THE ROLE OF SEIZURE-RELATED VARIABLES IN PEDIATRIC EPILEPSY: PERSPECTIVES FROM NEUROPSYCHOLOGY, PSYCHIATRY, AND SOCIAL AND EMOTIONAL COGNITION

by

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Abstract

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Heidi Allison Bender

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The role of seizure-related factors and psychopathology in neurocognitive functioning has been extensively studied throughout the literature. The present study, however, is the first to examine the multiple etiological determinants of neuropsychological dysfunction in pediatric epilepsy by assessing the individual and combined explanatory power of psychiatric status, behavioral social skills, and seizure-related factors. In so doing, our goal was to provide practitioners with an empirically-based guide for identifying children at elevated risk of impairment. It was hypothesized that seizure type, age of onset, and externalizing behavior problems would be robust predictors of neuropsychological dysfunction. Sixty participants, ranging from 6-17 years, comprised the sample. All subjects had a confirmed diagnosis of epilepsy; children with FSIQ scores <70 were excluded. A test battery assessing general intellectual, language, visuospatial, attentional, executive, and learning & memory abilities was administered. Two parent-report behavior rating scales (i.e., CBCL & BASC) were also completed. Covariance analysis was conducted to evaluate whether seizure-related variables moderate the effects of psychiatric and social impairment on

neuropsychological test performance. Ratings on global measures of psychiatric and behavioral symptomatology significantly contributed to diminished language abilities ($p \leq .05$) after seizure variables were accounted for; seizure type ($p \leq .05$) and treatment regimen ($p \leq .05$) both moderated this relationship. Elevated levels of depression, anxiety, and somatization contributed to language deficits and learning and memory impairment ($p \leq .01$); treatment regimen ($p \leq .01$) emerged as a consistent moderator of these relationships. Externalizing behaviors (as measured by the BASC) was one of the most robust scales in showing group differences with respect to neurocognitive performance. This scale significantly contributed to performance on the Executive Functioning ($p \leq .01$), Language ($p \leq .05$), and Learning & Memory ($p \leq .05$) domains. Age at seizure onset and treatment regimen appeared to significantly moderate the relationship between the BASC and the Learning & Memory and Language domains, respectively. Parent-report ratings of behavioral social skills did not significantly contribute to neuropsychological functioning when seizure variables were applied as covariates. This investigation identified several subgroups of children with epilepsy at increased risk for neuropsychological dysfunction. To this end, frequent assessment, psychoeducation, psychotherapy, and/or cognitive remediation may be warranted.

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CHAPTER ONE

I. INTRODUCTION

A. Research Question

The primary purpose of this study was to investigate the (a) neurocognitive functioning, (b) psychiatric status, and (c) social-behavioral functioning of children with epilepsy. The role of seizure-related variables was a particular focus of the present study. Four specific aims were addressed:

Aim #1 was to evaluate the combined and unique contributions of seizure-specific moderating variables on neurocognitive test performance in children with epilepsy. The majority of the extant literature reported that children with epilepsy often exhibit deficits on tests of intelligence and in several neuropsychological domains (e.g., language, attention, executive functioning, visuospatial skills, processing speed, learning, and memory; (Blennow, Heijbel, Sandstedt, & Tonnby, 1990; Bourgeois, Prensky, Palkes, Talent, & Busch, 1983; Dam, 1990; Farwell, Dodrill, & Batzel, 1985; Kolk, Beilmann, Tomberg, Napa, & Talvik, 2001; Stores, 1978; Williams, Griebel, & Dykman, 1998; Fedio & Mirsky, 1969; Masur & Shinnar, 1992) However, despite the known value of neuropsychological testing in populations with pediatric epilepsy (e.g., for pre-surgical planning and educational recommendations), much of the validity, reliability, and diagnostic utility of the obtained data may be confounded by the nature and treatment of the disease itself (B. P. Hermann & Whitman, 1984; Williams et al., 2001) That is, it is highly likely that seizure-related variables are significant moderators of neurocognitive functioning. We investigated the role of the following seizure-related moderating factors; a) epilepsy type, b) degree of seizure control, c) age at seizure onset, and d) anti-epileptic

drug therapy, either individually or in combination, on neuropsychological test performance. Based on findings from the extant literature, as well as preliminary studies conducted at the New York University Medical Center's Comprehensive Epilepsy Center (Bender & Auciello et al., 2006; Bender & Barr et al., 2007; Bender, Marks, Brown, Zach, & Zaroff, 2007; Bender & Zaroff et al., 2006; Zaroff & Bender et al., 2004), we posited that age at seizure onset and treatment regimen would each be significant moderators of neurocognitive performance in a sample of children with epilepsy. Once differences in neurocognitive performance based on seizure-related variables were established, regression analyses were performed to determine each variable's predictive power on performance in each neurocognitive test domain.

Aim #2 was to investigate the predictive value of seizure-related variables on the presence of psychiatric disturbance. In the classic Isle of Wight study, Rutter and colleagues (Graham & Rutter, 1968) reported "behavior problems" in 28.6% of children with uncomplicated epilepsies. More recently, the prevalence rate of psychological and maladaptive behavioral symptoms in children with epilepsy has been estimated at approximately 21-60%, representing an increased risk of ≥ 3-6 times that of the general population (Kolk et al., 2001; Ott et al., 2003). The frequency and specific presentation of psychiatric comorbidity(ies) are largely believed to be multifactorial in nature (e.g., due to adjustment to disability, delayed psychosocial development, external stressors, underlying neuropathology, and socioeconomic factors; (B. Hermann & Whitman, 1992; B. P. Hermann, Whitman, Hughes, Melyn, & Dell, 1988; B. P. Hermann, Whitman, Wyler, Anton, & Vanderzwagg, 1990). However, whereas the adult epilepsy literature suggests a significant relationship between the development of problem behaviors and

seizure-related variables (B. P. Hermann et al., 1988; Whitman, Hermann, Black, & Chhabria, 1982) similar studies in children have yielded inconsistent results (Caplan et al., 1998; Dunn, Austin, & Huster, 1999; B. P. Hermann et al., 1988; Ott et al., 2001). As a result, we investigated the effect of seizure-related variables on the frequency and the specific presentation of psychopathology (e.g., internalizing or externalizing disorders) in a child- and adolescent-aged sample. Two different parent-report measures, the Behavior Assessment System for Children and the Child Behavior Checklist, were employed as measures of psychiatric status in order to minimize the possible influence of measurement bias (e.g., developmental limitations, poor self-awareness of psychiatric symptomatology, and differences in instrument content and disorder conceptualization). It was hypothesized that children with more poorly controlled seizures, younger age at seizure onset, and those receiving polytherapy (i.e., prescribed more than one anti-epileptic drug) would exhibit comparatively higher rates of clinically-significant psychopathology. Group differences in problem behaviors reported were explored with *t*-tests or analyses of variance, for categorical seizure variables. Correlations were run where appropriate. Multiple regression analyses were then conducted to estimate which seizure-related variables predicted which measures of problem behavior, either uniquely or in combination.

Aim #3 was to describe the specific types of overt, atypical behavioral social skills often expressed in children with epilepsy. We further investigated the relationship between four specific seizure-related variables and social communication in this population. It has been widely reported throughout the pediatric literature that children with epilepsy are at increased risk of socially- and

developmentally-inappropriate behaviors and impaired social communication (Caplan et al., 1997). Both decreased opportunity for socialization and underlying neurological damage have been implicated in the development of these atypical behaviors. The present study investigated the "competence correlates" (Coie, Dodge, & Coppotelli, 1982) associated with atypical peer and social interaction in children with different seizure types, varying age at onset, seizure frequencies, and treatment regimens. More specifically, the present study defined "atypicality" through a more detailed and specific measure of stereotyped behaviors, uncommon linguistic and conversational characteristics, restricted range of interests, and negative reaction to change. The predictive power of the seizure variables on social competence was also a main focus of Aim #3. A small series of studies have reported that seizure-related variables do not appear to be consistent discriminators of social and behavioral functioning (Sabaz et al., 2003). However, the aforementioned studies were somewhat limited methodologically, assessing psycho-social difficulties through broad-band, non-specific measures of competence (e.g., the number of extracurricular activities joined), rather than with a more narrowly focused measure of clinically or theoretically relevant material (e.g., the child's ability to participate in reciprocal conversation). Based on the small available body of literature reviewed, we hypothesized that, as a whole, the studied sample would have diminished social skills and behavioral "appropriateness," as compared to a standardization sample of neurologically healthy children. Furthermore, we posited that regardless of epilepsy type and treatment, greater seizure frequency and younger age at seizure onset would be predictive of reduced social-behavioral functioning. Multiple t-tests and ANOVAs were conducted to assess observed differences on parent-report

measures of social skills based on seizure-related characteristics. Then, multiple regression analyses were performed to determine whether a reasonable pattern of prediction for seizure variables on social-behavioral functioning could be determined.

Finally, Aim #4 was to integrate the three previous Aims by examining the relationships among emergent psychopathology, social-behavioral functioning, and neurocognitive test performance as moderated by seizure-related variables. Despite the obvious benefits, the neuropsychological community at-large has been largely unable to establish a set of predictors of neurocognitive performance in children with epilepsy. Hermann et al. (1988) suggest a model which considers the multietiological determinants (e.g., biological, psychosocial, medication, and demographic) of psychopathology and social competence; however, these authors do not consider neuropsychological test data beyond a broad measure of intellectual functioning (i.e., Wechsler Full Scale IQ). In an effort to build upon the work of Hermann and others (Caplan et al., 2004; Schoenfeld et al., 1999), Aim #4 was to establish a set of variables with significant explanatory value in relation to neurocognitive test performance in this population. More specifically, the present study was unique in its attempt to establish predictors of test performance by evaluating the predictive value of psychiatric and social status on neurocognitive test performance with and without utilizing seizure-related variables as a covariate. It was hypothesized that the presence of clinically-impaired externalizing behaviors, impaired social competence, younger age at seizure onset, poor degree of seizure control, and multi-drug treatment regimen (i.e., polytherapy) would each have clinically significant explanatory value in relation to neuropsychological test performance. A series of analyses of covariances (ANCOVAs) were conducted to

explore whether seizure-related variables (either individually or in combination) moderate the effect of psychiatric symptomatology and social skills on neuropsychological test performance.

Taken together, these complementary findings would allow for the identification of seizure-related and psychiatric/social predictors of NP performance in children with epilepsy. To this end, it may be possible to identify a subgroup of children with epilepsy for whom additional treatment is warranted (e.g., early intervention) prior to their school performance being compromised.

B. Literature Review

Epidemiology and Diagnostic Classification

Epilepsy is the most prevalent neurological disorder in the pediatric population, affecting approximately 8 in 1,000 children and adolescents (David, 1998; Hauser, 1994). A recent epidemiological investigation reports that 4-10% of children suffer at least one seizure within their first 16 years of life (McAbee & Wark, 2000). From a diagnostic perspective, a seizure is characterized by a transient, paroxysmal behavior change resulting from a discharge of hyperexcitable cerebral neurons (Browne & Holmes, 2000). Such discharges occur when the firing threshold for the neuronal membrane is diminished below the capability of the cellular mechanisms in place to prevent depolarization (Browne & Holmes, 2000). For patients, these electrical disturbances may alter physical consciousness, psychic perception, sensori-motor activity, or autonomic function (Friedman & Sharieff, 2006; International League Against Epilepsy Commission Report, 1997). The specific manifestations of the seizure are largely determined by the function of the cortical neurons involved in the generation and spread of abnormal electrical activity. Beyond objectively and subjectively noted behavior changes, oxygen use,

glucose consumption, cerebral blood flow, lactic acid, and carbon dioxide production all increase during the sustained and synchronous neuronal firing involved in seizure activity (see Friedman & Sharieff, 2006 for review). Also, early systemic changes reportedly include tachycardia, hyperglycemia, hypoxemia, and hypertension. By extension, the term "epilepsy" describes the susceptibility for recurrent seizures (two or more) of any type or duration, unprovoked by any immediate, identified cause (International League Against Epilepsy Commission Report, 1997). However, multiple seizures occurring within a 24-hour period are considered one event. Based on their population-based survey of a pediatric sample, McAbee and Wark (2000) report that approximately 150,000 children per year will experience a first-time, unprovoked seizure; 20% of these children will develop epilepsy.

According to the International League Against Epilepsy's International Classification of Epileptic Seizures (1989, 1997), seizures are first classified by two broad categories, partial and generalized. Partial seizures refer to events during which epileptiform activity begins in a relatively small, circumscribed location in one brain hemisphere. Partial seizures can be further classified as either simple or complex, as determined by alteration of consciousness. Simple partial seizures are paroxysmal events without alteration of consciousness, whereas complex partial seizures, often referred to as psychomotor seizures, involve alteration of consciousness (e.g., automatisms such as lip smacking, facial grimacing, or repeated hand movements) and amnesia for the event (Shnecker & Fountain, 2003). As the electrical activity spreads throughout the cortex, partial seizures may secondarily activate neurons in both cerebral hemispheres, resulting

in a generalization of the seizure. Epidemiological studies suggest that simple and complex partial seizures secondarily generalize in up to 30% of children.

Generalized seizures are sudden electrical discharges without anatomic localization, affecting both hemispheres. The most common type of primary generalized seizure is generalized tonic-clonic (GTC), which was formerly referred to as "grand mal." At the onset of a GTC, individuals characteristically experience a loss of consciousness, as well as increased muscle tone (the tonic phase) followed by bilateral, rhythmic convulsions (the clonic phase; see Shnecker & Fountain, 2003 for review). Tonic and clonic activity may also be observed independently of GTCs during tonic and clonic seizures, respectively. Clinically, atonic seizures, more commonly referred to as "drop attacks," cause an individual to lose consciousness and muscle tone, often resulting in an immediate fall. Myoclonic seizures are also common in child and adolescent epilepsy populations; they are typically characterized by an acute head drop and upper extremity involvement. In addition to the aforementioned seizures in which motor involvement occurs, non-convulsive seizures may also arise. Non-convulsive generalized events, absence seizures (formerly referred to as "petit mal" seizures), are typically manifested as a brief staring episode occurring during an absence of activity.

Neurocognitive Comorbidities of Pediatric Epilepsy.

Neuropsychological, psychiatric, and social-behavioral skills impairment are important comorbidities of chronic epilepsy. Factors implicated in developing deficits in these areas include: underlying neuropathology (Caplan et al., 2002; Czochanska, Langner-Tyszka, Losiowski, & Schmidt-Sidor, 1994), seizure foci (Apter et al., 1991), seizure frequency (Austin et al., 1999), severity and duration of events (Smith, Elliott, &

Lach, 2002), age at seizure onset (B. Hermann & Seidenberg, 2002; Smith et al., 2002), anti-epileptic drug (AED) regimen (Bourgeois, 1998; Williams et al., 1996), the psychosocial burden of epilepsy (Beran, 1999; Freitag & Tuxhorn, 2005; Sabaz et al., 2003), and the direct effects of epileptogenesis (Holmes, 1991a, , 1991b).

Effects on General Intelligence.

The specific effect of childhood epilepsy on general intelligence is not clearly delineated in the literature. Although several researchers have reported that children with epilepsy exhibit intellectual functioning comparable to the general pediatric population (Camfield et al., 1984; Hauser & Hesdorffer, 1990b), several recent studies have found that IQ scores are skewed towards the lower end of the average range (i.e., Wechsler Full Scale IQ's in the mid- to low- 90's ; Moore & Baker, 2002; O'Leary, Burns, & Borden, 2006; Smith, Elliott, & Lach, 2002).

Children with malevolent epileptic syndromes (i.e., medically refractory epileptic encephalopathies with an onset in early childhood) more frequently exhibit mental retardation and progressive cognitive decline than children without symptomatic etiology (i.e., idiopathic). For example, Lennox-Gastaut syndrome and West syndrome, two epilepsy syndromes, are associated with an extremely high incidence of mental retardation, at 96% and 80%-90%, respectively (Gastaut, 1982; Murphy & Dehkharghani, 1994). Though other chromosomal, metabolic, and neurologic disorders often co-occurring with seizure disorders have a high incidence of mental retardation (e.g., neonatal meningitis or encephalitis, perinatal asphyxia, Angelman's syndrome, Tuberous Sclerosis Complex, and neurofibromatosis), epilepsy stemming from these etiologies are relatively rare and describe only a small segment of the population with this disorder.

Beyond the etiology of seizures, additional factors have been consistently associated with intellectual decline and impairment. A history of status epilepticus[1] (Delgado-Escueta, Wasterlain, Treiman, & Porter, 1983), febrile convulsions[2] (Dodrill, 1986), and multiple seizure types (Yung et al., 2000) are variables that have been shown to impact cognition. Also, age at seizure onset is frequently observed to be a significant indicator of performance on IQ tests, with children with earlier seizure onset exhibiting a poorer prognosis (Farwell et al., 1985). It is believed that an earlier age at seizure onset precludes normal brain development by inhibiting mitotic cell activity, consequently affecting myelination and reducing cell numbers and size (Renier, 1987). Farwell and colleagues (1985) report that degree of seizure control and duration of epilepsy (in years) are both related to cognitive function, such that children with better seizure control and shorter duration of epilepsy obtain higher scores on intelligence tests when compared to those with more poorly-controlled epilepsies and longer duration of seizures.

Paradoxically, although anti-epileptic drug (AED) treatment often reduces seizure frequency, its benefits may be offset by the drug's potential for side effects. Studies examining the effect of treatment regimen on cognitive functioning have produced contradictory and sometimes controversial findings (Dodrill, 1990). Two frequently replicated findings indicate that AED toxicity is predictive of deficits on intelligence tests (Bourgeois et al., 1983), as is treatment with multiple AEDs (i.e.,

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[1] "A condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition" (World Health Organization Dictionary of Epilepsy). Approximately 4-16% of individuals with epilepsy will experience one episode of status epilepticus throughout their lifetime (Riviello, 2003).

[2] Convulsions or seizures associated with fever in the absence of central nervous system infection or acute electrolyte imbalance in children (Nelson & Ellenberg, 1976). Approximately 3-8% of children under 7 years of age have experienced a febrile convulsion (Kjeldsen, Kyvik, Friis, & Christensen, 2002). The prevalence of febrile seizures is between 3% and 8% in children up to 7 years of age.

polytherapy/polypharmacy; (Corbett, Trimble, & Nichol, 1985; Thompson & Trimble, 1982). Given the inconsistencies in the literature, Meador (1994) suggests that methodological limitations (e.g., selection bias) preclude empirically sound assessment of the role of AED's on cognitive functioning.

Specific Neuropsychological Functions.

Deficits or relative weaknesses in specific aspects of cognitive functioning are often observed in children with epilepsy, even in the absence of impaired intellectual skills (Schoenfeld et al., 1999). Many children with epilepsy exhibit significant deficits in several neuropsychological domains, including attention, executive functioning, language, visuospatial processing, processing speed, learning, and memory (Farwell et al., 1985; Fedio & Mirsky, 1969; Kolk et al., 2001; Masur & Shinnar, 1992; Stores, Hart, & Piran, 1978). Evidence for the specific effects of seizures has been based on electroencephalographic (EEG) correlates of disruption in neurocognitive and motor performance (Kasteleijn-Nolst Trenite, Smit, Velis, Willemse, & van Emde Boas, 1990). Beyond the well-documented effects of seizures on test performance (during either brief or prolonged episodes, such as status epilepticus) impairment has also been noted in children experiencing subclinical seizure activity (Binnie, Channon, & Marston, 1990).

Attention.

With few exceptions (e.g., Oostrom, Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2002), the majority of studies have found attention difficulties within this population, implicating diffuse neurological dysfunction, frontal lobe damage, subclinical seizure activity, and/or underlying neuropathology as key features of the clinical picture in children with epilepsy (Masur & Shinnar, 1992; Mitchell et. al., 1992; Stores, 1992;

Williams et. al, 1996). Such findings are not surprising given that consistent, uninterrupted responsiveness is a prerequisite for attention (Oostrom et al., 2002). Conversely, seizure activity, by its very nature, may diminish responsiveness to external stimuli, resulting in significant behavioral or cognitively based attention deficits. In two well-designed studies, children with epilepsy were found to exhibit relative deficits in attention, temporary storage, and effortful manipulation of information, as measured by the Wechsler Intelligence Scale for Children – Revised (WISC-R) Digit Span subtest (Forceville, Dekker, Aldenkamp, Alpherts, & Schelvis, 1992; Williams et al., 1996). It is important to note, however, that unlike Williams et al.'s (1996) investigation, the study undertaken by Forceville and colleagues (1992) included children with mental retardation, thereby limiting the generalizability of the study findings.

The impact of seizure-related variables has also been shown to effect attentional abilities. Although seizure type does not appear to influence performance differences on measures of sustained attention (Hara, 1989), children receiving polypharmacy, particularly regimens including Phenobarbital or benzodiazepines (Stores, 1985), are at increased risk for hyperactivity and attention deficits. Additionally, children with an earlier age of seizure onset have exhibited diminished performance on frequently administered measures of attention, visual scanning, and graphomotor speed (e.g., Trails A; D. S. O'Leary et al., 1983).

Executive Functioning.

