PARENT-REPORTED ANXIETY IN CHILDREN WITH SECONDARY GENERALIZED SEIZURES

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To my family and friends for all the encouragement, support, and love.

PARENT-REPORTED ANXIETY IN CHILDREN WITH SECONDARY GENERALIZED SEIZURES

by

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This study examined the role of seizure type in determining different levels of parent-reported anxiety, when taking demographic, medically-related, and medication-related variables into account.

One-hundred nineteen children with epilepsy aged 4 to 17 years old underwent a retrospective chart review. Demographic, medically-related, and medication-related variables, such as age, gender, ethnicity, handedness, median household income, age of

onset, seizure etiology, lateralization, EEG findings, MRI findings, number of antiepileptic drugs prescribed, side-effect profile of medication, and therapy regimen, were reviewed as well as parent-reported anxiety and depression on the Behavior Assessment System for Children, Second Edition (BASC-2).

Findings of the current study replicated previous research suggesting that children with epilepsy have higher average levels of depression and anxiety than the normative population. Children with epilepsy had similar levels of depression, regardless of seizure type. Children with partial seizures with secondary generalization had higher levels of anxiety symptoms compared to children with generalized seizures, but similar levels to those with partial seizures.

The current study's findings could have occurred due to the possible cueing components associated with having partial seizures with secondary generalization. The findings suggest a negative impact that behavioral symptoms of depression and anxiety may have on seizure-related care.

The current study expanded upon previous research by using a parent-report measure in which both depression and anxiety scales were normed with the same sample of children. Furthermore, the current study focused on children with secondary generalized seizures as a unique subtype and addressed anxiety specifically, which has been less researched than depression.

TABLE OF CONTENTS

PRIOR PUBLICATIONS

Gatchel, R.J., Robinson, R.C., Peng, Y.B., Benitez, O.J. & Noe, C.E. (2008). Pain and the brain. *Practical Pain Management, 8*(5), 28-40.

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADAA	Anxiety Disorders Association of America
ADHD	Attention-Deficit/ Hyperactivity Disorder
AED	Antiepileptic drug
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APA	American Psychiatric Association
BASC-2	Behavior Assessment System for Children, Second Edition
CBCL	Child Behavior Checklist
CBT	Cognitive-behavioral therapy
CDI	Children's Depression Inventory
CMCD	Children's Medical Center Dallas
CT	Computerized tomography
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
EEG	Electroencephalogram
EMU	Epilepsy monitoring unit
FDA	Food and Drug Administration
5-HIAA	5-hydroxyindoleacetic acid
fMRI	Functional magnetic resonance imaging
FSIQ	Full Scale Intelligence Quotient

GABA	γ-aminobutyric acid
HPA	Hypothalamic-pituitary-adrenal
ICES	International Classification of Epileptic Seizures
ILAE	International League Against Epilepsy
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children
MANOVA	Multivariate analysis of variance
MAOI	Monoamine oxidase inhibitor
MRI	Magnetic resonance imaging
NMDA	*N*-methyl-*D*-aspartate
PASW	Predictive Analytics SoftWare
PET	Positron emission tomography
RCMAS	Revised Children's Manifest Anxiety Scale
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SES	Socioeconomic status
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
STAIC	State-Trait Anxiety Inventory for Children
VNS	Vagal nerve stimulation
WAIS-III	Wechsler Adult Intelligence Scale, Third Edition
WASI	Wechsler Abbreviated Scale of Intelligence
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition

CHAPTER ONE
Introduction

Pediatric seizure disorders are potentially debilitating and can affect a child's cognitive functioning and overall emotional well-being, which can pose difficulties for the child's academic performance and daily life during his or her formative years. By clarifying various seizure disorders' impact on both cognition and emotions, treatment can be tailored to meet the needs of the child. The link between aberrant behavior or emotions and seizure emanation has been well documented in animal models of epilepsy (Barnes, Magyar, Pinel, & Takahashi, 2004; Depaulis, Helfer, Deransart, & Marescaux, 1997; Jones et al., 2008). These researchers surmise that these disorders, namely depression and anxiety, may manifest due to a variety of underlying circuits in the brain associated with temporal lobe pathology. Researchers suggest that involvement of the amygdala and other limbic structures in temporal lobe epilepsy may partially explain the connection between seizure manifestation and mood and fear symptoms.

Although the majority of research assessing psychiatric sequelae of epilepsy revolves around depression and psychosis, some researchers have assessed anxiety in adults with epilepsy (Goldstein & Harden, 2000; Kobau, Gilliam, & Thurman, 2006; Manchanda, 2002; Piazzini & Canger, 2001; M. Scheepers & Kerr, 2003; Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007). They suggest that anxiety experienced alongside epilepsy may be related to any of the following: (1) an ictal component (e.g., an actual simple partial seizure), (2) anticipatory fear of experiencing a seizure related to onset of an aura, (3) anticipatory fear of having a seizure without warning, (4) postictally-related

symptoms (e.g., lack of memory for the seizure itself despite the loss of bowel control or extreme sleepiness), (5) a manifestation related to the underlying physical pathology of the seizure disorder, (6) an adjustment problem related to having epilepsy, (7) a social consequence to the adjustment of having epilepsy (e.g., stigma, lower quality of life), (8) side-effects of antiepileptic drugs (AEDs) (e.g., tremor, cognitive slowing), and (9) a comorbid, unrelated, psychiatric disorder.

A large body of research with adult samples also addresses the health-related quality of life experienced by individuals with epilepsy (Cramer, Brandenburg, & Xu, 2005; Gilliam, Hecimovic, & Sheline, 2003; Zeber, Copeland, Amuan, Cramer, & Pugh, 2007). This body of literature typically indicates that emotional symptoms of depression are more potent predictors of the quality of life in individuals with epilepsy as opposed to "epilepsy-related" variables such as the amount of seizures per month, seizure control, and so forth. Thus, emotional symptoms secondary to epilepsy need to be understood for more appropriate treatment planning.

In addition to the body of adult-focused literature on various emotional manifestations related to epilepsy, pediatric literature has provided support showing that depression and anxiety are common comorbidities of epilepsy (Adewuya & Ola, 2005; Caplan et al., 2005; Dunn & Austin, 2004; Freilinger et al., 2006; Ott et al., 2001; Ott et al., 2003; Pellock, 2004; Williams et al., 2003). The impact that these emotional manifestations have on children is quite apparent given the social stigma of epilepsy, the relationship of emotional symptoms and school performance, and the child's social competence. Despite

existing research in pediatric epilepsy, not much research has clarified the differences in psychiatric symptoms among different types of seizures (i.e., generalized, partial, partial with secondary generalization). Furthermore, of the literature that exists, studies do not address the unique symptomatology of partial seizures with secondary generalization. The current research study seeks to address different levels in parent-reported anxiety and depression in order to provide more proactive and clarified treatment recommendations for behavioral and emotional disturbances related to different seizure manifestations.

CHAPTER TWO
Review of the Literature

OVERVIEW OF EPILEPSY

What are Seizures and Epilepsy?

A seizure is defined as a "period of sudden, excessive activity of cerebral neurons" (Carlson, 2005, p. 435). Symptoms are variable and depend upon the type of seizure that is experienced. For instance, symptoms can range from brief lapses in attention or quick muscle jerks to prolonged convulsions. In addition to the symptom variability, the frequency of seizures individuals can experience ranges from one every few years to many each day. There are many causes for seizures, some of which include brain injury, alcohol withdrawal, and preventable parasitic diseases. One seizure does not constitute a diagnosis of epilepsy as 10% of the worldwide population experience at least one seizure in their lifetime. The International League Against Epilepsy (ILAE) has defined epilepsy as a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher et al., 2005, p. 470). This important distinction needs to be emphasized as the diagnosis of epilepsy cannot be made until an individual has experienced a recurrent history of seizures with some functional or structural evidence of neurological dysfunction.

Epilepsy is one of the most common neurological conditions and affects more than 50 million individuals worldwide (Jacoby, 2002). According to the World Health

Organization (2009), an estimated 2.4 million individuals are diagnosed with epilepsy worldwide every year. Notably, approximately half of all reported cases of epilepsy are childhood-onset cases (Sillanpaa, Jalava, Kaleva, & Shinnar, 1998). According to Ekinci, Titus, Rodopman, Berkem, and Trevatha (2009), epilepsy is the most common neurological condition that affects children with prevalence rates between 0.05 to 1%. Using epidemiological measures, researchers (Shinnar & Pellock, 2002) approximate that 20,000 to 45,000 children are diagnosed with epilepsy each year.

Historical Accounts of Epilepsy

The modern understanding of epilepsy is based on scientific knowledge of the structural and functional neurological signs and symptoms that accompany it. However, to fully appreciate the stigma associated with it and why individuals with epilepsy may have anxiety or depressive symptoms, it is important to have an understanding of the history of how epilepsy has been conceptualized.

Early Accounts

Indian Ayurvedic writing in 2000 B.C. and ancient Babylonians attributed epilepsy to various curses or spirits. In 400 B.C., the Greek philosopher and father of medicine, Hippocrates, wrote *On the Sacred Disease,* which suggested that epilepsy was the product of brain dysfunction and spurred the movement to characterize epilepsy as an organic disease. He stated, "It is thus with regard to the disease called Sacred: it appears to me to be nowise more divine no more sacred than other diseases, but has a natural

cause like other affections…" (Hippocrates & Fischer, 2008, p. 99). Religious connotations are also paired with epilepsy such as in the Bible, in the book of Mark 9:14-25 (New International Version). In these verses, Jesus casts a devil out of a boy with epilepsy:

> Teacher, I brought you my son, who is possessed by a spirit that has robbed him of speech. Whenever it seizes him, it throws him to the ground. He foams at the mouth, gnashes at his teeth, and becomes rigid. I asked your disciples to drive that spirit out, but they could not.

Malleus Maleficarum, written in the latter half of the 15th century, was a handbook on witch hunting that identified the presence of seizures as a characteristic of witches (Summers, 1928). This work guided persecution and is as an example of one of the theories between personality and epilepsy.

Epilepsy was termed *The Falling Disease* during the Renaissance era, which rejected the superstitious medical beliefs of the middle ages. This line of thought continued to develop during the Enlightenment period of the 1600's in which the belief that demons played a part in epileptic semiology faded.

Modern View

As modern medicine progressed, so did the knowledge of various aspects of epilepsy. The more educated modern view of epilepsy began in the early twentieth century with English neurologists Russell Reynolds, John Hughlings Jackson, and Sir William Richard Gowers. They suggested that seizures were related to the discharge of disorderly nerve

tissues (Hogan & Kaiboriboon, 2004). Biologically-based theories of epilepsy have been supported since that time in both animal and human models.

