an optimal level of age-appropriate independence, and help in the identification of children who are at risk of suboptimal adaptive functioning so that preventative interventions may be applied. The first specific aim of this study sought to establish the extent to which a measure of cumulative seizure severity as well as individual seizure and treatment variables were able to predict adaptive functioning. The second specific aim was designed to address whether seizure and treatment variables either directly affected adaptive functioning, or indirectly affected it through their effects on neuropsychological functioning. These aims were designed to highlight the key variables associated with positive adaptive outcome and quantify the effects of seizure and treatment variables on adaptive functioning.

### *Specific Aims*

**Aim 1: Establish how epilepsy and treatment variables were related to adaptive functioning.**

Hypothesis 1: More severe epilepsy history was hypothesized to be negatively related to adaptive functioning.

Hypothesis 2: Longer amount of time elapsed since first seizure, younger age at seizure onset, active seizures, multiple medications, and multiple seizure types were predicted to be negatively associated with independent living skills.

Hypothesis 3: Focal epilepsy surgery was hypothesized to be positively related to adaptive functioning.

**Aim 2: Establish the strongest neuropsychological predictors of adaptive functioning and whether neuropsychological functioning mediated the relationship between seizure and treatment variables and adaptive functioning.**

Hypothesis 1: Attention (California Verbal Learning Test-Children's Edition (CVLT-C, 1994) Trial 1), verbal learning (CVLT-C Learning Slope), and verbal memory (CVLT-C Long Delay Free Recall) at Time 1 were proposed to be positively related to adaptive functioning (Adaptive Behavior Assessment System-II (ABAS-II, 2003) Conceptual, Social, and Practical domains) at Time 2. Executive dysfunction (Behavior Rating Inventory of Executive Function (BRIEF, 2000) Behavioral Regulation Index and Metacognitive Index) was hypothesized to be negatively associated with adaptive functioning at Time 2.

Hypothesis 2: Behavior problems (Behavior Assessment System for Children-Second Edition (BASC-2, 2004) Internalizing and Externalizing Problems) at Time 1 were predicted to be negatively associated with independent living skills at Time 2.

Hypothesis 3: Based on the results of hypotheses 1 and 2, verbal learning (CVLT-C Learning Slope), executive functioning (BRIEF General Executive Composite (GEC)), and behavior problems (BASC-2 Behavior Problems Composite) at Time 1 were predicted to

mediate the relationship between Seizure History Scale (SHS) scores at Time 1 and adaptive functioning at Time 2 (see Figure 1a). Furthermore, this relationship was hypothesized to persist when neuropsychological functioning and SHS scores at Time 2 (both when SHS scores at Time 1 were controlled for and when they were not) were used (see Figure 1b).

As it is more traditional to divide children with epilepsy into groups according to their treatment status, an additional mediational model was tested using group membership as a predictor of adaptive functioning. A dummy coded variable represented group membership (Time 1: 0 = typically developing, 1 = monotherapy, and 2 = polytherapy; Time 2: 0 = typically developing, 1 = monotherapy, 2 = polytherapy, and 3 = surgical).

Hypothesis 4: Verbal learning (CVLT-C Learning Slope), executive functioning (BRIEF GEC), and behavior problems (BASC-2 Behavior Problems Composite) at Time 1 were predicted to mediate the relationship between Group at Time 1 and adaptive functioning at Time 2 (see Figure 2a). Furthermore, this relationship was hypothesized to persist when examining neuropsychological functioning and Group at Time 2 (both when Group at Time 1 was controlled for and when it was not; see Figure 2b).

With the ultimate goal of improving the lives of children with epilepsy, this study sought to increase our understanding of how the developing brain is affected by this chronic illness and its treatment and to suggest means by which to fine tune interventions to improve adaptive skills in order to assist children in achieving an optimal level of age-appropriate independence.

## Chapter 2

### METHOD

#### *Participants*

Children with epilepsy and their families were recruited from a larger group of children who were referred to Children's Healthcare of Atlanta (CHOA) for a neuropsychological evaluation. Children on monotherapy and polytherapy for seizure control were eligible to

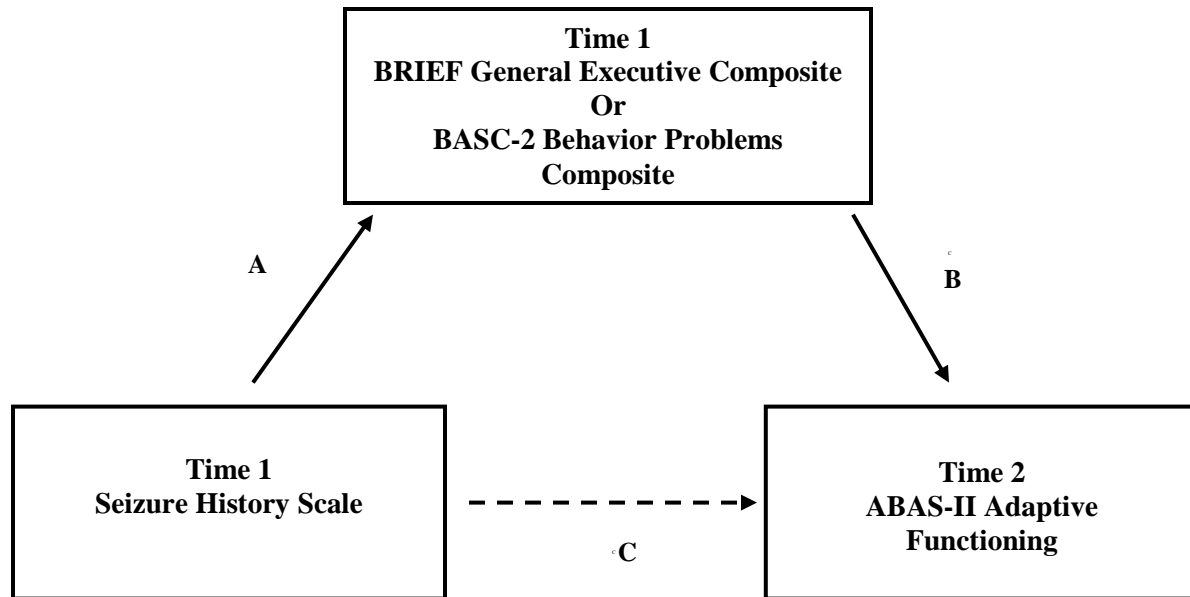


Figure 1a. Mediation model examining executive functioning or behavior problems at Time 1 as a mediator of the relationship between the Seizure History Scale at Time 1 and adaptive functioning at Time 2.

*Note.* Verbal learning was dropped as a mediator due to a non-significant correlation with the Seizure History Scale.

When executive functioning was examined as a mediator, behavior problems were controlled for and vice versa.

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Functioning; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.

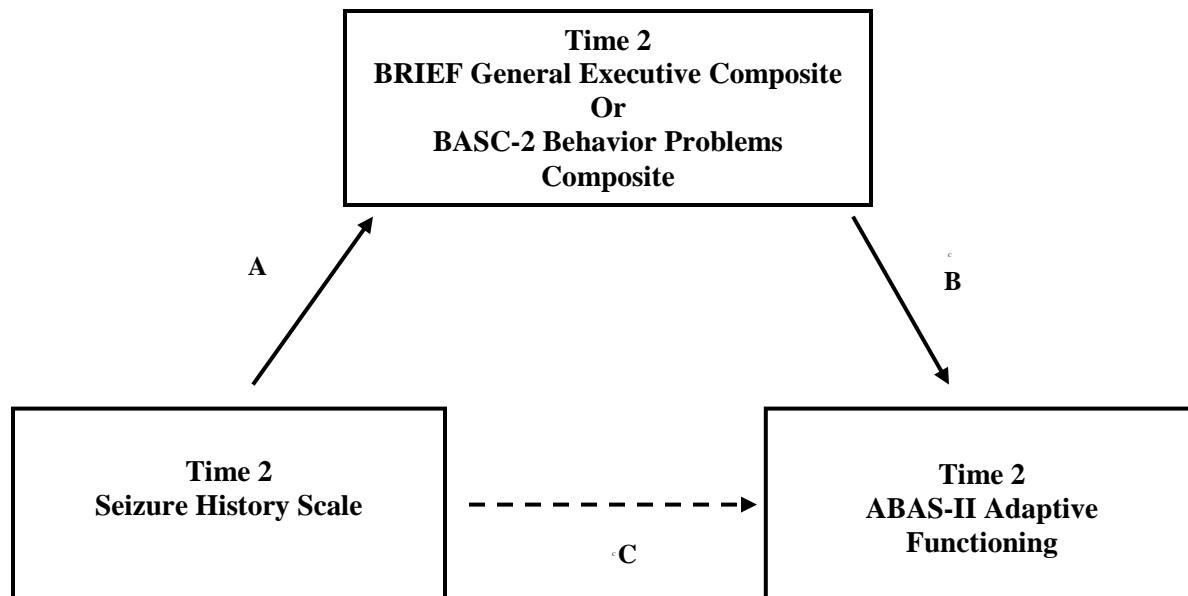


Figure 1b. Mediation model examining executive functioning or behavior problems at Time 2 as a mediator of the relationship between the Seizure History Scale at Time 2 and adaptive functioning at Time 2.

*Note.* Verbal learning was dropped as a mediator due to a non-significant correlation with the Seizure History Scale. When executive functioning was examined as a mediator, behavior problems were controlled for and vice versa. This model was tested both when performance on the Seizure History Scale at Time 1 was controlled for and when it was not to examine the effects of changes in seizure history between Time 1 and Time 2. Abbreviations: BRIEF, Behavior Rating Inventory of Executive Functioning; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.



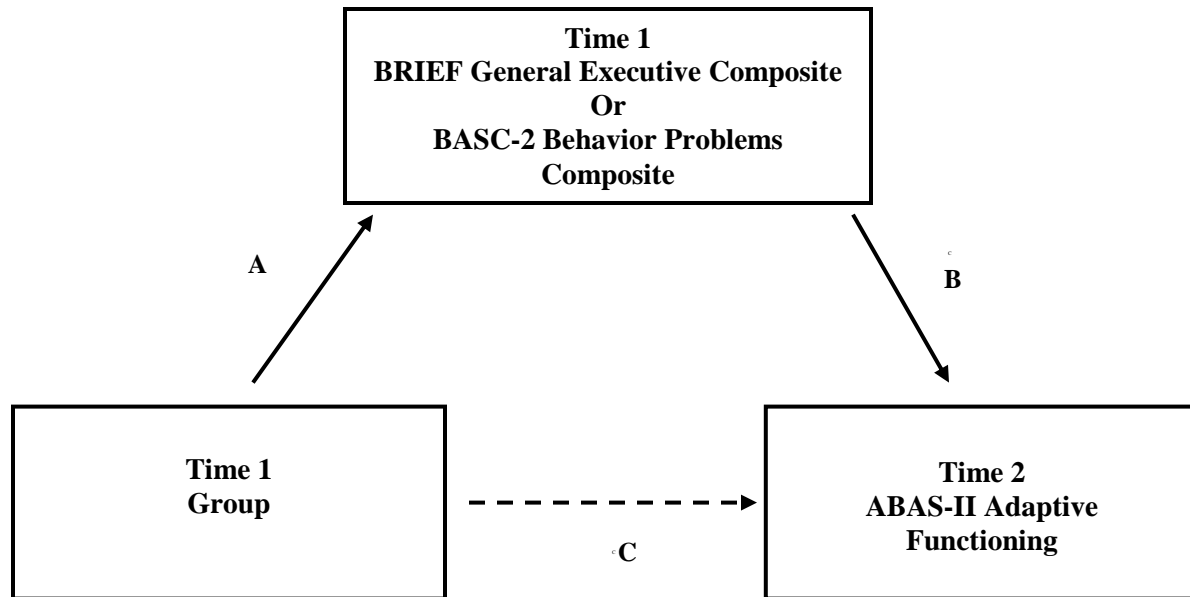


Figure 2a. Mediation model examining executive functioning or behavior problems at Time 1 as a mediator of the relationship between Group at Time 1 and adaptive functioning at Time 2.

*Note.* Verbal learning was dropped as a mediator due to a non-significant correlation with Group. Group represents whether the child belongs to the Typically Developing, Monotherapy, or Polytherapy group. When executive functioning was examined as a mediator, behavior problems were controlled for and vice versa. Abbreviations: BRIEF, Behavior Rating Inventory of Executive Functioning; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.

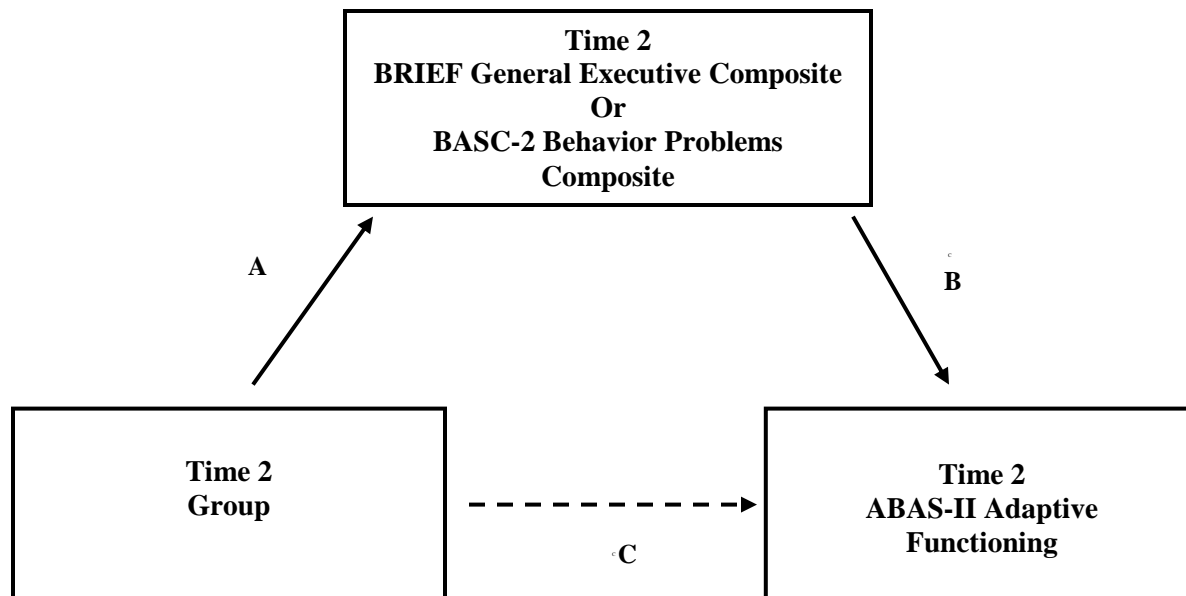


Figure 2b. Mediation model examining executive functioning or behavior problems at Time 2 as a mediator of the relationship between Group at Time 2 and adaptive functioning at Time 2.

*Note.* Verbal learning was dropped as a mediator due to a non-significant correlation with Group. Group represents whether the child belongs to the Typically Developing, Monotherapy, Polytherapy, or Surgery group. When executive functioning was examined as a mediator, behavior problems were controlled for and vice versa. This model was tested both when Group at Time 1 was controlled for and when it was not to examine the effect of changes in group membership between Time 1 and Time 2. Abbreviations: BRIEF, Behavior Rating Inventory of Executive Functioning; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.

participate. Children who underwent a focal resection for the purpose of seizure control also were eligible to participate. Presurgical neuropsychological assessments were used for this group in order to determine the extent to which their post-surgical functioning could be predicted by how participants were functioning prior to surgical intervention. Children who had more than one surgical resection were eligible for participation in the study provided that a neuropsychological evaluation was conducted prior to the initial resection. Typically developing children and their families who participated in another study at CHOA, were recruited for the comparison group. Inclusion in this group was contingent on not having received a diagnosis of epilepsy.

Regardless of group, inclusion in this study was contingent upon children being between the ages of 6 and 16 at the time of the initial neuropsychological evaluation (Time 1). At least one year, but fewer than five years, must have elapsed between the neuropsychological screening and the completion of parent-report questionnaires (Time 2). Only families who spoke English as a first language were eligible to participate. Children who were diagnosed with a brain tumor were eligible for participation only if they had not been treated with radiation or chemotherapy. Participants diagnosed with a specific learning disability ( $n = 5$ ; 1 spelling, 2 math, 2 reading), attention deficit/hyperactivity disorder ( $n = 12$ ) or with a history of traumatic brain injury ( $n = 1$ ) were eligible to participate given their high rates of comorbidity with epilepsy, and their diagnoses were noted to help characterize the sample. Children who were diagnosed with an additional distinct neurological disorder such as Neurofibromatosis or Autism or who had epilepsy associated with a neurodegenerative disorder (e.g., progressive myoclonic epilepsy) were excluded, because being diagnosed with an additional neurological disorder with known neurocognitive impairments would have undermined our ability to draw conclusions about the specific effects of epilepsy and seizure treatments on adaptive functioning. Children with Chiari Type 1 Malformations ( $n = 3$ ) were eligible to participate because this structural defect is not reliably associated with neurocognitive impairments, but rather is typically associated with

physical symptoms such as dizziness, headache, neck pain, and muscle weakness (NINDS, 2007). Furthermore, when the analyses were run without these participants, the results did not change appreciably.