The presence of neurological damage, particularly in the frontal lobes, may also account for the executive dysfunction often observed in this population (Levin et al., 1996). Executive function is an umbrella term referring to the ability to devise and

maintain a logical strategy for the attainment of purposeful future goals. According to Luria (1973), executive processes are critical for the synthesis of external stimuli, formulation of goals, preparation for action, and engagement of self-monitoring and review that strategies are implemented properly. In a series of recent studies, Slick and colleagues (Sherman, Slick, & Eyrl, 2006; Slick, Lautzenhiser, Sherman, & Eyrl, 2006) reported that approximately 40-50% of children with epilepsy exhibited clinically significant difficulties with planning or working memory. In both of these studies, scores on the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000), a parent-report questionnaire rating executive functioning in daily life, was utilized as the dependant variable. Although Gioia and colleagues' investigation was somewhat lacking in construct validity, as do many studies relying on parent-report rating scales of attention; in general, more objective, performance based measures of this construct (e.g., the administration of a continuous performance task) confirm response inhibition, set-shifting, problem-solving efficiency, and mental flexibility as areas of particular difficulty in this population. (B. P. Hermann et al., 1988; Kolk et al., 2001).

Assessing executive function in children is often considered a challenge in pediatric neuropsychology (Strauss et al., 2006), as many common, well-validated measures of this construct are not always developmentally appropriate for preschool and early childhood aged samples, particularly those with neurological impairments (i.e., Delis Kaplan Executive Function System; Delis, Kaplan, & Kramer, 2001). Perhaps as a result of this limitation, comparatively few group studies have attempted to investigate executive functions across a medically-diverse cross-section of children with epilepsy. Despite a relatively small sample size (n=32), Hernandez et al., (2002) reported

significantly diminished performance on measures of executive functioning (i.e., tasks assessing fluency, flexibility, impulse control, and planning) in children with epilepsy, as compared to healthy participants. A recent study conducted by Bender et al. (2007) is consistent with these findings. In the aforementioned study, children with frontal lobe seizure foci unsurprisingly exhibited the most substantial deficits, as compared to those with temporal lobe epilepsy and generalized seizures (absences). Task performance was also noted to be adversely impacted by antiepileptic medication, although no analyses of group differences between participants receiving polytherapy versus monotherapy were conducted.

Language.

Although severe communication deficits (e.g., acquired aphasia) are typically only observed in children with epileptic encephalopathies, such as Landau-Kleffner syndrome, less profound language deficits are fairly common in children with epilepsy. In their 1999 study, Schoenfeld and colleagues evaluated the language abilities of 7-16 year-old children with complex partial seizures and compared them to a cohort of age-matched sibling probands. Although all children with epilepsy were evaluated as having normal intelligence, language functioning, as measured by scores on the Kaufman Brief Intelligence Test (KBIT; Kaufman & Kaufman, 1990) was significantly lower than the scores obtained by the healthy controls. Moreover, language function (both expressive and receptive) was the most impaired neuropsychological domain evaluated.

A specific constellation of language-related deficits has been reported throughout the pediatric epilepsy literature in the areas of naming, comprehension, reading, and verbal fluency (Hermann et al., 1988b; Rutter et al., 1970; Schoenfeld et al., 1999;

Seidenberg et al., 1986). In a related finding, children with epilepsy reportedly average a one-year lag in reading ability, as measured by grade placement or chronological age (Rutter et. al., 1970). Given the potential for academic underachievement in children with language deficits, it is not surprising that this construct is predictive of future vocational adjustment and independent living in young adults with epilepsy (Dodrill & Clemmons, 1984).

While it is assumed that focal seizures disrupt hemisphere-specific functions (e.g., seizures arising from the left hemisphere result in a relative weakness in language abilities in most right-handers), empirical data supporting this theory are comparatively lacking throughout the pediatric epilepsy literature (Blackburn et al., 2007; Camfield et al., 1984; Cohen, 1992; Williams et al., 1996). The utility of using neuropsychological assessment in this manner has been particularly well-documented in adults (Andelman, Neufeld, & Fried, 2004; B. Hermann & Seidenberg, 2002; Loring & Meador, 2000) as studies have implicated epilepsy type and laterality as contributors to neuropsychological test performance (Bulteau et al., 2000; Pavone et al., 2001). In large part, the comparatively inconsistent findings cited throughout the pediatric literature may reflect the developmental aspects of cognition, as functional specialization is a more dynamic process in children due to cerebral plasticity. For instance, cerebral localization of language in a right-handed adult with left hemisphere epilepsy was speculated to reside in the right hemisphere (Rasmussen & Milner, 1977); however, this process may not become stable until after related developmental processes have occurred. Similarly, focal cerebral dysfunction may not produce its resultant behavioral deficit until a child has reached a certain age when that skill is thought to first manifest itself (Upton &

Thompson, 1997). Studies evaluating hemispheric specialization of function are further limited throughout the pediatric epilepsy literature due to the paucity of investigations utilizing sodium amytal procedures (e.g., Wada tests) in pediatric samples.

Visuospatial Processing.

Despite limited investigation in pediatric populations, visuospatial skills are yet another area in which children with epilepsy differ from normal controls (Pavone et al., 2001; Riva, Saletti, Nichelli, & Bulgheroni, 2002; Tymchuk, 1974). Pavone et al. (2001) report visuospatial skill impairment in children with absence seizures and posit that these deficits, when coupled with a relative sparing of language, are suggestive of right-hemisphere dysfunction. In contrast, a relatively small study (n= 8) conducted by Riva and collaborators (2002) report that children with a left-sided seizure focus performed significantly worse than children with a right-sided seizure focus on a task of "visuospatial analysis" as measured by Wechsler's Picture Completion subtest. It is important to note, however, that Riva's findings may be considered lacking in face and construct validity, as the Picture Completion subtest has high factor loadings on the domain of attention and is not a "pure" measure of visuospatial processing. In addition to laterality of seizure focus, epilepsy type also appears to be a significant risk factor for developing visuospatial and perceptual deficits. Children with epilepsy with occipital paroxysms (e.g., Benign Rolandic Epilepsy; Germano et al., 2005; Weglage, Demsky, Pietsch, & Kurlemann, 1997) and benign childhood epilepsy with centrotemporal spikes (Pinton et al., 2006) are at greater risk for developing difficulties in visuospatial abilities.

Processing Speed.

Similarly, in adults, progressive decline in psychomotor speed has been noted in individuals with temporal lobe epilepsy (Piazzini et al., 2006). Impairments in motor function (e.g., balance, coordination, gross- and fine-motor skills Beckung & Uvebrant, 1993; Cowan et al., 1989) and speed (Beckung, Steffenburg, & Uvebrant, 1997; Beckung & Uvebrant, 1993) have also been consistently reported in the pediatric epilepsy literature. While some studies directly attribute processing speed deficits to the neuronal effects of seizure activity (Vermeulen & Aldenkamp, 1995), other investigators suggest that the extent of psychomotor slowing is dependent on seizure frequency (Aldenkamp et al., 1999) and AED treatment regimen (Aldenkamp et al., 1993; Thompson, Huppert, & Trimble, 1980; Vermeulen & Aldenkamp, 1995). Along similar lines, a recent study evaluating the clinical utility of the NEPSY[3] (Korkman, Kirk, & Kemp, 1999) for use with pediatric epileptic populations, Bender and colleagues (H. A. Bender et al., 2007); Bender & Zaroff, 2005) found that children with epilepsy, particularly those receiving polytherapy, exhibited global difficulties on timed tasks (e.g., speeded naming, fingertip tapping, visual cancellation, auditory attention, and visuoconstruction).

Learning and Memory.

Deficits in verbal and visual learning and in memory have been well documented in children with epilepsy (Jambaque, Dellatolas, Dulac, Ponsot, & Signoret, 1993; Saykin, Gur, Sussman, O'Connor, & Gur, 1989; Signoret & Whiteley, 1979). It has been posited that epileptiform activity, even in the subclinical range, may disrupt the registration, storage, and recall of information (Scheffner & Weber, 1981). In general, memory function within this group appears to be commensurate with overall cognitive

[3] **NE**uro+**PSY**ch= NEPSY. The NEPSY is a relatively age-appropriate neuropsychological test battery appropriate for children aged 3:0:0 through 11:12:30.

abilities; however, even children with intact intellectual functioning can have academic difficulties resulting from memory disorders (Scheffner & Weber, 1981; Stores, 1981; Williams et. al., 1996). Even in cases where the initial memory disturbance is transitory, continuing abnormal activity may adversely impact the acquisition of academic skills, such as reading (Binnie et al., 1990). Although many hypotheses exist regarding the specific causes (e.g., alteration of the cerebral and neurobiological mechanisms underlying discrete cognitive functions), it has been widely suggested that children with partial seizures with temporal lobe and hippocampal involvement are especially vulnerable to memory deficits.

It is widely, yet inconsistently, documented throughout the adult epilepsy literature (see Bell & Davies, 1998, for review) that verbal memory deficits are frequently correlated with left temporal lobe epilepsy (Milner, 1966) and that right temporal lobe epilepsy characteristically produces non-verbal impairment (Smith, 1989). In contrast, similar investigations with pediatric populations report that memory is equally impaired in groups with left or right seizure focus (Williams et al., 1998; Cohen, 1992a,; Lendt, Helmstaedter, & Elger, 1999; Nolan et al., 2003). Jambaque et al. (1993) provided evidence for material-specific impairments in verbal and non-verbal memory in children with temporal lobe epilepsy. However, these authors emphasized the observed differences between children with left temporal lobe epilepsy and healthy participants, as opposed to directly comparing them to children with right temporal lobe epilepsy, thereby weakening the conclusion that verbal memory is impaired in children with left (but not right) temporal lobe epilepsy (Gonzalez, Anderson, Wood, Mitchell, & Harvey, 2007). In a recent publication, Jambaque, Lassonde, & Dulac (2001) suggest that the

equivocal relationship between verbal memory and children with left hemisphere damage may be the result of neuronal plasticity which may allow verbal memory functioning to shift to an undamaged right hemisphere.

Degree of seizure control and treatment regimen are both additional factors that have been associated with reduced performance on verbal and/or visual memory skills. Perhaps unsurprisingly, children with uncontrolled seizures appear to have significantly poorer recall of logical prose (Williams et al., 1996), given the sensitivity of the hippocampus to the effects of repeated or prolonged seizures (i.e., status epilepticus). It is often difficult to interpret the main effects of degree of seizure control and AED therapy on a given construct, as there is a significant degree of overlap between these two variables; individuals with poorly controlled epilepsy are commonly prescribed more than one AED (i.e., polytherapy), whereas monotherapy is more typically reserved for those with well-controlled symptoms. In general, polytherapy has been shown to have a negative impact on verbal and visual memory testing (Williams et al., 1996). Findings from Williams and colleagues (1996) support earlier results that reducing polytherapy to monotherapy leads to improvement in arousal, attention, concentration, and drive (Reynolds, 1983).

The Clinical and Diagnostic Utility of Neuropsychological Testing in Children with Epilepsy

Given the potential for deficits across several domains, neuropsychological testing is considered to be an integral component of a comprehensive epilepsy evaluation as determined by national epilepsy organizational guidelines (Gumnit & Walczak, 2001). In isolation, neurocognitive testing plays a relatively limited role in the diagnostic

process; rather, test findings are often viewed as "consistent with" clinical history and electroencephalogram data, as opposed to "diagnostic of" a seizure-related disorder (Loring & Meador, 2000). However, in clinical settings, neuropsychologists are frequently called upon to provide a baseline of cognitive functioning, predict postoperative cognitive and behavioral changes, and aid in seizure localization/lateralization. In pediatric populations, neuropsychological testing proves exceptionally valuable, as evaluations are often performed to identify early cognitive, academic, and psychosocial impairment, as well as to provide a basis for intervention strategies (Buelow & McNelis, 2002). Some critics cite high costs, the dangers of labeling a child as "learning disabled," and the potentially dire effects of false-positive findings as arguments in favor of limiting the use of testing to epileptic children with recognized deficits (Buelow & McNelis, 2002). However, proponents of comprehensive evaluations argue that early identification of primary neuropsychological deficits provides the best chance of maximizing the opportunity for effective interventions and arresting the development of secondary academic difficulties (Buelow & McNelis, 2002).

Traditionally, neuropsychological evaluations administered to children with epilepsy examine functioning in several major cognitive domains, including: language, attention, psychomotor speed, sensorimotor abilities, executive functioning, visuospatial skills, learning, and memory. Although beyond the scope of the current investigation, screenings of academic achievement are also commonly administered during neuropsychological evaluations. The necessity for academic testing is clear; an overwhelming body of literature suggests that children with epilepsy are at risk for subtle, but significant, learning disabilities (Stores, 1978; Stores et al., 1978; Stores & Hart,

1976) which can decrease the likelihood of future academic and vocational success (Sillanpaa, 2000).

Neuropsychological evaluation in pediatric epilepsy populations are beginning to include an assessment of psychiatric disorders and social skills functioning as part of a child's routine care. An urgent need for early identification and treatment of psychiatric disturbances exists within this population, as suicidal ideation with and without intent was reported in 4.3% and 11% of children with epilepsy, respectively (Ettinger et al., 1998). However, despite the known risk factors, emotional and behavioral functioning are too often overlooked and left unaddressed and untreated. In a recent study by Ott and colleagues (Ott et al., 2003), 61% of study participants met criteria for a DSM-IV psychiatric diagnosis although only 33% received mental health services.

Psychiatric Comorbities of Pediatric Epilepsy

Mood and Behavior-Related Disturbance.

In the classic, community-based Isle of Wight study, Rutter and collaborators (Graham & Rutter, 1968) reported "behavior problems" in 28.6% of children with uncomplicated epilepsies, as compared to 10.3% of children with chronic, non-neurological illnesses and to 6.6% of the general population. In studies comparing children with newly diagnosed epilepsy with other recently diagnosed chronic illness, it was found that children with epilepsy had higher rates of internalizing and externalizing behavior problems than children with diabetes mellitus (Hoare, 1984a), migraine (Brent, 1986), asthma (J. K. Austin, Smith, Risinger, & McNelis, 1994), and cardiac disorders (McDermott et al., 1995). Also, unlike other chronic illnesses with childhood onset (both with and without CNS involvement), epilepsy is unique because of the comparatively

early expression of maladaptive behaviors. Multiple studies have identified behavioral problems in children as early as 6 months *prior* to their first recognized seizure, with nearly 32% of children with newly diagnosed seizures having baseline levels of psychiatric symptomatology in the clinical or at-risk range (Austin et al., 2001; Dunn, Austin, & Huster, 1997). Behavioral problems antedating epilepsy diagnosis suggest that psychiatric disturbance may be integrally linked to the development of epilepsy (Ott et al., 2003).

Numerous studies have addressed the clinical heterogeneity of psychopathology frequently comorbid with pediatric epilepsy. Children with epilepsy frequently experience elevated levels of internalizing disorders (e.g., depression- and anxiety-related symptomatology; (Caplan et al., 1998; Ettinger et al., 1998). In a well-designed study by Ettinger et al. (1998), 26% of children with epilepsy had significantly higher rates of depression than healthy controls, and 16% met criteria for clinically significant anxiety-related disorders. These authors suggest that the incidence of internalizing disorders may be even higher than reported, as depression and anxiety may manifest themselves as irritability or disruptive behaviors in children (Ettinger et al., 1998). Anxiety, in particular, is reportedly difficult to recognize in this population, and is often left undiagnosed and untreated until more overt concomitant behaviors begin to occur (e.g., panic attacks, obsessive compulsive behaviors, and school refusal (Weisbrot & Ettinger, 2001).

Externalizing behavior disorders, such as Attention Deficit Hyperactivity Disorder (ADHD), may be the most commonly-reported behavioral problem in children with epilepsy. ADHD in this population occurs at 3-4 times the prevalence rate of the

general population (Dunn, 2003). More specifically, 28.1% to 39.0% of children with epilepsy exhibit symptoms of ADHD, Hyperactive/Impulsive subtype, and 42.4% exhibit problems with attention (Carlton-Ford, Miller, Brown, Nealeigh, & Jennings, 1995; McDermott et al., 1995).

Although far less frequent, formal thought disorders are also reportedly observed in children with epilepsy at a rate higher than expected based on community-based population estimates. More specifically, in a series of studies evaluating children with complex partial seizures, illogical thinking characteristic of thought disorder and schizophrenia-like symptoms were reportedly associated with early seizure onset and poor seizure control (Caplan, Guthrie, Shields, & Mori, 1992). Interestingly, according to Caplan and co-authors (1997), the thought and communication deficits often observed in this population appear to be the result of underlying neuropathology and unrelated to recurrent epileptogenesis.

Many authors have discussed the multi-etiological factors contributing to the development of emotional, behavioral, and adjustment-related disorders in children with epilepsy. Given the sometimes adverse, unexpected, and uncontrollable nature of seizures, the development of depression and anxiety can also be explained by a learned helplessness model (Dunn et al., 1999). By extension, the unpredictable nature of epilepsy may also contribute to the perception of lacking control (e.g., either an external locus of control or an unknown locus of control; (Dunn et al., 1999), fearfulness, anxiety, and a subjective need for continued parental dependence (Zeigler, 1981). Furthermore, depression in children with epilepsy is also associated with an increase in family stress (J. Austin, Dunn, Huster, & Rose, 1998; J. K. Austin, Risinger, & Beckett, 1992; Buelow et

al., 2003; Brent et al., 1986); report of family difficulties by mothers was a predictor of depression in children with epilepsy (Austin, 1988). Austin and Huberty (1993) posit that depression and epilepsy may be best understood through a cognitive diathesis-stress model of depression, where negative family attitudes towards epilepsy are related to behavior problems and poor self-concept.

From a more neuro-biological perspective, seizure-related variables are widely studied predictors of psychopathology in pediatric epilepsy (Caplan and Gillberg, 1998; Hermann et al., 1988; Ott et al., 2003). Similar to the effect on neuropsychological/cognitive functioning, a child's age at seizure onset is related to their future psychiatric functioning (Hermann et al., 1988). Both early age at onset and longer duration of epilepsy (i.e., number of years in a child's life that they have suffered from epilepsy) have been associated with an increased risk of behavioral disturbances (Caplan et al., 1992; Hermann et al., 1988). Likewise, poor seizure control (J. K. Austin et al., 2001; Dunn, 2003; Dunn et al., 1997; B. P. Hermann et al., 1988; Hoare, 1984; Williams et al., 1996) is a prognostic indicator of future psychopathology. Children receiving AED therapy, particularly those prescribed high treatment doses or more than one medication (i.e., polytherapy) are at additional risk for emergent psychopathology (Harbord, 2000; Ott et al., 2003). In comparison to the seizure-related factors discussed above, lateralization of epileptic foci and epilepsy type are historically weaker predictors of psychopathology in children (J. K. Austin et al., 1992; Camfield et al., 1984; Hoare et al., 1984a).

In addition to the risks of acute psychiatric disturbance and behavior-related academic under-achievement, potentially long-term consequences may result from early

psychological distress (Robertson & Trimble, 1983). More specifically, several authors have suggested that psychopathology in adults with epilepsy may, in some cases, originate in psychological disturbance in childhood and adolescence. Considering the elevated prevalence of psychopathology in adults with epilepsy, which has been estimated to be as high as 80% (Blumer, Montouris, & Hermann, 1995; Mendez, Cummings, & Benson, 1986), successfully identifying and treating emergent psychopathology in pediatric populations warrants close clinical and empirical recognition.

Impairment in Social Skills Functioning.

Although considerable attention has been paid to the psychiatric and psychosocial comorbidities in children with epilepsy, far less emphasis has been placed on evaluating the overt, behavioral social skills associated with peer and social acceptance (Meijer, S. A., Sinnema, G., Bijstra, J. O., Mellenbergh, G. J., & Wolters, W. H; La Greca, 1992; Spirito, DeLawyer, & Stark, 1991). Beyond the possible genetic and neuroanatomic underpinnings of impaired social communication (e.g., autism or pervasive developmental delay), children with chronic illnesses such as epilepsy may develop behavioral social skills impairments due to reduced peer socialization, restriction of physical activity, time-intensive treatment regimens (e.g., dialysis or chemotherapy), an inability to attend school on a consistent basis, actual or perceived stigma related to their medical condition, concerns about physical appearance, and/or interruption of activities of daily living (La Greca, 1990).

It is believed that children who experience difficulty with the pragmatic, organizational, and syntactical aspects of conversation may be viewed by peers as being

poor social communicators (Caplan et al., 2006), leaving them vulnerable to possible ridicule and isolation. Unfortunately, empirical examination of specific behaviors necessary to follow societal rules and social conventions has been largely ignored in the pediatric epilepsy literature. A recent study conducted by Bender and colleagues (Bender et al., 2006; Bender & Zaroff, 2006) reports that "atypical behavior" (e.g., odd or unusual social behaviors characteristic of autism or formal thought disorder) was observed in 36.7% of subjects evaluated. Behaviors of interest, as measured by a rationally-derived[4] parent-report behavior rating scale, included: disorganization of thought processes due to inadequate or inappropriate reasoning, unpredicted changes in conversation topics, restricted elaboration of an ongoing topic of conversation, capacity for change, and scrambled syntax (Bender et al., 2006; Bender & Zaroff, 2006).