Throughout the history of epilepsy, magical explanations of seizures faltered in favor of empirically-based biological explanations; however, remnants of the past still exist as some laypersons may not understand the biological nuances that contribute to an epileptic seizure. Since the inception of ILAE in 1909, global campaigns educating about epilepsy have become more apparent. This agency employs medical professionals and laypersons and aims to address various aspects of epilepsy.

Definitions and Classifications of Seizures

The task of defining various types of seizures and epileptic syndromes began in 1981 with ILAE's creation of the International Classification of Epileptic Seizures (ICES). Revisions to the classification system in 1985 focused on describing seizure syndromes as various clusters of signs and symptoms that occur together. Additional revisions in 2001 more clearly defined focal seizures and developed a multiaxial system with therapeutic implications. Consistent throughout each of the classifications systems is the differentiation of seizures according to localization (i.e., focal versus generalized) and etiology (i.e., symptomatic, idiopathic, or cryptogenic).

Localization

Seizures can be classified by the area of the brain that is affected. Two general types of seizures based on localization are focal seizures and generalized seizures.

Terms describing seizures that affect one side of the brain have changed from "partial" in 1981 to "localization-related" in 1989, and most recently have been termed "focal" in 2001. These terms describe seizures that are accompanied by clear evidence of functional or structural origin. Though the ILAE has proposed the term "focal" to describe seizures with lesions or paroxysmal activity in one cerebral hemisphere, "partial" is still commonly used in clinical settings and was used interchangeably in the current study. Pertinent to focal seizures, ictal behavior and symptoms reflect underlying brain regions that are affected by the seizure. For example, individuals with seizures that have focal abnormalities in the left temporal lobe may present with language difficulties.

Partial seizures can be further subdivided by those that do not involve an alteration in consciousness (i.e., simple) and those that involve an alteration or a loss in consciousness (i.e., complex). Alteration in consciousness is typically defined as amnesia for the events during a seizure occurrence. During simple partial seizures, although consciousness is intact, various motor, sensory, or autonomic symptoms may occur depending on cerebral location of pathology. Examples of simple partial seizures include focal motor and sensory seizures. These seizures typically happen during the day, occur relatively infrequently, and often disappear during adolescence (Crumrine, 2002). During complex partial seizures, patients often lose consciousness and experience automatisms (e.g.,

facial movements, movement of upper limbs, vocalizations) as well. Examples of complex partial seizures include temporal and frontal lobe seizures. Partial seizures with secondary generalization are a subtype of partial seizures in which the seizure begins in a specific location, but then spreads across both cerebral hemispheres.

Finally, with regard to localization, generalized seizures are those in which the nervous system changes or pathology involves both hemispheres of the cerebrum from the beginning of a seizure and lead to impairment in consciousness. Examples of these seizures include atonic, absence, and tonic-clonic seizures.

Etiology

In addition to classifying seizures by localization, clinicians have classified them by the etiology as well. Idiopathic, symptomatic, and cryptogenic are all terms commonly used to describe the underlying cause or causes of seizures.

The descriptor *idiopathic* is a term often used in medical nomenclature to describe a disorder not preceded or occasioned by another. Despite a lack of imaging evidence to suggest a structural or functional abnormality for idiopathic seizures, the ILAE suggests that there are genetic causes to such seizures. Idiopathic seizures are the most commonly cited etiology among children, affecting approximately six out of ten with epilepsy (World Health Organization, 2009).

A *symptomatic* seizure is a consequence of a known or suspected disorder of the central nervous system. For example, anoxic insults, traumatic brain injuries, and strokes are all common causes of central nervous system pathology that may contribute to the manifestation of seizures.

In 2001, the term *cryptogenic* was added to the 1985 classification system. This addition accompanied the previously defined symptomatic and idiographic terms to describe seizures presumed to be symptomatic without clearly defined etiology.

Diagnosis of Epilepsy

As noted above, the occurrence of one seizure does not necessarily mean that an individual has epilepsy. Because of the wide variety of medical conditions that can contribute to seizures, a formal diagnosis of epilepsy requires a series of medical procedures and steps. Though there are variations in how an individual receives a diagnosis of epilepsy, best practices have been described in previous research and is reviewed below (S. Brown et al., 1998; Johnston & Smith, 2008).

Semiology

Semiology describes behaviors or symptoms that an individual may exhibit immediately prior to (i.e., preictal), during (i.e., ictal), and after (i.e., postictal) a suspected seizure. Behaviors exhibited in the time periods in between seizures (i.e., interictal) have also been studied. Although these behaviors vary depending on the type of seizure

experienced and the location of the seizure, they can include any or all of the following: auras, confusion, amnesia, staring, rhythmic jerks, or tightening of the muscles. These outward manifestations of epilepsy make the disorder apparent to others. In one of the first steps toward the diagnosis of epilepsy, an individual will usually visit his or her primary care physician with these complaints. For instance, the individual may note that a witness described symptoms such as stiffening up, falling, and shaking uncontrollably for a few moments with confusion immediately following.

Physical Examination

Upon describing the semiology to their physician, a detailed medical history is taken including the symptoms and duration of the episodes. The description of semiology may help focus the physician on identifying whether or not the experienced seizure is epileptogenic in nature or is a symptom of another medical condition. Blood samples may be collected to screen for metabolic or genetic conditions as well as infections, anemia, or diabetes, which may contribute to seizure emanation. If lab results suggest dysfunction unrelated to a metabolic or genetic condition and if the primary care physician suspects the symptoms to be related to seizures, best practices lead the physician to make a provisional diagnosis of epilepsy and refer the patient to a neurologist who is more specifically trained in epilepsy. From here the epileptologist, a neurologist with extensive training in epilepsy, performs a neurological examination to assess the muscles, senses, and reflexes and typically orders an electroencephalogram (EEG) to help aid in diagnosis.

Electroencephalogram

An EEG is a functional technique that uses tiny electrodes placed on the scalp. These electrodes pick up electrical signals from communicating neurons, amplify them, and record them on telegraphic paper (Carlson, 2005). It is the most specific method to define the epileptogenic area of the brain and often reveals characteristic findings in several epilepsy syndromes (Noachtar & Remi, 2009).

The EEG process is classified based on the level of invasiveness: (1) noninvasive electrodes and (2) invasive electrodes (Noachtar & Remi, 2009). Noninvasive procedures involve placement of electrodes on the scalp. Invasive procedure EEGs are used when noninvasive procedures do not yield sufficient localization of the epileptogenic zone. Examples of noninvasive procedures include depth electrodes, which are very precise electrodes used to identify whether specific structures (e.g., cingulate gyrus) are involved in seizure emanation, and subdural electrodes which are grids or strips used to help localize seizure emanation more clearly than noninvasive procedures. Foramen ovule electrodes are another example of an invasive procedure in which electrodes may be placed in close proximity to the mesial temporal lobe for a more accurate localization of temporal lobe epilepsies. Although invasive procedures have clearer signal-to-noise ratios and little electromyographic artifact from movement (i.e., typical setbacks of traditional noninvasive EEG), there are a variety of disadvantages, such as risks of infection (2 to 3%), intracerebral hemorrhages (less than 1%), general surgery risks, and patient discomfort, which clinicians must consider (Blume, 1997).

During the EEG process, individuals may be asked to breathe deeply (i.e., hyperventilation), look at flashing or flickering lights (i.e., intermittent photoic stimulation), or open and close his or her eyes in rapid succession. Furthermore, EEGs can also be performed during sleep-deprived states. Techniques employed during EEG monitoring promote seizure activity so that symptoms may be observed by physicians. Furthermore, EEG monitoring helps describe the paroxysmal activity of seizure occurrences and guide treatment recommendations. For example, special precautions can be recommended to individuals with a propensity toward photospecific seizures. An epilepsy monitoring unit (EMU) may be used to guide diagnosis and treatment. An EMU is an area of a hospital or clinic that is dedicated solely to capturing interictal and ictal epileptiform activity and often involves extended stays and video telemetry in addition to EEG monitoring.

Despite the disadvantages of using EEG such as poor temporal stability and often diffuse electrical activity, it is one of the most useful tools for diagnosing epilepsy. Results from an EEG illustrate the electrical activity of the brain and help address epileptogenic location and efficacy of therapy (Noachtar & Remi, 2009). Depending on the type of seizure experienced, EEG findings have unique features that support clinical diagnoses. For example, simple partial seizures may show focal sharp waves during interictal periods or slow rhythmic discharges during ictal phases. Complex partial seizures may be recorded as focal EEG abnormalities including sharp waves or spikes during interictal periods and focal or bilateral rhythmic sharp waves during ictal periods. In generalized seizures there are typically generalized synchronous symmetrical discharges on both

sides of the cerebrum. Childhood and juvenile absence epilepsy are two types of idiopathic generalized epilepsy syndromes that often coincide with generalized 3-Hz spike and slow wave discharges upon EEG procedure (Siren et al., 2007). Finally, generalized polyspikes are common in myoclonic epilepsies (Noachtar & Remi, 2009).

A final issue worth mentioning with EEG use is that of necessity versus sufficiency. An abnormal EEG finding is neither necessary, nor is it sufficient, to diagnose epilepsy. A normal EEG does not automatically preclude a diagnosis of epilepsy as some types of simple partial seizures evidence normal EEG patterns. After patients have undergone EEG monitoring and experienced two or more seizures in the past, they may be diagnosed with epilepsy. However, there are other ancillary imaging techniques that may be used to strengthen the diagnosis, add to the clinical picture, and guide treatment options.

Anatomic Studies

In addition to EEG results, neurologists may rely on structural imaging results from computerized tomography (CT) and magnetic resonance imaging (MRI) to help aid in diagnosis. MRI is a relatively young imaging technique that is used to view the internal structure of a body. MRI resembles a CT scan but uses magnetic fields instead of standard x-rays. Unlike CT, MRI uses no ionizing radiation, but a powerful magnetic field to align the nuclear magnetization of hydrogen atoms in water in the body. Radio frequency fields are used to systematically alter the alignment of this magnetization, causing the hydrogen nuclei to produce a rotating magnetic field detectable by the

scanner. This signal can be manipulated by additional magnetic fields to build up enough information to construct an image of the body (Carlson, 2005). Since the 1970's, MRI has helped physicians visualize clearer depictions of soft tissue when compared to traditional CT. MRI has been helpful in diagnosing epilepsy as some individuals have clear neurostructural pathologies suggestive of brain dysfunction, such as in the case of mesial temporal sclerosis and cortical dysplasias.