One hundred and forty-one families were eligible to participate in this study. Twenty-six families were unable to be located (typically developing = 6, monotherapy = 17 (two of whom later underwent surgery) and, polytherapy = 3). Three families declined participation (all monotherapy), and thirty-four families (typically developing = 3, monotherapy = 23 and, polytherapy = 8) did not answer phone calls about participation. A total of 78 families consented to participate. Sixteen families of these families did not return packets (typically developing = 4, monotherapy = 8 (two of whom later underwent surgery) and, polytherapy = 4). Means, frequencies, and significant differences between children who participated in the study and those who did not are presented in Table 1. Children from the monotherapy group who participated in the study were more likely to have active seizures at Time 1, than children who did not participate ( $\chi^2(1, n = 75) = 7.07, p = .01$ ). Children treated with monotherapy who did not participate had significantly more executive problems as measured by the Behavioral Regulation Index of the BRIEF ( $t(72) = -2.18, p = .03$ ) than children who did participate, but mean scores for both groups were within normal limits. The age of seizure onset was found to be significantly lower for polytherapy participants compared to non-participants ( $t(36) = -2.30, p = .03$ ). Typically developing children who participated in the study had more externalizing ( $t(27) = 4.43, p < .001$ ) and executive problems (General Executive Composite  $t(27) = 2.41, p = .02$ ; Behavioral Regulation Index  $t(27) = 2.57, p = .02$ ) compared to non-participants, but still scored within normal limits.

Sixty two eligible families completed participation in this study (46 with children with epilepsy, 16 typically developing). Within the epilepsy group, at Time 1, 23 children were prescribed a single AED and 23 children were prescribed multiple AEDs. At Time 2, 17 children

Table 1. Means (standard deviations) and frequencies for children who participated in the study and those who did not at Time 1.

	Monotherapy		Polytherapy		Typically Developing	
	Participants <i>n</i> = 23	Non-Participants <i>n</i> = 51	Participants <i>n</i> = 23	Non-Participants <i>n</i> = 15	Participants <i>n</i> = 16	Non-Participants <i>n</i> = 13
Age at Neuropsychological Assessment (years)	12.01 (3.05)	10.91 (2.82)	11.22 (3.27)	11.84 (2.67)	11.75 (2.99)	11.40 (3.58)
Age at Seizure Onset (years)	7.07 (4.98)	6.15 (3.93)	4.87 (3.00) <sup>c</sup>	7.33 (3.54) <sup>c</sup>	-	-
Active: Controlled Seizures	21:2 <sup>a</sup>	31:20 <sup>a</sup>	22:1	15:0	-	-
Socioeconomic Status	1.91 (.90)	1.98 (.71)	1.91 (.95)	1.80 (.56)	1.25 (.45)	1.23 (.44)
Female:Male	7:16	24:27	8:15	4:11	7:9	6:7
Caucasian:African American	21:2	39:12	18:5	13:2	9:7	8:5
Right:Left Handedness	21:2	42:9	15:8	13:2	15:1	13:2
Number with IEP at School	9	25	14	7	0	0
Number in Accelerated Program at School	1	2	1	0	0	0

	Monotherapy		Polytherapy		Typically Developing	
	Participants <i>n</i> = 23	Non- Participants <i>n</i> = 51	Participants <i>n</i> = 23	Non- Participants <i>n</i> = 15	Participants <i>n</i> = 16	Non- Participants <i>n</i> = 13
CVLT-C Trial 1	93.48 (15.05)	94.71 (14.95)	86.30 (11.00)	95.00 (17.85)	103.75 (14.23)	95.96 (16.66)
CVLT-C Learning Sl.	94.78 (16.84)	95.29 (17.81)	99.35 (22.94)	86.50 (12.74)	99.53 (13.82)	107.50 (13.35)
CVLT-C LDFR	87.61 (24.83)	92.35 (17.26)	87.28 (20.53)	86.00 (21.93)	104.22 (11.93)	106.35 (9.61)
BASC-2 Internalizing	105.35 (17.13)	110.49 (19.36)	108.74 (19.64)	119.50 (21.54)	96.53 (7.66)	91.23 (6.53)
BASC-2 Externalizing	102.74 (18.14)	110.64 (19.19)	107.70 (18.61)	111.25 (19.14)	102.81 (7.35) <sup>d</sup>	91.23 (6.53) <sup>d</sup>
BRIEF GEC	112.78 (26.21)	123.33 (15.70)	120.22 (19.22)	127.10 (21.22)	100.94 (11.95) <sup>e</sup>	92.04 (6.46) <sup>e</sup>
BRIEF BRI	106.75 (21.88) <sup>b</sup>	117.53 (18.29) <sup>b</sup>	115.68 (20.08)	123.50 (22.82)	101.41(11.97) <sup>f</sup>	91.12 (8.95) <sup>f</sup>
BRIEF MI	115.75 (26.51)	124.12 (15.78)	121.00 (18.73)	126.10 (18.37)	100.47 (13.47)	92.38 (7.10)
Wechsler Full Scale IQ	94.00 (16.38)	89.48 (15.76)	87.74 (18.74)	81.07 (14.68)	114.50 (11.65)	108.15 (16.76)

Note. Non-participants included children who could not be located (*n* = 27), children whose parents did not return calls about participation (*n* = 36), children whose parents declined to participate (*n* = 3), and children whose packets were not completed (*n* = 16). Socioeconomic status was scored on a 5 point scale (Hollingshead, 1957) with 1 representing the highest socioeconomic status and 5 the lowest. Significant differences between groups are indicated by a superscript letter. Higher scores on the BASC-2 and BRIEF indicate worse functioning. Abbreviations: IEP, Individualized Education Plan; CVLT-C, California Verbal Learning Test-Children's Version; Learning Sl., Learning Slope; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of

Executive Functioning; GEC, Global Executive Composite; BRI, Behavioral Regulation Index; MI, Metacognition Index. Significant differences between groups are indicated by a superscript letter.

$$^a \chi^2 (1, n = 75) = 7.07, p = .01$$

$$^b t(72) = -2.18, p = .03$$

$$^c t(36) = -2.30, p = .03$$

$$^d t(27) = 4.43, p < .001$$

$$^e t(27) = 2.41, p = .02$$

$$^f t(27) = 2.57, p = .02$$

were prescribed a single AED, 15 children were prescribed multiple AEDs (one was also on the ketogenic diet), and 14 children had undergone a temporal lobectomy (nine right, five left;  $M = 2.42$  years ago,  $SD = 1.56$ , range = 1.00-5.00 years). Although children who underwent focal surgical resections in other areas of the brain were eligible to participate, only three other children underwent focal resections and were within the age-range of this study. All three were excluded for other reasons, namely for co-morbid neurological conditions. Demographic data are presented in Table 2. Socioeconomic status (SES) was assessed by the Hollingshead Two-Factor Index of Social Position (Hollingshead, 1957) which uses parental occupation and educational level to estimate SES. This is a five point scale with one representing the highest socioeconomic status and five the lowest. Mean SES was higher than average across all four groups.

T-tests and Fisher Exact tests were used to test for significant differences between groups. The surgery group was found to be significantly older than the monotherapy ( $t(29) = -2.32$ ;  $p = .03$ ), polytherapy ( $t(27) = -2.52$ ;  $p = .02$ ), and typically developing ( $t(28) = -2.27$ ;  $p = .03$ ) groups at the time parents completed the questionnaires, and may reflect the current view that surgery is a “last-resort” treatment. The amount of time elapsed between neuropsychological assessment and the completion of questionnaires (Times 1 and 2) was significantly longer for children in the monotherapy group compared to the polytherapy ( $t(30) = 3.13$ ,  $p = .004$ ) and typically developing ( $t(31) = -4.07$ ,  $p = .001$ ) groups and for children in surgery group compared to the polytherapy ( $t(27) = -3.01$ ,  $p = .09$ ) and typically developing ( $t(28) = -3.35$ ,  $p = .005$ ) groups. The surgery group had a significantly later onset of epilepsy than the polytherapy group ( $t(27) = -2.55$ ;  $p = .02$ ). SES was significantly higher for the typically developing group compared to the monotherapy ( $t(31) = -2.61$ ;  $p = .01$ ) and surgery ( $t(28) = -3.19$ ;  $p = .01$ ) groups. Compared to the typically developing group, the surgery group was found to be comprised of significantly more Caucasian children (*Fisher Exact* (1,  $n = 30$ ) = 5.12;  $p = .04$ ). Children in the polytherapy group were significantly more likely to be left handed than



Table 2. Demographic information according to group at Time 2.

	Monotherapy ( <i>n</i> = 17)	Polytherapy ( <i>n</i> = 15)	Surgery ( <i>n</i> = 14)	Typically Developing ( <i>n</i> = 16)
Age at Neuropsychological Assessment (years)	10.80 (3.16)	11.42 (2.98)	12.81 (3.19)	11.73 (2.95)
Age at Questionnaires (years)	12.90 (3.30) <sup>a</sup>	12.82 (2.84) <sup>b</sup>	15.53 (2.95) <sup>a,b,c</sup>	13.05 (3.03) <sup>c</sup>
Time between Neuropsychological Assessment and Questionnaires (years)	2.08 (.78) <sup>de</sup>	1.37 (.43) <sup>df</sup>	2.69 (1.58) <sup>fg</sup>	1.25 (.31) <sup>eg</sup>
Age at Seizure Onset (years)	5.17 (3.36)	4.46 (2.68) <sup>h</sup>	8.55 (5.41) <sup>h</sup>	-
Time between Seizure Onset and Questionnaires (years)	7.69 (4.12)	8.34 (3.84)	6.94 (5.31)	-
Active:Controlled Seizures	7:10	13:2	6:8	-
Socioeconomic Status	1.94 (.97) <sup>i</sup>	1.60 (.63)	2.21 (1.05) <sup>j</sup>	1.25 (.45) <sup>ij</sup>
Female:Male	8:9	2:13	5:9	7:9
Caucasian:African American	15:2	11:4	13:1 <sup>k</sup>	9:7 <sup>k</sup>
Right:Left Handedness	14:3	9:6 <sup>l</sup>	13:1	15:1 <sup>l</sup>
Number with IEP at School	9 <sup>m</sup>	9 <sup>n</sup>	5 <sup>o</sup>	0 <sup>mno</sup>
Number in Accelerated Program at School	0	2	1	0

*Note.* Socioeconomic status was scored on a 5 point scale (Hollingshead, 1957) with 1 representing the highest socioeconomic status and 5 the lowest. Abbreviations: IEP, Individualized Education Plan. Significant differences between groups are indicated by a superscript letter.

<sup>a</sup>  $t(29) = -2.32, p = .03$

<sup>b</sup>  $t(27) = -2.52, p = .02$

<sup>c</sup>  $t(28) = -2.27, p = .03$

<sup>d</sup>  $t(30) = 3.13, p = .004$

<sup>e</sup>  $t(31) = -4.07, p = .001$

<sup>f</sup>  $t(27) = -3.01, p = .09$

$$^g t(28) = -3.35, p = .005$$

$$^h t(27) = -2.55, p = .02$$

$$^i t(31) = -2.61, p = .01$$

$$^j t(28) = -3.19, p = .01$$

$$^k \text{Fisher Exact } (1, n = 30) = 5.12, p = .04$$

$$^l \text{Fisher Exact } (1, n = 31) = 5.04, p = .04$$

$$^m \text{Fisher Exact } (1, n = 33) = 11.65, p = .001$$

$$^n \text{Fisher Exact } (1, n = 31) = 13.53, p < .001$$

$$^o \text{Fisher Exact } (1, n = 30) = 6.86, p = .01$$

children in the typically developing group (*Fisher Exact* (1,  $n = 31$ ) = 5.04;  $p = .04$ ). Finally, children across the monotherapy (*Fisher Exact* (1,  $n = 33$ ) = 11.65;  $p = .001$ ), polytherapy (*Fisher Exact* (1,  $n = 31$ ) = 13.53;  $p < .001$ ), and surgery (*Fisher Exact* (1,  $n = 30$ ) = 6.86;  $p = .01$ ) groups were significantly more likely to have an Individualized Education plan (IEP) in place than children in the typically developing group.

Information regarding medications and seizure types is presented in Table 3. The number of participants currently prescribed specific AEDs (or combination of AEDs where applicable) is listed according to group membership. This is followed by the number of past AEDs a child has been prescribed, again presented according to the number of participants per group. Then the number of participants per group experiencing different seizure types is listed. Additionally, two children in the monotherapy group and one child in the surgery group had experienced infantile spasms. On average, children within the monotherapy group experienced 2.18 ( $SD = 1.13$ ) different types of seizures, children within the polytherapy group 2.13 ( $SD = 1.13$ ), and children within the surgery group 1.86 ( $SD = 1.03$ ). There were no significant differences in the mean number of seizure types experienced per group ( $t_{monotherapy\ vs.\ polytherapy}(30) = .11, p = .92$ ;  $t_{monotherapy\ vs.\ surgery}(29) = .82, p = .42$ ;  $t_{monotherapy\ vs.\ polytherapy}(27) = .69, p = .50$ ). The total number of current AEDs children were taking was significantly greater for the polytherapy group compared to the monotherapy group ( $t(30) = 16.00, p < .001$ ) and the surgery group ( $t(27) = 4.38, p = .001$ ). At time 1, 43 children had experienced at least one seizure in the last year (active), compared to three who had not experienced a single seizure in the last year (controlled; 2 monotherapy, 1 polytherapy). At Time 2, 26 children had active seizures (7 monotherapy, 13 polytherapy, 6 surgery) and 20 children had controlled seizures (10 monotherapy, 2 polytherapy, 8 surgery). Additionally, at Time 2, children in the polytherapy group were significantly more likely to have had one or more seizures in the last year compared to the monotherapy group (*Fisher Exact* (1,  $n = 32$ ) = 7.04,  $p = .01$ ) and the surgery group (*Fisher Exact* (1,  $n = 29$ ) = 6.15,  $p = .02$ ).

Table 3. Names of current Antiepileptic Drugs (AEDs), number of past AEDs, and seizure types at Time 2 according to group membership.

	Number of Participants		
	Monotherapy ( <i>n</i> = 17)	Polytherapy ( <i>n</i> = 15)	Surgery ( <i>n</i> = 14)
<b>Current AEDs</b>			
None	-	-	4
Keppra	5	-	4
Trileptal	3	-	1
Depakote	2	-	1
Lamictal	3	-	1
Zonegran	1	-	-
Topamax	3	-	-
Keppra & Zarontin	-	1	-
Keppra & Carbatrol	-	1	-
Keppra & Depakote	-	-	1
Depakote & Zonegran	-	2	-
Depakote & Dilantin	-	1	-
Depakote & Carbatrol	-	1	-
Depakote & Topamax	-	1	-
Depakote & Trileptal	-	-	1
Depakote & Lamictal	-	2	-
Lamictal & Topamax	-	2	-
Lamictal & Tranxene	-	2	-

	Number of Participants		
	Monotherapy ( <i>n</i> = 17)	Polytherapy ( <i>n</i> = 15)	Surgery ( <i>n</i> = 14)
Zonegran & Klonopin	-	1	-
Keppra, Topamax, & Lamictal	-	-	1
Trileptal, Phenobarbital, & Mysoline	-	1	-
<u>Number of Past AEDs</u>			
None	3	1	4
One	8	1	4
Two	4	1	2
Three	1	5	1
Four	-	1	0
Five or More	1	6	3
<u>Seizure Types</u>			
Partial			
Simple Partial	4	3	2
Complex Partial	9	7	10
Secondarily Generalized	1	1	-
Generalized			
Absence	11	7	6
Atypical Absence	1	1	1
Tonic-Clonic	11	7	7
Clonic	-	1	-
Myoclonic	1	1	-
Other			
Eyelid Myoclonia	-	1	-

Gelastic	-	1	-
Febrile	2	-	1
Status Epilepticus	1	1	-

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*Note.* Abbreviations: AEDs; Antiepileptic Drugs

A summary of neuropsychological functioning at both Times 1 and 2 is presented in Table 4. Although mean scores were typically within the average to low average range, a substantial percentage of children in each of the epilepsy groups was functioning below the 25<sup>th</sup> percentile (or above the 25<sup>th</sup> percentile on the BASC-2 and BRIEF where higher scores indicate more problems). Significant between group differences in neuropsychological functioning based on t-tests are presented in Table 5. The epilepsy groups did not differ significantly from each other on any measure of neuropsychological functioning at either time point. Between group differences were noted between the epilepsy groups and typically developing group, with the children in the typically developing group performing significantly better than children with epilepsy on many measures. Although children with epilepsy were found to have significantly poorer adaptive functioning compared to typically developing children, when IQ was controlled for an Analysis of Covariance showed that there were no longer significant differences between groups on adaptive functioning ( $F(3, 57) = .30, p = .83$ ).