It was found that children with epilepsy demonstrated a higher incidence of formal thought disorder and impaired social skills compared to neurologically healthy controls (Caplan et al., 1997). Interestingly, children of average intelligence with partial (complex partial seizures; CPS) and generalized seizures (primary generalized epilepsy; PGE) were observed to engage in illogical thinking and underused linguistic devices to connect contiguous sentences more frequently than children without epilepsy. In a more recent study (Caplan et al., 2002), formal thought disorder was related to lateralization of seizure focus, Full Scale IQ, and degree of seizure control. In contrast, impaired linguistic cohesion (e.g., linking sentences together through word repetition and tying together contiguous clauses) in this population was associated with lateralization of seizure focus. Caplan and others (2002) posit that CPS and PGE disrupt the neuronal

[4] According to Reynolds and Kamphaus (1992), "rationally-derived" rating scales include items focused on clinically or theoretically relevant material useful in arriving at DSM diagnoses. Furthermore, these items were derived by rational means, unlike the Child Behavior Checklist, which is empirically derived.

systems necessary for a child to properly organize and formulate their thoughts. Cortical dysfunction in the fronto-temporal region may play a role in the linguistic deficits that may, in turn, impair social competence (Caplan et al., 2002). Briefly, these areas are important in the integration of thought and language and continue to develop through adolescence (Demonet, Thierry, & Cardebat, 2005). The extensive diminution of neocortical white matter and disturbed metabolic patterns in individuals with childhood-onset temporal lobe epilepsy (B. Hermann & Seidenberg, 2002) further underscores the potential for social communication deficits in this population. In addition to more anterior involvement, an alternative hypothesis implicates dysfunction in posterior cortical areas; conditions such as benign rolandic epilepsy may obscure accurate recognition of emotional cues necessary for normal social development (Deonna & Roulet, 2006).

Additional risk factors for diminished social competence in children with epilepsy are multifactorial in nature (Caplan et al., 2005; Hermann et al., 1988). Some seizure-related variables have been shown to be significantly associated with diminished social competence. Poor seizure control, longer duration of illness, and AED regimen (including valproic acid; a GABA transaminase inhibitor; Hermann et al., 1988) are related to low social competence scores. Type of seizure disorder does not appear to be a robust discriminator of social functioning (Whitman et al., 1982; Williams et al., 1996); rather, a high proportion of children score within the clinically abnormal range in the domain of social competency regardless of seizure type (Sabaz et al., 2003). Children with low Full Scale IQ scores also frequently experience problems with social interactions and display difficulties when responding to social cues (Caplan et al., 2006 ;

Sabaz, Cairns, Lawson, Bleasel, & Bye, 2001). According to Buelow et al. (2003), epilepsy and low IQ may have an additive effect, resulting in even greater social problems.

C. Purpose of the Present Study

Given the potential consequences for the neuropsychological, psychiatric, and social/emotional well-being of children with epilepsy, further investigation into the frequency, severity, and relationships among these domains is warranted. Although several studies have commented on the effects of possible risk factors (e.g., biological, psychosocial, medicinal, and demographic) that have the potential for contributing to deficits in the domains mentioned above, very few studies have considered these data simultaneously in order to evaluate their relative explanatory power. In their 1988 investigation, Hermann and colleagues were the first to establish a set of prognostic indicators of psychopathology and social competence in children with epilepsy. While Hermann's early models are commendable for their consideration of a variety of independent variables, the use of only one parent-report instrument as their dependent measure (Child Behavior Checklist Total Social Competence, Total Externalizing Behavior Problems, and Total Internalizing Behavior Problems), significantly limits the generalizability of their findings. In an attempt to supplement and expand upon Hermann's original theoretical framework, the present study has placed a greater emphasis on neuropsychological functioning and has also added a more clinically-driven parent-report behavior rating scale (the Behavior Assessment System for Children; Reynolds & Kamphaus, 2004) to the model.

The primary purpose of the proposed study is to evaluate the (a) neuropsychological/cognitive functioning, (b) psychiatric status, and (c) social skills of children with epilepsy. In addition to expanding the body of research examining children with epilepsy in these three domains, the effect of seizure-related variables on these areas was also studied. Taken together, these findings allow for the identification of seizure-related and psychiatric predictors of diminished neuropsychological performance in children with epilepsy. To this end, it may be possible to differentiate a subgroup of children with additional treatment needs (e.g., early intervention) prior to school performance being compromised.

D. Hypotheses

Aim #1 was to evaluate the individual and combined contributions of seizure-specific moderating variables on neurocognitive test performance in children with epilepsy. As stated above, it has long been reported that neuropsychological impairment is an important, and often observed comorbidity of chronic epilepsy (for review, see Elger et al., 2004). The existing literature suggests diffuse neurocognitive difficulties in children with intractable seizures (Farwell et al., 1985; Kolk et al., 2001; Smith et al., 2002). Data from preliminary studies conducted at the New York University Medical Center's Comprehensive Epilepsy Center (Bender & Zaroff, 2005; Zaroff & Bender et al., 2004) were consistent with much of the extant literature. Bender and colleagues (2007, 2005, 2004) suggested that, overall, children with epilepsy are impaired in attention, executive functioning, and sensorimotor abilities, compared to non-neurologically impaired same-aged peers. Based on these findings, we posited that

children with chronic epilepsy would exhibit a higher rate of neurocognitive impairment than normative samples on the respective test measures.

For the reasons noted in previous sections, we investigated the potential impact of the following seizure-related variables a) epilepsy type, b) degree of seizure control, c) age at seizure onset, and d) anti-epileptic drug therapy, either individually or in combination, on neurocognitive performance. Based on the findings of multiple authors evaluating children with intractable epilepsy (Bourgeois et al., 1983; O'Leary et al., 1983; Smith et al., 2002; Vasconcellos et al., 2001), it was hypothesized that age at seizure onset would be positively correlated with test performance. Although polypharmacy has been suggested to have a negative impact on cognitive performance (Reynolds, 1983; P. J. Thompson & Trimble, 1982), many authors have concluded that AED's, when present in therapeutic ranges, produce little or no cognitive impairment (Devinsky et al., 1995; Dodrill & Clemmons, 1984). We hypothesized that polytherapy would significantly impact neurocognitive performance (as compared to monotherapy) when seizure frequency is not controlled for as a covariate; we do not predict a difference in performance findings related to number of AEDs when seizure frequency is used as a covariate. Given the broad classification system used to define seizure frequency (i.e., daily, weekly, monthly, and occurring in clusters), we posited that seizure frequency alone would not impact neurocognitive test performance. Given the findings of a similar study conducted by Williams et al. (1996), it was hypothesized that seizure type would not be a significant contributor to neurocognitive functioning in children with epilepsy.

Aim #2 was to investigate the predictive effects of seizure-related variables on the presence of psychiatric disturbance. Given the overwhelming body of evidence

suggesting elevated rates of psychopathology in children with epilepsy (J. K. Austin et al., 2001; Caplan et al., 1998; Caplan et al., 1992; Carlton-Ford et al., 1995; Dunn et al., 1997; Ettinger et al., 1998; Ott et al., 2003; McDermott et al., 1995), it was hypothesized that children with epilepsy would demonstrate a higher frequency of internalizing and externalizing problems than age- matched normative samples. Throughout the existing literature, the role of seizure-related variables on psychopathology remains somewhat equivocal (B. P. Hermann, 1982; Whitman et al., 1982). Due to the increased potential for neuroanatomic damage, developmental delay, and psychosocial impairment, it was hypothesized that younger age at seizure onset and poor seizure control would both be associated with increased rates of psychopathology. These hypotheses are consistent with the findings of many investigators (J. K. Austin et al., 1992; Caplan et al., 1998; Dunn et al., 1997; B. P. Hermann et al., 1988). Despite inconsistent findings throughout the literature (Brent, Crumrine, Varma, Brown, & Allan, 1990; Levinson & Devinsky, 1999), we also positted that children receiving polytherapy would exhibit comparatively higher rates of clinically-significant psychopathology than those receiving monotherapy. Lastly, in contrast to the "epileptic personality" suggested by Nuffield (1961; i.e., children with generalized epilepsy were characterized as neurotic and individuals with partial seizures were described as anti-social and aggressive), it was predicted that seizure type would not be associated with seizure-related disturbance.

Aim #3 was to describe the specific types of atypical overt, behavioral social skills often exhibited by children with epilepsy. We further investigated the relationship between four specific seizure related variables and social communication in this population. The present study investigated specific

"competence correlates" associated with atypical peer and social interaction in children with various seizure types, ages at onset, seizure frequencies, and treatment regimens. In many studies (Caplan et al., 2006; Hermann et al., 1988; Hoie, Mykletun, Waaler, Skeidsvoll, & Sommerfelt, 2006; Jakovljevic & Martinovic, 2006; Sabaz et al., 2003), behavioral social skills were evaluated using parent-report ratings assessing competence in the following domains: activities (e.g., sports and hobbies); social (e.g., friendships and interpersonal skills); and school (e.g., performance, ability, and school problems). Although each of the aforementioned studies concluded that epilepsy is a limiting factor for social competence in children with epilepsy, the scope of this construct (i.e., "social competence") may not fully capture the range of behaviors characteristic of some children with epilepsy. Rather, for the purposes of the present study, behavioral social skills were defined as the presence of illogical and irrational thought processes, stereotyped behaviors, uncommon linguistic and conversational characteristics, restricted range of interests, and negative reaction to change. A recent investigation by Bender, Auciello, and colleagues (2006) is the only known study to date which has evaluated social functioning in this manner with a sample of children with epilepsy. In our earlier investigation, a clinically-significant elevation on a parent-report scale measuring atypical behaviors was observed for 36.7% of the children evaluated. Based on the small available body of literature reviewed, as well as preliminary results from our own study, it was hypothesized that the present sample would have diminished social skills and behavioral appropriateness compared to a neurologically-healthy standardization sample. Furthermore, we posited that regardless of epilepsy type and treatment, increased seizure

frequency and younger age at seizure onset would be predictive of reduced social-behavioral functioning.

Finally, Aim #4 was to integrate the three previous Aims by examining the relationship among emergent psychopathology, social-behavioral functioning, and neurocognitive test performance as moderated by seizure-related variables. As discussed throughout, considerable debate exists regarding the relationships among epilepsy, neurocognitive performance, psychopathology, and social competence. According to Hermann and co-authors (1988), much of the discussion surrounds the role of seizure-specific variables in predisposing children with epilepsy to a range of neuropsychological, psychiatric, and behavioral comorbidities. In their 1988 investigation, Hermann et al. suggested a model which considers the multi-etiological determinants (e.g., biological, psychosocial, medication, and demographic) of psychopathology and social competence in children with epilepsy. While Hermann and colleagues (1988) did not integrate neuropsychological test performance and specific behavioral social skills into their model, these authors provided a framework for a better understanding of the moderators of psychopathology in this population.

In an effort to extend and expand upon Hermann's model, Aim #4 was to establish a set of predictors regarding test performance by evaluating the predictive value of psychiatric and social status on neurocognitive test performance with and without utilizing seizure-related variables as a covariate. We hypothesized that the presence of clinically-impaired externalizing behaviors, impaired social competence, younger age at seizure onset, poor degree of seizure control and multi-drug treatment regimen (i.e.,

polytherapy) would each have clinically significant explanatory value in relation to neuropsychological test performance.

CHAPTER TWO

II. Methods

A. Participants

The present study was approved by the Institutional Review Boards (IRBs) of New York University School of Medicine and Queens College, City University of New York. A total of 60 children and adolescents (six to 17 years of age) receiving a neuropsychological evaluation at New York University Medical Center's Comprehensive Epilepsy Center (NYUCEC) from 2004-2006 were included in the present study. In most cases, neuropsychological testing was administered in one to two testing sessions; however, some participants were tested over the course of several days due to medically-related interruptions (i.e., seizures, unavailability in hospital setting, and post-ictal fatigue). Fifty-four of these participants completed the parent-report rating scales during a single inpatient admission or outpatient visit at NYUCEC during which the neuropsychological testing was performed. Six subjects were contacted via telephone and were asked to complete the parent-report questionnaires independently and remit them to NYUCEC for analysis.

A diagnosis of epilepsy, as defined by the International Classification of Epilepsies, was required for inclusion. A Full-Scale IQ of $\geq$ 70 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), Wechsler Intelligence Scale for Children- Third Edition (WISC-III; Wechsler, 1991), or Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV; Wechsler, 2003) was also required. Exclusionary criteria included vision or hearing impairment (as noted in the participant's

medical chart), an invalid response profile on study measures (e.g., elevated "F" index on the Behavior Assessment System for Children – Parent Report Scale, an index of unusually extreme maladaptive behavior), and/or a history of intracranial surgical intervention for seizure disorder (i.e., craniotomy or hemispherectomy). As shown in Table 1, 60 children with epilepsy (22 male and 38 female) were selected to participate in this study. As presented in Table 2, participants had a mean age of 11.91 years (SD = 3.01) and a mean Wechsler Full Scale IQ of 93.63 (SD = 16.42). Six children currently receiving psychopharmacological intervention for an existing psychiatric condition were included for all analyses and subsequently excluded in order to compare findings in a treatment-naïve cohort.

B. Evaluation of Seizure-Related Variables

A review of medical history (as per the participant's chart) was conducted for each participant. Epilepsy type was categorized as either partial or generalized, based on reported clinical history and video-EEG evidence. Seizure frequency, often referred to as "degree of seizure control" was highly variable across the sample studied. Given this heterogeneity and the fact that some of the seizures occurred when the children were not actively observed by their parents, physicians, or inpatient video monitoring (e.g., nocturnal seizure or events occurring at school), it was not possible to provide an exact count of seizure frequency, even over a short period of time. As such, a categorical classification of seizure frequency was calculated for each study participant based on the following criteria: a) seizures occurring daily, b) seizures not occurring daily, but at least once per week, c) seizures not occurring each week, but at least once per month, d) seizures occurring in clusters, during which the child experiences more than two seizures

over a one-to-two-day period, followed by seizure-free intervals lasting more than 2 weeks in duration, and e) no current seizures. The above described classification system was first described by Smith, Elliott, and Lach (2002). Age at seizure onset was recorded as a continuous variable. AED treatment regimen was coded as a categorical variable; participants were receiving a) monotherapy, b) polytherapy, or c) medication-free. Due to the many combinations of AEDs represented in this sample, the role of individual AEDs (e.g., Keppra or valproic acid) was not evaluated in the present study.

C. Measures

The WASI, WISC-III, or WISC-IV was administered to each child individually. In addition to estimates of global intellectual functioning, the current study investigated performance in six major neuropsychological areas (i.e., attention, executive functioning, language, visuospatial processing, processing speed, learning and memory). As previously stated, the present study also sought to determine the predictive value of psychiatric status and behavioral social skills on neuropsychological test performance. Both empirically- (Child Behavior Checklist) and rationally-derived (Behavior Assessment System for Children) parent-report behavior rating scales were selected in order to evaluate level of functioning from two conceptually distinct perspectives.

The neuropsychological and behavioral data collected were obtained from routinely administered, non-invasive measures of cognition and psychiatric status. All test measures have well-established validity and reliability. The questionnaires, neuropsychological tests, and cognitive instruments were administered by psychologists-in-training (overseen by licensed clinical psychologists), graduate level project assistants,

or a senior clinical neuropsychologist. Descriptions of the specific tests administered are ennumerated below:

Intelligence Tests.

For the purposes of the present study, children were administered one of the following: Wechsler scales of intelligence, the four-subtest Wechsler Abbreviated Scale of Intelligence (WASI), the Wechsler Intelligence Scale for Children- Third Edition (WISC-III), or the Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV). In two cases, a Full Scale IQ was derived from a two-subtest administration of the WASI (Vocabulary and Matrix Reasoning subtests). For children receiving the two or four subtest WASI, participants were also administered two additional subtests, the Digit-Symbol Coding and Digit Span subtests, from either the WISC-III or WISC-IV.

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) is a brief, reliable measure of intelligence. This measure was administered to each child individually and yielded a Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). The Verbal Scale consistsed of Vocabulary and Similarities subtests, and the Performance Scale wa comrpised of Matrix Reasoning and Block Design Sutests. WASI subtests parallel Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997a) subtests in content. The four-subtest administration of the WASI took approximately 30-45 minutes to complete. As per the WASI manual (Wechsler, 1991), the standardization sample of the WASI is representative of the U.S. English-speaking population and consisted of 2,245 individuals ranging in age from 6-89 years of age. Concurrent validity studies comparing the WASI to other Wechsler scales, the Wechsler Adult Intelligence Scale-III, the Wechsler Intelligence Scale for Children-III, and Wechsler Intelligence Scale for

Children-IV suggested a high degree of correlation among these measures (Zhu, Tulsky, & Leyva, 1999). The composite Full Scale IQ (FSIQ) has a mean of 50 and a standard deviation of 10, whereas the individual subtests (e.g., Block Design) have a mean of 10 and a standard deviation of 3. The dependent variables of interest in this study were Full-Scale IQ Score, Vocabulary subtest Scaled Score, Block Design subtest Scaled Score, and Matrix Reasoning subtest Scaled Score.

Wechsler Intelligence Scale for Children- Third Edition (WISC-III; The Psychological Corporation) is a multifaceted test of intelligence that was used to generate an overall estimate of intelligence (FSIQ, M=100, SD=15). The dependent variables of interest were the Full-Scale IQ, Block Design subtest Scaled Score, Matrix Reasoning subtest Scaled Score, Vocabulary subtest Scaled Score, Digit-Symbol Coding subtest Scaled Score, and Digit Span subtest Scaled Score. A more detailed description of the individual subtests comprising the WISC-III are provided below, in their respective subsections.

Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV; The Psychological Corporation, 2003) The WISC-IV was recently normed on 2,200 English-speaking children and is the most updated revision of the scale. The dependent variables of interest were the Full-Scale IQ, Block Design subtest Scaled Score, Matrix Reasoning subtest Scaled Score, Vocabulary subtest Scaled Score, Digit-Symbol Coding subtest Scaled Score, and Digit Span subtest Scaled Score. A more detailed description of the individual subtests comprising the WISC-IV are provided below, in their respective subsections.

Neuropsychological Tests.

The present study evaluated neuropsychological functioning of children with epilepsy in the following domains: attention (timed visual sequencing and working memory), executive function (set-shifting and nonverbal abstract reasoning), language (vocabulary and confrontation naming), visuospatial skill (visual block construction and pattern analysis), psychomotor speed, verbal learning and memory (serial list learning), and nonverbal learning and memory (complex figure learning and memory).

Measures of Attention.

Trail Making Test – Trails A (Reitan & Wolfson, 1993) is a timed assessment of attention, visual scanning, and graphomotor speed. Part A required children to connect 25 numbered circles in ascending order as quickly, but as accurately as possible. A sample trial was completed prior to testing; teaching was permissible only during the sample period. Children were instructed that if they make an error during their performance on this task, they would be corrected by the Examiner. Total completion time in seconds for Trails A was the dependent measure of interest.

Digit Span subtest from the Wechsler Intelligence Scale for Children-III or Wechsler Intelligence Scale for Children- IV is a measure of attention span and mental control that was presented from either the WISC-III or WISC-IV. The Digit Span subtest is a core Working Memory subtest and is comprised of 2 parts, Digits Forward and Digits Backward.

On Digits Forwards, children were required to repeat a sequence of progressively longer number strings in the forward direction. On the WISC-III or IV, Digits Forward is comprised of sixteen items; the task was discontinued when two consecutive incorrect

responses were provided for a string with the same number of digits. Fifteen trials from Digits Forward from the WISC-III were retained on the WISC-IV.

The Digits Backward component of this subtest adds an additional level of complexity, as children were required to hold the presented digits in mind while simultaneously exhibiting the cognitive flexibility necessary to repeat the digits in the backwards direction. Like the Digits Forward, Digits Backward is also comprised of 16 items; 12 items from the WISC-III Digits Backward were retained on the WISC-IV. The dependent measure of interest was the total age-based Scaled Score generated by each participant.

Measures of Executive Functioning.

Trail Making Test – Trails B (Reitan & Wolfson, 1993) was administered to measure visual sequencing and set-shifting. Like Trails A, a sample trial was completed prior to testing and children were corrected if an error was made during task completion. Part B of the Trail Making Test required participants to connect 15 consecutively numbered and lettered circles by alternating between numbers (in ascending order) and letters (in alphabetical order). The dependent measure was the time taken to complete Trails B.

Matrix Reasoning subtest from the Wechsler Abbreviated Scale of Intelligence or the Wechsler Intelligence Scale for Children IV is a non-verbal task of visual information processing and abstract reasoning. This subtest is highly similar whether it is a component of the WASI or WISC-IV. On each of the Wechsler scales, the Matrix Reasoning subtest is comprised of 35 items; children were asked to complete the missing portion of an incomplete matrix from five response options. Matrices are arranged in

four patterns: continuous and discrete pattern completion, classification, serial reasoning, and analogical reasoning. The dependent measure was the total age-based Scaled Score.

Measures of Language Abilities.