*Special Studie*s

Clinicians may employ several other methods to assist in the diagnosis and treatment of epilepsy, including functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). These are all examples of functional imaging techniques, which may assist in determining language dominance and areas of cognitive deficit. For example, fMRI uses the change in blood flow and oxygenation in order to produce images of the brain's functions. It increases the probability of accurately identifying hemispheric language dominance in subgroups of individuals with epilepsy (Medina, Bernal, & Ruiz, 2007). Furthermore, fMRI's strength in spatial resolution compliments the EEG's strength in temporal resolution with regard to brain function and is occasionally used in diagnosis and determining targets for surgery.

PET is a nuclear imaging technique that produces three-dimensional images of the functional process of the brain. Unlike other techniques that are noninvasive in nature, PET uses radioactive tracer isotopes that are injected in the body. The most common

tracer is flurodeoxyglucose, a derivative of glucose, which gives tissue metabolic activity in terms of glucose uptake. More energy is used in areas of increased metabolic activities; in areas of little activity, less energy is used. In the event of a seizure a PET shows the area of increased glucose use. An advantage of PET includes more confidence in localizing seizure emanation when used in conjunction with EEG. Furthermore, if PET is used, the reliance on invasive procedures such as depth electrodes is reduced. However, PET imaging is not as commonly used in children as the use of radioactive substances poses ethical issues (Munson, Eshel, & Ernst, 2006).

Finally, SPECT is an imaging technique that uses gamma rays to produce a three-dimensional functional image of blood flow. A small amount of radioactive compound that is injected into an individual that binds to certain types of tissues. The combination of the compound and ligand are then imaged by a gamma camera and particles it emits are measured. The compound and ligand combination produces an image showing various levels of blood flow. The more blood flows through a certain area of the body, the more particles are emitted from the compound. SPECT is not as routinely used as previously mentioned imaging techniques; however, it can be helpful in showing the increased blood flow in areas of seizure emanation immediately before or after a seizure occurs.

In summary, a diagnosis of epilepsy requires an accurate description of clinical manifestations and symptoms, which leads to a series of medical tests to help rule out other possible etiologies. EEG findings, anatomical, and special studies help solidify the

diagnosis. Once epilepsy is diagnosed, a variety of treatments options are available that may decrease the amount of seizures experienced.

THE TREATMENT OF EPILEPSY

Like many chronic illnesses, epilepsy cannot be cured; however, seizures can often be successfully attenuated and managed with medication, lifestyle changes, medical interventions, and surgery. Although some patients with epilepsy do not obtain full seizure control with medication and other treatment, a percentage of individuals stop having seizures with proper treatment. The Collaborative Group for the Study of Epilepsy (1992) suggests that approximately 60 to 80% of seizures can be controlled with medication alone. Individuals who do not obtain adequate seizure relief with medication may obtain some seizure relief with ancillary treatments such as the ketogenic diet, vagal nerve stimulation (VNS), and neurosurgical procedures, which are beyond the scope of the study.

Treatment with Antiepileptic Drugs

In 1912, phenobarbital became the first AED offered to reduce seizures. Over the last century, many AEDs with different pharmacological properties have been developed to decrease or eliminate recurrent seizures. After much reliance on phenobarbital as a first-line AED, the development of valproic acid, phenytoin, and carbamazepine in the 1950s greatly broadened the choices for pharmacological treatment. Advances in the late 1980s

and into the 1990s allowed researchers and pharmaceutical companies to develop new generation AEDs, which act on different neurological systems and have "safer" side-effect profiles (Cramer et al., 2005).

Mechanisms of Action

At the basic molecular level, neurons are interconnected and communicate with each other via transmission at synaptic junctions. Furthermore, without the aid of inhibitory synapses, excitatory synapses stimulate each other, causing the brain to fire uncontrollably leading to seizure activity. In the central nervous system most synaptic communication is accomplished via two amino acid neurotransmitters, one with excitatory and one with inhibitory effects. Glutamate, an excitatory neurotransmitter, and γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, act as modulating neurotransmitters and often work with other neurotransmitters (e.g., serotonin, dopamine). The mechanism of action of AEDs varies depending on the physiological system with which the particular drug interacts. According to Davies (1995), AEDs are classified in three groups: (1) those that facilitate GABAergic transmission (e.g., phenobarbital and gabapentin), (2) those that are neuronal ion channel modulators (e.g., phenytoin, carbamazepine, oxcarbazepine, valproic acid, lamotrigine, and zonisamide), and (3) those with no conventional GABAergic, antiglutamatergic, or ion channel modulatory effect (e.g., levetiracetam). Furthermore, Glauser (2004a) suggested adding another group of drugs with a mixed GABAergic and antiglutamatergic mechanism of action (e.g., topiramate) to the classification system.

Antiepileptic Drugs Commonly Prescribed for Children

Antiepileptic drugs have a wide range of adverse side effects, which have a negative impact on an individual's well-being and daily life. Side effects such as sedation, irritability, and gastrointestinal symptoms are a just a few of the many that are associated with certain drugs. Selection of specific medication for pediatric epilepsy may depend on the experience of the clinician rather than research, given the relative absence of pediatric AED clinical trials, variability in clinical trials, population differences, investigator bias, and reliance on retrospection (Loring, 2005; Vinayan, 2006). Nevertheless, in a comprehensive study in 2004, Glauser reviewed the ten most commonly prescribed AEDs in children, which represented more than 95% of the AED prescriptions written for patients under the age of 20 at that time. In descending order by the rate of prescription, these drugs include valproic acid, carbamazepine, phenobarbital, lamotrigine, phenytoin, levetiracetam, oxcarbazepine, topiramate, zonisamide, and gabapentin. Due to the nature of the current study, an understanding of the types of epilepsy that are typically treated with certain drugs and the medical, cognitive, and behavioral side-effect profiles associated with those drugs is appropriate.

Introduced in 1978, the most commonly prescribed AED, valproic acid is an older generation AED typically prescribed to treat all types of seizures. It is prescribed at a high rate due to its efficacy in decreasing seizures such as myoclonic seizures (Crumrine, 2002). In general, valproic acid, when used in combination with carbamazepine, represents the standard AED indication for children and adolescents with newly diagnosed epilepsy (Donati et al., 2006). As stated, valproic acid is a neuronal ion

channel modulator and is typically associated with calcium channel, neuropeptide Y, and GABA interactions in very high doses. The medical side effects of valproic acid include weight gain, gastrointestinal upset, and tremors. Cognitive side effects of valproic acid most commonly include psychomotor slowing and decreases in attention and memory (Meador, 2005). However, in a recent study of children with newly diagnosed absence seizures, baseline measures of neuropsychological functioning were obtained to evaluate the cognitive impact of valproic acid (Siren et al., 2007). After a high percentage of children obtained full seizure relief from valproic acid they were retested. Results revealed that children with epilepsy who obtained seizure relief improved in fine-motor fluency, attention, and visual memory. Although this study employed a small sample size, it illustrates the importance of the attainment of remission in the development of cognitive abilities during childhood. Additionally, valproic acid is not typically associated with behavioral side effects, and the mood-stabilizing properties of the AED have also been instrumental in treating mood symptoms and Bipolar I Disorder (Post et al., 1996). However, it currently has a black box warning indicating that it may increase the risk for suicidal thoughts and behaviors. It should be noted that this warning comes from the U.S. Food and Drug Administration's (FDA) placebo-controlled clinical trials of the AEDs, which showed patients receiving medication were at twice the risk for experiencing suicidal thoughts or engaging in suicidal behavior than those who were not currently prescribed AEDs (U.S. Food and Drug Administration, 2008).

The second most commonly prescribed AED, carbamazepine, was introduced in 1953 and is an older generation AED that is favored in the treatment of all types of partial

seizures. It affects sodium channels and inhibits rapid fire of brain cells. The medical side effects of carbamazepine include blurred vision, weight gain, and hyponatremia. It is often prescribed with valproic acid to children and adolescents with newly diagnosed epilepsy as first line treatment. Much like valproic acid, cognitive side effects include decreases in attention and memory, and psychomotor slowing. Interestingly, carbamazepine causes EEG alpha wave slowing, which has been correlated with declines on tests of intelligence (Frost, Hrachovy, Glaze, & Rettig, 1995). Though there are typically no major behavioral side effects experienced when taking carbamazepine, it can indirectly affect psychiatric symptoms through P450 enzymes. Carbamazepine is a strong cytochrome P450 enzyme inducer that may interfere with the clearance of some tricyclic antidepressants and anxiolytics, indirectly contributing to psychiatric symptomatology (Glauser, 2004b). Additionally, like valproic acid, carbamazepine currently has an FDA black box warning for increasing suicidal thoughts and behaviors. Nevertheless, Post et al. (1996) have found that it has mood-stabilizing properties and is often used as an off-label treatment for Bipolar I Disorder.

Phenobarbital the oldest and third most commonly prescribed AED in children, is a barbiturate that increases the effects of GABA. Though it has been used to treat all types of seizures with the exception of absence seizures, because of the side effects associated with phenobarbital use, it is no longer recommended as a first or second line treatment in individuals with epilepsy. Despite the side effects, phenobarbital is still used as a first line AED in neonatal seizures. Like other barbiturates, the medical side effects include sedative and hypnotic properties as well as dizziness and nystagmus. Phenobarbital is the

most widely cited AED with cognitive side effects (Bourgeois, 2004; Bourgeois, Prensky, Palkes, Talent, & Busch, 1983; Loring, 2005; Loring & Meador, 2004; Vinayan, 2006). It is associated with declines in IQ, which are thought to reflect slowed mental growth rather than a loss of previously acquired cognitive function and is supported by some studies that have shown an improvement in IQ following the discontinuation of phenobarbital (Farwell et al., 1990). In a classic study, phenobarbital was compared to sodium valproate for cognitive effects in 21 children. The study used a double-blind crossover comparison and found that although there was no difference in seizure control between the two AEDs, while on valproate, children scored higher on Full Scale and Performance IQs (Vining et al., 1987). In addition to cognitive effects of Phenobarbital, other studies have shown that patients taking it are prone to increased levels of depression (Crumrine, 2002; Lambert & Robertson, 1999). Phenobarbital is also a strong cytochrome P450 enzyme inducer and may therefore interfere with the clearance of some antidepressants and anxiolytics (Glauser, 2004b).

Lamotrigine is the fourth most commonly prescribed AED, was released in 1994, and is a new generation AED that is indicated as a monotherapeutic treatment of all types of seizures in adults and as an adjunctive treatment in children. Though it is not as effective in decreasing myoclonic seizures, there are fewer adverse side effects compared to valproic acid. Medical side effects include dizziness, fatigue, and rash, with more severe medical side effects unusual. Lamotrigine has been associated with little cognitive impairment and may actually lead to improved alertness (Meador, 2005; Meador, Gilliam, Kanner, & Pellock, 2001). Furthermore, lamotrigine's mood-stabilizing

properties subsequently led to its clinical indication for the treatment of Bipolar I Disorder. Finally, despite black box warnings of increasing the risk of suicidal thoughts and behaviors, it is routinely used as an off-label adjunctive treatment for unipolar depression (Goldsmith, Wagstaff, Ibbotson, & Perry, 2003).