At Time 2, within the monotherapy group, seven children had experienced at least one seizure in the last year (active seizures) and 10 had not experienced any seizures in the last year (controlled seizures). In the polytherapy group, 13 children had active seizures, and two had controlled seizures. Within the surgery group, six had active seizures, and eight had controlled seizures. Scores on the Seizure History Scale (SHS; see Appendix A) were compiled to compare the severity of cumulative seizure history across participants. The range of possible scores was 0 to 22, with higher numbers indicating more severe seizure history. Overall, the mean score at Time 1 was 9.41 ( $SD = 3.33$ ), and 8.48 ( $SD = 4.58$ ) at Time 2. Mean scores on the SHS at Time 1 were 7.96 ( $SD = 3.17$ ) for the monotherapy group and 10.87 ( $SD = 2.87$ ) for the polytherapy group. At Time 2, mean scores on the SHS were 5.94 ( $SD = 3.60$ ) for the monotherapy group, 12.00 ( $SD = 4.00$ ) for the polytherapy group, and 7.79 ( $SD = 4.04$ ) for the surgery group.

Table 4. Mean neuropsychological performance in standard scores across groups and percentage below normal.

	Monotherapy <i>n</i> = 23		Polytherapy <i>n</i> = 23		Surgery <i>n</i> = 0		Typically Developing <i>n</i> = 16	
<b>Time 1</b>	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal
CVLT-C Trial 1	93.48 (15.05)	39	86.30 (11.00)	57	-	-	103.75 (14.23)	25
CVLT-C Learning Sl.	87.61 (24.83)	35	99.35 (22.94)	30	-	-	99.53 (13.82)	31
CVLT-C LDFR	90.54 (20.75)	39	87.28 (20.53)	48	-	-	104.22 (11.93)	13
BASC-2 Internalizing	105.35 (17.13)	35	108.74 (19.64)	43	-	-	96.53 (7.66)	0
BASC-2 Externalizing	102.74 (18.14)	39	107.70 (18.61)	30	-	-	102.81 (7.35)	19
BRIEF GEC	112.78 (26.21)	43	120.22 (19.22)	65	-	-	100.94 (11.95)	19
BRIEF BRI	106.75 (21.88)	35	115.68 (20.08)	57	-	-	101.41(11.97)	25
BRIEF MI	115.75 (26.51)	43	121.00 (18.73)	70	-	-	100.47 (13.47)	13
Wechsler Full Scale IQ	94.00 (16.38)	35	87.74 (18.74)	57	-	-	114.50 (11.65)	0



Time 2	Monotherapy <i>n</i> = 17		Polytherapy <i>n</i> = 15		Surgery <i>n</i> = 14		Typically Developing <i>n</i> = 16	
	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal	Mean (SD)	%age Below Normal
BASC-2 Internalizing	107.68 (15.27)	35	108.70 (16.54)	33	108.14 (24.70)	43	97.56 (10.40)	13
BASC-2 Externalizing	102.12 (16.70)	29	107.70 (17.34)	40	108.68 (20.38)	57	98.97 (11.43)	13
BRIEF GEC	118.18 (18.86)	65	120.30 (15.05)	73	115.00 (25.54)	57	98.69 (14.48)	25
BRIEF BRI	110.59 (16.92)	59	113.70 (16.93)	67	115.86 (27.06)	43	97.75 (12.49)	13
BRIEF MI	121.10 (20.68)	65	121.60 (14.05)	80	113.61 (23.24)	57	101.03 (16.95)	38
ABAS-II GAC	90.24 (22.43)	47	89.47 (14.62)	60	89.14 (23.76)	64	105.00 (13.64)	13
ABAS-II Conceptual	90.94 (20.00)	47	90.40 (15.38)	60	92.79 (23.33)	50	107.06 (10.56)	6
ABAS-II Social	91.53 (28.34)	35	91.33 (16.18)	33	92.64 (21.03)	43	104.44 (13.58)	6
ABAS-II Practical	86.35 (24.33)	53	89.93 (13.71)	73	89.14 (25.73)	64	103.25 (15.50)	25

*Note.* Higher scores on the BASC-2 and BRIEF indicate worse functioning. %age Below Normal was defined as the percentage of children in each group performing at or below the 25<sup>th</sup> percentile (SS ≤ 90; CVLT-C, IQ, ABAS-II) or at or above the 25<sup>th</sup> percentile (SS ≥ 110; BASC-2, BRIEF) based on norms.

Abbreviations: %age Below Normal, Percentage Below Normal; CVLT-C, California Verbal Learning Test-Children's Version; Learning SI., Learning Slope; BASC-

2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite; BRI, Behavioral Regulation Index; MI, Metacognition Index; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition; GAC, General Adaptive Composite.

Table 5. Significant differences between groups on neuropsychological measures at Time 1 and Time 2 according to t-tests.

	Monotherapy vs. Polytherapy	Monotherapy vs. Typically Developing	Polytherapy vs. Typically Developing
<b>Time 1</b>			
CVLT-C Trial 1	-	$t(37) = 2.14, p = .04$	$t(37) = 4.32, p < .001$
CVLT-C Learning Sl.	-	-	-
CVLT-C LDFR	-	$t(37) = 2.78, p = .01$	$t(37) = 2.96, p = .01$
BASC-2 Internalizing	-	$t(37) = -2.18, p = .04$	$t(37) = -2.36, p = .02$
BASC-2 Externalizing	-	-	-
BRIEF GEC	-	-	$t(37) = -3.86, p < .001$
BRIEF BRI	-	-	$t(37) = -2.73, p = .10$
BRIEF MI	-	$t(37) = -2.32, p = .03$	$t(37) = -3.75, p = .001$
Wechsler Full Scale IQ	-	$t(37) = 4.30, p < .001$	$t(37) = 5.06, p < .001$

	Monotherapy vs. Polytherapy	Monotherapy vs. Surgery	Monotherapy vs. Typically Developing	Polytherapy vs. Surgery	Polytherapy vs. Typically Developing	Surgery vs. Typically Developing
<b>Time 2</b>						
BASC-2 Internalizing	-	-	$t(31) = -2.21, p = .04$	-	$t(29) = -2.21, p = .04$	-
BASC-2 Externalizing	-	-	-	-	-	-
BRIEF GEC	-	-	$t(31) = -3.31, p = .002$	-	$t(29) = -3.31, p = .002$	-
BRIEF BRI	-	-	$t(31) = -2.47, p = .02$	-	$t(29) = -2.47, p = .02$	$t(28) = -2.30, p = .03$
BRIEF MI	-	-	$t(31) = -3.02, p = .01$	-	$t(29) = -3.02, p = .01$	-
ABAS-II GAC	-	-	$t(31) = 2.30, p = .03$	-	$t(29) = 2.30, p = .03$	$t(28) = 2.20, p = .04$
ABAS-II Conceptual	-	-	$t(31) = 2.92, p = .01$	-	$t(29) = 2.92, p = .01$	-
ABAS-II Social	-	-	-	-	-	-
ABAS-II Practical	-	-	$t(31) = 2.36, p = .03$	-	$t(29) = 2.36, p = .03$	-

*Note.* Abbreviations: vs., versus; CVLT-C, California Verbal Learning Test-Children's Version; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite; BRI, Behavioral Regulation Index; MI, Metacognition Index; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition; GAC, General Adaptive Composite.

With respect to comorbidities at Time 2, within the monotherapy group, five children had been diagnosed with ADHD, and four of these were taking stimulant medication. Of these five, one child had also been diagnosed with Obsessive Compulsive Disorder (OCD) and another child was noted to have a Chiari Type 1 Malformation, which was asymptomatic and had not been treated. Within the polytherapy group, five children were diagnosed with ADHD, and two of these were taking stimulant medication. An additional child in the polytherapy group had undergone decompression surgery for a Chiari Type 1 Malformation. Finally, one child within the polytherapy group had a history of traumatic brain injury preceding seizure onset. Within the surgery group, two children were diagnosed with ADHD, and both of these were taking stimulant medication. One child within the surgery group was noted to have a Chiari Type 1 Malformation, which was asymptomatic and had not been treated. Additionally, one child was diagnosed with OCD, and another child had a history of traumatic brain injury preceding seizure onset.

Seizure localization information was available on all children who had undergone video-EEG monitoring. Within the monotherapy group, three children were reported to have a bilateral frontal focus, one a left frontal focus, one a right frontal focus, one a bilateral temporal focus, one a left mesial temporal focus, three bilateral fronto-temporal, one right hemisphere focus, one child with left parietal-occipital and bifrontal foci, and four were found to have generalized seizure activity. One child in this group had not undergone any localization testing. Within the polytherapy group, two children were reported to have a bilateral frontal focus, one a left frontal focus, one left temporal focus, one bilateral fronto-temporal, one left hemisphere focus, one child with left parietal and right frontal foci, one child with a right posterior temporal-occipital focus, and five had generalized seizure activity. Two children in this group had not undergone localization testing. Within the surgery group, nine children underwent a right temporal lobectomy. Three of the children in the right temporal lobectomy group had been diagnosed with a brain tumor (2 ganglioglioma, 1 Dysembryoplastic Neuroepithelial tumor (DNET)). Two children were diagnosed with right mesial temporal sclerosis, and four children were noted to have

multifocal discharges within the temporal lobe, one of whom underwent a surgical revision 3 months after her initial surgery because of persistent seizures. Five children underwent a left temporal lobectomy all following diagnosis of a brain tumor (3 ganglioglioma, 1 astrocytoma, 1 DNET). No child diagnosed with a brain tumor had received adjuvant therapy prior to participating in this study.

Parents/guardians (the term parent will be used hereafter for simplicity) completed questionnaires on their children at both Times 1 and 2. Whenever possible, the same parent completed the questionnaires at both time points. At Time 1, 54 mothers, 7 fathers, and 1 grandmother completed the questionnaires. At time 2, 56 mothers, five fathers, and one grandmother completed the questionnaires. Three fathers and two mothers, who completed the questionnaires at Time 1, were unable to complete them at Time 2 due to work/time commitments. Additionally, one father was unable to complete the questionnaires at Time 2 due to neurological illness. In all of these cases, their spouse was able to complete the questionnaires at Time 2.

### *Experimental Design*

This study was approved by the Institutional Review Boards of Georgia State University (H08028) and CHOA (07-008). Both children and parents assented/consented prior to participating in this study. All children completed a neuropsychological screening (consisting of Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV, 2003;  $n = 24$ ) or Wechsler Abbreviated Scale of Intelligence (WASI, 1999;  $n = 38$ ) and California Verbal Learning Test-Children's Edition (CVLT-C, 1994)) and a parent completed the Behavior Assessment System for Children-Second Edition (BASC-2, 2004) and Behavior Rating Inventory of Executive Function (BRIEF, 2000) at Time 1. Between one and five years later ( $M = 1.83$ ,  $SD = 1.04$ ), at Time 2, a parent completed the Adaptive Behavior Assessment System-II (ABAS-II, 2003), BASC-2, and BRIEF as well as a seizure information form. All families were recruited through CHOA. Prior to contacting families, medical records were reviewed to determine study eligibility.

Eligible families were then contacted by telephone, and those who consented to participate completed the ABAS-II, BASC-2, and BRIEF. Three parents requested to complete the questionnaires over the phone because it was easier for them, and one because they were recovering from hand surgery. Completion of these questionnaires took approximately 45 minutes. Prior neuropsychological testing results were collected from participant's medical records in order to understand how these results related to children's current level of functioning. Previous testing results were collected for the following measures: (1) WISC-IV or WASI, (2) CVLT-C, (3) BASC-2, and (4) BRIEF.

Typically developing children were recruited through a database maintained on children who have previously served as comparison participants for other studies at CHOA. This database was examined to identify children who met the inclusion criteria for this study. These families were contacted by telephone, and, if they consented to participate, completed the ABAS-II, BASC-2, and BRIEF. As an incentive to participate, parents were offered a summary of their child's strengths and weaknesses based on the results of the questionnaires.

### *Measures*

#### *Adaptive Functioning*

The Adaptive Behavior Assessment System-II (Harrison & Oakland, 2003) was administered at Time 2 and is designed to assess whether an individual displays the functional skills necessary for age-appropriate daily living without the assistance of others. This measure includes a General Adaptive Composite (GAC), which is comprised of 3 domains: Conceptual, Social, and Practical. The Conceptual domain is comprised of the communication, functional academics, and self-direction skill areas, and assesses skills such as taking turns during conversations, reading menus at restaurants, and saving money to buy something special. The Social Domain is made up of the leisure and social skill areas and assesses behavior such as participating in an organized program for a sport or hobby, inviting others home for a fun activity, and offering assistance to others. The Practical Domain is comprised of the community use,

home living, health and safety, and self-care skill areas and assesses skills such as folding clean clothes, calling for help if someone is hurt, and tying one's shoes. The ABAS-II has numerous applications including diagnosis and classification, identification of adaptive strengths and weaknesses, as well as the identification of service needs and planning and monitoring of progress.

Although the few studies examining adaptive functioning in this population primarily have used the Vineland Adaptive Behavior Scales (VABS; Sparrow et al., 1984; Sparrow et al., 2005), the ABAS-II was chosen for this study for a number of reasons. The first is because of the better reliability of the ABAS-II as compared to the VABS-II. Internal consistency, test re-test reliability and inter-rater reliability are all higher for the ABAS-II (.97-.99, .90, .90 respectively) than for the VABS-II (.93-.97, .80, .75). The second is to increase the likelihood of participation. The ABAS-II is a parent-report questionnaire that takes less than 30 minutes to complete and can be completed at the parent's convenience, while the VABS-II is a survey form that takes approximately 60 minutes to complete and must be administered by a trained researcher. Additionally, the ABAS-II GAC has been shown to correlate significantly ( $r = .78$ ) with the Adaptive Behavior Composite of the VABS-II suggesting that there is substantial overlap in the construct they measure. The two measures cluster adaptive skills differently, but correlations among domains measuring similar content range from .60 to .74 for the age range of this study.

With respect to validity of the ABAS-II, factor analysis has confirmed the presence of a unified single factor of adaptive functioning (GAC) as well as a close-fitting three-factor model. Within a typically developing sample, the parent report version of the ABAS-II has been shown to correlate moderately with FSIQ on the WISC-IV ( $r = .41$ ). At the domain level, the Conceptual Domain is most highly correlated with FSIQ ( $r = .49$ ), followed by the Social Domain ( $r = .35$ ), and the Practical Domain ( $r = .28$ ). Similar correlations are reported for the WASI. Adaptive functioning was shown to be more highly correlated with FSIQ as assessed by the WISC-IV when using a mixed clinical sample. The correlation between FSIQ and ABAS-II GAC was



moderate ( $r = .58$ ), with performance on the Conceptual Domain most highly correlated with FSIQ ( $r = .63$ ), followed by the Practical Domain ( $r = .53$ ), and the Social Domain ( $r = .43$ ).

### *Learning and Memory*

The California Verbal Learning Test (CVLT) assesses the ability to encode information, store it, and later retrieve it. Participants completed the CVLT-Children's Version (CVLT-C; Delis et al., 1994) at Time 1. Learning Slope and the Long Delay Free Recall Trial were used to assess verbal learning and memory. List A of the CVLT-C is comprised of 15 words, with five words from each of 3 semantic categories. The Learning Slope quantifies the mean number of new words per trial that an examinee acquires across the five immediate recall trials of List A. This variable has been shown to be sensitive to certain types of memory impairment, such as a "flat learning curve" where performance on List A, Trial 1 is normal or close to normal, but few words are learned on subsequent trials (Luria, 1981 in Delis et al., 1994). The Long Delay Free Recall Trial is a measure of free recall after a 20 minute delay (filled with nonverbal testing).

On the CVLT-C, test-retest reliability is modest, ranging from .59 to .73 on the selected variables. These reliability coefficients are not surprising given the nature of the measure, as re-administration of the test within a short time (a median of 28 days) might allow children to build upon their learning from the initial administration. Factor analysis indicated that the multiple variables of the CVLT-C cluster into theoretically meaningful factors consistent with the constructs they were designed to measure. In children with epilepsy, performance on the CVLT-C has not been shown to differ significantly from typically developing children when seizures are well-controlled (Williams et al., 2001), but children whose seizures are poorly controlled show reduced overall learning relative to controls (Hernandez et al., 2003).