Boston Naming Test (BNT - 2nd Edition; Kaplan, Goodglass, & Weintraub, 1983) is a 60-item measure of confrontation naming which evaluates a child's ability to spontaneously name line-drawn pictures of objects, as well as their responses following semantic and/or phonemic cueing. Items were scored as "correct" if they were named spontaneously or after a stimulus (semantic) cue. The dependent measure in this study was the total number of correct responses (spontaneous + semantic) provided.

Throughout the adult literature, measures of confrontation naming are believed to be particularly sensitive to left hemisphere dysfunction. Numerous studies have found group differences on confrontation naming measures between participants with left (dominant) and right (non-dominant) seizure foci, with individuals with left-sided dysfunction obtaining lower scores on such tasks (Busch, Frazier, Haggerty, & Kubu, 2005; B. P. Hermann & Wyler, 1988; B. P. Hermann, Wyler, & Somes, 1991; Mayeux, Brandt, Rosen, & Benson, 1980). Though findings in the pediatric literature are somewhat less convincing regarding the diagnostic utility of confrontation naming tasks in lateralization of seizure focus (Fedio & Mirsky, 1969 ; Jambaque et al., 1993), the BNT is arguably one of the most frequently administered measures of this construct across all age groups (i.e., early childhood through adulthood; (Busch et al., 2005).

Vocabularly subtest from the Wechsler Abbreviated Scale of Intelligence or the Wechsler Intelligence Scale for Children is a measure of expressive vocabulary. Participants were presented with written words which they were asked to define. The WASI and WISC-IV

are both slightly different in administration from the WISC-III because the latter does not include picture items which extend the floor of the subtest. On the WISC-III, if the child failed to receive full credit on either of the first two items administered, they were then asked to name pictures displayed in the Stimulus Book. While the difference in administration was only evident when the "reverse rule" was used (i.e., when the first two items failed to receive full credit), the picture vocabulary items were used for several of the participants in the studied sample. Twenty-seven verbal items from the WISC-IV were retained from the WISC-III; five new verbal items were added (WISC-IV Technical Report, The Psychological Corporation). The dependent measure was the total age-based Scaled Score.

Measures of Visuospatial Functioning.

Rey Osterreith Complex Figure Test – Copy Condition (ROCFT; Osterreith, 1944) is a measure of visuoconstructional ability; due to the complexity of the figure, the ROCFT copy condition also reflects the participant's organizational and planning abilities. This task required the child to copy a complex geometric design with numerous embedded details. Based on the accuracy and placement of the items, scores ranging from 0 points to 2 points (i.e. 0 points, .5 point, 1 point, and 2 points) were assigned to each of the 18 figure components (Meyers & Meyers, 1995), for a total possible score of 36. The dependent measure was the total number of points the child received on the ROCFT Copy condition.

Block Design subtest from the Wechsler Abbreviated Scale of Intelligence or the Wechsler Intelligence Scale for Children The Block Design subtest is a visual construction task which requires participants to view either a three-dimensional

Examiner-constructed model or a two-dimensional picture and to re-create the designs within a specified time limit. Relatively intact visual perceptual and spatial skills are necessary to perform this task successfully (Sattler, 1988). Designs were constructed using four or nine six-sided square blocks; two sides were red, two sides were white, and two sides were red and white, divided diagonally. As predicated by the discontinuation rule, the subtest was discontinued after three consecutive designs were produced for which no credit was given. Although the principles of this task remain the same regardless of the Wechsler scale that it belongs to, ten items from the WISC-III were retained on the WISC-IV, and four new items were created. The dependent measure was the total age-based Scaled Score.

Measures of Processing Speed.

Digit-Symbol Coding subtest from the Wechsler Intelligence Scale for Children –III or Wechsler Intelligence Scale for Children IV is a graphomotor coding task measuring sustained attention and processing speed. On this task, the child was required to copy symbols that are paired with numbers. Using a key located at the top of the page, the child then drew a symbol (based on its corresponding number) in each box within a specified time limit. Both forms of Digit-Symbol Coding on the WISC-IV were retained from the WISC-III. The dependent measure was the total age-based Scaled Score.

Measures of Learning and Memory.

Rey Osterreith Complex Figure Test – Delayed Recall Condition (ROCFT; Osterreith, 1944). After copying the presented geometric figure (see Rey Osterreith Complex Figure Test – Copy Condition discussed above), the child was asked to reproduce the figure from memory following a 30-minute delay; no prior warning was given. As stated, based

on the accuracy and placement of the items, scores ranging from 0 points to 2 points (i.e., 0 points, .5 point, 1 point and 2 points) were assigned to each of the 18 figure components (Meyers & Meyers, 1995). The dependent measure was the total number of points the child received on the ROCFT Delayed Recall condition.

California Verbal Learning Test- Children's Version (CVLT-C; Delis, Kramer, Kaplan & Ober, 1994). The CVLT-C is a frequently administered list-learning test that assesses a child's ability to learn and recall items from a serially presented word list. Children were read a "shopping list" (List A) of 15 items (belonging to 3 conceptual categories) over the course of five consecutive presentations. Items were presented in a fixed order. The ability to recall the previously presented word list was measured immediately following each of the five list presentations. Following the five learning trials, a second list, comprised of new words from similar conceptual categories, was then presented for "interference." Recall of items from the interference list was also measured immediately following presentation. Participants were then asked to recall items from the first list (presented five times), with and without the aid of semantic cues. Semantic cues were then given to provide a concrete framework for categorical clustering. After a 20-minute delay, the ability to recall and recognize the words was again tested, first with free-recall and then with semantic cues. A forced-choice recognition trial was then administered by presenting children with a list of 45 words, including the 15 words belonging to the initial list. Participants were asked whether each word was on List A or not. The CVLT-C was scored with the assistance of a computer program. While numerous variables were generated (n= 27) through computer-scoring, for the purposes of the present study, the dependent measures were the total number of correct, spontaneously recalled words

generated during the learning trials (e.g., Total Trials T-score, M= 50, SD= 10) and the total number of spontaneously recalled words generated during the delayed-recall trial (Long Delayed Recall Z-score, M=0, SD= 1).

Measures of Psychiatric Symptomatology and Social-Emotional Processing

In addition to the neuropsycholgical test data described above, scores from routinely administered parent-report behavior ratings were also collected. All proposed measures of psychiatric functioning and social-emotional processing behavior have well-established validity and reliability. Brief descriptions of these measures are provided below.

The Child Behavior Checklist/Ages 6 -18 (Achenbach & Rescorla, 2001) is a parent-report behavior rating scale appropriate for 6 -18 year-old children. Parents responded to 118 items by rating their child on a three-point scale (e.g., 0= "not true," 1= "somewhat or sometimes true," and 2= "very true"). In several cases, the same item contributed to more than one scale. This measure yielded an overall symptom index (i.e., Total Problems), two broad-band dimensions (i.e., Internalizing, Externalizing), and eight narrow-band syndrome scales (i.e., Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior). Computer software available from the Achenbach System of Empirically-Based Assessment was used to score the checklists. In a method similar to Dorenbaum and colleagues (Dorenbaum, Cappelli, Keene, & McGrath, 1985), normative comparisons were based on the standardization sample provided by the CBCL scoring program.

Scores for the CBCL consisted of raw scores and converted T-scores (M = 50, SD = 10) using age-appropriate normative data. For the broad-band scales, T scores from 60 to 63 represented "Borderline Clinical" symptoms and T scores ≥64 represented "Clinical" range symptoms. For the syndrome scales, T scores from 65 to 69 represented "Borderline Clinical" symptoms whereas T scores ≥70 represented "Clinical" range symptoms.

The Behavior Assessment System for Children – 2 - Parent Rating Scales (BASC-2-PRS) (Reynolds, 1983) is a parent-report adaptive functioning and behavior rating scale that has developmentally-appropriate versions for preschool (2-5 years), child (6-11 years), and adolescent (12-21 years) age groups. Parents responded to 130 items by rating their child on a 4-point scale of behavior frequency (ranging from "never" to "almost always"). Individual items assess aspects of childhood behavior and personality across home, community, and school settings. There are also scales assessing the validity of individual's responses.

The Behavior Assessment System-Parent Report System (Reynolds, 1983) was administered to five participants who were evaluated prior to the release of the BASC-2-PRS. The original and revised versions of the BASC are very similar in their item scope, content, and scoring, and have strong correlations between their resultant broad- and narrow-band scales (Reynolds, 1983). As noted in the BASC manual, the Parent-Report Scale has excellent internal consistency, test-retest reliability, and content and construct validity (Reynolds, 1983).

Broad-band composite scores on the BASC-2-PRS included the Behavioral Symptoms Index and the Internalizing and Externalizing Symptom Indices. Narrow-

band scales included Aggression, Anxiety, Attention Problems, Atypicality, Conduct Problems, Depression, Hyperactivity, Withdrawal, and Somatization. Unlike the Achenbach scales, the BASC scales were developed so that each item contributed to only one narrow-band scale, thereby allowing each scale to remain a distinct measure of that specific construct (Reynolds, 1983).

As stated in Specific Aims #3 and #4, assessment of behavioral social skills is one of the other major foci of the present study. This construct was measured via parent-report data assessing odd and unusual behaviors reflective of possible psychosis, formal thought disorder, or autism. When assessing behavioral social skills, the dependent varible of interest was the total score from the BASC Atypicality Scale. Items loaded on the BASC-PRS Atypicality Scale include, but are not exclusive to: "does strange things," "babbles to self," "repeats one thought over and over," "seems out of touch with reality, " "acts if other children are not there," "seems unaware of others," "says things that make no sense," and "shows feelings that do not fit the situation."

Scores for the BASC-2-PRS consisted of raw scores and converted T-scores (M = 50, SD = 10) obtained using age-appropriate norms. T-scores falling between 40 and 60 were considered to be within normal limits. T scores of 60-69 (1-2 standard deviations above the mean) on the clinical scales were considered "At-risk," whereas T-scores of 70 or above fall in the "Clinical" range. The Anxiety scale (both child and adolescent) has lower cut-off scores for the "Clinical" range; scores 60-64 were considered "At-risk," and scores 65 and above were within the "Clinical" range.

D. Plan for Statistical Analyses

Results were analyzed using the Statistical Package for the Social Sciences (SPSS) - Windows version, 11.5.

Aim #1

Descriptive statistics were obtained for all 13 neurocognitive measures administered. Mean z-scores were computed for each neurocognitive domain (intelligence, attention, executive functioning, language, visuospatial processing, processing speed, learning and memory) and served as the primary dependent measures analyzed for Aim #1. Z-scores, rather than raw scores, were selected for this purpose in order to analyze data in a standard metric, instead of comparing raw data normed with different standardization samples. Group differences based on demographic characteristics (e.g., race and years of education) were determined via independent sample t-tests or one-way analyses of variance (ANOVAs), as appropriate. Where indicated, analyses were adjusted for heterogeneity of variance. As the primary goal of Aim #1 was to determine whether seizure-related variables have differential effects in children with epilepsy across a variety of neurocognitive measures, a series of t-tests and one-way ANOVAs were also performed with seizure-related variables as the dependent measures. Group comparisons were made based on the following seizure-related characteristics: a) epilepsy type, b) degree of seizure control, c) age at seizure onset, and d) anti-epileptic drug therapy. A series of multiple regressions were also conducted to investigate the predictive effect of each seizure-related variable on neuropsychological test performance. The assumptions underlying regression analysis (e.g., homogeneity of

variance, independence, and normalcy of error variance) were evaluated both graphically and statistically before any conclusions were drawn.

Since analyses undertaken in previous studies (Bender et al., 2007) have indicated considerable variability in performance across all neurocognitive measures, these data were also examined by establishing ranges in terms of clinical criteria for performance. Similar to the analyses performed by Smith, Elliott, and Lach (2002), scores less than 1 SD below the mean or above for the normative data was classified as "average or above," scores between 1-2 SDs below the mean were classified as representing "mild to moderate impairment," and scores more than 2 SDs below the mean were considered indicative of "severe impairment." The percentage of participants within each group in each of these performance ranges was calculated, and the potential differences were explored through χ^2 analyses.

Aim #2

Descriptive statistics included the means and standard deviations of scores on the BASC-PRS and CBCL/6-18. For the purposes of Aim #2, the T-scores of the following broad- and narrow-band scales were analyzed to examine psychiatric and behavioral maladjustment; "B" denotes a broad-band scale and "N" denotes a narrow-band scale. From the CBCL, the following dependent variables were analyzed: Internalizing Problems Scale score (B), Externalizing Problems score (B), Total Problems score (B), Withdrawn/Depressed Scale score (N), Anxious/Depressed Scale score (N), and Attention Problems score (N). From the BASC, the following data were also evaluated: Internalizing Problems score (B), Externalizing Problems score (B), Behavioral Symptoms Index score (B), Depression Scale score (N), Anxiety Scale score (N),

Attention Problems score (N), and the Hyperactivity Scale score (N). The percentage of the sample obtaining scores in the clinically significant range, denoted "Clinical," was computed for each scale. For the BASC-2, the term "At-risk" was adopted for those scores falling in the "At-risk" range on the BASC-2 and for scores falling in the "Borderline Clinical" range on the CBCL. The classification system of both the BASC and CBCL interpreted scores as falling within the "normal," "borderline," or "clinically significant" ranges according to their respective test manuals. In addition to conducting all analyses using the three aforementioned classifiers, all analyses were repeated, with psychiatric functioning classified as either "normal" or "abnormal" (collapsing the borderline and clinically significant ranges). Additional exploration involved segregating subjects into groups based on clinical ranges on the CBCL and BASC and then comparing across these groups.

As the primary goal of Aim #2 was to investigate whether observed subject differences on parent-report measures of psychiatric symptomatology related to differences in seizure-related characteristics, multiple t-tests and ANOVAs were conducted. Multiple regression analyses were then performed to determine which seizure-related variables, if any, significantly predicted elevated levels of psychopathology on broad-band (e.g., global evaluations of internalizing and externalizing symptomatology on the CBCL and BASC) and narrow-band behavior scales (e.g., CBCL Withdrawn/Depressed scaled score). The above analyses were repeated excluding children receiving psychopharmacologic intervention for psychiatric and behavioral disturbance (n = 4) in order to evaluate the data with a treatment-naïve cohort.

Aim #3

For the purposes of Aim #3, T-scores on the following broad- and narrow-band scales were again analyzed to examine relationships to social skills functioning and overt, behavioral social communication. From the CBCL, the Thought Problems (N) score was analyzed and from the BASC-PRS, the Social Skills Problems score (N) and Atypicality Scale score (N) were evaluated. Independent samples t-tests and one-way ANOVAs were conducted to evaluate whether observed subject differences on parent-report measures of social skills were related to categorizations of seizure-related characteristics. Then, multiple regression analyses were performed to determine whether there was a pattern of prediction for seizure variables on social-emotional development. Similar to procedures undertaken for Aim #2, indicators of social functioning were also classified as "normal" or "abnormal;" subjects were segregated into groups based on these classifications, and seizure-related variables were compared across these groups. Again, the above analyses were repeated excluding children receiving psychopharmacologic intervention for psychiatric and behavioral disturbance in order to evaluate the data in a treatment-naïve cohort.

Aim #4

The fourth and final aim was the combination of all of the aims explored in #1 through #3. An analysis of covariance (ANCOVA) was conducted to evaluate whether seizure-related variables (either individually or in combination) mediate the effect of psychiatric symptomatology and social skills on neuropsychological test performance.

CHAPTER THREE

III. Results

A. Sample Characteristics

Table 1 summarizes the IQ, demographic (i.e., sex, race, and SES), educational (i.e., years of education and special education status), and seizure-related characteristics (i.e., seizure type, age at seizure onset, duration of seizures, seizure frequency, and treatment regimen) of the studied sample.

As shown in Tables 1 and 2, 60 children with epilepsy (22 male and 38 female) were selected to participate in this study. Participants had a mean age of 11.91 years (SD = 3.01), an average of 6.71 years of education (SD = 3.02), and a mean Wechsler Full Scale IQ of approximately 94 (SD = 16). The majority of participants were Caucasian (77%); the remaining participants were Hispanic (12%), African-American (7%), and Asian (5%)[5]. The following seizure variables were examined: a) age of seizure onset, b) duration of seizures, c) seizure frequency, d) seizure type, and e) treatment regimen. Where appropriate, these variables were further collapsed or dichotomized in order to conduct chi-square and regression analyses, and to increase power in the ANOVAs (i.e., by increasing group sizes). This variable was collapsed from six (i.e., no seizures currently, cluster seizures, at least 1 seizure per year, at least 1 seizure per month, at least 1 seizure per week, at least one seizure daily) to four groups (i.e., no seizures currently, >1 seizure per year and cluster seizures, weekly or monthly seizures, and daily seizures) for the ANOVAs and for chi-square and regression analyses.

[5] Percentages do not add up to 100% due to rounding.

It was noted that there were several extreme outliers in five of the seven neurocognitive domains. As these participants met all inclusion criteria, there was no methodological basis to exclude them from further analyses. However, additional analyses that excluded outliers with domain scores of $z \leq -5.00$ were conducted to assess their impact on the findings. Where applicable, the differences in findings are discussed. Table 4 reports sample size, means (z-score), and standard deviations of neurocognitive domains with outliers excluded.

B. Results of Individual Aims

Aim #1

As stated in the Methods section, all instruments were administered according to the standardized procedures for each test, as outlined in their respective manuals. Subtest scores were converted to age-corrected standardized scores (e.g., scaled scores, standard scores, T-scores, and *z*-scores) by using the respective normative data for each. In an effort to reduce the number of variables and thereby maximize statistical power, individual subtest data were combined, *a priori,* into seven broader neurocognitive domains (See Table 3). Individual subtests were grouped by domain based on the putative constructs they are believed to measure (Lezak, 2004). Similar to methods employed by Mandelbaum and Burack (1997), domain summary scores were created for the seven cognitive domains for each participant by taking the mean of the *z*-scores across the related neuropsychological tests. Means and standard deviations of each of the 15 individual subtest scores and seven broader neurocognitive domains for the total sample and by seizure variable are presented in Table 4.

Preliminary Analyses.

In order to ensure that the results of the main analyses were not confounded by demographic factors, the effects of age, sex, race, SES, and Special Education status on all seven neurocognitive domains were tested using ANOVAs or independent sample t-tests (2-tailed), where applicable. Descriptive statistics and results for these analyses are presented in Table 5. Of note, the assumption of equal variances was examined using Levene's test. In cases where variances were found to be unequal, appropriate statistics were applied[6]. In cases where a significant F-ratio was identified ($p<.05$; 2-tailed) post-hoc, multiple comparisons were conducted. The Games-Howell statistic was selected to conduct such analyses because it is robust in populations with unequal variances, differing sample sizes between groups, and when normality cannot be assumed (Games and Howell, 1976).

As illustrated in Table 5, sex was identified as a potential covariate in analyses of processing speed, as boys (M = -.45, SD = 1.17) were found to be significantly faster than girls (M= -1.23, SD =1.01; p< .01). The implications of this finding will be discussed below. As expected, the children receiving special education services represented the majority of the children obtaining with domain scores of $z \leq -5.00$. Prior to removal of these outliers, Special Education status was significantly associated ($p <$ .05) with diminished performance across many neurocognitive domains (e.g., Full Scale IQ, Visuospatial Skills, and Attention). When outliers were excluded, the effect of special education status only retained statistical significant affects on FSIQ ($p< .05$). Additionally, the effect of race was significant in 5 of the 7 cognitive domains: FSIQ, Language, Visuospatial Skills, Attention, and Learning and Memory. Post-hoc analyses

[6] Browne-Forsythe (F^*)

revealed that Asian-Americans performed significantly better than Caucasians, African-Americans, and Hispanics in all cases. It is important to note that Asian-Americans comprised only 5% of the total studied sample (n = 3), and that the individual scores received by members of this racial/ethnic group were relatively homogenous when compared to the three other groups studied. Furthermore, there were no significant differences in performances among the remaining racial groups. The effect of SES was significant with respect to FSIQ; children belonging to the lower SES group (M = -1.49, SD = .43) scored lower than children from middle (M = -.57, SD = 1.11) and upper (M = -.16, SD = 1.09) SES groups ($p < .05$). Pearson Product Moment Correlations were performed to evaluate the relationship between continuous demographic and educational variables (i.e., age and years of education) and neurocognitive test performance; none were statistically significant.

Chi-square tests were conducted to evaluate the relationship between neurocognitive performance and the following seizure-related variables: age at seizure onset, seizure frequency, seizure type, and treatment regimen. Cutoff scores were set up to divide neurocognitive performance into the following three groups: 1.) Average or above ($z > -1$); 2.) Mild to Moderate Impairment ($-2 < z < -1$); and 3.) Severe Impairment ($z < -2$). As indicated in Table 6, the association between seizure type and scores on the Learning and Memory domain approached significance ($p = .09$), this relationship no longer trended towards significance when outliers were removed from the sample ($p < .10$). No other significant associations between seizure type and neurocognitive test performance were noted. The relationship between treatment regimen and the Learning and Memory domain score was significant ($p = .04$) both with

and without the exclusion of outliers, with poorer performances seen for those participants receiving polytherapy versus those who were prescribed one or fewer antiepileptic medications. Treatment regimen was not associated with performance on any of the remaining six neurocognitive domains. Age at seizure onset was not associated with performance on any of the remaining neurocognitive domains. None of the associations between age at seizure onset, seizure frequency, and neurocognitive performance was significant within the total sample. However, when outliers were excluded, the relationship between language and age at seizure onset approached statistical significance ($p = .06$).