The fifth most commonly prescribed pediatric AED, phenytoin is an older generation AED introduced in 1939 and is currently indicated in the treatment of generalized tonic-clonic and complex partial seizures, and prevention and treatment of seizures following neurosurgery. As stated, the mechanism of action of phenytoin is by voltage-gated sodium channels. The medical side effects of phenytoin include neurological, hematological, and gingival problems. Furthermore, more recently it has been proposed to be a teratogen, causing similar physical and cognitive abnormalities as fetal alcohol syndrome; however, definitive statements about the teratogenicity are unclear at this time. Like older generation AEDs already reviewed (e.g., valproic acid and carbamazepine), phenytoin has a cognitive side-effect profile that includes decreases in memory, attention, and psychomotor speed (Meador, 2005). Like other drugs that are strong P450 enzyme inducers, phenytoin can indirectly contribute to psychiatric symptoms despite the findings that show it may contribute to decreases in anxiety and better mood (Glauser, 2004a).

Levetiracetam is a new generation AED introduced in 1999, is the sixth most commonly prescribed AED for children, and is indicated as an adjunctive therapy in the treatment of partial seizures, myoclonic seizures and juvenile myoclonic epilepsy, and primary

generalized tonic-clonic seizures and idiopathic generalized epilepsy. Common medical side effects of levetiracetam are asthenia, dizziness, and insomnia. Compared to older AEDs such as carbamazepine, levetiracetam has fewer cognitive side effects as found by a recent randomized, double-blind, two-period crossover study using a sample of healthy individuals (Meador et al., 2007). In the study, individuals who were given levetiracetam performed better on tests of attention, memory, language, motor speed, graphomotor coding, and naming speed compared to those given carbamazepine. Though the cognitive side effects of the drug are very minimal, behavioral side effects have been cited in numerous studies, especially in pediatric samples. In numerous studies, levetiracetam has induced irritability in the individuals for which it was prescribed (Abou-Khalil, 2005; Bourgeois, Holder, & Valencia, 2001; Glauser et al., 2002; Sheless & Ng, 2002). Furthermore, it has been associated with reports of aggression (Loring, 2005), and currently has an FDA black box warning for increasing the risk of suicidal thoughts and behaviors. A comprehensive study of the psychiatric and behavioral side effects of the newer AEDs was carried out recently (Weintraub, Buchsbaum, Resor, & Hirsch, 2007). In this chart review of 1,394 adult patients who were newly prescribed an AED, the focus was to measure the level of self-reported psychiatric side effects (i.e., defined as behavior change, depression, irritability, and anxiety) and control for numerous non-AED predictors of psychiatric disturbance (e.g., previous mental health history, demographics, past medical history). The researchers found that overall only 16% of the sample experienced adverse psychiatric or behavioral events. However, the most psychiatric symptoms were endorsed in individuals prescribed levetiracetam. Despite the overwhelming majority of studies reporting untoward behavioral effects, it should be

noted that there are a few studies that suggest limited behavioral side effects (Meador et al., 2007); however, these studies are minimal.

Oxcarbazepine is a new generation AED that was released in 2000, is the seventh most commonly prescribed AED in children, and is similar in structure and mechanism of action to carbamazepine. It is indicated as a monotherapeutic or adjunctive therapeutic treatment for partial seizures in adults and as an adjunctive therapeutic treatment for children with epilepsy. Studies have frequently shown it to be as effective as its older AED counterpart and with fewer side effects. Despite the lower incidence of side effects, it carries the risk of increasing hyponatremia. Although it is structurally similar to carbamazepine, it does not lead to declines in cognitive functioning (Donati et al., 2006, 2007). Oxcarbazepine currently has a black box warning for increasing the risk of suicidal thoughts and behaviors; however, most studies show that oxcarbazepine has a relatively safe behavioral side-effect profile (Weintraub et al., 2007). Some studies have also shown that oxcarbazepine can have a slight anxiolytic effect as well (Mazza et al., 2007).

Topiramate is a new generation AED that was released in 1996, is the eighth most commonly prescribed pediatric AED, and is indicated as an adjunctive therapy to treat partial and primary generalized tonic-clonic seizures in children and adults. It has several mechanisms of action, including interactions with both GABA and glutamate. The medical side effects most commonly associated with topiramate include glaucoma, kidney stones, headaches, parathesias, and upper respiratory tract infections. The most

pronounced declines in cognitive ability in the new generation AEDs have been found with topiramate use, which has been associated with difficulties in memory, speech, attention, concentration, and psychomotor slowing (Drane & Meador, 2002; Loring, 2005; Meador, 2005). In a study comparing adults and children with epilepsy who were prescribed either levetiracetam or topiramate, researchers found that 15% more patients discontinued topiramate due to the higher reports of perceived negative neurocognitive effects (Bootsma et al., 2006). In another study, topiramate was studied in multi-dose formulations as a monotherapeutic regimen in adults (Lee, Jung, Suh, Kwon, & Park, 2006). These researchers obtained self-reports of cognitive functioning prior to administration and at one-year follow-up. Results revealed that over 40% of the individuals in the study had progressive subjective complaints of cognitive problems after the administration of topiramate. Objective results revealed dose-dependent cognitive difficulties with auditory attention and verbal fluency tests, illustrating that even at lower doses of topiramate, cognitive side-effects occur. Though more rare than the documented cognitive side effects, there is currently a black box warning for topiramate stating that it may increase the risk of suicidal thoughts and behaviors. Additionally, a few studies have suggested that topiramate contributes to endogenous depression in individuals with epilepsy (Lambert & Robertson, 1999); however, this is not a common finding.

Zonisamide is a new generation AED that was introduced in 2000 and is the ninth most commonly prescribed AED for children. It is approved for use as an adjunctive treatment in adults with partial seizures and is often used in children with infantile spasms, Lennox-Gastaut syndrome, and myoclonic and generalized tonic-clonic seizures. The mechanism

of action of zonisamide is a neuronal ion channel modulator, particularly sodium ion channels. The known medical side effects of zonisamide include drowsiness, loss of appetite, dizziness, headache, and nausea. Although some cognitive side effects have been documented within the first three months of titration, these side effects typically remit by six months. However, perhaps more apparent than the cognitive side effects are the psychiatric and behavioral effects that accompany its use. For example, numerous studies have shown that after titration with zonisamide, psychotic or obsessive-compulsive symptoms typically manifest (Miyamoto, Koshsaka, & Koyama, 2000). Similar to other AEDs, zonisamide also carries a black box warning, suggesting it increases the risk of suicidal thoughts and behaviors.

Gabapentin is a new generation AED introduced in 1994, is the tenth most commonly prescribed pediatric AED, and is indicated as an adjunctive treatment for partial seizures. The mechanism of action includes the facilitation of GABAergic transmission. The medical side effects of gabapentin include weight gain, fatigue, and dizziness. It has been associated with minimal cognitive side effects (Meador et al., 2001), despite similar slowing of EEG patterns found in individuals who are prescribed carbamazepine (Salinsky et al., 2002). Despite black box warnings for increasing the risk of suicidal thoughts and behaviors, the behavioral and psychiatric side effects of gabapentin are reportedly minimal. In a recent study addressing self-report of psychiatric side effects, individuals who were prescribed gabapentin had the fewest number of psychiatric symptoms compared to those prescribed other AEDs (i.e., levetiracetam, zonisamide) (Weintraub et al., 2007). Gabapentin is also sometimes prescribed for mental health

disorders such as Bipolar I Disorder, anxiety disorders, and treatment-resistant depression (Chouinard, 2006).

As reviewed, there are a wide variety of medical, cognitive, and behavioral side effects of commonly prescribed AEDs for children. These side effects, particularly the behavioral effects, are important and were taken into account in the current study to address whether they have an interactive effect with seizure type in understanding parent-reported anxiety and depression. The side effects of commonly prescribed pediatric AEDs are summarized in Table 1.

The Issue of Monotherapy and Polytherapy

In addition to the biological mechanism of action, the number of medications prescribed to an individual also has an effect on seizure control and the behavioral and psychiatric side effects an individual may experience. In 2002, Oguz, Kurul, and Dirik found support for higher levels of anxiety in children on AED polytherapy compared to those on monotherapy. Dodrill (1992) found that seizure frequency was positively correlated with the number of prescribed AEDs. In other words, polytherapy is often used to treat patients with less seizure control and therefore the most basic proxy for seizure severity may be the number of AEDs that an individual is prescribed. More specifically, an individual who is prescribed one AED and obtains adequate seizure control may be well-adjusted relative to someone else who is prescribed three AEDs for poorer seizure control and experiences the additive side-effects of being prescribed numerous AEDs.

Polytherapy has routinely been associated with higher adverse events in both cognitive

and behavioral side effects (Adewuya & Ola, 2005; Bourgeois et al., 1983; Freilinger et al., 2006; Glauser, 2004a; Mendez, Doss, Taylor, & Salguero, 1993; Thompson & Trimble, 1982; Vinayan, 2006). Finally, others have found monotherapy pivotal in minimizing cognitive side effects (Drane & Meador, 2002).

THE NEUROPSYCHOLOGY OF EPILEPSY

Given the involvement of the central nervous system, evaluations for epilepsy often involve assessment of cognitive abilities over the course of the disease process (Nelson & Fischer, 2007). Neuropsychological evaluations often assist in providing descriptions of current abilities, determining which interventions to prescribe, and predicting prognosis over time. Neuropsychological functioning may be affected by epilepsy in a variety of ways including: (1) underlying neurological compromise that accounts for symptoms of epilepsy as well as the cognitive deficit, (2) post-ictal confusion and memory difficulties during the course of an epileptic event, and (3) interictally during bouts of subclinical epileptiform discharges. Understanding the intellectual, neuropsychological, and academic compromises and challenges that accompany epilepsy help provide a better perspective on the psychosocial adjustment to the disease.

Intellectual Correlates

Though it was long thought that children with epilepsy had significant brain damage that interfered with intellectual abilities, it was not until Ellenberg, Hirtz, and Nelson (1986) suggested that the full-scale intelligence of children with epilepsy was no different than their normal siblings that researchers began conceptualizing children with epilepsy as having generally no gross intellectual deficits. Their study was longitudinal in nature and they were able to address full-scale intelligence scores before and after the onset of seizures, typically ranging between 4 and 7 years of age. The finding that the majority of pediatric patients with uncomplicated epilepsy do not suffer from any permanent deficiencies in intelligence has also been found in several seminal long-term studies that address intelligence and the course of pediatric epilepsy (Bourgeois et al., 1983; Ellenberg, Hirtz, & Nelson, 1986; Guimaraes et al., 2007; Hauser & Hersdorffer, 1990; Rodin, Schmaltz, & Twitty, 1986). In studies that assessed intelligence in addition to specific neuropsychological measures, IQ is generally intact in children with childhood epilepsy regardless of the type of seizure experienced (Fedio & Mirsky, 1963; Jambaque, Dellatolas, Dulac, Ponsot, & Signoret, 1993; Nolan et al., 2004; Siren et al., 2007).