### *Attention*

List A, Trial 1 of the CVLT-C was used as a measure of attention. It is the first immediate recall trial of List A and is a measure of auditory attention span (Delis et al., 1994). It is a supraspan measure because participants are presented with more stimuli than the immediate

attention span can hold. This overload condition is believed to be especially sensitive to deficits in attention (Lezak et al., 2004).

### *Executive Functioning*

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) is a parent questionnaire assessing executive functioning behaviors in children 5-18 years old and was completed at Times 1 and 2. Executive functions are responsible for directing and managing cognitive, emotional, and behavioral functions which are typically involved in problem-solving behavior. For this study, parents completed the questionnaire, and the Behavioral Regulation (BRI) and Metacognition (MI) Indices and Global Executive Composite (GEC) were used. The BRI is a reflection of the child's ability to shift cognitive set and use inhibitory control to modulate emotions and behavior. This index is comprised of the Emotional Control, Shift, and Inhibit scales. The MI reflects a child's ability to initiate, plan, organize, and sustain future-oriented problem solving in working memory. This index is comprised of the Initiate, Working Memory, Plan/Organize, Monitor, and Organization of Materials scales. The BRIEF GEC assesses a child's ability to shift set, use inhibitory control to modulate emotions and behavior, and ability to initiate, plan, organize, and sustain future-oriented problem solving in working memory. Test-retest reliability is high, with coefficients in the mid to upper .80s for both indices and the composite.

There are two validity scales: the Inconsistency Scale examines the extent to which similar items are answered differently and the Negativity Scale examines the extent to which items are answered in an unusually negative manner. Scores on these two scales were examined to ensure test profiles were valid. Scores on the Inconsistency Scale were within acceptable limits. Scores on the Negativity Scale were elevated for 8 children (number of typically developing children = 0; monotherapy = 4; polytherapy = 2, surgery = 2; number of children with active seizures = 4, controlled seizures = 4), and consistent with the guidelines presented in the Users' Manual (Gioia et al., 2000), these children's profiles were reviewed

more closely and examined within the broader context of their previous neuropsychological assessment and any additional commentary from parents. In all cases, children were reported to be experiencing substantial levels of executive dysfunction, which was most likely the underlying reason for the elevation on this scale (Gioia et al., 2000), so their data were retained. Good convergent and divergent validity of the BRIEF scales has been demonstrated through correlations with scales from the Behavior Assessment System for Children-2, Child Behavior Checklist, and Conner's Rating Scale. Furthermore, the BRIEF has been shown to be highly correlated with an objective measure of executive functioning, the Delis-Kaplan Executive Function System, in children with epilepsy (Parrish et al., 2007). Factor analysis has confirmed the two factor model supporting the presence of the BRI and MI (Gioia et al., 2000).

### *Behavior Problems*

The Behavior Assessment System for Children-Second Edition (BASC-2; Reynolds & Kamphaus, 2004) measures many aspects of behavior and child personality. Parents completed the Parent Ratings Scale of the BASC-2 at Times 1 and 2. This study used the Externalizing and Internalizing Problems composite scores. The Externalizing Problems composite is comprised of the hyperactivity, aggression, and conduct problems scales, which are all characterized by disruptive behavior. The Internalizing Problems composite consists of the anxiety, depression, and somatization scales. Children with internalizing problems are likely to excessively monitor their own actions and to be excessively compliant, so their symptoms may be more likely to go unnoticed. At the scale level, T-scores in the 60-69 range are considered At-Risk, and T-scores of 70 or above are considered Clinically Significant. Test-retest reliability for the BASC-2 for the Internalizing and Externalizing Problems composites is typically in the mid .80s to low .90s for children and adolescents. Interrater reliabilities are in the high .60s to the high .70s. Symptoms of externalizing behaviors are usually more obvious than internalizing behaviors, which may account for slightly higher levels of interrater agreement on the Externalizing Behaviors composite. The validity of composite scores has been confirmed

through factor analysis. The BRIEF GEC correlates moderately to highly with parent-report of externalizing problems.

Validity of the report is assessed through an F index which assesses whether a parent rates their child in a highly negative fashion. Profiles with an F Index in the Caution or Extreme Caution range suggest that a negative response set may have skewed the results. A Consistency Index identifies cases where differing responses are given on questions typically answered similarly. Scores on these indices were examined, and all test profiles were found to be valid.

Recent research has suggested that parent-report measures of internalizing behavior problems that include a measure of physical symptoms may be erroneously elevated in chronically ill children with the potential for real physical complaints being mislabeled as reflecting psychosocial disturbance (Friedman et al., 2007). The Internalizing Problems composite of the BASC-2 is comprised of the somatization, anxiety, and depression scales. Prior to including the Internalizing Problems composite in our analyses, scores on the individual scales were examined to determine whether they were significantly elevated relative to norms and/or significantly more elevated than other scales on children's profiles according to critical values provided in the manual. Scores on this scale were not found to be significantly elevated relative to norms or scores on other scales of the Internalizing Problems composite. Therefore, the somatization scale was retained as part of the Internalizing Problems composite.

### *Intellectual Functioning*

Intellectual functioning was assessed for all participants in this study at Time 1. IQ was used for general description of cognitive functioning, but was not used as a predictor in the models. This was because of the greater theoretical interest in examining the predictive utility of specific constructs, rather than general measures of cognitive integrity, where it would be harder to tease apart the key ability (or abilities) accounting for significant findings. Furthermore, IQ has

been reported to be highly correlated with adaptive functioning, particularly in clinical samples (Harrison & Oakland, 2003).

Participants in this study were administered either the Wechsler Intelligence Scale for Children-IV (WISC-IV; Wechsler, 2003;  $n = 24$ ) or the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999;  $n = 38$ ). The WISC-IV provides a measure of general intellectual functioning as well as four composite scores for children: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed (PSI). This measure has 10 core subtests and can be administered to children from ages 6 years 0 months to 16 years 11 months. WISC-IV scores possess adequate test-retest reliability (Wechsler, 2003). Reliability coefficients are particularly robust for the four composite scores as well as the FSIQ. Factor analysis confirmed the existence of one core factor (FSIQ) as well as four factors (index scores). The WISC-IV FSIQ is highly correlated with both the FSIQ-4 ( $r = .83$ ) and FSIQ-2 ( $r = .86$ ) of the WASI. Subtest correlations range from the low to high .70s.

The WASI is a short and reliable measure that provides an estimate of an individual's general level of intellectual functioning. It consists of four subtests: Vocabulary, Block Design, Similarities, and Matrix Reasoning from which a Full Scale IQ-4 (FSIQ-4), VIQ, and PIQ can be generated. For children, test-retest reliability coefficients were .93, .94, and .96 for the VIQ, PIQ and FSIQ-4 respectively.

### *Seizure Variables*

In some analyses, participants were grouped according to their epilepsy status. The groups were: monotherapy, polytherapy, surgery, and typically developing. When group membership was examined as a predictor of adaptive functioning, group was treated as an ordinal variable with typically developing membership coded as 0, monotherapy as 1, polytherapy as 2, and surgery as 3. The following seizure and treatment variables were included in the analyses: age at seizure onset, amount of time elapsed since first seizure, active seizures, more severe epilepsy history, multiple medications, multiple seizure types, and

whether or not focal epilepsy surgery was performed. This information was collected from medical record review and a parent questionnaire (see Appendix B). Age at seizure onset was measured in months. The amount of time elapsed since first seizure was calculated by subtracting the date the Time 2 questionnaires were completed from the date of the participant's first known seizure and was measured in months. Active seizures was a dichotomous variable with 0 defined as no seizures in the past 12 months (controlled) and 1 defined as one or more seizures in the past 12 months (active; Fastenau et al., 2004).

Multiple medications was a continuous variable reflecting the number of medications a child was taking for the purpose of seizure control at Time 2. Multiple seizure types were entered in the model as a continuous variable that reflected the number of different seizure types a participant had experienced since being diagnosed with epilepsy. A value of 1 represented that a participant had only experienced one type of seizure, a value of two that a participant had experienced 2 different types of seizures and so on. Whether or not focal epilepsy surgery was performed was a dichotomous variable with 0 representing no surgical intervention and 1 representing that focal epilepsy surgery was conducted. All children in this study had their resections completed by the same neurosurgeon at CHOA.

Although researchers have created seizure severity scales to assess current seizure severity (e.g., Baker et al., 1998; Breau et al., 2008; Carpay et al., 1996), no scale could be identified that examined the cumulative effects of seizure history since the time of diagnosis in children. For this purpose, the Seizure History Scale (SHS; see Appendix A) was created to compare the severity of seizure history across participants. This measure is comprised of items that assess seizure frequency broadly, lifetime seizure types, lifetime history of status epilepticus, current number of AEDs, AED history, and surgical intervention for seizure control. The range of possible scores was 0 to 22, with higher numbers indicating more severe seizure history.

## Chapter 3

### RESULTS

Scores were converted to Standard Scores so that all data were on the same quantitative scale for ease of interpretation. Prior to conducting our analyses, the assumptions of regression were tested (Lewis-Beck, 1980). Data were visually inspected to ensure that a linear model was applicable. There was one outlier (an outlier was defined as a Standard Score of  $\leq 40$  or  $\geq 160$ ) on the BRIEF GEC (SS = 175). When the analyses were re-run without this participant, the results did not change appreciably, so this participant was retained in the analyses. The assumptions of homoskedasticity and that the residuals are approximately normally distributed were met. Correlation analyses were conducted with those measures chosen for inclusion in the models to confirm the absence of multicollinearity (see Tables 6-9). Age at seizure onset and the amount of time elapsed between seizure onset and completion of the parent questionnaires were found to be highly correlated ( $r = .72$ ;  $p < .001$ ), therefore the latter was dropped from our model. Descriptive statistics for BASC-2, BRIEF, and CVLT-C at Time 1 and the BASC-2, BRIEF, and ABAS at Time 2 are presented in Table 4.

For our first specific aim and the first two hypotheses of our second aim, linear regression analyses were used. For the remaining hypotheses of specific aim 2, mediation was tested. With a mediational model, there are a number of different pathways of interest (see Figures 1 & 2). The total effect, or  $c$  pathway, denotes the relationship between the independent variable (IV) and dependent variable (DV).  $c'$ , or the direct effect, refers to the effect of the IV on the DV after controlling for the mediator. The  $a$  pathway refers to the effect of the IV on the mediator and the  $b$  pathway to the effect of the mediator on the DV. The  $ab$  pathway, or indirect effect, is the product of the  $a$  and  $b$  pathways (also  $c - c'$ ). The significance of the  $ab$  pathway was tested according to Preacher and Hayes (2004; 2008), which calculates the direct and indirect effects similarly to the Baron and Kenny method, but affords greater statistical power through its use of bootstrap estimation (Mallinckrodt et al., 2006). Bootstrapping is a

Table 6. Correlation matrix between seizure and treatment variables at Time 2 and adaptive functioning.

	ABAS-II Conceptual	ABAS-II Practical	ABAS-II Social	Age at Seizure Onset	Active Seizures	Number of Current AEDs	Number of Past AEDs	Number of Seizure Types
ABAS-II Practical	.92**	-						
ABAS-II Social	.66**	.71**	-					
Age at Seizure Onset	.20	.16	.14	-				
Active Seizures	-.46**	-.43**	-.47**	-.12	-			
Number of Current AEDs	-.28	-.18	-.19	-.30*	.44**	-		
Number of Past AEDs	-.07	-.26	-.30	-.25	.26	.43**	-	
Number of Seizure Types	-.15	-.07	-.12	-.03	.14	-.03	.14	-
Temporal Lobe Surgery	.05	.03	.00	.41**	-.18	-.33*	-.12	-.13

Note. Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition; AEDs, Antiepileptic Drugs.

\* $p(\text{one-tailed}) < .05$ , \*\* $p(\text{one-tailed}) < .01$



Table 7. Correlation matrix for variables at Time 1.

	Group	Active Seizures	SHS	CVLT-C Trial 1	CVLT-C Learning Slope	CVLT-C Long Delay Free Recall	BASC-2 Internalizing	BASC-2 Externalizing
Active Seizures	.76**	-						
SHS	.83**	.86**	-					
CVLT-C Trial 1	-.46**	-.38	-.41*	-				
CVLT-C Learning Slope	.01	.00	-.01	.35*	-			
CVLT-C Long Delay Free Recall	-.29*	-.34*	-.37	.40**	-.28*	-		
BASC-2 Internalizing	.28*	.25*	.35*	.30*	.11	-.03	-	
BASC-2 Externalizing	.13*	.07	.07	-.04	-.20	-.05	.48**	-
BRIEF GEC	.35*	.28*	.31*	-.24*	-.16	-.18	.60**	.75**

*Note.* Active seizures denotes whether or not a child has had one or more seizures in the last year. Abbreviations: SHS, Seizure History Scale; CVLT-C, California Verbal Learning Test-Children's Version; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite.

\* $p(\text{one-tailed}) < .05$ , \*\* $p(\text{one-tailed}) < .001$ .

Table 8. Correlation matrix for variables at Time 2.

	Group	Active Seizures	SHS	BASC-2 Internalizing	BASC-2 Externalizing	BRIEF GEC	ABAS-II Conceptual	ABAS-II Social
Active Seizures	.07	-						
SHS	.62**	.77**	-					
BASC-2 Internalizing	.21*	.32*	.44**	-				
BASC-2 Externalizing	.23*	.15	.22*	.44**	-			
BRIEF GEC	.29*	.44**	.50**	.67**	.73**	-		
ABAS-II Conceptual	-.26*	-.54**	-.47**	-.42**	-.50**	-.70**	-	
ABAS-II Social	-.26*	-.43**	-.41*	-.45*	-.59**	-.60**	.80**	-
ABAS-II Practical	-.21	-.50**	-.40*	-.41**	-.44**	-.64**	.92**	.81**

*Note.* Group represents whether the child belongs to the Typically Developing, Monotherapy, Polytherapy, or Surgery group. Active seizures denotes whether or not a child has had one or more seizures in the last year. Abbreviations: SHS, Seizure History Scale; CVLT-C, California Verbal Learning Test-Children's Version; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite.

\* $p(\text{one-tailed}) < .05$ , \*\* $p(\text{one-tailed}) < .001$ .

Table 9. Correlation matrix between variables at Time 1 and Time 2.

		Time 2								
Time 1		Group	Active Seizures	SHS	BASC-2 Internalizing	BASC-2 Externalizing	BRIEF GEC	ABAS-II Conceptual	ABAS-II Social	ABAS-II Practical
		Group	.71**	.59**	.78**	.37*	.21	.41**	-.42**	-.32*
	Active Seizures	.74**	.42**	.65**	.24*	.13	.36*	-.31	-.19	-.20
	SHS	.71**	.53**	.86**	.39*	.17	.40*	-.34*	-.28*	-.26*
	CVLT-C Trial 1	-.40**	-.40**	-.43**	-.36*	-.09	-.31	.30*	.12	.29*
	CVLT-C Learning Slope	.06	.16	.09	.02	-.14	-.03	-.13	-.03	-.08
	CVLT-C Long Delay Free Recall	-.34*	.01	-.28*	-.24	-.08	-.21	.20	.07	.19
	BASC-2 Internalizing	.24*	.34*	.41**	.69**	.41**	.60**	-.43**	-.42**	-.42**
	BASC-2 Externalizing	.08	.18	.19	.28*	.73**	.59**	-.46**	-.19	-.42**
	BRIEF GEC	.17	.39*	.40*	.45**	.59**	.78**	-.69**	-.51**	-.65**

*Note.* Group at Time 1 represents whether the child belongs to the Typically Developing, Monotherapy, or Polytherapy group. Group at Time 2 represents whether the child belongs to the Typically Developing, Monotherapy, Polytherapy, or Surgery group. Active seizures denotes whether or not a child has had one or more seizures in the last year. Abbreviations: SHS, Seizure History Scale; CVLT-C, California Verbal Learning Test-Children's Version; BASC-2, Behavior Assessment

System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite; ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.

\* $p(\text{one-tailed}) < .05$ , \*\* $p(\text{one-tailed}) < .001$ .

nonparametric approach to hypothesis testing that can be used with small samples with greater confidence than the Baron and Kenny method. The number of bootstrap samples was set to 20,000 (Preacher & Hayes, 2008) meaning that 20,000 samples of our  $n$  of 62 were taken and the  $ab$  pathway was calculated for each. The mean of the 20,000  $ab$  pathways was then used to calculate confidence intervals. When zero is not within the confidence interval, the null hypothesis that the  $ab$  pathway is not significantly different from zero can be rejected. Bias corrected and accelerated 95% confidence intervals were used.

### *Primary Analyses*

#### **Aim 1: Establish how epilepsy and treatment variables were related to adaptive functioning.**

Hypothesis 1: More severe epilepsy history was hypothesized to be negatively related to adaptive functioning.