Descriptive statistics and results across neurocognitive domains for specific seizure-related variables are presented in Table 6. Group means were then compared using ANOVAs for age of onset, seizure frequency, and treatment regimen, and t-tests for seizure frequency in order to compare the degree to which seizure variables impacted neurocognitive performance. Neither age at seizure onset, seizure type, nor seizure frequency significantly impacted neurocognitive performance in any domain. With respect to the potential impact of medication regimen on cognitive performance, the number of AEDs was associated with a significant difference in performance on the Learning and Memory domain ($p = .007$), with children receiving polytherapy achieving lower scores than those receiving monotherapy (or who were unmedicated). Linear trends ($p < .10$) were also observed within the Learning and Memory domain, as children with partial seizures and those with an earlier age at seizure onset (0-2 years) receivied lower scores than children with generalized seizures or with seizure onset occurring after 3 years of age.

Hierarchical regression analyses were conducted to examine the extent to which the four seizure-related variables predicted neurocognitive test performance of children with epilepsy. These data are presented in Table 7. Based on findings presented throughout the literature (e.g., Williams et al., 1996), age of seizure onset was hypothesized to be the strongest predictor of neurocognitive functioning, followed by seizure frequency, seizure type, and treatment regimen; therefore, predictors were entered into the model in this order. Of the seven regression analyses, the combination of these seizure variables only explained a significant amount of variance in performance for the Learning and Memory domain. In the final model, age at seizure onset, seizure frequency, seizure type, and treatment regimen explained 29.8% of the total variance in performance in this domain ($p < .01$). However, it should be noted that only age at seizure onset and treatment regimen predicted significant amounts of unique variance in performance (10.8% and 18.2%, respectively). Though not statistically significant, the amount of unique variance in performance on the Language domain that was explained by age at seizure onset approached significance (7.9%; $p = .08$), although none of the remaining variables contributed a significant amount of additional variance, and in combination, the amount of variance explained by all four variables was not significant (14.2%, $p = .201$).

Aim #2 and #3

Tables 8 and 9 show the CBCL and BASC overall scale means for the entire studied sample. With the exception of the Attention Problems scale on the CBCL (M= 60.38), none of the overall mean T-scores fell in the Borderline Clinical or Clinical ranges. None of the total mean T-scores fell in the At-risk or Clinical ranges on the

BASC. On both the CBCL and BASC, study participants were at approximately 1.5-2.5 times greater risk for developing Internalizing and Externalizing Problems within the clinically elevated range, when compared to the normative sample (16.0%). Mean scores on the CBCL were, in general, uniformly higher than theoretically similar scales on the BASC, with a mean difference of 3.41. Additionally, greater variability was observed on the BASC, as all of the standard deviation scores were $\geq$10, whereas on the CBCL, only two of seven standard deviation scores were >10.

All seizure-related variables that have previously been discussed were examined with respect to CBCL and BASC problem scale endorsement (see Table 8). Differences between group means (*T*-scores) on the psychiatric and overt behavioral communication problems scales were examined using ANOVAs and *t*-tests (Table 10). Among the broad-band measures of psychiatric symptomatology (i.e., CBCL and BASC Internalizing and Externalizing Problem scales, CBCL Total Problems scales, and BASC Behavioral Symptom Index), participants with partial seizures exhibited significantly more externalizing behaviors and total problems than their counterparts with generalized seizures (p <.05). Although not statistically significant, children receiving monotherapy scored higher than those receiving polytherapy on a measure of externalizing problem behaviors (BASC Externalizing Problems M= 58.5, S.D. = 20.37, p = .076). On the narrow-band syndrome scales, seizure type trended towards significance for both the Hyperactivity and Atypicality syndrome scales, with children with partial seizures exhibiting a greater degree of psychiatric and behavioral impairment than children with generalized seizures. The aforementioned analyses were repeated excluding participants currently receiving psychopharmacologic intervention for psychiatric and behavioral

disturbance (n = 4). There was no change in the significance of the results that were seen, with the exception of the effect of seizure type on the Behavioral Symptom Index on the BASC, which no longer reached statistical significance (p = .12).

Chi-square tests were also conducted to evaluate the relationship between level of psychiatric symptomatology and behavioral social skills with seizure-related variables (e.g., age at seizure onset, seizure type, seizure frequency, and treatment regimen) for the entire sample, and treatment naïve subgroup, respectively. None of the relationships between age at seizure onset and measures of psychiatric and social skills behavioral functioning were statistically significant. The relationship between seizure frequency and broad- and narrow-band parent-report measures did not reach statistical significance in either the treatment included or treatment naïve subgroup. When diagnostic categories were collapsed into two groups (e.g., "normal," which comprised all participants with scores falling WNL, and "abnormal," which included participants falling into either the sub-clinical or clinically significant ranges), the BASC Atypicality Problem scale trended towards significance (p = .09). Seizure type and many subscales of the CBCL and BASC were also significantly related. When participants receiving psychopharmacologic intervention were included, scales reflecting thought problems (CBCL Thought Problems scale), hyperactivity (e.g., BASC Hyperactivity Problem scale) and a broad spectrum of emotional and behavioral impairment (e.g., BASC Behavioral Symptoms Index) all reached statistical significance (p < .05). Measures assessing seizure type and externalizing behaviors (e.g., CBCL Externalizing Problems and BASC Externalizing Problems scores) also trended towards significance. Similarly, in the treatment-naïve subgroup, there was an association between seizure type and thought problems,

hyperactivity, atypical behaviors, and a global measure of psychiatric and behavioral symptomatology (e.g., BASC BSI $p = .005$). Lastly, there was not a significant relationship between treatment regimen and level of psychiatric and behavioral impairment. However, degree of internalizing behaviors approached significance in the treatment included group ($p = .09$).

Hierarchical regression analyses were also computed for each dependent measures (i.e., broad- and narrow-band syndrome scale scores) using 4 independent variables (i.e., seizure type, age at seizure onset, seizure frequency, and treatment regimen; see Table 11). Homogeneity of variance, as well as the independence and normalcy of error variance were verified so that additional transformations were not necessary. As before, age of seizure onset was hypothesized to be the strongest predictor of impairment, followed by seizure frequency, seizure type, and treatment regimen; therefore, predictors were entered into the regression equation in this order. In combination, age at seizure onset, seizure frequency, seizure type, and treatment regimen served as a significant predictor for the all three broad-band scales of the BASC. Specifically, the combination of the four aforementioned seizure-related variables explained 25.9% ($p < .05$) and 37.3% ($p = .005$) of the variance of the Internalizing and Externalizing Problems, respectively. With respect to the former, seizure frequency was the only variable to explain a significant amount of unique variance in the final model ($p < .05$), although treatment regimen approached significance ($p < .10$). Regarding Externalizing Problems, seizure type and treatment regimen both explained a significant amount of unique variance in the final model ($p < .05$), while the contribution of seizure frequency approached significance ($p < .10$). Additionally, the combination of these four

variables significantly predicted degree of symptom endorsement on the Behavioral Symptom Index, as it explained 29.7% of the variance ($p < .05$). Seizure frequency and seizure type both explained a significant amount of unique variance in the final model ($p < .05$). None of the seizure-related variables, either independently or in combination, predicted broad-band syndrome scales on the Child Behavior Checklist. The pattern of statistically significant results of the stepwise regression was unchanged when evaluating a treatment-naïve sample.

Aim #4

One-way ANOVAs were conducted to examine between-group differences (i.e., "normal" vs. "abnormal" range of functioning on the BASC and CBCL) on neurocognitive domains, without taking into account the effects of seizure-related variables. Results of the ANOVAs that examined the six broad-band scales (i.e., CBCL Internalizing Problems, CBCL Externalizing Problems, CBCL Total Problems score, BASC Internalizing Problems, BASC Externalizing Problems, and BASC Behavioral Symptom Index) and the two narrow-band scales assessing behavioral social skills (i.e., BASC Social Skills and Atypicality Problem Scales) across seven neurocognitive domains yielded no statistically significant results. Participants who were rated in the "abnormal range" (i.e., Borderline Clinical and Clinically significant ranges combined) on the CBCL Internalizing Problems scale exhibited lower performances on the Visuospatial Skills domain, although the difference between groups did not reach statistical significance ($p < .10$). Similarly, there was a trend for participants who were rated in the abnormal range on the BASC Atypicality scale to score lower than those in the normal range on the Language domain ($p <. 10$).

Next, analyses of covariance (ANCOVA) were conducted to evaluate whether seizure-related variables (either individually or in combination) moderated the effects of psychiatric symptomatology and overt behavioral social skills on neuropsychological test performance (see Table 12). Of note, none of the correlations between seizure variables was significant; therefore, multicollinearity was not an issue in subsequent analyses.

Broad band ratings of psychiatric symptomatology.

CBCL Total Problems Scale and BASC Behavioral Symptoms Index

Although one-way ANOVAs did not achieve statistical significance, ratings on the CBCL Total Problems scale were found to contribute to performance on the Language domain ($p < .05$) after seizure-related variables were accounted for in the analysis, and there was a trend towards significance in the Learning and Memory domain ($p = .10$); however, neither were significant when outliers were removed. Seizure type and treatment regimen were both found to be significant moderating variables ($p < .05$) in differences in performance on the aforementioned cognitive domains; seizure type no longer retained statistical significance as a covariate when outliers were removed ($p < .10$). Age at seizure onset also trended towards significance when utilized as a covariate ($p = .10$) in the Learning and Memory domain; this relationship achieved statistical significance when outliers were removed. Additionally, when outliers were removed, ratings on the CBCL Total Problems scale approached statistical significance ($p < .10$) in the Visuospatial and Attention domains after accounting for the effect of treatment regimen.

ANCOVAs that examined the association between neurocognitive performance and ratings on the BASC Behavioral Symptoms Index did not yield a significant main

effect for group, with the exception of performance on the domain of executive functioning ($p < .05$).

CBCL and BASC Internalizing and Externalizing Problems Scales

Although the results of ANOVAs were not statistically significant among the broad-band Internalizing and Externalizing scales of the CBCL and BASC, a significant association was seen between ratings on the CBCL Internalizing Problems scale and performance on the Learning & Memory domain ($p < .01$); treatment regimen ($p < .01$) and seizure type ($p < .05$) emerged as significant moderators to this relationship. The CBCL Internalizing Problems scale also approached significance in its contribution to performance on the Language and Learning & Memory domains after accounting for seizure variables (treatment regimen and age at seizure onset, respectively), although none of the seizure-related variables was found to be a significant moderator in this effect when examined alone. It should be noted that when outliers were removed, this broadband scale did contribute significantly to performance ($p < .05$) on the Learning and Memory domain, with seizure duration being a significant moderating variable in this relationship. Linear trends were also noted in the Language and Attention domains, with seizure type and treatment regimen identified as significant covariates.

The broad-band BASC Internalizing Problems scale was a significant contributor to neurocognitive performance in two domains (e.g., Language and Learning & Memory) and approached statistical significance in two domains (e.g., Visuospatial Skills and Attention), with treatment regimen identified as a significant covariate in these relationships. These relationships remained significant when outliers were removed.

Seizure type emerged as a significant covariate ($p < .05$) in the relationship between this scale and the Visuospatial Skills domain when outliers were excluded from the analyses

The relationship between ratings on the CBCL Externalizing Problems scale and neurocognitive performance still did not reach statistical significance alone; however, it was a significant contributor to neurocognitive performance in the domains of Language and Learning and Memory when treatment regimen was entered as a covariate.

Although no statistically significant relationships emerged under the one-way ANOVA, the BASC Externalizing Problems Scale emerged as one of the more robust scales to show consistent group differences with respect to neurocognitive performance. Parent-report ratings on this scale significantly contributed to performance on the Executive Functioning ($p < .01$), Language ($p < .05$), and Learning & Memory domains ($p < .05$) and approached significance on in the area of Processing Speed ($p < .10$). Age at seizure onset moderated the relationship between this scale and the Learning & Memory domain ($p < .01$). Treatment regimen also appeared to significantly moderate the relationship between BASC externalizing behaviors and performance on the Language ($p < .01$) and Attention ($p < .05$) domains. When outliers were excluded from these analyses, the relationship between BASC Externalizing Problems and the Language domain ceased to be statistically significant, as did the moderating effect of seizure type on the Executive Function domain.

Narrow band ratings of psychiatric symptomatology

Lastly, ratings on the BASC narrow-band scales of behavioral social communication (e.g., BASC Social Skills Problems Scale and Atypicality Problems

scale) still did not contribute to performance on neurocognitive tests when seizure variables were included as covariates.

CHAPTER FOUR

IV. Discussion

In recent years, many investigators have examined the role of seizure-related factors (for review see Masur & Shinnar, 2001) and of psychopathology (Caplan et al., 2004; B. P. Hermann et al., 1988) in the neurocognitive functioning of children with epilepsy. Uniquely, the present study was the first to examine several known risk factors of neuropsychological impairment (e.g., seizure-related factors, psychiatric functioning, and behavioral social skills) and allowed them to "'compete'" with each other, both individually and in combination, to assess their respective explanatory power. In so doing, a multi-etiological model was proposed to further explore the mechanisms underlying neuropsychological dysfunction in children with epilepsy. In terms of the potential clinical applications, our goal was to provide practitioners with an empirically-based guide for identifying children with epilepsy who have the highest risk of neurocognitive impairment. Hermann et al. (B. P. Hermann & Whitman, 1984; B. P. Hermann et al., 1988; B. P. Hermann et al., 1990) were among the first to explore this type of risk assessment modeling in both adults and children. However, though the present study and others (Caplan et al., 2004; B. P. Hermann & Whitman, 1984; B. P. Hermann et al., 1988; B. P. Hermann et al., 1990; Schoenfeld et al., 1999) shared several overarching goals, the methodological design, breadth, and range of the tests administered across studies differs considerably. As such, the ability to draw direct comparisons was substantially limited.

A. Discussion of Results

Aim #1 **To evaluate the combined and unique contributions of seizure-specific moderating variables on neurocognitive test performance in children with epilepsy.** The obtained findings were consistent with others throughout the literature suggesting that intellectual performance in children with epilepsy is skewed towards the lower end of the average range (S. D. O'Leary et al., 2006; Williams et al., 1998). In fact, the observed mean FSIQ of the total sample, approximately 94 (S.D. = 16), was likely an overestimation of mean intelligence of children seeking treatment at a tertiary care facility like NYU Comprehensive Epilepsy Center due to the exclusionary criteria of this study (e.g., FSIQ < 70 were not included).

Interestingly, and contrary to prediction, treatment regimen was significantly related to performance on learning and memory measures. These findings were somewhat inconsistent with the literature indicating little or no cognitive impairment related to AEDs in therapeutic doses (Devinsky et al., 1995; Smith et al., 2002). However, like Williams et al. (1996), the results of the present study suggest diminished performance on both visual and verbal memory measures for children receiving polytherapy. Conceptually, it was not surprising that children receiving many medications exhibitted lower scores than their counterparts receiving monotherapy, due to the formers' high correlation with difficult-to-control seizures, underlying brain pathology, and increased risk of blood serum toxicity (Williams et al., 1996). This group's relatively poorer encoding, recall, and retention may have also stemmed from the lowered alertness, concentration, drive, and mood often observed in children receiving multiple epilepsy medications (Reynolds, 1983), as these are all neurobehavioral

processes that underlie learning and memory. Also, the observed performance differences may be attributable to a reduction in cerebral blood flow and glucose metabolic rate (mechanisms directly caused by AEDs, like vigabatrin), which, in turn, may have adversely affected neurocognitive functioning (Hosking, Roff Hilton, Embleton, & Gupta, 2003).

Although not significant ($p \leq .10$), it is important to note the relationship between seizure type and Learning and Memory test performance; children experiencing partial seizures exhibitted lower performance than those with generalized epilepsy. Though only a trend, these data were somewhat skewed due to the greater number of participants with generalized seizures, and therefore, may otherwise have reached statistical significance. The performance differences observed between seizure types (CPS and PGE) may represent underlying neuroanatomical damage to areas associated with intellectual capacity. For example, early damage to focal areas, which may ultimately result in the development of partial seizures, has been shown to have deleterious long-term effects on learning and memory. In animal models, early seizures have been shown to alter the hippocampal connectivity and typical neuronal arrangement, even in cases where neurogenesis or cell loss is absent (R. A. Bender, Dube, Gonzalez-Vega, Mina, & Baram, 2003).

Surprisingly, and contrary to expectation, seizure frequency and age at seizure onset were not significantly related to neurocognitive dysfunction in children with epilepsy. Although the impact of seizure-frequency on test performance may have been significantly limited by the artificially-created classification system used in this study and in others (Smith et al., 2002), historically, age at seizure onset has been found to be a

robust indicator of neurocognitive dysfunction (Chevrie & Aicardi, 1978; Dikmen, Matthews, & Harley, 1975; D. S. O'Leary et al., 1983). In contrast, the negative impact of early seizures on neurocognitive development was observed to only approach statistical significance in the correlations between age at seizure onset and memory abilities. Although unexpected, these findings were consistent with those of Smith et al. (2002) and support data from animal studies suggesting that the developing brain is less likely to suffer irreparable damage from continuous hippocampal stimulation than is the mature brain (Holmes, 1991a, , 1991b).

Aim #2 **To investigate the prognostic value of seizure-related variables on the presence of psychiatric disturbance.** In terms of the obtained self-report data, it was not surprising that internalizing and externalizing behavioral problems profoundly affected children with epilepsy. These findings were consistent with our *a priori* hypotheses, as well as with a large-scale epidemiological investigation (Rutter et al., 1970). The particularly high rate of attentional problems in this sample (irrespective of pharmacotherapy status) was also consistent with our earlier findings (H. A. Bender et al., 2007; Bender et al., 2005, 2007) and likely reflects transitory attentional impairment caused by interictal discharges (Aarts, Binnie, Smit, & Wilkins, 1984; Binnie & Marston, 1992). In fact, the presence of attentional difficulties has also been considered to be a prodromal feature before the first episode of seizure in children; in two large scale studies, behavioral difficulties (e.g., attention problems) were 2.4 times more common before the identification of a child's first seizure, as compared to seizure-free sibling controls (Austin et al., 1997; Dunn et al., 1997).

Contrary to our predictions, age at seizure onset, degree of seizure control, and AED treatment regimen were largely unrelated to increased rates of psychopathology. Rather, the present findings indicated that seizure type was the most consistent indicator of psychiatric and behavioral disturbance: children with partial seizures exhibited higher rates of internalizing and externalizing disorders than children with generalized epilepsies. Although recent studies regarding the association of seizure-type with psychopathology remain equivocal (Caplan et al., 1998; Oguz, Kurul, & Dirik, 2002; Ott et al., 2001), historically, children with CPS have been described as antisocial and aggressive, (Nuffield, 1961; Rutter et al., 1970), and patients with PGE were characterized as "neurotic." The results of the present study loosely supports Nuffield's (1961) conceptualization of the "epileptic personality," as children with CPS exhibited more behavioral impairment, attention problems, and atypical behaviors (i.e., odd or unusual behaviors reflective of possible psychosis, formal thought disorder, and/or autism) than the PGE group. The present study; however, did not indicate a significant relationship between neurotic behavior (e.g., affective disorders assessed by the Internalizing Problems Total scores of the CBCL and BASC) and PGE.

From a neuroanatomical perspective, the significant positive relationship between partial seizures and the development of psychiatric disturbance was not entirely unexpected. First, there is evidence that even a single complex partial seizure with secondary generalization may cause substantial neuronal damage (Rabinowicz et al., 1996) and result in extracellular glutamate cytotoxicity, both of which are known predictors of behavior problems (During & Spencer, 1993). Second, abnormal rates of metabolism in the cingulate gyrus and amygdala, both structures frequently affected by

epileptogenesis in partial epilepsies, have also been implicated in the development of psychopathology. Third, by definition, the CPS group represents a localization-related type of epilepsy, typically involving or restricted to the temporal lobe(s) (Williamson, 1987); limbic system disturbance is believed to be the most important cause of organically-based (endogenous) psychopathology in patients with epilepsy. However, comparing the risk of psychiatric disturbance in children with CPS to those with PGE is difficult, if not impossible, without consideration of the presence and extent of limbic involvement. According to Bear (1979), comparing the predisposition of psychopathology in: a) individuals with PGE (which may or may not involve seizure activity in the limbic structures), b) children with CPS with an extra-temporal seizure focus, and c) patients with highly focal temporal lobe epilepsy, is troublesome without some objective measurement of known seizure localization and EEG correlates. Instead, it is suggested that the presence of interictal involvement, rather than seizure type, may be a more robust determinant of the probability of psychiatric and behavioral disturbance in children with epilepsy.