Despite children with epilepsy, as a whole, having normal levels of intelligence, some individuals with certain subtypes of epilepsy (i.e., temporal lobe epilepsy) have lower scores on standardized tests of intelligence (Cormack et al., 2007). There has been speculation as to why intellectual abilities may present in children with epilepsy. Generally, deficits in gross intellectual ability are related to neurological pathology such

as in tuberous sclerosis, neurofibromatosis, cortical dysplasias, and encephalitis (Aarts, Binnie, Smit, & Wilkins, 1984; Bourgeois et al., 1983; Guimaraes et al., 2007; Williams & Sharp, 2000).

In addition to studying the type of seizure and how that may impact intellectual measures, children with certain epileptic syndromes have also been studied to address their intellectual function as well. For example, benign rolandic epilepsy and juvenile myoclonic epilepsy are typically associated with a normal intellectual profile with minimal progressive decline in abilities (Nelson & Fischer, 2007; Williams & Sharp, 2000). Other syndromes are more strongly correlated with mental retardation, as is addressed in a later section. As previously noted, there are certain AEDs that hinder overall intellectual functioning. Some AEDs cause declines in processing speed, attention, and critical thinking abilities and may be the most pronounced in phenobarbital at toxic levels (Bourgeois et al., 1983).

Finally, according to previous research, age of onset has been the best predictor of intellectual dysfunction in pediatric epilepsy, with onset in early childhood, particularly in the first year of life, resulting in a high incidence of intellectual impairment (Cormack et al., 2007). Children with age of onset after the fifth year of life seem to be at significantly reduced risk for intellectual deficiencies. Nevertheless, previous studies suggest that early insults to the neurological system may contribute to intellectual difficulties. To date, no studies specifically address intellectual correlates and children affected by partial seizures with secondary generalization.

The Issue of Intellectual Disability

Mental retardation has been defined as a generalized disorder with impaired cognitive functioning, disruptions in two areas of adaptive functioning, and onset prior to 18 years of age (American Psychiatric Association, 2000). Although intelligence is only one aspect of the diagnosis, for the purpose of the present study, the term intellectual disability refers to the intellectual aspect of the diagnostic triad of mental retardation. Intellectual ability is generally intact in children with epilepsy, though children with certain epileptic syndromes are more susceptible to mental retardation, such as in the progressive deterioration of intellectual abilities in Lennox-Gastaut syndrome and high incidence (i.e., 90%) of mental retardation in West Syndrome (Murphy & Dehkharghani, 1994). Epilepsy and mental retardation occur in association in 9 to 30% of cases; however, it is unclear to what the association is related (Hauser & Hersdorffer, 1990). Additionally, in a longitudinal study, mental retardation was more common in children with pediatric epilepsy compared with their siblings and was associated with children with documented neurological abnormalities prior to their first seizure (Ellenberg et al., 1986). Though many research studies propose that an earlier age of onset contributes to lower levels of intelligence, critics often note that these studies include children with early epileptic syndromes (e.g., West Syndrome) high in mental retardation incidence, which often skew the data to lower intelligence levels (Williams & Sharp, 2000).

Adaptive Behavior

As medical interventions for epilepsy have evolved to promote increasing seizure control, there has been a shift to focus on functional (i.e., social and psychological) outcomes (Berg et al., 2004). Among the functional outcomes that need to be taken into account is adaptive behavior, which is defined as the ability to perform daily activities required for personal and social sufficiency (Sparrow, Balla, & Cicchetti, 1984). Adaptive behavior includes receptive, expressive, and written communication, activities of daily living, socialization, and motor functioning (Strang, 1990).

One may have deficits in adaptive behavior without the formal diagnosis of mental retardation, as found in children with epilepsy. For example, a recent prospective, longitudinal study that employed a large sample evaluated adaptive behavior in children with newly-diagnosed epilepsy (i.e., prior to when the child was three years old) over time (Berg et al., 2004). The researchers assessed whether seizure type, etiology, and seizure control affected adaptive behavior as measured by the Vineland Adaptive Behavior Scales. They found that at the initial diagnosis, adaptive behavior was somewhat below average and continued to decline over the course of three years. However, baseline and declining effects were related to symptomatic etiology, intractability, and encephalopathies as children with none of these factors had average adaptive function at baseline with no declines over time. Among the domains of adaptive behavior studied, daily living and communication seemed to be the most affected.

The failure to acquire age-appropriate skills over time leads to detriments in the child's ability to lead a functional daily life, which may contribute to psychiatric symptomatology, which is reviewed in a later section.

Neuropsychological Correlates

A number of studies on the neuropsychology of children with epilepsy have used intelligence as a proxy for overall cognitive ability; however, numerous research studies have shown cognitive dysfunctions in the areas of attention, vigilance, and mental and psychomotor speed (Dam, 1990; Meador, 2002). In general, the cognitive deficits that result from epilepsy have been explained by abnormal effects from the specific site of emanation, a more generalized epileptogenic underlying factor, and associated effects from AED treatment (Williams & Sharp, 2000). Often subclinical discharge, epileptiform discharge as evidenced by EEG monitoring without the accompaniment of semiology, occur in certain epilepsies. Evidence obtained during EEG monitoring often supports cognitive deficits resulting from specific sites during subclinical discharges. Some suggest that upwards of 50% of children experience brief cognitive impairment during such discharges, often termed transitory cognitive impairment (Aarts et al., 1984). Furthermore, complex tasks such as working memory and language are most likely to be affected during bouts of transitory cognitive impairment.

In the current body of research, two characteristic neuropsychological patterns are typically found in pediatric epilepsy. Some research finds more generalized patterns of

inattention regardless of the type of seizure and other research finds hemisphere-specific disruption of cognitive skills (Schoenfeld et al., 1999; Williams, Griebel, & Dykman, 1998). Much of the neuropsychology of pediatric epilepsy is not definitive as many studies refute others and within each study, variable profiles exist.

Epilepsy and Attention

The ability to attend to information and encode it is an important aspect of cognitive functioning that is related to all other spheres of cognition. In general, attention is the most compromised and consistently described aspect of cognitive functioning affected in pediatric epilepsy (Williams & Sharp, 2000). This pattern of dysfunction has been found in children of both normal and lower intellectual functioning and has been supported by results on tests of attention as well as from parent-reported attention problems (Williams, Bates et al., 1998). Furthermore, it has been found in both community (Williams et al., 1996) and tertiary care samples of children with epilepsy (Williams, Griebel et al., 1998).

Attention problems in children with epilepsy have been used as an explanation for other cognitive or academic deficits and this viewpoint supports the pattern of more diffuse neurological dysfunction rather than lateralized deficits. For example, the researchers suggest that difficulties with attention may decrease performance on tests of reading and writing, which rely highly on rapid automatic processing (Bender, Marks, Brown, Zach, & Zaroff, 2007). The overall reduced ability to attend to information and encode properly may produce a generalized dampened neuropsychological profile. In one of the earliest theories of attentional dysfunction, Stores and Hart (1976) suggested that disruption in

subcortical or cortical mechanisms contributed to difficulties with attention, which explain attention problems regardless of seizure type. Sturniolo and Galletti (1994) suggest that most cognitive dysfunction can be explained by decreased attentional skills. In a study addressing the overall neuropsychological status of children with epilepsy, researchers found that reduced attention skills were related to measured ability in several areas including memory tasks sensitive to attention and encoding of information (Williams, Griebel et al., 1998). Interestingly, these findings remained even after children diagnosed with Attention-Deficit/ Hyperactivity Disorder were excluded from statistical analyses. Like the majority of studies reviewed thus far, no studies address attention in children affected by partial seizures with secondary generalization; however, attention deficits seem to occur in children with epilepsy regardless of seizure type.

Epilepsy and Executive Function

Executive functioning is a "broad term that refers to a multidimensional set of abilities ranging from planning to self-monitoring to working memory, and involving cognitive and emotional components as well as overt behaviors" (Donders, 2002, p. 29). It is a generally accepted principle that the frontal lobes, especially the prefrontal areas, have a significant role in mediating motor coordination and executive functioning (Carlson, 2005). In a recent study, the majority of the children with epilepsy had dysexecutive symptoms and these symptoms were the second most compromised aspect of cognition affected with only attention problems impacting more children (Bender, Marks, Brown, Zach, & Zaroff, 2007). In a study that addressed executive function deficits in children with epilepsy, researchers separated children with frontal lobe epilepsy, temporal lobe

epilepsy, and generalized epilepsy (i.e., absence seizures) and administered multiple tests of executive function (Hernandez et al., 2002). Like most adult studies, they found support that children with frontal lobe epilepsy manifested impairments in motor coordination, verbal fluency, mental flexibility, impulse control, and planning, all aspects of executive functioning, at a higher rate than those with temporal lobe epilepsy or generalized seizures. However, compared to the normative population, children with temporal lobe epilepsy or generalized seizures also had deficits, which suggested that epilepsy can have a deleterious effect on a child's executive function regardless of the areas involved in seizure emanation.

In a study using a parent-report measure of executive function, children with medically-refractory epilepsy had higher levels of executive dysfunction than did the standardization sample (Slick, Lautzenhiser, Sherman, & Eyrl, 2006). Specifically, the most commonly elevated scales included those of working memory, planning, and organizing; however, almost a third of the sample did not have any clinically elevated scales, suggesting that executive dysfunction may be frequent, but not characteristic, of children with epilepsy. Limitations included issues of sample selection (i.e., not representative of children with controlled epilepsy) and reliance on parent-report; however, the results suggest that children with epilepsy may have executive function deficits that need to be addressed.

A recent study found that children with newly-diagnosed epilepsy, regardless of seizure type (i.e., localization-related and generalized), were more impaired on tests of executive

function versus a control group (Parrish et al., 2007). In this study, measures used to quantify deficits in executive function included a standardized set of objective cognitive measures that assesses executive function as well as parent-reported executive dysfunction. Children in the "at-risk" group based on results from the parent-report measure were significantly more impaired than the "low-risk" group on the objective cognitive measure, illustrating the utility of using parent ratings during neuropsychological assessment. Guimaeres et al. (2007) conducted neuropsychological evaluations with children with temporal lobe epilepsy. The pattern of results suggested deficits in executive function, memory, language, visuospatial skills, and attention. The deficits that presented were diffuse, suggesting that the cerebral dysfunction may lie in the temporal and frontal lobes. This hypothesis is supported by previous studies, which shows the functional and structural connectedness of the temporal and frontal lobes (Spencer, 2007).