To examine the cumulative and interactive effects of seizure and treatment severity, three regressions were conducted with the SHS as the independent variable and the three domains of the ABAS-II as the dependent variables. This measure was able to explain 10%, 8%, and 8% of the variance in the Conceptual ( $b = -1.58$ ,  $SE = .74$ ,  $p$  (one-tailed) = .02), Social ( $b = -1.63$ ,  $SE = .85$ ,  $p$  (one-tailed) = .03), and Practical ( $b = -1.64$ ,  $SE = .83$ ,  $p$  (one-tailed) = .03) domains.

Hypothesis 2: Longer amount of time elapsed since first seizure, younger age at seizure onset, active seizures, multiple medications, and multiple seizure types were predicted to be negatively associated with independent living skills.

Hypothesis 3: Focal epilepsy surgery was hypothesized to be positively related to adaptive functioning.

Linear regressions were conducted to examine the relationship between seizure and treatment variables and adaptive functioning. Age at seizure onset, active seizures, multiple medications, multiple seizure types, and whether or not focal epilepsy surgery was performed.

were entered as independent variables. This model was run with the 3 different domains of the ABAS-II as dependent variables: Conceptual, Social, and Practical scores. The model was able to explain 28%, 26%, and 23% of the variance across the three domains. Active seizures emerged as the only significant predictor of adaptive functioning across domains, with active seizures associated with lower adaptive functioning (see Table 10 and Figure 3). The active seizures variable was uniquely able to explain 14%, 9%, and 15% of the variance across the three domains.

**Aim 2: Establish the strongest neuropsychological predictors of adaptive functioning and whether neuropsychological functioning mediated the relationship between seizure and treatment variables and adaptive functioning.**

Hypothesis 1: Attention (CVLT-C Trial 1), verbal learning (CVLT-C Learning Slope), and verbal memory (CVLT-C Long Delay Free Recall) at Time 1 were proposed to be positively related to adaptive functioning (ABAS-II Conceptual, Social, and Practical domains) at Time 2. Executive dysfunction (BRIEF BRI and MI) was hypothesized to be negatively associated with adaptive functioning at Time 2.

Due to the high correlation between the BRI and MI ( $r = .79, p < .001$ ) of the BRIEF, the composite score (BRIEF GEC) was used instead. Linear regression analyses were used. The BRIEF GEC was a significant predictor of adaptive functioning across domains with greater executive dysfunction associated with reduced adaptive functioning (see Table 11). The BRIEF GEC was uniquely able to explain 45%, 26%, and 39% of the variance across the three domains. Learning Slope from the CVLT-C was a significant predictor on the Conceptual and Practical domains explaining 6% and 3% of the variance respectively, and was positively related to adaptive functioning. The overall model was able to explain 55%, 28%, and 48% of the variance across the Conceptual, Social, and Practical domains respectively.

Hypothesis 2: Behavior problems (BASC-2 Internalizing and Externalizing Problems) at Time 1 were predicted to be negatively associated with independent living skills at Time 2.

Table 10. Unstandardized b coefficients (standard error) showing the ability of seizure variables to predict the three domains of the ABAS-II.

	Conceptual	Social	Practical
Age at Seizure Onset	.08 (.06)	.07 (.06)	.06 (.07)
Active Seizures	-16.18 (5.94)**	-12.84 (5.95)*	-18.87 (7.05) **
Number of Current AEDs	-4.37 (4.75)	-1.60 (4.75)	2.79 (5.64)
Number of Past AEDs	1.43 (1.43)	-1.70 (1.43)	-1.77 (1.69)
Number of Seizure Types	-2.39 (2.52)	-.76 (2.53)	0.10 (3.00)
Temporal Lobe Surgery	-6.57 (6.50)	-9.48 (6.51)	-4.70 (7.72)

Note. Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition; AEDs, Antiepileptic Drugs.

\*  $p(\text{one-tailed}) \leq .05$  \*\* $p(\text{one-tailed}) \leq .01$

Figure 3.

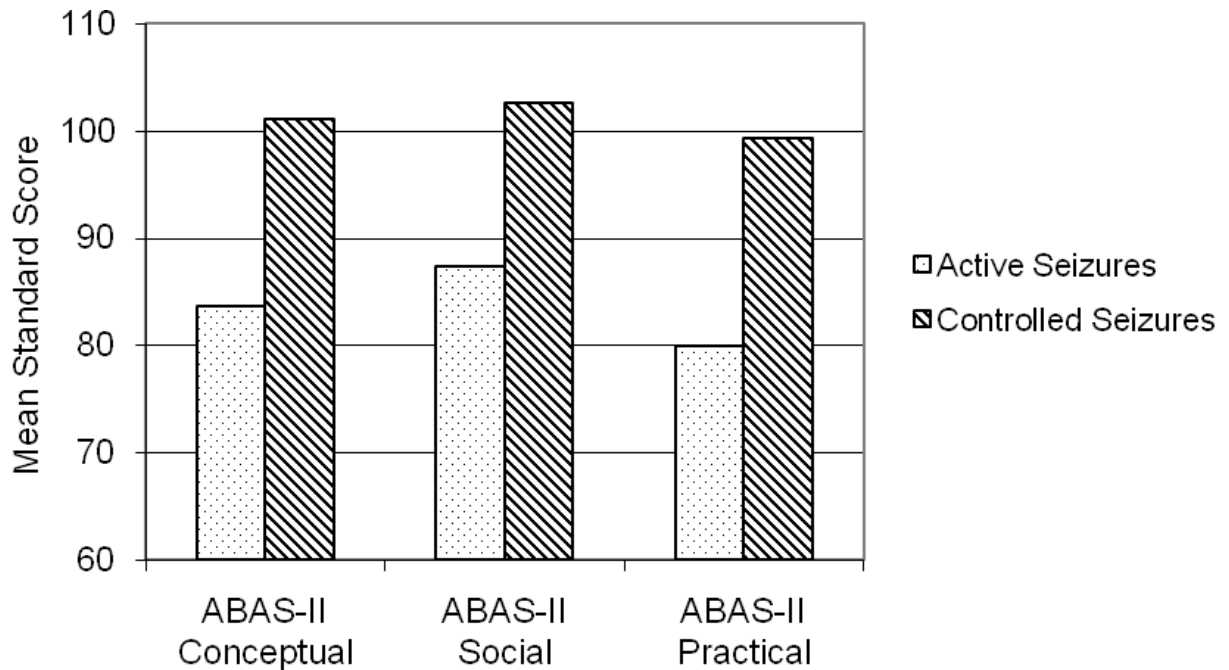


Figure 3. Bar graph showing the differences in adaptive functioning according to whether seizures are active ( $n = 26$ ) or controlled ( $n = 20$ ).

*Note.* Active seizures denotes whether or not a child has had one or more seizures in the last year. Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition.



Table 11. Unstandardized b coefficients (standard error) showing the ability of neuropsychological variables to predict the three domains of the ABAS-II.

	Conceptual	Social	Practical
CVLT-C Trial1	-.06 (.15)	-.10 (.19)	.01 (.18)
CVLT-C Learning Slope	-.31 (.11)**	-.16 (.14)	-.25 (.14)*
CVLT-C Long Delay Free Recall	.15 (.10)	.04 (.12)	.13 (.12)
<b>BRIEF GEC</b>	<b>-.62 (.08)**</b>	<b>-.46 (.10)**</b>	<b>-.64 (.10)**</b>

*Note.* Abbreviations: ABAS-II, Adaptive Behavior Assessment System 2<sup>nd</sup> Edition; CVLT-C, California Verbal Learning Test-Children's Version; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite.

\*  $p(\text{one-tailed}) \leq .05$  \*\* $p(\text{one-tailed}) \leq .01$

Linear regression analyses were used to determine the extent to which behavior problems were able to predict adaptive functioning. Internalizing Problems significantly predicted the Conceptual ( $b = -.31$ ,  $SE = .14$ ,  $p$  (one-tailed) = .02,  $r^2 = .06$ ), Social ( $b = -.32$ ,  $SE = .14$ ,  $p$  (one-tailed) = .01,  $r^2 = .07$ ), and Practical ( $b = -.35$ ,  $SE = .16$ ,  $p$  (one-tailed) = .02,  $r^2 = .06$ ) domains. Similarly, Externalizing Problems significantly predicted the Conceptual ( $b = -.38$ ,  $SE = .15$ ,  $p$  (one-tailed) = .01,  $r^2 = .08$ ), Social ( $b = -.31$ ,  $SE = .15$ ,  $p$  (one-tailed) = .02,  $r^2 = .06$ ), and Practical ( $b = -.37$ ,  $SE = .17$ ,  $p$  (one-tailed) = .02,  $r^2 = .06$ ) domains. Overall, the model was able to explain 27%, 24%, and 24% of the variance respectively.

Hypothesis 3: Based on the results of hypotheses 1 and 2, verbal learning (CVLT-C Learning Slope), executive functioning (BRIEF GEC), and behavior problems (BASC-2 Behavior Problems Composite) at Time 1 were predicted to mediate the relationship between SHS scores at Time 1 and adaptive functioning at Time 2 (see Figure 1a). Furthermore, this relationship was hypothesized to persist when neuropsychological functioning and SHS scores at Time 2 (both when SHS scores at Time 1 were controlled for and when SHS scores were not controlled for) were used (see Figure 1b).

In light of the large number of potential mediational models (18) and the resulting increased risk of finding an effect purely by chance, the decision was made to test each proposed mediational model with the General Adaptive Composite (GAC) of the ABAS-II as the dependent variable first. If a significant indirect effect was found, the model was then tested with each of the three domains. If no significant indirect effect was found, testing of that model was discontinued. Prior to testing the significance of the indirect effect, the correlations between the independent variable and the mediators were examined (see Table 7). Learning Slope was found to be non-significantly correlated with SHS ( $r = -.01$ ), and, therefore, was dropped from the model. Owing to the significant correlation between Externalizing and Internalizing Problems of the BASC-2 ( $r = .48$ ,  $p$ (one-tailed) < .001 at Time 1 and  $r = .44$ ,  $p$ (one-tailed) < .001 at Time 2), the decision was made to combine the two scales into a Behavior Problems

Composite when testing for mediation to reduce the likelihood of suppression: the indirect effects remained non-significant when both scales were entered as mediators, but there was evidence of suppression as the relationships between some variables were in the direction opposite to previous research of these constructs. In light of greater theoretical interest in examining the independent contributions of measures of executive functioning and behavior problems in explaining the relationship between seizure history and adaptive functioning and the high correlations between the BASC-2 and the BRIEF, the decision was made to examine the significance of the indirect effects of executive functioning while controlling for behavior problems and vice versa.

Controlling for behavior problems, the *c* pathway, or total effect, between SHS scores at Time 1 and the ABAS-II GAC and three adaptive domains was significant (see Table 12), but when the mediator, executive functioning at Time 1, was introduced, SHS scores dropped from significance (*c'*). The *ab* pathway was significant with 95% confidence intervals that indicated that the coefficient for this pathway was significantly different from zero. Thus, there was full mediation of the relationship between SHS scores at Time 1 and adaptive functioning at Time 2 by executive functioning at Time 1. Similarly, when the model was re-run with SHS scores and executive functioning at Time 2, the *ab* pathway was significant, indicating full mediation of the relationship between SHS scores and adaptive functioning by executive functioning at Time 2. Mediation was not evident, however, for the Social domain, as there was not a notable change from *c* to *c'* when executive functioning was entered into the model. The model was also run controlling for SHS scores at Time 1, in order to test whether the relationship between changes in SHS scores and adaptive functioning was also mediated by executive functioning. For this model, partial mediation was evident for both the ABAS-II GAC and the Practical domain. Partial mediation occurs when there is a drop from *c* to *c'*, but *c'* prime continues to be significant. Full mediation was found for the conceptual domain. Behavior problems were not found to mediate

Table 12. Coefficients (standard errors) for mediation with the Seizure History Scale (SHS) as the Independent Variable at either Time 1 or Time 2 (both when Time 1 scores on the SHS are controlled for and when they were not).

Time	Mediator	DV	a	b	c	c'	ab	Confidence Intervals for ab
<u>1</u>	BRIEF	GAC	.76 (.35)*	-.59 (.16)**	-.86 (.46)*	-.41 (.43)	-.44 (.20)	-.87 to -.09
		Conceptual	.76 (.35)*	-.59 (.14)**	-.96 (.43)*	-.50 (.39)	-.45 (.19)	-.85 to -.11
		Social	.76 (.35)*	-.26 (.16)	-.65 (.44)	-.46 (.45)	-.18 (.12)	-.58 to -.03
		Practical	.76 (.35)*	-.76 (.35)*	-.66 (.51)	-.12 (.46)	-.55 (.26)	-1.11 to -.09
	BASC-2	GAC	.02 (.24)	.00 (.22)	-.48 (.40)	-.48 (.40)	.00	-.12 to .11
<u>2</u>	BRIEF	GAC	.87 (.29)**	-.55 (.18)**	-1.12 (.41)**	-.64 (.41)	-.48 (.23)	-1.07 to -.13
		Conceptual	.87 (.28)**	-.63 (.16)**	-1.16 (.40)**	-.61 (.38)	-.55 (.23)	-1.12 to -.19
		Social	.87 (.28)*	-.12 (.17)	-.84 (.37)*	-.73 (.40)*	-.10 (.16)	-.49 to .15
		Practical	.87 (.29)**	-.67 (.20)**	-1.01 (.47)*	-.43 (.47)	-.59 (.29)	-1.34 to -.16
	BASC-2	GAC	-.06 (.23)	-.03 (.23)	-.53 (.39)	-.53 (.40)	.00 (.06)	-.11 to .13
<u>2 controlling for Time 1</u>	BRIEF	GAC	1.10 (.52)*	-.53 (.18)**	-1.94 (.73)**	-1.35 (.71)*	-.59 (.33)	-1.46 to -.12

Time	Mediator	DV	a	b	c	c'	ab	Confidence Intervals for ab
2 controlling for Time 1	BRIEF	Conceptual	1.10 (.52)*	-.62 (.16)**	-1.75 (.71)*	-1.06 (.66)	-.68 (.32)	-1.53 to -.20
		Social	1.10 (.52)*	-.11 (.17)	-1.57 (.66)**	-1.45 (.69)*	-.11 (.21)	-.67 to .22
		Practical	1.10 (.52)*	-.65 (.20)**	-2.07 (.84)**	-1.36 (.80)*	-.74 (.41)	-1.81 to -.15
	BASC-2	GAC	-.21 (.41)	-.05 (.23)	-1.25 (.70)*	-1.26 (.70)	.00 (.10)	-.14 to .28

Note. When the BRIEF was examined as a mediator, performance on the BASC-2 was controlled for, and when the BASC-2 was examined as a mediator, performance on the BRIEF was controlled for. See Figures 1 and 2 for an illustration of pathways. Pathway a represents the path from SHS to BASC-2 or BRIEF. Pathway b denotes the path between BASC-2 or BRIEF and adaptive functioning (Adaptive Behavior Assessment System-II GAC and domains). Pathway c represents the path from SHS to adaptive functioning, while pathway c' represents the pathway from SHS to adaptive functioning controlling for BASC-2 or BRIEF scores. Pathway ab denotes the pathway from SHS to BASC-2 or BRIEF to adaptive functioning. Abbreviations: DV, Dependent Variable; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite; GAC, General Adaptive Composite.

\**p* (one-tailed) ≤ .05 \*\**p* (one-tailed) ≤ .01

the relationship between SHS scores and adaptive functioning at either Time 1 or Time 2 (see Table 12).

Hypothesis 4: Verbal learning (CVLT-C Learning Slope), executive functioning (BRIEF GEC), and behavior problems (BASC-2 Behavior Problems Composite) at Time 1 were predicted to mediate the relationship between Group at Time 1 and adaptive functioning at Time 2 (see Figure 2a). Furthermore, this relationship was hypothesized to persist when examining neuropsychological functioning and Group at Time 2 (both when Group at Time 1 was controlled for and when it was not; see Figure 2b).

As with hypothesis 3, each model was tested first with the ABAS-II GAC as the DV, and only if the indirect effect was significant did testing of the model continue at the domain level. Prior to testing the significance of the indirect effect, the correlations between the IV and the mediators were examined. Learning Slope was found to be non-significantly correlated with Group ( $r = .01$ ), and, therefore, was dropped from the model. As with the above model, when executive functioning was tested as a mediator, behavior problems were controlled for and vice versa.

Controlling for behavior problems, the c pathway, or total effect, between group membership at Time 1 and the ABAS-II GAC and Conceptual and Practical domains was significant (see Table 13), but when the mediator, executive functioning at Time 1, was introduced, this relationship (c') dropped from significance (ABAS-II GAC and the Practical domain) or remained significant but was substantially reduced in size (the Conceptual domain). The ab pathway was significant with 95% confidence intervals that indicate that the coefficient for this pathway was significantly different from zero. Thus, there was full mediation of the relationship between Group at Time 1 and scores on the ABAS-II GAC and Practical domain at Time 2 by executive functioning at Time 1. There was partial mediation of the relationship between Group at Time 1 and scores on the Conceptual domain at Time 2 by executive functioning at Time 1. Executive functioning at Time 2 did not mediate the relationship between

Table 13. Coefficients (standard errors) for mediation with Group as the IV at either Time 1 or Time 2 (both when Time 1 group membership is controlled for and when it was not).