Aim #3 **To describe the specific types of overt, atypical behavioral social skills often expressed in children with epilepsy. We further investigated the relationship between four specific seizure-related variables and social communication in this population.** Consistent with our hypotheses, as a whole, the studied sample exhibited diminished social skills and behavioral appropriateness, compared to the neurologically-healthy standardization samples described in both the CBCL and BASC manuals. The percentage of children exhibiting diminished social skills and atypical behaviors was comparable to that in our previous investigation (Bender et al., 2007, 2005), regardless of

whether or not children receiving pharmacotherapy were included in the analyses. In terms of the specific seizure-related variables, seizure type and seizure frequency both approached statistical significance in their relationship with disordered social skills behaviors and to impaired social communication in children. Children with partial seizures and those with more difficult-to-control epilepsies were found to be at a greater risk for atypical thinking, behavior, and social communication. These findings were highly consistent with the body of work presented by Caplan and colleagues (Caplan et al., 1997; Caplan et al., 2002; Caplan et al., 1992; Caplan et al., 1991; Caplan et al., 1992; Caplan & Guthrie, 1994; Caplan et al., 1997; Caplan et al., 2002). In their seminal 1997 investigation, Caplan et al. demonstrated that children with CPS displayed significantly more illogical thinking and atypical behavior patterns than those with PGE, although, overall, children in both seizure groups exhibited a higher incidence of formal thought disorder than did healthy controls. Furthermore, Caplan and colleagues also found seizure frequency to be significantly related to the severity of the illogical thinking in the PGE group.

Several theories have been proposed to explain the relationships among impaired social communication, partial epilepsies, and uncontrolled seizures. Many investigators have provided electrophysiological (EEG; Lieb, Dasheiff, & Engel, 1991), structural (MRI; B. Hermann, 2003), and functional evidence (PET scan; Azari et al., 1999) in support of the predisposition of social communication and behavioral deficits in CPS patients. Briefly, the indirect effect of CPS on the frontal lobes, via epileptogenic propagation from the temporal lobe to the contralateral frontal lobe, and/or disturbed metabolic patterns in Broca's and Wernike's areas, implicates partial seizures in

promoting frontal lobe dysfunction. Additionally, the presence of hippocampal abnormalities, which may underlie complex partial seizures, has also been shown to cause diffuse disruption of the corticolimbic structures, including areas of the prefrontal cortex (PFC; Engel, Wilson, & Lopez Rodriguez, 2002). It has been well established that frontal lobe areas, particularly the prefrontal cortex, are responsible for monitoring conversation, organizing one's thinking, making inferences, processing speech, and processing higher-order thinking (see McGrath, 1991 for review). Damage occurring in these areas may have negative social and behavioral consequences ino children with CPS.

Neurodevelopmentally, it was not unforeseen that children with more frequent seizures would exhibit impaired social and emotional development. Poorly controlled seizures in childhood may disrupt the typical course of language and social skills acquisition, which largely occurs between toddlerhood and adolescence (Caplan et al., 2002; Peterson & Dodsworth, 1991). However, from a more practical perspective, it wais also not surprising that increased seizure frequency was related to poor social competence, as children with more severe, impairing seizures often face restrictions on the extent and quality of their social interactions. More specifically, children with chronic seizures are often hospitalized, have extended school absences, and are faced with physical activity restrictions. These, and other illness factors, may limit a child's exposure to, and participation in, sports, extracurricular activities, and other opportunities for play and association. As such, decreased opportunity to participate in activities is often a limiting factor in the epileptic child's ability to learn and practice age-appropriate social behaviors and societal rules (Harper, 1991; Parker & Asher, 1987).

Aim #4 **To integrate the three previous Aims by examining the relationships among emergent psychopathology, social-behavioral functioning, and neurocognitive test performance as moderated by seizure-related variables.** Behavioral research is often most meaningful when explaining causal inferences; however, suggestions of causality are often threatened by the presence of extraneous relationships. More specifically, the presence of confounding factors often obscures the effect of the independent variable when these confounds are not adequately understood and controlled for *a priori*. Epilepsy research is particularly vulnerable to the effects of these potential confounding factors due to the nature and treatment of the disease itself. Indeed, while many of the study's specific methodological limitations are addressed in detail below (see the *Limitations* subheading), careful theoretical interpretation of the potential impact of these factors should first be explored. In the current study, the presence of specific seizure-related variables was hypothesized to modify the relationship between independent and dependent variables, and therefore, cofactor adjustment was statistically accounted for through multivariate analyses (i.e., stepwise regression analyses and analysis of covariance).

Rather than reflecting direct or cumulative effects of seizures, the results of the present study suggest that neurocognitive dysfunction in children with epilepsy is multi-etiological in nature. More specifically, our findings demonstrated that neurocognitive dysfunction in children with epilepsy is modestly, but significantly, associated with both psychopathology and seizure-related factors. Perhaps most interestingly, these data argue for the key role of seizure-related variables as predictors of neurocognitive performance. Although psychiatric and behavioral status were hypothesized to affect neurocognitive

performance, in actuality, this relationship was only statistically significant under certain covariates. For example, a child's score on the CBCL Internalizing Problems scale significantly contributed to performance on the Learning and Memory domain; however, treatment regimen and seizure type each made significant independent contributions to the explanatory power of this broad-band measure.

The development of a set of individual or combined prognostic indicators through complex statistical modeling warranted thorough consideration before accurate conclusions can be drawn. Conceptually, there has been a great deal of variability throughout the pediatric epilepsy literature when describing the direction and strength of relationships between predictors and outcomes. More specifically, the terms "moderating variable" and "mediating variable" have been used interchangeably, and often incorrectly, when evaluating the effects of covariates, such as demographic, or sociocultural factors in a risk assessment model (Findley & Cooper, 1983). In the past two decades, many investigators have commented on the need for terminological, conceptual, and statistical consistency when describing moderated and mediated effects (Baron & Kenny, 1986; Holmbeck, 1997; Rose, Holmbeck, Coakley, & Franks, 2004; Shadish & Sweeney, 1991). These investigators, and others, have suggested that a "moderator" causes an interaction effect and that a moderating variable affects the relationship between two predictor variables and has an impact of the level of the dependent variable. In contrast, mediating variables are more relationally enmeshed; the independent variable causes the "mediator," which, in turn, causes the outcome. The seminal work of Baron and Kenny (1986) further suggests that three conditions (including one subcondition) must be met for a variable to be correctly termed as a

meditator: a) the predictor must be significantly associated with the hypothesized mediator, b) the predictor must be significantly associated with the dependent variable, c) the mediator must have a significant association with the dependent variable, and d) the impact of the predictor on the dependent measure is less after controlling for the mediator.

Based on the obtained findings, the model proposed herein that the impact of psychopathology on neuropsychological dysfunction was *moderated* by seizure-related variables. From a more theoretical perspective, the presumed lack of influence of the predictor variable (e.g., psychiatric and social communication functioning) on the covariate (e.g., seizure-related variable) also precluded the definition and conceptualization of seizure-related variables as a "mediator" of neurocognitive performance in our theoretical model. Designating seizure-related variables as moderators of neuropsychological dysfunction further refined the model as one that predicts risk for maladaptive outcomes. From a clinical perspective, full awareness and understanding of the variables that moderate the potential outcomes facilitates the development of highly specific intervention plans tailored to the patient and their specific set of needs.

B. Potential clinical applications

The need for early intervention of children with newly diagnosed epilepsy has been described by many authors (Berg et al., 2005; Devinsky et al., 1999 ; Hoare et al., 2000). Several large scale, population-based longitudinal studies of adults with an onset of epilepsy in early childhood suggest increased rates of school failure (Camfield et al., 1984; (Sturniolo & Galletti, 1994), social isolation (Camfield et al, 1984), behavioral

difficulties (J. K. Austin & Dunn, 2002; J. K. Austin et al., 2001; J. K. Austin et al., 1994), and neuropsychological deficit (Neyens, Aldenkamp, & Meinardi, 1999), when compared with neurologically-healthy populations. Similarly, poor social and educational outcomes were also observed in seizure-free adults with epilepsy remitting in childhood (Sillanpaa, Jalava, Kaleva, & Shinnar, 1998). It has been further posited that there is a small period of vulnerability for irreversible neurocognitive decline in early childhood (Battaglia et al., 1999; Vasconcellos et al., 2001). These, and other studies, clearly underscore the urgency for proactive neurorehabilitative, psychiatric, and psychosocial interventions in children with newly diagnosed epilepsy.

Model building is often key to identifying optimal targets for intervention programs (Dishion & Patterson, 1999). More specifically, thorough evaluation of the explanatory power of factors related to behaviors, events, and/or outcomes is frequently necessary to fully understand its antecedents. Like the model proposed herein, conceptual and theoretical frameworks of impairment in this population directly and indirectly inform clinical practice. As suggested by the present findings, the potential for neuropsychological dysfunction in children with epilepsy is multifactorial in nature. For example, seizure-related variables, such as age at seizure onset and seizure frequency often affected treatment regimen, which in turn, impacted neurocognitive abilities, and, as a result, psychological and psychosocial functioning. Though treatment and rehabilitation geared for children with epilepsy is a highly individualized, holistic endeavor, several common themes emerge across the literature.

Beyond determining a profile of strengths and weaknesses for diagnostic purposes, neuropsychological test data are often used to translate test data into more

functional terms (Ylvisaker, 1985) and estimate a patient's capacity to benefit from cognitive remediation (Ben-Yishay, 1983). Although, from an intervention standpoint, there is little that mental health professionals can do about treating the biologically- and structurally-based contributors to neurocognitive dysfunction (e.g., seizure type or AED treatment regimen), neuropsychologists clearly have the potential to improve a patient's functional deficits through intensive remediation (see Fletcher-Jantzen and Kade, 1997, for a comprehensive review).

Given the findings of the present study, as well as other investigations evaluating the neuropsychological impairment frequently comorbid in children with epilepsy, there is clearly a need for compensatory strategies and techniques aimed at remediating deficits in the domains of attention, memory, and organization. Attentional abilities, often a mediating variable for all neurocognitive functions, can be strengthened in both visual and auditory modalities. Remediation in the attention domain often involves some form of cognitive self-control, which involves teaching the patient to self-monitor their own ability to remain "on task." Once some degree of self control in this area has been mastered, tasks, such as those proposed by Ben-Yishay and colleagues (Ben-Yishay, Diller, & Ratook, 1978; Ben-Yishay et al, 1980) may then be used to improve selective attention by practicing the discrimination of auditory and visual stimuli among distractors. Compensatory strategies aimed at improving encoding, storage, and/or retrieval deficits have also been effective in attenuating memory impairment in children (Hallahan & Sapona, 1983). The use of mnemonic devices and self-generated cueing strategies are specific remediation techniques that have been utilized with significant degrees of success in brain-damaged populations (Bauer, 1977; Gianutsos & Gianutsos,

1979). In a similar vein, cognitive retraining and "behavioral engineering" (Diller & Gordon, 1981) in the areas of organization and planning are also warranted for many children with epilepsy. While little research has been conducted in this area, organizational skills interventions similar to those successfully employed in ADHD populations (e.g., notebook training, motivational coaching, organizational skills drills) (Stevenson et al., 2002) will likely be useful remediation strategies. It is important to note however, that the success of cognitive remediation and other early cognitively-based interventions is largely tied to the child's emotional and psychosocial health. Specifically, many authors suggest that children with neurological disorders are vulnerable to maladaptive emotional coping and adjustment when faced with the stress of "cognitive failure" (Bender, 1985; Lezak & O'Brien, 1990).

In addition to interventions aimed at improving cognitive and neuropsychological functioning, the elevated incidence of clinically-significant psychopathology in the sample studied emphasizes the need for intensive psychological and psychosocial support, as well as social skills intervention. According to Krishnanmoorthy (2003), a combined treatment approach, incorporating both pharamacotherapy and psychotherapy, is the most effective method of managing internalizing and externalizing disorders. As was the case with the studied sample, pharmacotherapy was sometimes provided as a treatment for emotional and behavioral disturbance in children with epilepsy. In many cases, children receiving methylphenidate or dextroamphetamine exhibit improvements on objective measures of attention (Semrud-Clikeman & Wical, 1999), as well as a decrease in AD/HD-related symptomatology on parent-report measures. Affective disorders in children with epilepsy are also commonly treated with psychotropic

medications (Ambrosini et al., 1999; Baumgartner, Emslie, & Crismon, 2002 ; Keller et al., 2001). Although prescribed with caution due to the potential for contraindications with AEDs, selective serotonin reuptake inhibitors (SSRI) are often prescribed to children exhibiting clinically-significant depression- and anxiety-related symptomatology. Non-fluoxetine SSRIs, such as sertraline and paroxetine have been shown to be particularly effective in this population (Barry, Huynh, & Lembke, 2000).

Ideally, psychological interventions should aim to prevent behavioral problems in children with epilepsy, rather than be initiated after the emergence of emotional or behavioral disturbance. Educational programs are often helpful in proactively assisting parents and children to cope with the diagnosis of epilepsy by raising awareness of potential difficulties and problem behaviors before they arise (Lewis et al., 1990). If behavior problems and/or adjustment difficulties still develop, many authors have also reported improvements in behavior and reductions in seizure frequency following cognitive behavior therapies teaching relaxation and self-control (Williams et al., 1979; Dahl et al., 1985). Individual and group counseling designed to decrease emotional stress has also been successful in reducing adjustment difficulties in children with epilepsy (Snead et al., 2004). Regardless of the techniques used, the present findings suggest that a reduction in psychiatric and behavioral disorders may also affect the exacerbation of concomitant neurocognitive dysfunction.

Beyond more traditional psychotherapeutic approaches, the finding of the current study, as well as of previous work by Bender and colleagues (2006, 2007) underscores the need for interventions geared at improving socialization and psychosocial adjustment. Yet, despite the need for this type of treatment, the quality of the child's social

information-processing skills and social interactions are largely unevaluated and unremediated in this population. One of the few studies that focused on increasing socially-appropriate interactions among children with epilepsy through group activities reported an improvement in health-related quality of life issues (Snead et al., 2004). Though outcome measures of the aforementioned study did not include elevations of neurocognitive or psychiatric functioning, as neither were relevant study goals, it can be assumed that there may have also been some improvement in skills in these areas as well, given their known correlation with health-related quality of life (Miller, Palermo, & Grewe, 2003).

Though additional empirical investigation of treatment efficacies are highly warranted for the interventions and therapies described above, developing models useful for evaluating risk in children with epilepsy are also critical to facilitate early identification. To date, very few studies have used multivariate techniques to establish the relative importance of demographic, seizure-related, and psychosocial variables in predicting need of more intensive clinical attention. Given the paucity of literature in this area, it is not surprising that more than 60% of children and adolescents with epilepsy have unmet psychiatric needs (Ott et al., 2003). If left untreated, children with undiagnosed or underdiagnosed psychological, behavioral, or social-emotional disturbances often continue to suffer from their disorder(s) well into adulthood.

C. Study Limitations

Despite the potential contributions, much of the research exploring the cognitive, psychological, and social skills functioning of children with epilepsy is limited, in large part, due to methodological constraints. This study is no exception.

Most broadly, epilepsy research is often limited in its scope and generalizability due to the potential confounds inherent in evaluating a heterogeneous sample of children with known neurological disorders. Selection bias is often considered to be one of the most salient methodological concerns discussed throughout the extant literature (B. P. Hermann & Whitman, 1984; Williams et al., 1996). As was the case in the present study (which was conducted at a tertiary care center), children with more malevolent epilepsies, representing approximately 17-20% of the entire epileptic population (Eriksson & Koivikko, 1997; B. P. Hermann & Whitman, 1984), were selected as research participants. As a result, there is believed to be an oversampling of children with more frequent, impairing, and less-controlled epilepsies than would be represented in a community-based sample. Additionally, such selection biases likely increased the reported incidence of mental retardation and the number of children receiving polypharmacy (Hoare & Kerley, 1991; Williams et al., 1996). From a more behavioral and social-emotional perspective, this bias may have also increased the estimated/presumed incidence of psychological and behavioral disturbances within the studied sample (Hoare & Kerley, 1991). As such, caution should be exercised before generalizing the present findings to a less symptomatic cohort. According to Hermann and Whitman (1992, pp. 1135), "studying *patients* with epilepsy does not necessarily inform us about *people* with epilepsy."

Moreover, considerable caution should be used in interpreting these data due to the relatively small sample size. Moreover, the large number of multiple comparisons increased the risk of Type I error; future studies may wish to employ a Bonferroni correction procedure in order to minimize the risk of measurement error. Additionally,

the lowered statistical power resulting from the factors above also limited the number of variables that could be entered into the model. Specifically, race and SES, which were both observed to significantly impact several areas of neuropsychological functioning within the studied sample, were not included in either the stepwise regressions or ANCOVA models due to concerns regarding sample size. Though presently more parsimonious, incorporating the explanatory power of race and culture as factors into our model may have significantly impacted the obtained findings. Additionally, the present study was hindered by the lack of an appropriate control group. Future studies may wish to recruit chronically ill children without a primary neurological diagnosis in order to examine which psychological and behavioral risk factors are specific to an epilepsy diagnosis, rather than to the presence of a long-term physical illness.

The obtained findings underscored the difficulty in making precise attributions regarding the determining factors of cognitive status in a pediatric sample with a neurological anomaly. Unlike adults, whose neurobehavioral deficits may be more stable, the neurobehavioral status in children is more dynamic, reflecting not only continued development, but also the complex interaction between epilepsy-associated variables and development. For instance, children with epilepsy differ from their neurologically-healthy age-matched peers not only as a direct result of epileptiform activity, but also due to differing rates of maturational growth and neuroanatomical development, often secondary to the varying influence of neuronal plasticity (Giza & Sankar, 1998). However, the present study findings suggest that functional outcome is not the direct result of developmental impairment resulting solely from neurogenic factors, as the current sample contained children with grossly intact intellectual abilities

(many of whom possessed intellectual skills falling in a range above their age-related peers lacking neurological dysfunction). Rather, the obtained findings can be used to indicate the need for caution when using psychometric data to infer functional anatomical deficits. It is further suggested that such inferences are more appropriate to the adult epilepsy population where a psychometric pattern of strengths and weaknesses is more consistently tied to localized cerebral dysfunction (Milner, 1970).

Given the wide array of deficits observed in pediatric epilepsy, standardized multidimensional assessment is required for a comprehensive evaluation. To this end, numerous investigations, including the present one, have utilized a battery consisting of several individual measures of neuropsychological functioning (Gleissner et al., 2002; Hernandez et al., 2002; Smith et al., 2002). However, combining a number of tests from various sources poses an inherent threat to methodological and psychometric reliability (Korkman & von Wendt, 1995; Wilson & Risucci, 1986). Most notably, standardized scores yielded by multiple individual tests, each with different standardization samples, may obscure true patterns of strengths and weaknesses (Korkman & von Wendt, 1995). While much of this concern can be obviated by transforming data into a standard metric (the present study converted all data into z-scores), differences in the subject characteristics of standardization samples and variable age ranges across measures should be considered when interpreting study findings.

Yet another limitation intrinsic to the neuropsychological assessment of children with epilepsy is the questionable clinical and ecological validity of the measures appropriate for this population. As previously stated, children with epilepsy, particularly those receiving more than one antiepileptic medication, exhibited difficulties on time-

dependent tasks (H. A. Bender et al., 2007 ; Bender & Zaroff, 2005). Although timed tasks provide useful information regarding a child's performance on tasks assessing psychomotor speed (e.g., WISC or WASI Digit Symbol Coding,), attention (e.g., Trailmaking Test, Trails A), executive functioning (e.g., Trailmaking Test, Trails B), visuospatial skills (e.g., WISC or WASI Block Design), and sensorimotor abilities (e.g., Purdue pegboard; a commonly-administered task administered by pediatric neuropsychologists), content-based limitations may underestimate actual level of abilities. While similar comparisons were not feasible in the present study due to the diversity of test measures and accompanying normative data, previous investigations suggest that scores on highly time-dependent subtests (e.g., NEPSY Speeded Naming and Visuomotor Precision) were approximately two standard deviations below each of the means obtained by the age-matched normative sample (H. A. Bender et al., 2007 ; Bender & Zaroff, 2005) . Based on a broader view of study findings, it is quite possible that the sample studied would have exhibited deficits on these subtests even if administration modifications had been used, as core deficits in the language and sensorimotor abilities were still observed on non-time dependent tasks. However, when assessing children with epilepsy, it is critical to acknowledge that processing speed deficits can compromise the extent to which a given task measures its putative cognitive construct.

Beyond the difficulties encountered during the interpretation and administration of neuropsychological test measures in this population, there were also multiple theoretical, developmental, and methodological challenges inherent in assessing psychiatric and social-emotional functioning in children with epilepsy. Questionnaires

such as the BASC and CBCL are problematic for several reasons. Apart from the issues of chronological age and concomitant cognitive developmental level, the ability to obtain reliable and valid self-report assessments may be compromised by a child's limited verbal skills and/or lack of insight. Clinically, much of this concern can be reduced by obtaining parent-report ratings, instead of self-report evaluations, which were used in the present study. However, quantitative parent-report rating scales, such as the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), may not accurately capture the true level of psychopathology in chronically ill populations. Although typically administered in studies of children with medical illnesses, including cystic fibrosis (Simmons et al., 1987), diabetes mellitus (Brown, Kaslow, Sansbury, Meacham, & Culler, 1991), cancer (Brown et al., 1992), asthma (Reichenberg & Broberg, 2004), and inflammatory bowel disease (De Boer, Grootenhuis, Derkx, & Last, 2005), concern exists regarding the usefulness of the CBCL in populations with chronic somatic complaints. At the very least, the interpretation of somatic symptom scales within larger broadband measures needs to be qualified in such populations.