In conclusion, although executive function deficits are typically found in adults with frontal lobe epilepsy, patterns of executive dysfunction are not as clear cut in children with epilepsy. Many studies suggest that patterns include frontal deficits, a variety of studies suggest similar levels of pathology in those with temporal lobe and generalized epilepsies. As with most neuropsychological studies, researchers do not separate children affected by partial seizures with secondary generalization, which creates difficulty in conceptualizing the possible deficits in this subtype.

Epilepsy and Memory

Memory deficits are a common symptom reported in certain types of adult epilepsy (i.e., temporal lobe epilepsy); however, it is not as extensively studied in pediatric samples. Most adult studies provide support for lateralized deficits depending on the areas of dysfunction and are examples of material-specific memory models. For example, verbal memory deficits are typically associated with left temporal lobe epilepsy and nonverbal memory dysfunction is more commonly reported in individuals with right temporal lobe epilepsy (Bell & Davies, 1998).

In general, memory deficits may reflect the underlying compromise to a neurological substrate involved in memory such as the hippocampus in temporal lobe epilepsy. For instance, some studies have found that children with partial seizures emanating from the left temporal lobe have difficulties with verbal memory, suggesting that there may be an association between memory and the site of emanation (Cohen, 1992; Jambaque et al., 1993). However, within the same studies, children with extratemporal epilepsies had similar levels of memory deficits and there were no differences in verbal memory deficits among children with left and right-sided neurological dysfunction. This finding contrasts with adult literature that typically shows clear memory lateralization and suggests that memory deficits may be more diffuse during early childhood (Nolan et al., 2004; Williams, Griebel et al., 1998).

A recent study assessed the localization (i.e., mesial versus lateral) and lateralization (i.e., left vs. right) of memory deficits in children with temporal lobe epilepsy (Gonzalez,

Anderson, Wood, Mitchell, & Harvey, 2007). Although the researchers found no differences among children with left and right temporal lobe epilepsy in almost all memory tasks, facial recognition was poorer in right temporal lobe epilepsy. Despite this finding, the researchers also found that those with mesial pathology, rather than lateral pathology, were more impaired in associative learning and complex figure recall, regardless of the side of the brain of dysfunction. They suggested memory is bitemporal in nature early in life and epileptogenic lesions disrupt the lateralization of the memory system.

Children with frontal lobe epilepsy often present with worse short-term memory versus those with temporal lobe epilepsy, suggesting that cerebral specialization may not have yet occurred (Lendt et al., 2002). It may be too simplified to correlate verbal and nonverbal memory deficits with left- and right-sided pathology, respectively. Cerebral nonspecialization could be explained by less lateralization in brain organization during early childhood or the cerebral reorganization after early brain insults that led to the development of epilepsy. Additionally, numerous aspects of memory within the verbal and non-verbal memory constructs need to be studied specifically in order to fully understand memory deficits in children with epilepsy. Because most previous studies do not address children affected by partial seizures with secondary generalization as a separate subtype, it is difficult to speculate as to how memory functions may be affected. Nevertheless, because most studies suggest that memory dysfunction in children with epilepsy may be more diffuse than clear-cut modality-specific memory dysfunction in

adults, children with secondary generalized seizures may have similar levels of memory dysfunction relative children with other types of seizures.

Epilepsy and Language

Language encompasses many aspects of cognitive ability such as receptive and expressive vocabulary, verbal fluency, and naming. It is used on an everyday basis to communicate with others and exchange ideas. Language is typically intact in children who experience certain epileptic seizures, but children with complex partial seizures, regardless of the lateralization of emanation, have lower language scores as compared with similar-aged siblings (Schoenfeld et al., 1999).

In a study assessing the neuropsychological profile of temporal lobe epilepsy in children, those with epilepsy obtained significantly lower scores on tests of verbal learning, naming, verbal fluency, and verbal memory, suggesting a similar pattern often found in adults with epilepsy (Guimaraes et al., 2007). Language functions are also heavily affected in children with Landau-Kleffner syndrome, which is also known as acquired aphasia with convulsive disorder (Williams & Sharp, 2000). Following a period of normal development, children with Landau-Kleffner syndrome develop auditory agnosias, which affect responsiveness to oral communication and lead to progressive impairments in expressive speech and vocabulary. Researchers have suggested that the language impairment in Landau-Kleffner syndrome is due to the underlying neurological impairment in areas of the brain associated with language and a result of the seizures

themselves (Gordon, 1990). In children with Landau-Kleffner syndrome, nonlanguage abilities are typically intact.

An example of a complex relationship between cognitive testing and epilepsy is left-handedness syndrome, which occurs as a result of early insults to the left hemisphere (Nelson & Fischer, 2007). Because the majority of individuals have language specialization in the left hemisphere, early injuries to this side of the brain may cause reorganization of language to the right side. This often leads to "crowding," which suggests that the dysfunction of typically right-sided skills (e.g., visuospatial abilities) occur as traditionally left-sided functions become dominant (Gleissner et al., 2003; Strauss & Satz, 1990). Deficits in visuospatial abilities and motor performance with the right hand often result despite preserved language. The authors suggest that early seizure onset, left-hemisphere epileptogenic focus, and left-hand dominance without a family history of left-handedness are part of the profile included in this syndrome. Research has shown that individuals with left temporal lobe epilepsy had greater activation in the right hemisphere for language tasks and greater atypical language lateralization in adult and pediatric samples (Sveller et al., 2006; Thivard et al., 2005).

In 2002, Saltzman, Smith, and Scott found a much higher proportion of children with atypical language lateralization if seizures began prior to five years of age, suggesting a reorganization of skills. The researchers used the intracarotid amytal procedure and assessed the neuropsychological status of those with left temporal lobe epilepsy and atypical (i.e., right-sided) and typical (i.e., left-sided) language dominance. They found

support that those with right-sided language dominance had relatively lower visual memory versus verbal memory scores, and higher verbal memory versus those with typical language dominance, supporting the crowding hypothesis. Other studies found that more than 80% of children with left temporal lobe epilepsy and atypical language dominance had seizure onset prior to the age of six, which is considered the age of the main development of the corpus callosum and important functional brain asymmetries (Battaglia et al., 2006; Gleissner et al., 2003). Regarding specific seizure types in the current study, studies have not specifically addressed language in children affected by partial seizures with secondary generalization. However, in previous research, children affected by complex partial seizures, specifically those with temporal lobe epilepsy, have been shown to have higher levels of language dysfunction. One can surmise that children secondary generalized seizures would likely evidence similar levels of language dysfunction.

Epilepsy and Visuospatial Abilities

Visuospatial abilities encompass many aspects of nonverbal intelligence including part-to-whole conceptualization and discerning relationships among spatial objects. Despite the reliance on this aspect of cognition for daily activities such as physically navigating the environment, a dearth of research addressing visuospatial abilities in a pediatric population exists (Schoenfeld et al., 1999). In a recent study assessing overall neuropsychological functioning using a comprehensive developmental instrument in children with epilepsy, researchers found that visuospatial abilities were relatively intact (Bender et al., 2007). Interestingly, the visuospatial abilities found were similar to

neurologically normal peers. However, in the Guimaeres et al. (2007) study, children with temporal lobe epilepsy had more deficits in tests of visuoconstructive praxis (i.e., Block Design) versus a control group of peers. Like studies addressing other aspects of cognition, there seem to be as many studies that support visuospatial problems in children with epilepsy as those that do not. Therefore, because of the lack of studies and variable findings in those that exist that address visuospatial abilities in pediatric epilepsy, it is difficult to know what patterns would emerge in children affected by partial seizures with secondary generalization.

Academic Achievement

Children with epilepsy are undoubtedly affected academically by the behavioral and cognitive sequelae of seizures as well as the side effects of treatments aimed at reducing those very seizures. Children with epilepsy are often diagnosed with learning disabilities (Aldenkamp, Alpherts, Dekker, & Overweg, 1990; Seidenberg, 1996). One issue in assessing the etiology of academic difficulties is that the terms learning disorders, learning disabilities, educational problems, and scholastic problems have been used interchangeably in previous studies (Vinayan, 2006). Most studies use hospital-based tertiary care samples rather than large-scale population studies, which creates sampling bias.

Nevertheless, what can be supported by previous research is the overall academic underachievement that occurs in children with epilepsy as compared to same-aged peers

(Bailet & Turk, 2000; Sturnilio & Galletti, 1994). One research study that assessed academic achievement of children with epilepsy found that they were placed in special education and repeated their grade twice as frequently as control groups (Farwell, Dodrill, & Batzel, 1985). Low educational achievement often continues into adulthood for adults who were diagnosed with childhood epilepsy (Kokkonen, Kokkonen, Saukkonen, & Pennanen, 1997; Sillanpaa et al., 1998).

Researchers have hypothesized about the actual etiology of academic difficulties, including the location of seizure emanation, seizure severity, and presence of status epilepticus (Williams & Sharp, 2000). As previously reviewed, the multitude of side effects from various AEDs may contribute to sedation, double vision, and reduced vigilance during the school day, indirectly affecting academic performance. Furthermore, Vinayan (2006) reviewed variables that may be associated with decreased academic functioning such as medically-related variables including the presence of mental retardation; neuropsychological variables including attention deficits and presence of learning disabilities; and psychosocial variables including reduced learning opportunities. Stigma from having epilepsy may actually cause parents and teachers to lower their academic expectations for the child, contributing to the child's academic underachievement (Williams, 2003).

Much research shows multiple variables contribute to the underachievement of children in the academic setting. Researchers have suggested using a multivariate approach that takes into account cognitive, psychosocial, seizure-related, and medication-related

variables when attempting to explain or address academic underachievement (Austin, Huberty, Huster, & Dunn, 1998; Seidenberg, 1996). Particularly pertinent to this study, a previous study found that anxiety and depression predicted academic performance similarly, and had more predictive utility than intelligence did (Rapport, Denney, Chung, & Hustace, 2001). In a recent study, the impact of epilepsy characteristics and behavior problems were examined in relation to school placement (El Sabbagh, Soria, Escolano, Bulteau, & Dellatolas, 2006). In this study, children with epilepsy in traditional school environments were compared to those in specialized placement on a multitude of variables. Results showed that those who had an earlier age of onset, who were prescribed multiple AEDs, and who experienced behavioral problems had lower academic achievement and, subsequently, more placement in specialized schools. This finding illustrates that clinicians must consider variables beyond that of intelligence and cognitive ability when making school-related recommendations. Furthermore, with regard to seizure types, the researchers found that those with nonidiopathic generalized epilepsy and refractory localized epilepsy had higher level of exclusion from regular school. However, the relationship was mediated by the level of intelligence and no separation of children affected by partial seizures with secondary generalization was used.