Time	Mediator	DV	a	b	c	c'	ab	Confidence Intervals for ab
<u>1</u>	BRIEF	GAC	5.37 (2.14)**	-.55 (.16)**	-7.25 (2.77)**	-4.28 (2.66)	-2.90 (1.31)	-6.12 to -.84
		Conceptual	5.37 (2.14)**	-.56 (.14)**	-7.72 (2.57)**	-4.69 (2.41)*	-3.03 (1.32)	-6.10 to -.84
		Social	5.37 (2.14)**	-.23 (.16)	-5.08 (2.69)*	-3.82 (2.80)	-1.11 (.99)	-4.26 to .03
		Practical	5.37(2.14)**	-.67 (.17)**	-6.45 (3.06)*	-2.85 (2.87)	-3.52 (1.57)	-7.07 to -.89
	BASC-2	GAC	-.67 (1.54)	-.02 (.22)	-4.54 (2.55)*	-4.56 (2.57)	.14 (.49)	-1.41 to .85
<u>2</u>	BRIEF	GAC	1.39 (1.39)	-.63 (.17)**	-2.37 (1.96)	-1.50 (1.78)	-.89 (.91)	-2.90 to .76
	BASC-2	GAC	.35 (1.01)	-.01 (.23)	-1.51 (1.76)	-1.50 (1.77)	-.01 (.24)	-.63 to .43
<u>2 controlling for Time 1</u>	BRIEF	GAC	-1.02 (1.89)	-.59 (.17)**	.84 (2.68)	.24 (2.46)	.64 (1.08)	-1.23 to 3.12
	BASC-2	GAC	-.50 (1.37)	-.02 (.23)	-.12 (2.39)	-.11 (2.41)	.02 (.27)	-.77 to .44

*Note.* Group at Time 1 represents whether the child belongs to the Typically Developing, Monotherapy, or Polytherapy group. Group at Time 2 represents whether the child belongs to the Typically Developing, Monotherapy, Polytherapy, or Surgery group. When the BRIEF was examined as a mediator, performance on the BASC-2 was controlled for, and when the BASC-2 was examined as a mediator, performance on the BRIEF was controlled for. See Figures 1 and 2 for an illustration of pathways. Pathway a represents the path from Group to BASC-2 or BRIEF. Pathway b denotes the path between BASC-2 or BRIEF and adaptive functioning (Adaptive Behavior Assessment System-II GAC and domains). Pathway c represents the path from Group to adaptive functioning, while pathway c' represents the pathway from Group to adaptive functioning controlling for BASC-2 or BRIEF scores. Pathway ab denotes the pathway from Group to BASC-2 or BRIEF to adaptive functioning. Abbreviations: DV, Dependent Variable; BASC-2, Behavior Assessment System for Children 2<sup>nd</sup> Edition; BRIEF, Behavior Rating Inventory of Executive Functioning; GEC, Global Executive Composite; GAC, General Adaptive Composite.

\* $p(\text{one-tailed}) \leq .05$  \*\* $p(\text{one-tailed}) \leq .01$



Group at Time 2 and adaptive functioning at Time 2 either when controlling for Group at Time 1 or when not controlling for prior group membership. Controlling for executive functioning, behavior problems did not serve as a mediator of the relationship between group and adaptive functioning at either Time 1 or Time 2 (see Table 13) suggesting the unique importance of executive functioning.

### *Supplementary Analyses*

A strong relationship was found between executive and adaptive functioning, with executive functioning mediating the impact of seizure history on adaptive functioning. This raised the question of whether this strong relationship between executive and adaptive functioning was present only in typically developing children, only in children with epilepsy or both. We hypothesized that the relationship between executive functioning and adaptive functioning at both Times 1 and 2 would be moderated by an epilepsy variable indicating whether or not the child had ever experienced a seizure such that the relationship between adaptive and executive functioning would be stronger for children with epilepsy.

Prior to the creation of interaction terms, executive functioning was mean centered for both Times 1 and 2 (Holmbeck, 2002). At Time 1, executive functioning ( $B = -.56$ ,  $SE = .09$ ,  $p$  (*one-tailed*)  $< .001$ ) was significantly associated with the ABAS-II GAC, but seizure status was not ( $B = -6.68$ ,  $SE = 4.56$ ,  $p$  (*one-tailed*)  $= .08$ ). The interaction term was not significant ( $B = -.05$ ,  $SE = .34$ ,  $p$  (*one-tailed*)  $= .45$ ). At Time 2, executive functioning ( $B = -.64$ ,  $SE = .10$ ,  $p$  (*one-tailed*)  $< .001$ ) was significantly associated with the ABAS-II GAC, but seizure status was not ( $B = -2.99$ ,  $SE = 4.56$ ,  $p$  (*one-tailed*)  $= .27$ ). The interaction term for this model was significant ( $B = -.57$ ,  $SE = .28$ ,  $p$  (*one-tailed*)  $= .02$ ;  $R^2_{\Delta} = .04$ ) with executive functioning better predicting adaptive functioning for the children with epilepsy ( $B = -.73$ ,  $SE = .11$ ,  $p$  (*one-tailed*)  $< .001$ ), versus typically developing children ( $B = -.16$ ,  $SE = .25$ ,  $p$  (*one-tailed*)  $= .26$ ). It should be noted that higher scores on the BRIEF are indicative of more difficulties with executive functioning, while higher adaptive scores indicate better adaptive functioning (see Figure 4).

Figure 4.

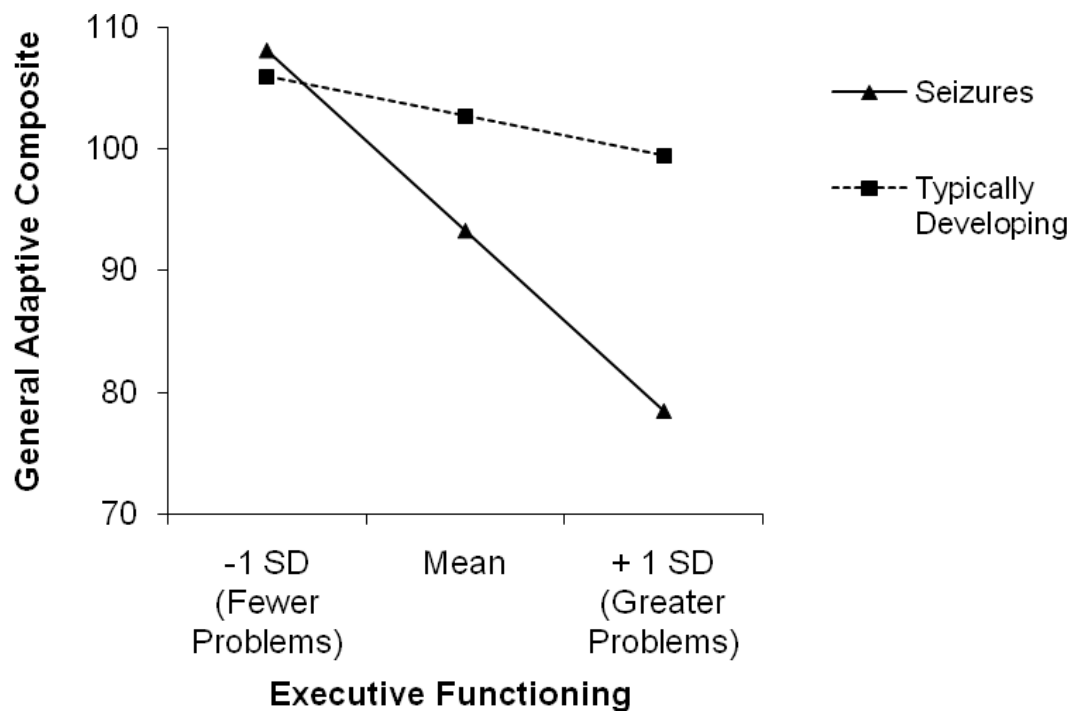


Figure 4. Regression lines for the relationship between executive functioning and adaptive functioning as moderated by whether children have epilepsy or are typically developing (a 2-way interaction).

*Note.* Seizures  $b = -.73$ ; Typically Developing  $b = -.16$ . Abbreviations: SD, standard deviation.

In light of significantly higher intellectual functioning in the typically developing group as compared to the children with epilepsy, the above models were re-run controlling for intellectual functioning to confirm that the stronger relationship between executive and adaptive functioning was not simply due to the lower level of functioning in children with epilepsy. The results were similar. For Time 1, intellectual functioning was entered in step 1 and found to be significantly predictive of the ABAS-II GAC ( $B = .49$ ,  $SE = .12$ ,  $p$  (one-tailed)  $< .001$ ). Entered at step 2, executive functioning ( $B = -.51$ ,  $SE = .09$ ,  $p$  (one-tailed)  $< .001$ ) was significantly associated with the ABAS-II GAC, but seizure status was not ( $B = -1.44$ ,  $SE = 5.04$ ,  $p$  (one-tailed)  $= .39$ ). The interaction term was not significant ( $B = .07$ ,  $SE = .33$ ,  $p$  (one-tailed)  $= .42$ ). At Time 2, intellectual functioning ( $B = -.64$ ,  $SE = .10$ ,  $p$  (one-tailed)  $< .001$ ) and executive functioning ( $B = -.59$ ,  $SE = .11$ ,  $p$  (one-tailed)  $< .001$ ) were significantly associated with the ABAS-II GAC, but seizure status was not ( $B = -.50$ ,  $SE = 5.09$ ,  $p$  (one-tailed)  $= .46$ ). The interaction term for this model was significant ( $B = -.54$ ,  $SE = .27$ ,  $p$  (one-tailed)  $= .03$ ;  $R^2_{\Delta} = .03$ ) with executive functioning better predicting adaptive functioning for the children with epilepsy ( $B = -.67$ ,  $SE = .11$ ,  $p$  (one-tailed)  $< .001$ ), versus typically developing children ( $B = -.13$ ,  $SE = .25$ ,  $p$  (one-tailed)  $= .30$ ).

Across measures, there was less variability in performance in the typically developing group. To help clarify whether this reduced range was the reason for the finding of moderation, this model was also tested with internalizing and externalizing behavior problems from the BASC-2, which evidenced similar rates of variability compared to the BRIEF GEC. The interaction terms for Internalizing (T1  $B = -.49$ ,  $SE = .61$ ,  $p$  (one-tailed)  $= .22$ ; T2  $B = -.09$ ,  $SE = .46$ ,  $p$  (one-tailed)  $= .43$ ) and Externalizing (T1  $B = .19$ ,  $SE = .61$ ,  $p$  (one-tailed)  $= .38$ ; T2  $B = .001$ ,  $SE = .40$ ,  $p$  (one-tailed)  $= .50$ ) Behavior Problems were not significant at either time point indicating that the relationship between behavior problems and adaptive functioning did not differ according to whether or not a child had been diagnosed with epilepsy.

Given the predictive utility of the active seizures variable, we further hypothesized that the relationship between executive and adaptive functioning would be stronger for children with active seizures as they would be at greater risk of both executive and adaptive dysfunction as compared to children with controlled seizures. At Time 1, executive functioning ( $B = -.56$ ,  $SE = .10$ ,  $p$  (one-tailed)  $< .001$ ) was significantly associated with the ABAS-II GAC, but the active seizures variable was not ( $B = 8.47$ ,  $SE = 9.42$ ,  $p$  (one-tailed)  $= .19$ ). The interaction term was not significant ( $B = .19$ ,  $SE = .45$ ,  $p$  (one-tailed)  $= .35$ ). At Time 2, executive functioning ( $B = -.65$ ,  $SE = .11$ ,  $p$  (one-tailed)  $< .001$ ) and the active seizures variable ( $B = -10.43$ ,  $SE = 4.25$ ,  $p$  (one-tailed)  $= .01$ ) were significantly associated with the ABAS-II GAC. The interaction term was not significant ( $B = .30$ ,  $SE = .22$ ,  $p$  (one-tailed)  $= .10$ ) indicating that the relationship between executive and adaptive functioning is not altered by whether children have active or controlled seizures.

## Chapter 4

### DISCUSSION

The overarching aim of this study was to identify the seizure, treatment, and neuropsychological variables associated with adaptive functioning in children with epilepsy to not only better characterize adaptive functioning in this population, but also to aid in the identification of children with epilepsy at risk of suboptimal adaptive functioning. The findings from the first specific aim suggest that more severe history of epilepsy, as evidenced by the cumulative and interactive effects of active seizures, higher numbers of current and past AEDs, more seizure types, and surgical intervention, is associated with reduced adaptive functioning. With respect to the ability of specific seizure and treatment variables to predict adaptive capabilities, this study showed that children who have had one or more seizures in the past year are at greater risk of suboptimal adaptive functioning according to parent-report. Inconsistent with what was hypothesized, and somewhat surprisingly, no other specific seizure and treatment variables were significantly associated with adaptive functioning.

The findings from the second specific aim indicate that verbal learning, behavior problems, and executive functioning were significant neuropsychological predictors of later adaptive functioning. Executive functioning and behavior problems were tested as mediators of the relationship between seizure severity and adaptive functioning. Mediation was confirmed for executive functioning only, suggesting that seizure severity affects executive functioning abilities, which, in turn, affect adaptive skills. This means that children with a more severe history of epilepsy are at greater risk of executive deficits, and that more executive dysfunction places children at greater risk of adaptive deficits. A further hypothesis postulated that executive functioning and behavior problems would mediate the relationship between group membership and adaptive functioning. This hypothesis was only supported for executive functioning at Time 1 mediating the relationship between group at Time 1 and adaptive functioning at Time 2. This indicated that group membership has a weaker influence on executive functioning abilities than seizure severity, and may be a reflection of the grouping variable being a poor way of classifying seizure status. This finding also may indicate the greater importance of seizure status over treatment (i.e., monotherapy, polytherapy) group.

Forty-four percent of eligible families participated in this study, and this sample of 62 was, for the most part, representative of the larger pool of potential participants. There were, however, some significant differences at Time 1 between children who participated and those who did not. Children treated with monotherapy who participated in the study were more likely to have active seizures and fewer executive problems, than children who did not. Children who were treated with polytherapy and participated in the study had a significantly younger age at seizure onset than those who did not participate. Among typically developing children, those who participated in the study had more externalizing and executive difficulties than those who did not, but mean scores for both groups on these measures remained within normal limits. Overall, this indicates that the families who participated in this study were a representative sample, however, the higher incidence of active seizures at Time 1 for monotherapy participants

and the earlier age at seizure onset for polytherapy participants suggests that children with more severe epilepsy histories may have been more likely to participate. Nevertheless, there were no significant differences between those who participated and those who did not with respect to IQ and performance on the CVLT-C, and minimal differences on the BASC-2 and BRIEF suggesting similar levels of functioning regardless of participation status.

Among those who participated, significant between group differences on some demographic variables were noted. The surgery group was significantly older than the monotherapy, polytherapy, and typically developing groups at the time the parent questionnaires were completed. There was a significantly longer amount of time between Times 1 and 2 for children in the monotherapy ( $M = 2.08$ ,  $SD = .78$  years) and surgery ( $M = 2.69$ ,  $SD = 1.58$  years) groups as compared to the polytherapy ( $M = 1.37$ ,  $SD = .43$  years) and typically developing groups ( $M = 1.25$ ,  $SD = .31$  years). Although early surgical intervention for intractable seizures is becoming increasingly popular, the older age of the surgery group likely reflects the more prevalent view that surgery is a last-resort treatment (Sheth et al., 2000). Age at seizure onset was significantly older for the surgery group compared to the typically developing group, with children in the surgery group having their first seizure when they were approximately 4 years older than children in the polytherapy group. Nevertheless, the duration of epilepsy was similar across all three groups: monotherapy ( $M = 7.69$  years,  $SD = 4.13$ ), polytherapy ( $M = 8.34$  years,  $SD = 3.84$ ), and surgery ( $M = 6.94$  years,  $SD = 5.31$ ). Socioeconomic status (SES) was significantly greater for the typically developing group compared to the monotherapy and surgery groups, however, mean SES was above the midpoint of the scale for all groups. The surgery group was comprised of significantly more Caucasians than African Americans compared to the typically developing group. This may result from a number of potential factors including hospital demographics and racial disparities in access to healthcare, healthcare information, and parent advocacy regarding their child's treatment. Participants in the polytherapy group were significantly more likely to be left-handed

than typically developing children, which may reflect greater neurological disruption and/or reorganization in this group. Finally, all three epilepsy groups were more likely to have an Individualized Education Plan in place compared to the typically developing group. This is consistent with research showing that children with epilepsy are at risk of reduced academic achievement (Bailet & Turk, 2000; Caplan et al., 2004; Tromp et al., 2004). Overall, these demographic differences are likely to reflect real differences between groups on these variables.