Another methodological concern arises when evaluating overt, behavioral social skills via parent-report ratings. The majority of the literature reviewed measured competence with the CBCL, a parent-report rating scale evaluating social competence in the following domains: activities (e.g., sports and hobbies), social (e.g., friendships and interpersonal skills), and school (e.g., performance, ability, and school problems) (Caplan et al., 2006; B. P. Hermann et al., 1988; Hoie et al., 2006; Jakovljevic & Martinovic, 2006; Sabaz et al., 2003). Moreover, given the physical and medical limitations placed on children with chronic medically-refractory epilepsy, participation in school activities,

hobbies, and sporting events, each viewed as indicative of "social competence" on the CBCL, may not be possible for reasons beyond the child's control.

D. Areas for future study

The current study suggested multiple avenues for future analysis and study. First, investigators may wish to expand the scope of the study by increasing the sample size. In so doing, more complex, and sophisticated statistical modeling procedures would be possible. More specifically, the additional number of subjects and resultant increase in statistical power would allow for exploratory factor analyses (EFA) to be conducted to determine subtest loadings for each of the seven cognitive domains. Statistically evaluating factor loadings, rather than assigning subtests to their putative cognitive domains would enable investigators to make more empirically-driven decisions during data reduction. Once EFA are conducted, confirmatory factor analyses could then be used to examine the initial factor structure so that correlation parameters could be added to the measurement model (where necessary) to obtain a better model fit. Inasmuch, such analyses would enhance the meaningfulness of the statistical and theoretical conclusions drawn from the data obtained.

Along similar lines, a larger sample size would facilitate multiple group comparisons through structured equation modeling (SEM; for a review, see (Morris, Bergan, & Fulginiti, 1991). According to Peyrot (1996), SEM is often preferable to other multivariate methods due to the degree of model "fit" after measurement error is controlled; SEM strategies often afford investigators a less biased assessment of moderator effects. The conventional regression modeling employed in the present study

did not account for measurement error, but instead presumed the composite variables would provide an accurate measurement of latent abilities.

Alternatively, large scale investigations, such as those conducted by multi-center epilepsy research studies (e.g., the Bozeman Epilepsy Consortium), may also consider analyzing their data using a statistical modeling procedure first outlined by Hermann and Whitman (1986). Hermann suggests that if variables related to the development of psychopathology in epilepsy are trichotomized into a) brain-related factors, b) non-brain-related factors, and c) treatment-related factors, then each group would explain different proportions of the variance for various behavioral disorders. By providing a regression equation to both researchers and clinicians, consumers of the literature would be able to develop an *a priori* hypothesis regarding the child's level of neurocognitive functioning when each of the trichotmoized terms are at their minimum, maximum, and all variations in between. As a result, the degree of behavioral change could then be statistically predicted when risk factors are modified (e.g., when a child initially receiving monotherapy is then prescribed polytherapy). Though similar procedures were undertaken in the present study, future workers in this area may wish to apply Hermann and Whitman's (1986) three-step process of data analysis to obtain an alternative understanding of the precursors of neurocognitive dysfunction.

It is important to note that even statistically significant variables in the present study were of relatively modest explanatory power. Beyond the application of more sophisticated statistical methods, evaluating a broader range of known moderators of neurocognitive functioning is also likely to be a worthwhile endeavor. Objectively assessing a child's coping strategies, cognitive appraisal factors, perception of control,

and other health-related quality of life issues, are believed to have additional prognostic value, as parent- and self-report ratings of these constructs are predictive of developing comorbid psychopathology (Wagner & Smith, 2006), neuropsychological status, and emotion/behavioral adjustment difficulties (J. K. Austin et al., 1992). It has also been widely reported that the psychosocial factors listed above are significantly related to seizure- related variables (Stores, 1980; Whitman et al., 1982). For example, as a child's seizure frequency increases, there is often a concurrent decrease in the child's locus of control, independence from their caregivers, and feelings of self-efficacy (Devinsky et al., 1999; Dunn et al., 1999). By further exploring this relationship in the context of neuropsychological test performance, investigators may have a better understanding of the psychosocial determinants of cognitive dysfunction in this population.

Furthermore, the inclusion of a more objective measure of social communication and behavioral social skills (rather than information collected by proxy) would be a useful addition to this line of investigation. To this end, administering an age-appropriate measure of meta-linguistic skill, such as the Test of Language Competence (TOLC-3; Wiig & Secord, 1999), would provide investigators with a direct assessment of a child's skills in pragmatics, syntax and semantics. In addition to assessing linguistic capability, the TOLC-3 could be used as a representative measure of social and emotional processing/cognition by evaluating a child's ability to interpret ambiguity, to understand inferences, to speak conversationally, and to comprehend figural expressions. According to Caplan and colleagues (Caplan et al., 1994), these above mentioned areas of linguistic communication are areas of concern for some children with epilepsy.

Lateralization of seizure focus has also been identified throughout the literature as contributing to, and predictive of, specific patters of neurocognitive dysfunction (Fedio & Mirsky, 1969; Kemp et al. 2001; Korkman & von Wendt, 1995). Although the present study was unable to evaluate lateralization due to the relatively small number of participants with a right-hemisphere seizure focus, future investigators may wish to incorporate lateralization and localization of epileptogenic focus as additional factors in their statistical modeling. Evaluation of seizure lateralization would be of particular interest to future studies examining prognostic indicators of neurocognitive dysfunction, due to the widely-discussed relationships between hemispheric specialization, psychological presentation, and emotional processing (Sackheim, 1982). In addition to more conventional means of assessing laterality of seizure focus (i.e., EEG and intracarotid sodium amytal testing), ictal perfusion single photon emission computed tomography (SPECT), interictal flurodeoxyglucose (FDG), and positron emission tomography (PET) may be valuable tools in more clearly defining ictal onset zones and ictal propagation pathways (Van Paesschen, Dupont, Sunaert, Goffin, & Van Laere, 2007).

Clearly, one of the primary goals of statistical modeling is to facilitate the prediction of long-term outcome. However, it is highly unlikely that a successful model can be developed when prediction (i.e., "risk assessment") is limited solely to static, conceptually-based contemporaneous factors. To this end, longitudinal studies can provide more concrete evidence and insight into the proposed interactional processes. Though a limited number of investigators have attempted to prospectively follow cohorts of children with epilepsy over time (MacDonald et al., 2000 ; Mitchell et al., 1994;

Shafer, Hauser, Annegers, & Klass, 1988; Shinnar et al., 2000; Sillanpaa et al., 1998) multiple authors of cross-sectional studies have considered longitudinal designs as worthwhile future endeavors (Meijer, Sinnema, Bijstra, Mellenbergh, & Wolters, 2000 Smith, Elliot, & Lach, 2002). Given the present investigation's goal of exploring the multiple determinants of neurocognitive functioning in children with epilepsy, systematic, long-term follow-up would be useful in determining which (if any) of the variables studied could predict test performance over time.

The development of epilepsy-specific test measures and sets of normative data produced by epilepsy patients are also worthwhile areas of future study. For example, the effect of treatment regimen on neurocognitive performance (see the results of Aims #2-4) may result in the underestimation of neuropsychological performance, particularly when children receiving polypharmacy are compared to non-medicated, neurologically-healthy normative samples. As such, traditional measures of neurocognitive functioning may lack sensitivity and specificity when evaluating dysfunction in this, and other neurologically-compromised populations (H. A. Bender et al., 2007). Whereas administration modifications, such as untimed testing, may obviate some of these concerns, the paucity of appropriate normative data remains a distinct handicap in this field of research. The development of disorder-specific scales or age-appropriate, disease-specific normative groups, though daunting from a pragmatic perspective, would facilitate more valid, reliable assessment in this population.

E. Summary

Although a multi-etiological model of psychopathology has been proposed by investigators studying adults (Hermann & Whitman et al. 1986; Hermann et al., 1991) and children (Caplan et al., 2004; B. P. Hermann et al., 1988) with epilepsy, very few studies to date have similarly explored the multiple determinants of neuropsychological dysfunction in a pediatric population. The present findings highlight the need to evaluate and control for the effects of seizure-related factors, psychiatric functioning, and behavioral social skills when evaluating neuropsychological functioning in children with epilepsy. To this end, early intervention, neurorehabilitation, and psychoeducational/psychosocial treatment therapies are highly warranted for the subgroups of children with epilepsy who are at particular risk for developing neurocognitive dysfunction, prior to their intellectual, academic, and developmental functioning being compromised.

V. TABLES

Table 1. Participant characteristics (frequencies) for the total sample

	N	N (%)
Sex		
Females	38	63.33
Males	22	36.67
Total	60	100.00
Race		
Caucasian	46	76.67
African-American	4	6.67
Hispanic	7	11.67
Asian	3	5.00
Total	60	100.00
Socioeconomic Status		
Lower	5	8.33
Middle	24	40.00
Upper	17	28.33
Missing	14	23.33
Total	60	100.00
Special Education Status		
Yes	27	45.00
No	32	53.33
Missing	1	1.67
Total	60	100.00
Seizure Type		
Partial	15	25.00
Generalized	32	53.33
Mixed	3	5.00
Missing	10	16.67
Total	60	100.00
Seizure Onset		
0 to 2 years	12	20.00
3 to 5 years	12	20.00
6 to 9 years	14	23.33
10 to 14 years	17	28.33
\ Missing	5	8.33
Total	60	100.00
Seizure Frequency		
None currently	9	15.00
Clusters	3	5.00
At least 1/year	10	16.67
At least 1/month	6	10.00
At least 1/week	11	18.33
Daily	10	16.67
Missing	11	18.33
Total	60	100.00
Treatment Regimen		
No Medication	18	30.00
Monotherapy	28	60.00
Polytherapy	6	10.00
Total	60	100.00

Table 2. Participant characteristics (mean and standard deviation) for total sample

	Mean	SD
Age	11.91	3.01
Years of Education	6.71	3.02
Full Scale IQ (SS)	93.63	16.42
Age at Seizure Onset (in years)	6.55	4.12
Duration of Epilepsy (in years)	5.39	4.11

Table 3. Neuropsychological test battery arranged by neurocognitive domain

Domain	Ability	Tests
Intelligence	● Verbal and non-verbal ability	● Wechsler Abbreviated Scale of Intelligence (WASI) or Wechsler Intelligence Scale for Children (WISC-III or WISC-IV)
Lanugage	● Confrontation naming	● Boston Naming Test
	● Expressive vocabulary	● WASI or WISC Vocabulary subtest
Visuospatial	● Visuoconstructional ability	● Rey Osterreith Complex Figure Test – Copy Condition
	● Visual perceptual and spatial skills	● WASI or WISC Block Design subtest
Attention & Concentration	● Visual attnetion, scanning, and motor speed	● Trail Making Test – Trails A
	● Attention span, mental control, and flexibility	● WISC Digit Span subtest
Executive Functioning	● Visual sequencing and set-shifting	● Trail Making Test – Trails B
	● Visual information processing and abstraction	● WASI or WISC Matrix Reasoning subtest
Psychomotor Speed	● Sustained attention and processing speed	● WISC Digit-Symbol Coding subtest
Learning & Memory	● Delayed visual memory	● Rey Delay Z
	● Verbal learning	● California Verbal Learning Test-Children's Version (Trials 1-5)
	● Delayed verbal memory	●California Verbal Learning Test-Children's Version (Long Delay Free Recall)

Table 4. Descriptive statistics for neurocognitive domains and individual subtests (z-scores) for the total sample (with outliers excluded*)

	Total Sample						Outliers Excluded		
						Transformed to z-scores			Transformed to z-scores
Test Name (unit of measure)	N	Min	Max	Mean	SD	Mean	SD	N	Mean	SD
Intelligence Domain	60	-2.50	1.77	-0.36	1.05	-0.36	1.05	N/A	N/A	N/A
Full Scale IQ (SS)	60	70.00	129.00	93.63	16.42	-0.42	1.09			
Verbal IQ (SS)	60	60.00	134.00	95.55	18.23	-0.30	1.22			
Performance IQ (SS)	60	65.00	131.00	93.63	16.15	-0.42	1.08			
Language Domain	60	-4.33	1.85	-1.05	1.45	-1.05	1.45	57	-.88	1.29
Boston Naming Test	55	-6.85	1.70	-1.60	1.97	-1.60	1.97			
Wechsler Vocabulary (T)	60	22.00	70.00	44.93	12.57	-0.51	1.26			
Visuospatial Skills Domain	60	-5.80	1.59	-1.39	1.50	-1.39	1.50	55	-1.09	1.13
Wechsler Block Design (T)	60	27.00	68.00	44.92	10.76	-0.51	1.08			
Rey-Osterreith Copy (Z)	53	-9.80	1.37	-2.42	2.48	-2.42	2.48			
Attention and Concentration Domain	59	-5.27	1.32	-0.59	1.42	-0.59	1.42	56	-.35	1.00
Wechsler Digit Span (SS)	53	1.00	17.00	8.32	3.49	-0.56	1.16			
Trails A (Z)	51	-8.88	1.61	-0.69	2.35	-0.69	2.35			
Executive Functioning Domain	60	-11.80	2.30	-0.73	1.87	-0.73	1.87	59	-.54	1.19
Wechsler Matrix Reasoning (T)	59	20.00	68.00	46.49	11.85	-0.35	1.19			
Trails B (Z)	49	-22.80	3.30	-1.24	3.62	-1.24	3.62			
Psychomotor Speed Domain	59	-3.00	2.00	-0.94	1.13	-0.94	1.13	N/A	N/A	N/A
Wechsler Digit-Symbol Coding (SS)	59	1.00	16.00	7.17	3.38	-0.94	1.13			
Learning and Memory Domain	58	-3.70	0.83	-0.95	0.92	-0.95	0.92	57	-.90	.85
Rey-Osterreith Delay (Z)	52	-4.17	0.72	-1.93	1.16	-1.93	1.16			
CVLT-C, Trials 1-5 (T)	58	20.00	73.00	45.16	11.09	-0.48	1.11			
CVLT-C, Delayed Recall (z-score)	58	-4.50	2.00	-0.50	1.17	-0.50	1.17			

*Only outliers on the domains were excluded (i.e., outliers on individual subtests were not excluded if score for domain was above z = -5.00

Abbreviations: SS = Standard Score; T = T-Score; Z = z-score; CVLT-C = California Verbal Learning Test for Children

Table 5. Comparison of mean performances (t-tests and ANOVAs) on neurocognitive domains across demographic categories

	FSIQ t/F M (SD)	Language t/F M (SD)	Visuospatial t/F M (SD)	Attention t/F M (SD)	Executive Functioning t/F M (SD)	Processing Speed t/F M (SD)	Memory & Learning t/F M (SD)
Sex	0.34	-0.10	-0.02	-0.59	-0.50	-2.71**	0.10
Females	0.39 (1.15)	-1.06 (1.41)	-1.39 (1.4)	-0.67 (1.49)	-0.82 (2.21)	-1.23 (1.01)	-0.94 (0.85)
Males	-0.49 (1.00)	-1.02 (1.54)	-1.39 (1.69)	-0.44 (1.32)	-0.57 (1.08)	-0.45 (1.17)	-0.96 (1.03)
Race	3.60*	4.06**	3.25*	3.35*	2.04	0.34	2.95*
Caucasian	-0.46 (1.03)	-1.11 (1.28)	-1.36 (1.43)	-0.51 (1.2)	-0.63 (1.11)	-0.89 (1.13)	-1.09 (0.88)
AA	-0.38 (1.35)	-0.28 (1.54)	-1.65 (0.46)	-0.09 (0.87)	-0.09 (0.72)	-0.75 (1.71)	-0.56 (0.97)
Hispanic	-0.97 (1.01)	-1.97 (1.82)	-2.35 (1.86)	1.9 (2.37)	2.18 (4)	1.29 (1.04)	-0.78 (0.85)
Asian	1.33 (0.41)	1.07 (0.71)	0.7 (0.45)	0.69 (0.54)	0.35 (2.56)	1.22 (0.69)	0.34 (0.42)
Socioeconomic Status	3.24*	1.81	0.37	0.73	0.30	0.36	0.68
Low	-1.49 (0.43)	-1.31 (1.38)	-1.54 (0.37)	-0.6 (0.58)	-0.91 (0.59)	-0.73 (1.64)	-1.15 (0.2)
Middle	-0.57 (1.11)	-0.76 (1.6)	-1.63 (1.36)	-0.99 (1.82)	0.97 (2.58)	-1.18 (1.09)	1.13 (0.92)
High	-0.16 (1.05)	-1.2 (1.54)	1.22 (1.85)	-0.41 (1.1)	-0.48 (1.21)	1.19 (0.97)	0.99 (0.25)
Special Education	5.50*	2.98	0.98	0.79	1.27	0.42	0.01
Yes	-0.76 (0.85)	-1.34 (1.14)	-1.91 (1.58)	-1.24 (1.39)	-1.01 (1.05)	-1.22 (1.02)	-1.21 (0.93)
No	-0.13 (1.21)	-0.77 (1.64)	1 (1.32)	-0.06 (1.24)	-0.46 (2.36)	-0.71 (1.19)	-0.76 (0.86)

Note: ANOVAs were conducted for race and socioeconomic status and t-tests were conducted for sex and special education status

* $p \leq .05$

* * $p \leq .01$

Table 6: Descriptive statistics and ANOVAs across neurocognitive domains for specific seizure-related variables (z-scores)

	FSIQ		Language		Visuospatial Skills		Attention		Executive Functioning		Processing Speed		Learning & Memory	
	F		F		F		F		F		F		F	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Seizure Type	0.83		1.04		0.05		0.26		0.66		0.33		2.3†	
Partial	-0.31	1.07	-0.76	1.36	-1.22	1.53	-0.50	1.71	-1.22	3.10	-0.89	1.24	-1.22	1.20
Generalized	-0.67	1.03	-1.36	1.43	-1.36	1.38	-0.83	1.43	-0.83	1.17	-0.86	1.18	-0.91	0.81
Mixed	-0.07	1.80	-0.65	2.20	-1.21	2.49	-0.52	0.92	0.17	1.24	-1.44	0.69	-0.02	0.28
Age of Onset (years)	2.01		1.71		0.63		0.62		0.12		0.21		1.15†	
0 to 2 years	-0.62	0.93	-1.38	1.42	-1.42	1.18	-0.89	1.52	-0.88	1.07	-0.77	0.99	-1.34	0.57
3 to 5 years	-0.68	0.99	-1.17	1.21	-1.91	1.45	-0.54	1.20	-0.43	1.06	-1.12	0.75	-0.9	0.82
6 to 9 years	-0.73	1.18	-1.54	1.50	-1.20	1.65	-0.91	1.67	-0.77	1.15	-1.07	1.39	-1.04	0.98
10 to 14 years	0.07	1.09	0.49	1.40	-1.17	1.80	-0.27	1.48	-0.77	3.11	-1.01	1.22	0.70	1.15
Seizure Frequency	0.81		1.35		0.47		1.91		1.75		0.58		0.93	
None currently	-0.24	1.17	-0.47	1.25	-1.96	1.26	-0.58	1.2	-0.68	1.17	-0.85	0.5	-1.12	1.07
Clusters	-0.53	0.99	-1.42	1.78	-0.64	0.7	-0.28	1.32	-0.69	0.88	-0.56	0.51	-0.76	0.47
At least 1/year	-0.63	1	-1.14	1.44	-1.56	1.42	-0.14	1.07	-0.46	1.02	-1.04	0.84	-0.64	1.03
At least 1/month	-0.91	0.87	-2.25	1.74	-1.53	1.08	-1.89	2.14	-2.7	4.61	-1.56	1.72	-0.51	0.90
At least 1/week	-0.59	0.97	1.09	1.46	-1.74	2.01	-0.97	1.54	-0.99	1.33	-0.82	1.56	-1.33	0.74
Daily	0.09	1.47	-0.60	1.36	-1.11	1.98	0.01	0.8	0.1	1	-0.6	1.15	-1.14	1.12
Treatment Regimen	1.01		1.36		1.98		2.14		1.39		0.64		5.6*	
No Medication	-0.37	1.15	-1.21	0.95	-1.77	1.60	-0.53	1.23	-0.22	1.45	-0.56	0.81	-1.43	0.42
Monotherapy	-0.82	0.88	-0.86	1.40	-1.02	1.30	-0.28	1.03	-0.53	1.28	-0.86	1.13	-0.56	0.90
Polytherapy	-0.39	1.21	-1.57	1.61	-1.89	1.76	-1.10	1.68	-1.39	2.73	-1.15	1.36	-1.35	0.90

* = $p \leq .01$
† = trend ($p \leq .10$)

Table 7. Hierarchical regression with seizure-related variables as predictors and neurocognitive domain scores as the criterion (total sample)[1]

Criterion	*Predictors*	*Beta*	*t*	*Sig. t*	*F*	*Sig. F*	R^2 / $R^2\Delta$
Language	Step 1				2.82	n.s.	.06 / .06
	Age at Seizure Onset	0.25	1.68	n.s.			
	Step 2				1.56	n.s.	.07 / .06
	Age at Onset	0.27	1.76	†			
	Seizure Frequency	-0.09	-0.59	n.s.			
	Step 3				1.29	n.s.	.02 / .09
	Age at Onset	0.26	1.62	n.s.			
	Seizure Frequency	-0.08	-0.48	n.s.			
	Seizure Type	-0.14	-0.88	n.s.			
	Step 4				1.57	n.s.	.14 / .05
	Age at Onset	0.28	1.80	†			
	Seizure Frequency	-0.09	-0.60	n.s.			
	Seizure Type	-0.17	-1.12	n.s.			
	Treatment Regimen	-0.23	-1.51	n.s.			
Learning & Memory	Step 1				0.20	n.s.	.05 / .05
	Age at Onset	0.22	1.41	n.s.			
	Step 2				1.45	n.s.	.07 / .02
	Age at Onset	0.25	1.59	n.s.			
	Seizure Frequency	-0.15	-0.98	n.s.			
	Step 3				1.83	n.s.	.12 / .06
	Age at Onset	0.28	1.81	†			
	Seizure Frequency	-0.18	-1.15	n.s.			
	Seizure Type	0.24	1.57	n.s.			
	Step 4				4.03	**	.30 / .17
	Age at Onset	0.33	2.33	*			
	Seizure Frequency	-0.21	-1.49	n.s.			
	Seizure Type	0.17	1.24	n.s.			
	Treatment Regimen	-0.43	-3.07	**			

[1]Non-significant analyses were not included in the table above (FSIQ, Visuospatial Skills, Attention, and Processing Speed domains were not significant)

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$).