In conclusion, though the majority of studies show that children with epilepsy have a relatively normal intellectual profile, intellectual disability and subtle cognitive deficits are associated with certain types of seizures. Age of onset seems to be a predictor of cognitive difficulties as children with epilepsy with an earlier age of onset of seizures are

more susceptible to intellectual, cognitive, and academic difficulties. Although the overall neuropsychological sequelae of pediatric epilepsy is not as clear as what is found in adult studies, detriments in attention and executive functioning have been consistently found across different subtypes. It is difficult to address how these differences may be apparent in children affected by partial seizures with secondary generalization as this subtype has not been routinely examined in previous research. Neuropsychological testing is an important component of the diagnosis and management of pediatric epilepsy as it may help aid in locating seizure emanation, predict neuropsychological outcomes, and track cognitive outcomes over the course of the disease process. Additionally, behavioral and emotional symptoms are often experienced as a result of having epilepsy or undergoing epilepsy treatment. Though depression in children with epilepsy has been studied more extensively, studies have shown that anxiety is also a major concern. A better understanding of these two unique psychiatric symptoms is important in order to understand it as it relates to pediatric epilepsy and seizures.

ANXIETY

Unrealistic, unfounded, persistent fear and worry typically characterize the broad spectrum of anxiety disorders (Carlson, 2005). From a clinical perspective, anxiety can be understood as hypervigilant behavioral, emotional, and cognitive reactions to the overestimation of perceived threat and underestimation of the perceived coping resources to ward off those threats (Kaplan, Sadock, & Grebb, 2007). From an evolutionary and adaptive perspective, anxiety is been described as “a means to detect signals, a way to

discriminate those that denote danger, and the capacity to initiate phylogenetically derived and ontogenetically learned behavior that results in avoidance of that danger" (Goldstein & Harden, 2000, p. 230). Anxiety can be conceptualized in both negative and positive valences, but for the purposes of the current study, anxiety was conceptualized as excessive worries that interfere with the daily life of the individual.

According to the APA's DSM-IV-TR (2000), anxiety disorders are comprised of twelve separate, yet theoretically similar, disorders. Interesting among these disorders is that the etiology ranges from the very specific (e.g., the identified trauma in Posttraumatic Stress Disorder, or cocaine in Cocaine-Induced Anxiety Disorder) to the unknown (e.g., Generalized Anxiety Disorder). Anxiety is a prevalent psychiatric condition, affecting nearly 40 million Americans each year with a lifetime prevalence of approximately 15 to 25% depending on the study cited (Kessler, Chiu, Demler, & Walters, 2005; Regier et al., 1988). The impact of anxiety disorders is apparent given the effect that it has on decreasing the quality of life of the individuals diagnosed (Mendlowicz & Stein, 2000). Although certain anxiety diagnoses (i.e., Obsessive-Compulsive Disorder, Social Phobia) show no clear gender bias, Generalized Anxiety Disorder, Specific Phobia, and Posttraumatic Stress Disorder tend to be twice as prevalent in females (Bell-Dolan, Last, & Strauss, 1990; Robins & Regier, 1991). Furthermore, pertinent to this study, many of the anxiety disorders develop during childhood and adolescence (Beesdo, Knappe, & Pine, 2009).

Anxiety in Children

Anxiety disorders are some of the most prevalent mental health issues that affect children, with most studies indicating lifetime prevalence of over 10% of children (Costello & Angold, 1995) and as high as 15% of children when anxiety disorders are grouped as a whole (Benjamin, Costello, & Warren, 1990; Bernstein, Borchardt, & Perwien, 1996). Anxiety disorders are the most commonly diagnosed mental health disorders in children with a rate of 4 to 7% of adolescents (Substance Abuse and Mental Health Services Administration, n.d.). According to the Anxiety Disorders Association of America (ADAA, 2009), younger children are more at risk than older children for experiencing specific phobias and separation anxiety disorder, with generalized anxiety disorder and social phobia more common in middle childhood and adolescence. With the change from APA's DSM-III to DSM-IV, Overanxious Disorder of Childhood was subsumed into Generalized Anxiety Disorder and Avoidant Disorder was subsumed into Social Phobia. Clinically, this change has allowed practitioners to compare adults and children on the same plane, thereby narrowing the developmental gap in the conceptualization of anxiety (Bernstein et al., 1996).

Although children are developmentally different than adults, the two age groups may experience anxiety in similar ways. For instance, the majority of the symptoms in the shared anxiety diagnoses, with the exception of duration specifiers, are similar among children and adults. However, because of their developmental level, children with anxiety disorders may experience unique symptoms. A previous study by Bell-Dolan, Last, and

Strauss (1990) addressed developmental issues unique to children with anxiety. They found that over 30% of children reported subclinical symptoms of generalized anxiety. Nonreferred children reported developmentally-normal worries such as fear of the dark and of harm. This finding may complicate the diagnostic process as the separation between developmentally-normal and pathological worries in children may seem difficult to distinguish at times. Additionally, due to younger children's limited verbal skills, anxiety symptoms may occasionally manifest as headaches, muscle tension, stomach pain, and gastrointestinal symptoms (Ginsberg, Riddle, & Davies, 2006). These somatic symptoms could also be accompanied by behavioral symptoms such as reliance on structured schedules, tantrums, and school avoidance (Field & Seligman, 2004). Although school avoidance may represent developmentally-normal school worries, approximately 2 to 5% of school-aged children avoid school due to anxiety (ADAA, 2009). During adolescence, developmentally-normal fears shift to worries about sexuality, social acceptance, and independence (Bernstein et al., 1996). During the time of adolescence, Panic Disorder and Social Phobia become more prevalent than in childhood and often persist into adulthood if untreated. Though these unique aspects of anxiety disorders in children may be present, a large majority of interventions for anxiety in child and adolescent populations have been adapted from therapeutic works with adults (Hinkle, 2004).

Theories of Anxiety

Numerous theories from all paradigms of psychiatry and psychology have conceptualized from where anxiety stems and the factors that facilitate its persistence. Relevant to the current study, the neurobiological theory and the learning, cognitive, and behavioral theories, are of importance and are the few major schools of thought regarding the etiology of anxiety (Hinkle, 2004). A conceptualization of these theories may help elucidate treatment considerations for children affected by anxiety.

Neurobiological Theory

Neurobiological theories encompass various biological aspects in explaining psychiatric symptomatology. Multiple scientific methodologies have been used to evaluate the neurobiological underpinnings of anxiety and have included neuroanatomy, neurochemistry, hormones, and genetics.

One of the most studied neuroanatomical structures related to anxiety is the amygdala, located within the mesial temporal lobe. It has been theorized to be from where anxiety stems, integrating external stimuli with internal appraisal (Garakani, Mathew, & Charney, 2006). Animal studies of anxiety, typically employing rodents, have identified the amygdala and connections with the prefrontal cortex, thalamus, and hippocampus as important in fear processing. Numerous research studies have shown that electrical stimulation of or ablation of the amygdala produces fear responses or deficits in fear appraisal in both humans and animals (Vasa & Pine, 2004). Additionally, much research

is devoted to identifying the different nuclei within the amygdala that play a role in fear recognition, appraisal, and response.

The amygdala is made up of 13 separate nuclei with the lateral and basal areas important for fear conditioning. The lateral amygdala seems to be responsible for memory consolidation and fear conditioning at the neuronal level; the basal amygdala is responsible for the behavioral aspects of the fear response (Garakani et al., 2006). The central nucleus of the amygdala is one of the most important parts of the brain for the expression of emotion evoked by aversive experiences (Carlson, 2005). In preclinical studies, after the central nucleus of the amygdala is ablated, animals do not show fear responses after previously showing fear to stimuli that were paired with aversive events. Furthermore, they have lower levels of stress hormones and appear more tame (LeDoux, 1992). However, when the central nucleus is stimulated, animals tend to show exaggerated behavioral and physiological signs of fear (Davis, 1992). The central nucleus is particularly important in aversive emotional learning and may play a role in consequent anxiety experienced in situations that were anxiety-provoking in the past, such as in stage fright or the anxiety experienced by someone with Posttraumatic Stress Disorder.

Studies involving humans also implicate the amygdala in stressful fear responses. In a correlational study, researchers interviewed patients with Alzheimer's disease about their memory of a witnessed earthquake in 1955, a particularly traumatic event (Mori et al., 1999). Results of the study revealed that memories of the anxiety-inducing event were inversely correlated with amygdala damage. The more damaged a patient's amygdala

was, the less the individual remembered and, subsequently, the less anxiety they endorsed about witnessing the event. Various studies involving PET have shown the activation of the right amygdala when individuals are presented with fear-provoking films or words (Carlson, 2005). One study using PET assessed blood flow in the brain in individuals with Social Phobia versus non-diagnosed individuals (Tillfors et al., 2001). Results showed that although normal subjects had increased blood flow to areas of the brain associated with thinking and evaluation during speaking tasks, subjects with Social Phobia had the most blood flow to their amygdala.

In addition to the neuroanatomy of anxiety symptoms, neurotransmitters have also been used to explain the etiology of anxiety. Neurotransmitters are important chemical messengers that allow the brain to make meaningful connections. However, dysfunction in neurotransmitter systems can arise when an overabundance, underabundance, underutilization, or rapid breakdown of certain neurotransmitters occurs. Serotonin, which affects a range of behavior, and GABA, which inhibits arousal and moderates emotional responses, have been implicated in the etiology of anxiety disorders (Carlson, 2005; Erk, 2004; Mash & Wolfe, 2002). When benzodiazepine medication binds with $GABA_A$ receptors, anxiolytic effects typically result. Research with adults has shown that individuals with Panic Disorder, an anxiety disorder that consists of recurrent unexpected panic attacks which are a concern to the person experiencing it, may have a reduction in the number of $GABA_A$ receptors, thereby making it more difficult for the anxiolytic properties of GABA agonists to work efficiently (Malazia et al., 1998). Norepinephrine has also been implicated in anxiety as it controls alarm reactions, short-term effects of

stress, and plays a role in behavioral regulation. Lastly, memory consolidation of fear occurs when calcium enters the neuron via *N*-methyl-*D*-aspartate (NMDA) glutamate receptors. Various animal studies using NMDA receptor antagonists show a decrease in fear acquisition (Garakani et al., 2006). Lamotrigine, a glutamate antagonist, has been shown to provide a reduction in anxiety in those with bipolar disorder. Though the neurochemical aspects of anxiety are not as relatively well understood, they are represented by the FDA-indicated medications for various anxiety disorders such as selective serotonin reuptake inhibitors (SSRI), benzodiazepines, and selective norepinephrine reuptake inhibitors.