Consistent with other studies examining adaptive functioning in epilepsy (Chapieski et al., 2005; Culhane-Shelburne et al., 2002), children with epilepsy in this study were found to be functioning in the lower end of the average to the low average range overall with respect to the mastery of age-appropriate independent living skills. Between one third and three quarters of children with epilepsy were functioning below the 25<sup>th</sup> percentile on adaptive functioning domains, suggesting that while mean scores are not that poor, a significant percentage of children are functioning below the average range. For the typically developing group, performance was in the average range across domains, with 25% or fewer children functioning below the 25<sup>th</sup> percentile across domains. At the domain level, there was a weak trend for children across both the epilepsy and typically developing groups to be functioning at a lower level relative to normative data on the ABAS-II Practical Domain, which includes skills such as folding clean clothes, calling for help if someone is hurt, and tying one's shoes.

Verbal learning and memory as well as auditory attention were assessed at Time 1 and were found to be in the average to low average range across epilepsy groups. Between 30% and 60% of children in the monotherapy and polytherapy groups were functioning below the 25<sup>th</sup> percentile on these measures. Verbal learning and memory as well as auditory attention were within the average range for the typically developing group. Between 13% and 31% were functioning below the 25<sup>th</sup> percentile in the typically developing group with the greatest percentage of children performing below average on verbal learning. From Time 1 to Time 2, there was a trend for increasing executive dysfunction, and, at Time 2, children with seizures

were, overall, one standard deviation above the mean indicative of greater executive difficulties. Ratings of behavior problems remained fairly consistent over time in the children with epilepsy, with externalizing and internalizing problems equally as common and slightly elevated relative to norms, but not in the clinically significant range overall. Nevertheless, approximately one third of children with epilepsy were above the 25<sup>th</sup> percentile indicative of more behavior problems, as compared to fewer than 25% of typically developing children. For the typically developing group, mean ratings of behavior problems and executive functioning were within normal limits at both Times 1 and 2. Although intellectual functioning was only assessed at Time 1, IQ scores were generally commensurate with adaptive functioning abilities at Time 2 for children with epilepsy, with 35% of children in the monotherapy group and 57% of children in the polytherapy group functioning below the 25<sup>th</sup> percentile. Intellectual functioning for the typically developing group was in the high average range with no children performing below the 25<sup>th</sup> percentile, and their adaptive functioning, assessed at Time 2, was in the average range across domains and the ABAS-II GAC, suggesting that adaptive skills were somewhat weaker than intellectual functioning.

No significant between group differences on neuropsychological functioning were found between the epilepsy groups at either Time 1 or Time 2. This suggests that, as a whole, children are not performing significantly differently according to a broad measure of their epilepsy status (monotherapy, polytherapy, surgery), and raises questions about the utility of grouping children in this way. Significant between group differences were observed between the typically developing group and epilepsy groups. At Time 1, children on monotherapy and polytherapy were found to display significantly more internalizing problems (BASC-2) and more executive problems (BRIEF; monotherapy: BRI, polytherapy: GEC, BRI, and MI) than children in the typically developing group. Children in both the monotherapy and polytherapy groups were found to have significantly poorer attention (CVLT-C Trial 1), memory (CVLT-C Long Delay Free Recall), and intellectual functioning (Wechsler Full Scale IQ) compared to typically developing



children. Although IQ was assessed at Time 1, and adaptive functioning at Time 2, these abilities were generally commensurate, and when controlling for IQ, there were no significant differences in adaptive functioning across groups. This is consistent with the typically reported moderate correlations between IQ and adaptive functioning, and attests to the lower level of functioning in children with epilepsy compared with typically developing children.

At Time 2, no differences were observed between the epilepsy groups. Children on both monotherapy and polytherapy were found to be displaying significantly more internalizing problems (BASC-2) and executive dysfunction (BRIEF GEC, BRI, and MI) and significantly poorer adaptive functioning (ABAS-II GAC and Conceptual and Practical domains) compared to typically developing children. Children in the surgery group differed from the typically developing group on a component of executive functioning (BRIEF BRI) and with respect to overall adaptive functioning (ABAS-II GAC). The lack of more significant differences between the surgery and typically developing groups is likely due to the higher standard deviations for the surgery group indicative of greater variability in functioning in this group. The prevalence of significant differences between children in the typically developing group compared to children with epilepsy is consistent with other studies reporting neurocognitive and behavioral difficulties in children with epilepsy (Adams et al., 2002; Bailet & Turk, 2000; Caplan et al., 2004; Prahbhjoy & Pratibha, 2005; Williams et al., 1998a).

#### *Specific Aim 1*

Consistent with what was hypothesized, more severe epilepsy history was significantly associated with reduced adaptive functioning across domains. This finding expands upon previous research, which has shown that more severe epilepsy is associated with poorer cognitive functioning including in the areas of intellectual functioning and academic achievement (Bailet & Turk, 2000; Caplan et al., 2004; Lah, 2004; Tromp et al., 2004), by providing evidence that the deleterious effects of more severe epilepsy extend to adaptive functioning as well. This result also supported the utility of using a measure of cumulative seizure history in predicting

outcome in children with epilepsy. This measure, however, was not able to explain as much variance in adaptive functioning as a conglomeration of individual seizure and treatment variables.

The extent to which specific seizure and treatment variables were related to adaptive functioning also was tested. The results indicated that the relationship between the active seizure variable and adaptive functioning was strong and present across adaptive domains. Children with active seizures were shown to be functioning at a lower adaptive level than their healthy peers as well as their peers with controlled seizures. As illustrated in Figure 3, in the controlled seizure group, adaptive functioning was consistently in the average range overall. In the active seizure group, adaptive functioning ranged from the low end of the low average range to the borderline range. This suggests that there is a strong association between active seizures and suboptimal adaptive functioning.

At Time 1, 43 of 46 children had active seizures, while at Time 2, 26 children had active seizures. This indicates that a significant proportion of children are likely to attain seizure control over time. Adaptive functioning appears to be at greater risk for those children who do not attain seizure control over time, and may indicate a more severe course of epilepsy and potentially an associated risk of poorer neuropsychological development. Consistent with what would be expected, children in the polytherapy group were significantly more likely than children in either the monotherapy or surgery groups to have active seizures, suggesting that this group may be particularly vulnerable to adaptive deficits. Furthermore, this group had a higher percentage of children who were functioning below the 25<sup>th</sup> percentile across both the Conceptual and Practical domains, but not the Social domain, compared to the monotherapy and surgery groups.

The lack of significant predictive utility for the remaining seizure and treatment variables was surprising, but suggests that they may contribute little additional variance to understanding adaptive functioning in this population. Specific seizure and treatment variables have been

found to be predictive of other outcome variables in different studies, and the lack of findings here may be due to the heterogeneity of this sample, which did not exclusively examine children with a specific site of seizure focus (e.g., left temporal), with a specific type of seizure (e.g., complex partial), or children who belonged to a specific subgroup (e.g., children with new-onset epilepsy). Thus the variability in our sample's epilepsy history may have favored a cumulative measure of seizure severity over individual variables. It also is possible that specific seizure and treatment variables, such as age at diagnosis, which have been shown to significantly impact other domains of neuropsychological functioning, may not be as strongly associated with performance on measures of adaptive functioning. This may be related to the acquisition of new adaptive skills being less dependent on the mastery of prior adaptive skills (which is in contrast to measures of, for example, of intellectual functioning or academic achievement). More specifically, being able to make your own bed is a developmentally more demanding adaptive task compared to picking up and throwing away trash or paper at home, but being able to perform the latter is not contingent on the former. In contrast, being able to subtract using double digits is likely to be dependent on the ability to successfully subtract using single digits. This lack of a hierarchical relationship may mean that age at diagnosis has less of a clear effect on the acquisition of adaptive skills over time. With the remaining seizure and treatment variables entered into the model (number of past and present AEDs, number of seizure types, and surgery), it is possible that they were proxy measures of epilepsy severity and the potential for associated neurological dysfunction. The active seizures variable may have been the most direct assessment of this underlying neurological dysfunction, and may explain its stronger association with adaptive functioning. Additionally, adaptive behaviors require the integration of more basic cognitive processes, and because of this complexity, cumulative measures of seizure severity may be better able to account for adaptive outcome than single seizure variables excluding the active seizures variable, which was significantly predictive of adaptive

functioning across domains. More studies are needed to both confirm and extend the association between active seizures and adaptive functioning.

Reduced adaptive functioning in children with active seizures may be a result of a combination of both environmental and neurological factors. With respect to environmental factors, it is possible that parents place greater restrictions on their child's independence while they continue to have seizures to ensure their child's safety and well-being. Additionally, children who continue to have seizures may be more socially isolated as a result of stigmatization (Adams et al., 2002), resulting in reduced opportunities to develop age-appropriate independent living skills. With respect to neurological factors, the brain's continued abnormal functioning as evidenced by persistent seizures and the potential for continued inter-ictal disturbance may be interfering with the development of children's adaptive skills and/or their ability to evidence adaptive behavior in age-appropriate circumstances. Furthermore, the active seizures variable was positively correlated with the number of AEDs a child was taking ( $r = .44, p < .01$ ), suggesting a potentially confounding effect of AEDs and their side effects or possibly the medically refractory nature of some seizures to multiple medications. Although the results of this study do not allow for a clear determination of the degree of influence of these potential environmental and neurological factors, children with active seizures were significantly more likely to have an Individualized Education Plan (IEP) in place at school than children with controlled seizures (65% versus 17%). The greater prevalence of IEPs may be a marker of more pervasive neurological dysfunction or disruption in children with active seizures.

The predictive utility of this active seizure variable warrants attention, particularly as researchers are challenging the accuracy of patient report of seizure frequency (e.g., Hoppe & Elger, 2007). While no studies could be found that examined the accuracy of parent report of children's seizure frequency, many parents reported that they had difficulty calculating anything more than a broad estimate of seizure frequency (e.g., whether or not their child was having one or more seizures a month). This was a particular issue when children experienced absence or

nocturnal seizures or seizures at school. Parents were, however, able to report the specific date of their child's last known seizure allowing for the calculation of whether or not a child had one or more seizures in the last year to be made with more confidence than a measure of seizure frequency. The findings of this study suggest that categorizing seizures as active or controlled may be a meaningful estimate of current seizure burden that is easier for parents to report than frequency, and that this measure may be subject to less measurement error and increased reliability.

### *Specific Aim 2*

Consistent with what was hypothesized, executive functioning, verbal learning, and internalizing and externalizing behavior problems were found to be significantly associated with adaptive functioning. More specifically, we found that better executive functioning abilities and verbal learning as well as fewer internalizing and externalizing behavior problems were associated with better adaptive functioning. Contrary to what was hypothesized, significant relationships were not found between attention or verbal memory and adaptive functioning. The lack of significant relationships between adaptive functioning and attention and verbal memory is surprising, and may be due to a number of factors. The lack of significant relationships may be due to the specific measures used. Trial 1 of the CVLT-C is considered a supraspan measure of attention, and this may not be the most ecologically valid measure of attentional functioning. It also is possible that the cognitive processes assessed by these variables may be too specific and, therefore, not as strongly associated with adaptive functioning as measure of broader constructs such as executive functioning.

With respect to mediation, verbal learning was dropped from the model owing to non-significant correlations with both the Seizure History Scale (SHS) and group membership. In light of significant correlations between executive functioning and behavior problems, when executive functioning was tested as a mediator, behavior problems were controlled for and vice

versa to allow for the examination of the specific contributions each variable could make to understanding the relationship between epilepsy and adaptive functioning.

### *Mediation*

Executive functioning at Time 1 fully mediated the relationship between scores on the SHS at Time 1 and adaptive functioning at Time 2 across domains and the ABAS-II GAC. Full mediation also was evident when executive functioning and SHS scores from Time 2 were used for the ABAS-II GAC and the Conceptual and Practical domains, but not the Social domain. Full mediation occurs when the relationship between the IV and DV becomes non-significant when the mediator is entered into the model. The coefficient for the ab pathway, or indirect effect, was significantly different from zero based on 95% confidence intervals, meaning that SHS scores can best explain adaptive functioning through their effect on executive functioning. Thus, more severe seizure history is associated with more executive dysfunction, which, in turn, is associated with reduced adaptive functioning. This means that children with higher scores on the SHS, indicative of a more severe seizure history, are at greater risk for deficits in executive functioning, and these deficits in executive functioning are, successively, associated with suboptimal adaptive functioning. Based on these findings, children with more severe epilepsy history should be monitored closely for both executive and adaptive functioning issues.

The above model was re-run when SHS scores at Time 1 also were controlled for in order to examine whether the change in cumulative seizure history from Time 1 to Time 2 was predictive of adaptive functioning, and if this relationship was mediated by executive functioning. Partial mediation was found for the ABAS-II GAC and the Practical domain. Partial mediation occurs when there is a weakening in the relationship between the IV and DV, but it is still significant. The presence of partial mediation here means that changes in seizure severity from Time 1 to Time 2 are associated with adaptive functioning, and that this effect is partially explained by the influence these changes in severity have on executive functioning. In other words, executive functioning was partially, but not fully, able to explain the association between

changes in seizure severity and adaptive functioning as measured by the ABAS-II GAC and the Practical domain. This might mean that adaptive functioning is more susceptible to changes in seizure severity than executive functioning. If these findings were confirmed, it might point to adaptive functioning being more amenable to change, and therefore, more responsive to interventions. The relationship between performance on the Conceptual domain and changes in cumulative seizure history was found to be fully mediated by executive functioning, suggesting that performance on this domain may be more susceptible to executive difficulties associated with changes in seizure status.

#### *Issues with Using Group Membership to Denote Epilepsy Severity*

Mediation was more elusive when testing the model with group membership as the IV. The relationship between Group at Time 1 and adaptive functioning at Time 2, was found to be fully mediated by executive functioning at Time 1 for the ABAS-II GAC and the Practical domain, and partially mediated for the Conceptual domain. At Time 2, executive functioning was not able to mediate the relationship between Group and adaptive functioning whether group membership at Time 1 was controlled for or not. The lack of mediation may be related to the addition of a surgery group at Time 2. These results indicate that grouping children according to their current treatment status may sometimes, but infrequently, be an appropriate method of denoting epilepsy severity. At time 1, children in the polytherapy group performed, as a whole, more poorly than the monotherapy group, who, in turn, performed more poorly than the typically developing group on many neuropsychological measures. This hierarchical relationship is likely what accounted for the finding of mediation by executive functioning at Time 1 because there was a clearer, ordinal relationship between group membership and degree of impairment. However, this linear relationship did not appear to hold at Time 2 when children who had undergone temporal lobectomies for seizure control were designated as the fourth group. This is likely because there was a great deal more heterogeneity in seizure severity within this group that included children with a long-standing history of intractable epilepsy and children who

underwent a surgical resection of a brain tumor within a short period of time from their first documented seizure.

Additionally, problematic for examining functioning according to group membership was that there did not appear to be a clear relationship between group membership and adaptive functioning. Instead, all three seizure groups performed similarly suggesting that group membership alone is not able to explain variability in adaptive performance. Thus, although it is more traditional to place children in groups for ease of comparison, considering group membership as an ordinal variable does not appear to be an appropriate way of studying the effects of epilepsy in children. Instead, the scale developed in this study to examine cumulative seizure history, the SHS, seemed to better capture the relationship between epilepsy, neuropsychological functioning, and adaptive functioning.

Across mediational models, behavior problems did not mediate the relationship between SHS scores or Group and adaptive functioning once executive functioning was controlled for. Although behavior problems were significantly predictive of adaptive functioning, this effect was no longer apparent when executive functioning was also part of the model. It seems that the overlapping variance between behavior problems and executive functioning was what accounted for the predictive utility of behavior problems, but that only the BRIEF General Executive Composite (GEC) was able to contribute additional, unique, variance towards explaining adaptive capabilities.

#### *Supplementary Analyses*

Supplementary analyses were designed to examine whether the strong relationship observed between executive and adaptive functioning is a normal part of development or further evidence of disrupted development in children with epilepsy. Moderation was not found when examining the relationship between executive functioning at Time 1 and adaptive functioning at Time 2. This means that the ability of executive functioning to predict later adaptive functioning was not significantly different according to whether a child had epilepsy or not. The relationship



at Time 2, however, between executive and adaptive functioning was found to be moderated by whether or not a child had experienced seizures. In light of the significant difference in intellectual functioning between the typically developing children and those who had experienced seizures, this model was also tested when intellectual functioning was controlled for to ensure that the observed relationship between executive and adaptive functioning in children with epilepsy was not a product of their lower intellectual functioning. The interaction persisted when intellectual functioning was controlled for, suggesting that this was not the case and that the relationship between executive and adaptive functioning was stronger in children with epilepsy than typically developing children regardless of intellectual ability. We further examined whether the relationship between executive and adaptive functioning abilities would be stronger for children with active seizures compared to children with controlled seizures. Moderation was not found at either Time 1 or Time 2, suggesting that the relationship between executive and adaptive functioning was not altered by current seizure status.