Table 8. Descriptive statistics for CBCL scales (T Scores), by seizure variable for all participants

	Internalizing		Externalizing		Total Problems		Withdrawn/ Depressed		Anxious/ Depressed		Attention Problems		Thought Problems	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Seizure Type														
Partial	58.13	8.45	55.67	12.69	60.40	10.03	57.27	6.98	59.00	6.38	62.53	9.52	59.93	9.33
Generalized / Mixed	55.91	10.42	50.22	7.70	54.53	8.43	57.94	8.77	57.22	6.81	59.25	8.97	56.38	7.17
Age at Sz Onset (years)														
0 to 2 years	60.42	6.67	55.42	7.86	59.00	6.22	58.56	7.53	61.00	7.26	58.78	9.86	60.33	4.87
3 to 5 years	57.83	8.07	49.75	8.83	56.25	8.74	60.08	7.72	58.00	6.94	60.33	9.82	56.25	7.77
6 to 9 years	52.31	11.67	49.62	10.05	53.54	10.07	57.08	11.83	54.33	5.58	60.75	9.09	55.92	8.98
10 to 14 years	58.00	11.46	51.20	12.59	56.27	12.57	59.93	8.74	59.20	8.98	58.53	10.43	58.27	10.12
Seizure Frequency														
None currently	59.38	8.11	51.00	10.18	57.88	7.95	60.13	7.77	60.63	6.70	59.63	5.50	59.75	8.29
Clusters	56.67	11.06	47.00	5.20	50.33	8.15	52.00	2.00	53.33	5.77	53.33	1.53	55.67	5.69
At least 1/year	54.11	6.51	49.22	7.24	54.22	5.97	56.44	6.17	54.44	4.75	60.22	8.50	57.33	5.96
At least 1/month	59.33	52.50	52.50	72.42	57.67	6.06	57.67	6.09	59.83	6.85	58.50	5.93	53.33	5.09
At least 1/week	57.20	52.50	52.20	12.41	57.10	13.63	58.80	7.39	57.90	8.14	60.80	12.64	60.10	11.84
Daily														
Treatment Regimen														
No Medication	56.50	9.51	54.13	11.03	58.69	10.44	56.56	6.19	57.88	7.54	60.75	10.55	59.00	9.99
Monotherapy	63.00	9.30	55.00	13.25	58.50	11.85	64.67	5.79	61.50	8.53	60.83	11.02	57.33	7.15
Polytherapy	56.81	11.02	51.37	9.05	56.04	9.42	59.04	10.34	57.89	7.61	61.04	9.46	58.17	9.56
Total	57.73	10.00	25.14	10.25	56.86	9.83	59.13	8.64	58.41	7.54	60.38	9.71	57.91	8.16

Table 9. Descriptive statistics for BASC scales, by seizure variable for all participants

	Internalizing		Externalizing		Behavioral Symptoms Index		Depressed		Anxiety		Attention Problems		Hyperactivity		Social Skills		Atypical	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	S
Seizure Type																		
Partial	57.00	11.99	56.90	17.89	63.80	16.71	60.10	17.28	58.45	11.24	61.36	8.56	60.64	18.75	44.64	7.74	63.09	1
Generalized[1]	51.59	13.00	47.37	8.41	53.43	11.70	52.50	15.37	52.68	12.90	55.11	12.45	51.31	11.90	46.00	13.54	54.04	1
Age at Sz Onset (years)																		
0 to 2	53.00	14.86	51.00	12.09	57.00	12.70	57.00	15.51	55.00	13.19	54.88	13.19	56.57	13.18	46.00	14.89	56.50	1
3 to 5	52.40	9.55	47.40	8.46	55.40	13.03	54.50	14.07	53.90	9.69	53.20	12.21	48.30	14.51	45.80	11.12	58.20	1
6 to 9	50.82	11.60	47.27	10.83	54.18	11.20	48.60	10.28	52.30	13.55	57.70	8.97	49.80	13.69	46.40	14.26	55.70	1
10 to 14	53.17	12.97	50.83	15.95	55.69	16.30	55.69	18.21	53.54	12.21	55.83	13.30	54.42	18.22	47.23	8767	53.23	1
Seizure Frequency																		
None	52.33	12.24	48.20	10.71	54.17	12.12	54.83	12.40	53.14	8.76	54.86	10.67	50.43	11.93	51.29	9.07	53.14	
Clusters	42.50	10.61	40.00	8.49	45.50	3.54	42.00	1.41	47.50	19.09	54.50	6.36	41.50	16.26	54.50	20.50	43.50	
≥ 1/year	46.75	5.95	44.63	6.35	50.13	6.27	46.38	6.41	48.75	7.36	58.13	10.67	44.88	13.31	45.88	12.82	48.63	
≥ 1/month	56.50	5.20	48.25	4.19	55.50	9.47	55.00	7.53	64.50	11.15	51.25	9.64	57.25	8.96	47.50	7.90	58.00	1
≥ 1/week	56.20	11.93	50.40	14.28	55.80	15.35	56.20	13.64	54.00	12.33	55.10	13.87	54.22	18.04	45.50	10.50	58.90	1
Daily	62.33	16.93	59.50	19.09	66.43	19.06	65.71	23.96	58.29	13.66	58.33	15.55	62.17	21.18	45.14	14.03	63.57	1
Treatment Regimen																		
None	57.07	11.20	52.79	11.34	58.86	12.75	58.86	14.90	56.57	10.37	56.93	9.72	56.93	14.23	47.29	7.03	59.71	1
Monotherapy	59.33	20.43	58.50	20.37	62.33	21.43	66.00	25.63	57.50	15.62	58.67	15.27	61.83	23.27	40.50	13.69	56.17	1
Polytherapy	51.30	10.34	46.15	9.82	54.45	12.29	52.50	12.16	52.62	11.61	57.86	11.97	50.45	12.38	45.71	13.41	54.24	1
Total	53.70	12.20	49.83	12.31	56.15	13.43	55.42	15.30	54.08	11.99	56.58	12.01	53.15	15.14	46.10	11.67	55.71	1

[1]Includes 3 patients with mixed seizures (partial and generalized)

Table 10. Results of group mean comparisons (ANOVA), with seizure variables as the independent variable and BASC/CBCL scores as the dependent variable (all participants)

	Age of Seizure Onset		Seizure Frequency		Seizure Type		Treatment Regimen	
CBCL	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Internalizing T	1.54	n.s.	0.31	n.s.	0.52	n.s.	0.98	n.s.
Externalizing T	0.86	n.s.	0.29	n.s.	3.33	†	0.53	n.s.
Total Problems T	0.64	n.s.	0.33	n.s.	4.38	*	0.41	n.s.
Withdrawn/Depressed T	0.45	n.s.	0.56	n.s.	0.07	n.s.	1.88	n.s.
Anxious/Depressed T	1.42	n.s.	1.06	n.s.	0.73	n.s.	0.58	n.s.
Attention Problems T	0.13	n.s.	0.34	n.s.	1.32	n.s.	0.01	n.s.
Thought Problems T	0.89	n.s.	0.60	n.s.	2.07	n.s.	0.20	n.s.

	Age of Seizure Onset		Seizure Frequency		Seizure Type		Treatment Regimen	
BASC	F	Sig.	F	Sig.	F	Sig.	F	Sig.
Internalizing T	0.08	n.s.	1.83	n.s.	1.31	n.s.	1.41	n.s.
Externalizing T	0.35	n.s.	1.25	n.s.	4.61	*	2.77	†
Behavioral Symptoms Index T	0.07	n.s.	1.42	n.s.	4.57	*	0.88	n.s.
Depressed T	0.48	n.s.	1.71	n.s.	1.69	n.s.	1.93	n.s.
Anxiety T	0.01	n.s.	1.38	n.s.	1.70	n.s.	0.66	n.s.
Attention Problems T	0.34	n.s.	0.23	n.s.	2.31	n.s.	0.05	n.s.
Hyperactivity T	0.57	n.s.	1.14	n.s.	3.38	†	1.64	n.s.
Social Skills T	0.08	n.s.	0.26	n.s.	0.10	n.s.	0.72	n.s.
Atypicality T	0.28	n.s.	1.60	n.s.	3.86	†	0.73	n.s.

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$).

Table 11. Hierarchical regression analyses with seizure-related variables as the predictor and CBCL and BASC scores as the criterion (total sample)[1]

Criterion	*Predictors*	*Beta*	*t*	*Sig. t*	*F*	*Sig. F*	R^2 / $R^2\Delta$
	Step 1				0.31	n.s.	.01 / .01
CBCL Total Problems T	Age at Seizure Onset	-0.09	-0.56	n.s.			
	Step 2				0.21	n.s.	.01 / .00
	Age at Onset	-0.09	-0.62	n.s.			
	Seizure Frequency	0.06	0.65	n.s.			
	Step 3			n.s.	1.63	n.s.	.11 / .10
	Age at Onset	-0.14	-0.92	n.s.			
	Seizure Frequency	0.09	0.60	n.s.			
	Seizure Type	0.32	-2.12	*			
	Step 4				1.28	n.s.	.12 / .01
	Age at Onset	-0.15	-0.96	n.s.			
	Seizure Frequency	0.10	0.64	n.s.			
	Seizure Type	-0.31	-1.98	†			
	Treatment Regimen	0.09	0.56	n.s.			
BASC	Step 1				0.01	n.s.	.000 / .00
Internalizing T	Age at Onset	-0.02	-0.10	n.s.			
	Step 2				2.54	†	.13 / .13
	Age at Onset	-0.09	-0.60	n.s.			
	Seizure Frequency						
	Step 3				2.49	†	.19 / .06
	Age at Onset	0.37	2.25	*			
	Seizure Frequency	0.41	2.45	*			
	Seizure Type	-0.24	-1.49	n.s.			
	Step 4				2.71	*	.26 / .07
	Age at Onset	-0.16	-1.01	n.s.			
	Seizure Frequency	0.42	2.64	*			
	Seizure Type	-0.19	-1.25	n.s.			
	Treatment Regimen	0.27	1.71	†			

[1]CBCL Internalizing and Externalizing Scales not included due to results being non-significant

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$).

Table 11 (*cont.*). Hierarchical regression analyses with seizure-related variables as the predictor and CBCL and BASC scores as the criterion (total sample)[1]

Criterion	*Predictors*	*Beta*	*t*	*Sig. t*	*F*	*Sig. F*	R^2 / $R^2\Delta$
BASC Externalizing T	Step 1				0.00	n.s.	.00 / .00
	Age at Seizure Onset	0.00	0.02	n.s.			
	Step 2				1.94	n.s.	.11 / .11
	Age at Onset	-0.07	-0.42	n.s.			
	Seizure Frequency	0.33	1.97	†			
	Step 3				3.73	*	.26 / .15
	Age at Onset	-0.13	-0.79	n.s.			
	Seizure Frequency	0.38	2.41	*			
	Seizure Type	-0.40	-2.58	*			
	Step 4				4.61	**	.37 / .11
	Age at Onset	-0.16	-1.11	n.s.			
	Seizure Frequency	0.41	2.75	†			
	Seizure Type	-0.34	-2.36	*			
	Treatment Regimen	0.35	2.37	*			
BASC Behavioral Symptoms Index	Step 1				0.10	n.s.	.00 / .00
	Age at Onset	-0.05	-0.32	n.s.			
	Step 2				2.12	n.s.	.11 / .12
	Age at Onset	-0.13	-0.77	n.s.			
	Seizure Frequency	0.34	2.03	*			
	Step 3				3.84	*	.26 / .15
	Age at Onset	-0.18	-1.17	n.s.			
	Seizure Frequency	0.38	2.47	*			
	Seizure Type	-0.39	-2.57	*			
	Step 4				3.38	*	.30 / .04
	Age at Onset	-0.20	-1.32	n.s.			
	Seizure Frequency	0.40	2.59	**			
	Seizure Type	-0.36	-2.36	*			
	Treatment Regimen	0.20	1.32	n.s.			

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$).

Table 12. Results of ANCOVAs with CBCL/BASC as independent variables, seizure-related variables as covariates, and neurocognitive test performance as dependent variables.

	Neurocognitive Domain											
	Language		Visuospatial		Processing Speed		Attention		Executive Functioning		Learning & Memory	
Psychosocial Variable	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.
CBCL - Internalizing (n = x)	1.29	n.s.	2.26	n.s.	0.05	n.s.	0.71	n.s.	0.19	n.s.	6.98	**
Sz Onset	0.39	n.s.	1.19	n.s.	0.79	n.s.	0.85	n.s.	0.01	n.s.	2.98	†
Sz Duration	0.42	n.s.	0.00	n.s.	0.71	n.s.	0.15	n.s.	0.08	n.s.	0.08	n.s.
Sz Frequency	0.02	n.s.	0.46	n.s.	0.00	n.s.	0.16	n.s.	0.00	n.s.	2.46	n.s.
Sz Type	2.54	n.s.	0.01	n.s.	0.00	n.s.	0.04	n.s.	0.43	n.s.	4.08	*
Treatment Regimen	3.26	†	1.76	n.s.	0.22	n.s.	2.22	n.s.	0.35	n.s.	9.17	**
CBCL - Externalizing (n = x)	0.32	n.s.	0.38	n.s.	0.74	n.s.	1.24	n.s.	0.99	n.s.	1.60	n.s.
Sz Onset	0.32	n.s.	1.26	n.s.	0.57	n.s.	0.60	n.s.	0.00	n.s.	2.92	†
Sz Duration	0.41	n.s.	0.02	n.s.	0.58	n.s.	0.11	n.s.	0.14	n.s.	0.17	n.s.
Sz Frequency	0.06	n.s.	0.56	n.s.	0.01	n.s.	0.13	n.s.	0.03	n.s.	1.38	n.s.
Sz Type	2.38	n.s.	0.01	n.s.	0.14	n.s.	0.39	n.s.	0.05	n.s.	4.23	*
Treatment Regimen	4.09	*	3.80	†	0.38	n.s.	2.32	n.s.	0.44	n.s.	5.36	*
CBCL - Total (n = x)	4.28	*	0.28	n.s.	0.13	n.s.	0.15	n.s.	1.71	n.s.	3.27	†
Sz Onset	0.27	n.s.	1.07	n.s.	0.79	n.s.	0.79	n.s.	0.00	n.s.	2.96	†
Sz Duration	0.12	n.s.	0.01	n.s.	0.48	n.s.	0.12	n.s.	0.27	n.s.	0.03	n.s.
Sz Frequency	0.01	n.s.	0.13	n.s.	0.01	n.s.	0.31	n.s.	0.02	n.s.	1.35	n.s.
Sz Type	5.72	*	0.06	n.s.	0.05	n.s.	0.10	n.s.	0.00	n.s.	5.92	*
Treatment Regimen	5.35	*	2.76	n.s.	0.21	n.s.	2.86	†	0.64	n.s.	5.11	*
BASC - Internalizing (n = x)	0.01	n.s.	0.37	n.s.	0.02	n.s.	0.23	n.s.	0.50	n.s.	0.18	n.s.
Sz Onset	0.49	n.s.	0.65	n.s.	1.61	n.s.	1.19	n.s.	0.14	n.s.	5.29	*
Sz Duration	0.11	n.s.	0.00	n.s.	1.29	n.s.	0.61	n.s.	0.05	n.s.	2.31	n.s.
Sz Frequency	1.55	n.s.	0.03	n.s.	0.04	n.s.	0.91	n.s.	0.01	n.s.	0.29	n.s.
Sz Type	0.89	n.s.	0.00	n.s.	0.00	n.s.	0.44	n.s.	0.14	n.s.	0.12	n.s.
Treatment Regimen	4.76	*	2.91	†	0.40	n.s.	3.90	†	0.29	n.s.	8.55	**

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$)

Table 12 (*cont.*). Results of ANCOVAs with CBCL/BASC as independent variables, seizure variables as covariates, and neurocognitive performance as dependent variables.

	Neurocognitive Domain											
	Language		Visuospatial		Processing Speed		Attention		Executive Functioning		Learning & Memory	
Psychosocial Variable	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.	F	Sig.
BASC - Externalizing (n = x)	4.50	*	0.03	n.s.	3.52	†	1.46	n.s.	9.46	**	4.27	*
Sz Onset	1.77	n.s.	0.42	n.s.	0.67	n.s.	1.74	n.s.	0.47	n.s.	9.19	**
Sz Duration	0.08	n.s.	0.00	n.s.	1.08	n.s.	0.71	n.s.	0.29	n.s.	3.26	†
Sz Frequency	3.97	†	0.24	n.s.	0.11	n.s.	1.29	n.s.	1.18	n.s.	0.86	n.s.
Sz Type	0.23	n.s.	0.01	n.s.	1.54	n.s.	1.40	n.s.	7.39	**	2.29	n.s.
Treatment Regimen	8.45	**	2.50	n.s.	1.50	n.s.	4.94	*	2.62	n.s.	13.28	**
BASC - BSI (n = x)	0.08	n.s.	0.01	n.s.	0.23	n.s.	0.11	n.s.	4.16	*	0.70	n.s.
Sz Onset	0.54	n.s.	0.38	n.s.	1.85	n.s.	1.00	n.s.	0.00	n.s.	5.76	*
Sz Duration	0.14	n.s.	0.00	n.s.	1.19	n.s.	0.45	n.s.	0.02	n.s.	1.98	n.s.
Sz Frequency	1.88	n.s.	0.27	n.s.	0.12	n.s.	0.78	n.s.	1.49	n.s.	0.49	n.s.
Sz Type	0.75	n.s.	0.07	n.s.	0.05	n.s.	0.35	n.s.	2.75	n.s.	0.28	n.s.
Treatment Regimen	5.14	*	2.43	n.s.	0.40	n.s.	3.76	†	1.22	n.s.	9.33	**
BASC - Social Skills* (n = x)	0.23	n.s.	0.83	n.s.	0.28	n.s.	1.21	n.s.	0.16	n.s.	0.76	n.s.
Sz Onset	0.67	n.s.	0.48	n.s.	1.78	n.s.	1.14	n.s.	0.00	n.s.	5.78	*
Sz Duration	0.18	n.s.	0.01	n.s.	1.52	n.s.	0.62	n.s.	0.09	n.s.	2.07	n.s.
Sz Frequency	1.52	n.s.	0.32	n.s.	0.08	n.s.	0.57	n.s.	0.04	n.s.	0.03	n.s.
Sz Type	0.85	n.s.	0.28	n.s.	0.00	n.s.	0.17	n.s.	0.85	n.s.	0.06	n.s.
Treatment Regimen	4.56	*	3.24	†	0.42	n.s.	4.21	*	0.50	n.s.	8.61	**
BASC - Atypicality (n = x)	0.35	n.s.	0.00	n.s.	0.02	n.s.	0.67	n.s.	2.24	n.s.	1.60	n.s.
Sz Onset	0.53	n.s.	0.38	n.s.	1.83	n.s.	1.16	n.s.	0.00	n.s.	6.31	*
Sz Duration	0.19	n.s.	0.00	n.s.	1.56	n.s.	0.41	n.s.	0.03	n.s.	1.70	n.s.
Sz Frequency	0.70	n.s.	0.18	n.s.	0.08	n.s.	1.24	n.s.	0.85	n.s.	0.60	n.s.
Sz Type	0.94	n.s.	0.14	n.s.	0.01	n.s.	0.53	n.s.	1.74	n.s.	0.40	n.s.
Treatment Regimen	4.11	†	2.94	†	0.37	n.s.	4.32	*	0.81	n.s.	9.57	**

[a]Adjusted Mean

* = $p \leq .05$; * * = $p \leq .01$; † = trend ($p \leq .10$)

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