Across measures, there was less variability in performance for children in the typically developing group. In order to better determine whether the observed interaction between executive and adaptive functioning was related to differing levels of variability in performance across children who have epilepsy compared to those who did not, moderation was also tested using Internalizing and Externalizing Behavior Problems of the BASC-2, which evidenced similar levels of variability to the BRIEF GEC. An interaction was not found at either Times 1 or 2. This suggested that the observed interaction between executive and adaptive functioning is not simply a byproduct of differing levels of variability. Nevertheless, confirmation of the presence of this interaction with a typically developing sample with more variability in adaptive performance is warranted.

Thus, concurrent executive and adaptive functioning appear to be much more closely intertwined in children with epilepsy, regardless of whether seizures were active or controlled, compared to typically developing children. This more highly correlated relationship between

executive and adaptive functioning also has been shown in children with autism (Gilotty et al., 2002) and children with a history of traumatic brain injury (Mangeot et al., 2002) suggesting that it may not be unique to children with epilepsy, and instead may be apparent across pediatric clinical populations. The observed association between adaptive and executive functioning may be, in part, related to the design of both measures which seek to assess children's day-to-day functioning as opposed to measures which test a child's maximal level of functioning in an environment with minimal distractions. There is also likely to be overlap in the demands of adaptive or executive tasks as both are dependent on the ability to respond appropriately to new environments and tasks.

There was only a weak relationship between adaptive and executive functioning within the typically developing group. Among children with seizures, however, there was a much steeper slope with higher adaptive performance strongly associated with fewer executive problems (i.e., lower scores on the BRIEF) and lower adaptive performance strongly associated with more executive problems (higher scores on the BRIEF). This finding underscores the importance of using control groups in clinical research. Having a typically developing comparison group in this study allowed for the testing of how the observed relationship between executive and adaptive functioning differed in typically developing children and children with epilepsy. A better understanding of how cognitive development is altered by epilepsy is important, not only for increasing our understanding of pediatric epilepsy, but also to help clinicians develop and refine the most effective interventions. Overall, these results suggest a significant concurrent association between adaptive and executive functioning in children with epilepsy that may not be present in typically developing children.

There are limitations to using a parent-report measure to predict another parent-report measure (e.g., shared variance). The BASC-2, however, is also a parent-report measure and did not demonstrate the same utility as the BRIEF in predicting adaptive functioning, which suggests that there are more to the findings of this study than simply parents completing both

the BRIEF and ABAS-II. Additionally, research has shown correlations between the BRIEF and a widely used objective, laboratory measure of executive functioning, the Delis-Kaplan Executive Function System (D-KEFS), in children with epilepsy (Parrish et al., 2007). Furthermore, among objective, laboratory measures of attention, verbal memory, nonverbal memory, and executive functioning, measures of executive functioning were found to be the strongest correlates of adaptive functioning (Culhane-Shelburne et al., 2002). Additionally, the ecological validity of parent-report measures of executive functioning is asserted to be greater than objective, laboratory measures of executive functioning, as the BRIEF is based on real-world, as opposed to laboratory, functioning. Thus, although there are some limitations to parent-report measures, there are also benefits and the BRIEF has been shown to correlate highly with objective, laboratory measures of executive functioning suggesting substantial overlap across methodologies for assessing executive functioning.

Although a strong relationship between executive and adaptive functioning was observed for children with epilepsy as compared to typically developing children, it is possible that there may be alternate explanations for this finding. The lack of sufficient variability in performance within the typically developing group may have been responsible for the weak relationship observed between executive and adaptive functioning in typically developing children. Although moderation was not found for the relationship with behavior problems, which had similar rates of variability to the BRIEF GEC, and adaptive functioning, it remains possible that the lack of variability in adaptive functioning in typically developing children may have accounted for the weak relationship between executive and adaptive functioning in this group. Future research will be needed to confirm if there is a stronger relationship between adaptive and executive functioning in children with epilepsy.

#### *Remediation of Adaptive Functioning Deficits*

The findings of this study suggest that a subset of children with epilepsy are at risk of significant adaptive impairments, and that this risk is associated with continued seizures and

executive dysfunction. In fact, 57% of children with epilepsy in this study were performing at or below the 25<sup>th</sup> percentile with respect to overall adaptive functioning compared to only 13% of the children in the typically developing group. Furthermore, for children with intractable seizures, research has shown significant declines in adaptive functioning over time (Berg et al., 2004), thereby bolstering the need for remediation. With the potential to identify children at risk of suboptimal adaptive functioning, comes the responsibility to find ways to boost adaptive functioning for these children. Based on the findings of this study, complete seizure control appears to be necessary for optimal adaptive development, and may be the first step in reducing the likelihood that children will evidence adaptive deficits. For children displaying adaptive deficits, interventions could be aimed at directly addressing adaptive deficits or indirectly addressing them through remediating other cognitive functions, such as executive functioning, that adaptive skills may be reliant on.

Within the realm of directly addressing adaptive deficits, there is new evidence to suggest that attending an epilepsy-specific overnight camp can produce not only more adaptive behaviors but also improve social interactions in children with epilepsy from ages 7 to 17 (Cushner-Weinstein et al., 2007). This study found that adaptive skills increased over the course of the weeklong camp experience and that attending the camp the following year was able to build upon those initial gains. There was not a no treatment group, rather all campers were assessed both at the start and finish of the camp. These findings are preliminary, but promising, with the authors describing the camp experience as a time for empowerment and inclusion for children with epilepsy (Cushner-Weinstein et al., 2007). More research into the potential utility of epilepsy camps in bolstering adaptive functioning is needed particularly as children did not appear to maintain these gains over the course of the subsequent year, which may be the result of the short duration of the camp (one week) being insufficient for creating lasting change or result from bias in pre- and post-camp adaptive assessments.

The existence of moderation of the relationship between executive and adaptive functioning by seizure status, indicates that remediation of executive skills might be another potential avenue through which to raise adaptive skills. This would seem a particularly fruitful approach to study, in light of the widely reported findings of executive dysfunction in children with epilepsy (Culhane-Shelburne et al., 2002; Parrish et al., 2007; Slick et al., 2006). Indeed, studies have reported that executive functioning is a vulnerable domain of cognition even in children with new-onset epilepsy whose seizures are well-controlled (Parrish et al., 2007) as well as in a substantial subset of children with intractable epilepsy (Slick et al., 2006). Furthermore, executive deficits may be apparent on both parent-report and neuropsychological tests even in the absence of any impairment in intellectual functioning (Culhane-Shelburne et al., 2002; Parrish et al., 2007). Culhane-Shelburne and colleagues (2002), for example, found IQ to be in the average range, adaptive functioning to be in the low-average to borderline range, and executive functioning to be in the average to low average range, suggesting that adaptive deficits may be one of the most vulnerable domains of functioning in children with epilepsy.

Research on the success of executive function remediation strategies is sparse and frequently limited to case-studies or small samples and lacking control groups. Meta-analyses of studies have sought to extrapolate guidelines from these studies. For example, Kennedy and colleagues (2008) reported evidence for improvements in executive functioning following Metacognitive Strategy Instruction in adults with a Traumatic Brain Injury, but determined that there was insufficient evidence to support the utility of specific remediation strategies in children with a Traumatic Brain Injury, a finding echoed by Limond & Leeke (2005). No research studies, however, could be found that examined the remediation of executive deficits in children with epilepsy. This will be an important area of future research, not only to determine the most efficacious ways to remediate executive functioning, but also to study whether there are secondary gains in adaptive functioning following remediation of executive deficits.

### *Limitations*

This study is limited by its part retrospective nature which precluded us from having a assessments of adaptive functioning at both Times 1 and 2. Without information about adaptive functioning at Time 1, no commentary can be made about changes in adaptive functioning over time or how adaptive functioning might change following surgical intervention. This study would have benefited from the use of a broader neuropsychological battery that included objective assessment of executive functioning, academic achievement, visual learning and memory, working memory, and additional measures of attention. Additionally, our modest sample size and the diversity in epilepsy history prevented the examination of whether and how seizure foci might differentially affect adaptive functioning. In light of the variability in AEDs prescribed, this study was unable to examine whether specific medications, particularly those more commonly reported to have cognitive side effects such as Topamax, might differentially affect adaptive functioning or the relationship between executive and adaptive functioning.

Although the use of a typically developing comparison group in this study allowed for commentary on how relationships between variables differ in children with epilepsy as compared to typically developing children, there were some limitations to the comparison group used. Intellectually, this comparison group was functioning in the high average range overall. Although mean performance on the other measures used in this study was in the average range (CVLT-C, BASC-2, BRIEF, and ABAS-II), it would be beneficial to replicate these findings with a sample of typically developing children functioning consistently in the average range. Additionally, it would have been advantageous to have had a non-neurological chronic illness comparison group (e.g., asthma) that had a similar range in severity (i.e., active versus controlled) in order to control for the effects of frequent school absences and hospital stays.

### *Future Research*

In light of the limited research on adaptive functioning in children with epilepsy, there are numerous directions for potential research. These might include confirming the utility of the

active seizures variable in explaining adaptive functioning, and testing whether this variable also may be of use in explaining variance in other areas of neuropsychological functioning. A better understanding of the underlying reason for the strong predictive utility of the active seizures variable is warranted. There is some evidence that children with more severe epilepsy histories may have been more likely to participate in this study, thus future studies may want to offer an incentive, potentially financial, to encourage wider participation.

Future research also should seek to examine other aspects of neuropsychological functioning (e.g., visual memory, processing speed, and motor skills) as well as more comprehensive measures of constructs examined in this study (e.g., attention, memory, executive functioning). This study used parent-report measures (ABAS-II, BASC-2, and BRIEF), which have been shown to be advantageous as they offer a higher degree of ecological validity than can be easily attained with direct assessment in testing conditions (Ris, 2007). Future research should, however, examine whether objective, laboratory measures of the same constructs produce similar results. With respect to the relationship between executive and adaptive functioning, it will be important for future studies to confirm these findings both with parent-report measures, as well as with teacher report and objective neuropsychological testing. Should this relationship be shown to occur consistently in children with epilepsy, and differ from that found in typically developing children or in children with other neurological disorders, the clinical implications will need to be evaluated and greater attention paid to evaluating methods for remediating both adaptive and executive functioning deficits. Additionally, longitudinal studies will be of interest to further characterize how adaptive functioning trajectories are influenced by seizures and their treatments over time. Such studies also could examine how adaptive functioning trajectories might be altered by changes in epilepsy status and/or treatments including epilepsy surgery.

### *Conclusions*

In spite of the aforementioned limitations, this study was able to provide more clarification on the poorly understood adaptive functioning capabilities of children with seizures. In particular, this study showed that adaptive functioning abilities were in the lower end of the average to the low average range across domains for children with epilepsy. Cumulative seizure history using the Seizure History Scale was able to significantly predict adaptive functioning across domains. Additionally, whether or not a child had experienced one or more seizures in the last year was best able to account for adaptive functioning compared to other individual seizure and treatment variables. Of note, although no pre-surgical measure of adaptive functioning was available, whether or not a child had undergone focal surgery was not found to be significantly associated with adaptive functioning, suggesting that surgical intervention in and of itself may not significantly affect adaptive functioning. Furthermore, children with active seizures were shown to have adaptive functioning scores more than one standard deviation below their peers with controlled seizures, suggesting that children who continue to experience seizures, even if only as infrequently as once in the prior year, are still at risk of adaptive deficits. Children with greater seizure burden are already known to be at greater risk of poorer neurocognitive outcome, and this study extends those findings to include adaptive outcome.

This study also identified the best neuropsychological predictors of adaptive functioning, which were found to be executive functioning, verbal learning, and internalizing and externalizing behavior problems. Mediation was found, indicating that increased severity of epilepsy history was associated with executive dysfunction which, in turn, was associated with suboptimal adaptive functioning. To better examine the reported relationship between epilepsy and adaptive functioning, the potential for moderation of this relationship by whether or not a child had epilepsy was assessed. Moderation was found, and confirmed the presence of a significantly stronger relationship between executive and adaptive functioning in children with epilepsy, such that level of functioning in one area was strongly associated with level of



functioning in the other. This relationship was not found in typically developing children. The strength of this association in children with epilepsy coupled with research consistently reporting that this population is at risk of executive deficits underscores the need for more research not only into executive functioning, but also into adaptive functioning in children with epilepsy and potential ways to reduce the risk of suboptimal functioning in these domains in children at risk.

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APPENDIX A  
SEIZURE HISTORY SCALE



**Seizure History Scale**

ID # \_\_\_\_\_

\_\_\_\_\_ Seizures in last 12 months

- 0 No
- 2 One-Four
- 4 Five-Ten
- 6 More than Ten

\_\_\_\_\_ Seizure Types

- 0 Single Seizure Type
- 1 Two Seizure Types
- 2 Three Seizure Types
- 3 Four Seizure Types
- 4 Five or more Seizure Types

\_\_\_\_\_ Status Epilepticus

- 0 Never
- 1 One-two times
- 2 Three or more times

\_\_\_\_\_ Medication

- 0 Currently No Medication
- 1 Currently Monotherapy
- 2 Currently 2 Medications
- 3 Currently 3 or More Medications

\_\_\_\_\_ Medication History

- 0 No past AEDS
- 1 1 Past AED
- 2 2 Past AEDs
- 3 3 Past AEDs
- 4 4 Past AEDs
- 5 5 or more past AEDs

\_\_\_\_\_ Surgery

- 0 No Surgical Intervention
- 1 Removal of Brain Tumor
- 2 No evidence of tumor, removal of identified seizure focus

Total Score \_\_\_\_\_

Range = 0 - 22

APPENDIX B

SEIZURE INFORMATION FORM SENT TO PARENTS FOR COMPLETION

### Seizure Information Form

Please complete and return in the enclosed envelope.

When was your child's first seizure (Month/Day/Year)? \_\_\_\_\_

When was your child's most recent seizure (Month/Day/Year)? \_\_\_\_\_

What medication(s) is your child currently taking for epilepsy?

Name \_\_\_\_\_ Dosage \_\_\_\_\_

Name \_\_\_\_\_ Dosage \_\_\_\_\_

Name \_\_\_\_\_ Dosage \_\_\_\_\_

Name \_\_\_\_\_ Dosage \_\_\_\_\_

Has your child taken any other medications for epilepsy in the past? \_\_\_\_\_

When was your child's last seizure medication change (Month/Day/Year)? This includes changes in the kind or amount of seizure medication your child is taking. If there have not been any changes, answer from the time your child was first prescribed seizure medication.

*Since your child's most recent medication change, how many and what types of seizures has your child had in the:*

Examples: seizure type absence how many a month? 5  
 seizure type tonic-clonic how many a month? 1

#### First Month After Medication Change?

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

#### Two-6 Months After Medication Change?

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

#### 7-12 Months After Medication Change?

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

#### 13-24 Months After Medication Change?

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

Please circle all types of seizures your child has had:

Tonic-Clonic/Grand Mal	Clonic	Tonic	Absence/Petit Mal
Atypical Absence	Spasms	Myoclonic	Simple Partial
Complex Partial	Eyelid Myolonia	Myoclonic Atonic	Negative Myoclonus
Atonic/Akinetic	Febrile	Focal Sensory	Focal Motor
Gelastic	Hemiclonic	Secondarily Generalized	Reflex
	Nonepileptic	Status Epilepticus	

Other, please specify: \_\_\_\_\_

Is your child currently taking any other medication (not for seizure control)? \_\_\_\_\_

Has your child tried any other treatments for epilepsy (for example, ketogenic diet)? \_\_\_\_\_

Has your child had any significant medical issues since their last appointment at the Department of Neuropsychology at Scottish Rite? If yes, please describe. \_\_\_\_\_

*If your child has had surgery to help reduce seizures, what was the date of their surgery (month/day/year)?* \_\_\_\_\_

*If your child has had surgery to help reduce seizures: since having surgery, how many and what types (e.g. absence, complex partial) of seizures did your child have in the:*

**First month after surgery?**

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_  
 seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_  
 seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

**Two-6 months after surgery**

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_  
 seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_  
 seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

**7-12 months after surgery?**

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

**13-24 months after surgery?**

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

**Before having surgery**, how many and what types (e.g. absence, complex partial) of seizures did your child have in a *typical*:

**Week?**

seizure type \_\_\_\_\_ how many a week? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a week? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a week? \_\_\_\_\_

**Month?**

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

seizure type \_\_\_\_\_ how many a month? \_\_\_\_\_

**Thank you!**