Hormonal explanations have also been offered to explain anxiety symptomatology. For example, the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in stressful responses and subsequent stress dysregulation. During stressful experiences a cascade of biological effects occurs. Short-term activation of the sympathetic nervous system prepares the individual for the stressor. Additionally, long-term physiological changes occur as the hypothalamus secretes corticotropin-releasing hormone, which then stimulates the pituitary gland to release adrenocorticotropic hormone. The adrenal glands are then alerted to release cortisol, a corticosteroid, by adrenocorticotropic hormone and arouse the body to prepare itself for a “fight or flight” situation. This biologically-driven response to stress is adaptive during short bouts of stress (i.e., cortisol helps store carbohydrates and reduce inflammation in case of injury), but continued activation of the HPA axis ultimately leads to a compromise in functioning. Daily stress leads to cortisol dysregulation and to long-term effects such as reduced immunological functions.

Interestingly, individuals who experience chronic stressors and subsequent HPA axis activation also experience prolonged release of cortisol, which contributes to hippocampal degeneration (Taylor, 2006). Simply put, individuals who experience stress or anxiety over a long period of time may have degeneration of the hippocampus, an important brain structure in memory consolidation. Over time, these individuals may have difficulty remembering the specific stressors that they actually experience, inadvertently contributing to generalized anxiety. Some researchers have studied HPA axis activity specifically with regard to a pediatric population (Kallen et al., 2008). The researchers found that HPA axis activity was positively correlated with scores on dimensional scales of anxiety indicating that greater activity was associated with poorer functioning; however, the scores were not correlated with specific anxiety diagnoses.

Neurobiological theories of anxiety also offer genetic explanations as to how anxiety symptomatology could occur. Of the diagnosable conditions, some anxiety disorders have a greater genetic basis than others. For instance, individuals with Panic Disorder are eight times more likely to have a biological relative with the disorder, and up to 20 times more likely to have a biological relative with the disorder if Panic Disorder is diagnosed before the age of 20 in their relatives (APA, 2000). Furthermore, concordance rates for monozygotic twins are higher for Obsessive-Compulsive Disorder. Individuals are at higher risk of developing Social Phobia, Specific Phobia, or Generalized Anxiety Disorder if first-degree relatives had been diagnosed with the disorders. Generally, the genetics of anxiety disorders as a whole have been reviewed and are represented by the observation that children with parents who have anxiety disorders are at higher risk for

developing anxiety than children who have parents without disorders. Furthermore, twin studies show moderate heritability (i.e., 0.20 to 0.42) depending on the anxiety disorder (Arnold, Zai, & Richter, 2004). Numerous studies have addressed Obsessive-Compulsive Disorder and Panic Disorder at the molecular genetic level, which is beyond the scope of the present study.

Neurobiological theories of anxiety have received much support over the years; however, some have criticized these theories as they do not explain certain anxiety disorders such as specific phobias, which may have a more cognitively-based origin. Furthermore, the majority of neurobiological research in anxiety has used adult samples with very limited studies evaluating the neurobiological factors in samples of children.

Learning, Cognitive, and Behavioral Theory

Behavioral models suggest that behavioral or learning perspectives shape adaptive and dysfunctional behavior (Erk, 2004). Furthermore, behavioral models assume that environmental influences are the primary determinants of behavior. Russian physiologist Ivan Pavlov (Pavlov, 1927) first described classical conditioning, one of the earliest behavior change principles identified. He discovered that pairing an unconditioned stimulus with a conditioned stimulus eventually produced a conditioned response. Specifically, dogs learned to salivate (i.e., unconditioned response) to a bell (i.e., newly conditioned stimulus) that was previously paired with a pleasant but unconditioned stimulus (i.e., food).

Later research illustrated that in addition to classical conditioning learning with pleasant stimuli, learning also takes place with aversive situations, known as fear conditioning, which is pertinent to the current study. An early preclinical study of aversive conditioning showed that rats could be conditioned for certain taste aversions (Garcia, Hankins, & Rusiniak, 1974). The father of American behaviorism, John Watson, alongside colleague Rosalie Rayner (1920), explained anxiety as a generalized form of a conditioned response. In their early studies they found that even young children are able to generalize fear-inducing situations with similar situations.

After literature bridged the gap between laboratory-induced anxiety in animals and in human subjects, cognitive theory emerged (Beck, Emer, & Greenberg, 1985). At the very basic level, Beck (1976) suggested that cognitive distortions revolving around danger or threat contribute to experienced anxiety. Two cognitive distortions involved in excessive anxiety include *probability overestimation* and *catastrophic thinking*. These two ways of thinking describe the tendency to overestimate a negative event and the tendency to view events as intolerable or unmanageable, respectively (T. A. Brown, O'Leary, & Barlow, 2001). Although cognitive models focus on the role of maladaptive thought patterns in child psychopathology, cognitive-behavioral models reflect the importance of both thought patterns and environmental determinants of behavior. Various cognitive distortions, insufficient cognitive mediation, attributional styles, and expectations are critical determinants of behavior in this model. Belief systems, known as schemas, are formed as individuals process life experiences.

Numerous ways of conceptualizing anxiety from a cognitive-behavioral perspective have been studied and some researchers have reviewed various aspects of an individual's cognition (e.g., pre-attentive bias to threat, negative images, and worried thinking) that drive behavioral responses such as threat avoidance and slowed decision-making (Newman & Borkovec, 1995). The interaction between subtle cognitive distortions and behavioral reactions used to protect against appraised threats leads to an intensification of anxiety. Kendall's (1985) theory of childhood anxiety posits that anxiety and fear are a reaction from the chronic overactivity of thoughts revolving around the themes of danger and death. This theory emphasizes distorted thoughts such as attentional bias (i.e., hypervigilance toward threatening material) and interpretational bias (i.e., tendency to impose negative interpretations on ambiguous situations). Furthermore, Kendell (1993) noted that cognitive distortions in childhood include concerns about the self, evaluation from others, and likelihood of severe negative consequences. Children often misperceive or misjudge the demands of the environment; children with anxiety are no exception as they often focus on threatening stimuli (Vasey, Dalieden, Williams, & Brown, 1995).

In a recent study, researchers investigated trait and state anxiety in children and addressed whether these factors had an influence on threat perceptions (Muris, Rapee, Meesters, Schouten, & Geers, 2003). Children between 8 and 13 years old completed self-report measures of anxiety symptomatology (i.e., state) and chronic anxiety (i.e., trait) and were subsequently interviewed using an ambiguous story to derive threat perception. The researchers found that general trait anxiety levels accounted for a larger proportion of variance related to increased perception of threat and lower levels of threat threshold.

State anxiety also accounted for a unique proportion of threat perception variance, albeit at a lower level than trait anxiety. Finally, girls displayed higher levels of anxiety disorders, trait and state anxiety, and perceived the stories as more threatening than did boys.

Learning, cognitive, and behavioral theories of anxiety are represented in treatment interventions by cognitive-behavioral therapy (CBT), which addresses cognitive distortions, uses breathing exercises and muscle relaxation, and provides psychoeducation to build and foster coping resources (Hinkle, 2004). Due to the high prevalence rates in the general population, the impact on daily life functioning, and negative consequences associated with it, anxiety is a particularly important issue to study. Finally, evidence has even shown that subclinical symptoms of anxiety may manifest in 20 to 30% of children who have never been diagnosed with a psychiatric disorder, illustrating the far-reaching implications of anxiety (Bell-Dolan et al., 1990).

DEPRESSION

Depression is defined as a "serious mood disorder that consists of unremitting depression or periods of depression that do not alternate with periods of mania" (Carlson, 2005, p. 475). Depression affects nearly 2 to 5% of people in the United States and is twice as common in females than males (Blazer, 2000). Furthermore, it is a very serious disorder, as it tends to be recurrent, life threatening, and a major cause of morbidity. Research

suggests that over 15% of individuals with depression have attempted suicide (Schneider, Muller, & Philipp, 2001).

The study focused on depressive symptomatology, however, knowledge about the dynamics of a few diagnosable depressive disorders may help with conceptualizing what individuals with depressive symptoms experience. According to the DSM-IV-TR (APA, 2000), a major depressive episode consists of a constellation of symptoms that include depressed mood, loss of interest, significant weight loss or gain, insomnia or hypersomnia, psychomotor changes, fatigue, feelings of worthlessness or guilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicide attempts. Symptoms must represent a change from previous functioning and cause distress or impairment in functioning. Although most people describe episodes of sadness in their lifetime, a diagnosis of a major depressive episode requires symptoms be present for at least two weeks. Left untreated, symptoms can last up to four months regardless of the age of onset.

There are many types of depression depending on the predominant constellation of presenting symptoms. Dysthymic Disorder is a milder form of depression with a more protracted course. It typically has an insidious onset earlier in life than depression and is not as prevalent as Major Depressive Disorder. It is a disorder that is characterized by depressed mood, more days than not, for at least two years. Finally, a diagnosis of Depressive Disorder Not Otherwise Specified is given when depressive symptoms are the hallmark of the psychiatric symptom presentation, but individuals do not meet criteria for

a diagnosable disorder. Examples of disorders fitting the Depressive Disorder NOS diagnosis include a minor depressive disorder in which depressive episodes last two weeks, but do not meet full criteria for a Major Depressive Episode or if a depressive disorder is present, but the clinician is unable to determine whether it is primary or due to a general medical condition. In the current study, depression was not conceptualized as a single entity, but rather as a heterogeneous syndrome comprised of different subtypes as suggested by Nestler et al. (2002).

Depression in Children

The diagnostic criteria for Major Depressive Disorder and Dysthymic Disorder in the DSM-IV-TR are primarily geared to an adult population and clinicians have increasingly appreciated the need to accurately diagnose depression in children and adolescents (Field & Seligman, 2004). Prevalence rates of depression in children range between 1 and 8%, with higher rates during adolescence and in medically-ill youth, as is explored later (Birmaher et al. 1996; K.D. Stark, 1990). Although from a diagnostic perspective, Major Depressive Disorder is no different in children than in adults, there are unique developmental issues that may be observed in depressed youth (APA, 2000).

K.D. Stark et al. (1999) suggested that youth who are depressed are likely to experience emotional, cognitive, motivational, and vegetative symptoms of depression, much like adults. There are no current diagnostic differences in major depressive episodes in adults and children; however, due to the developmental level of a child, symptoms may

manifest in unique ways. Atypical features such as mood reactivity, weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity are more common in children. In addition, irritability, social withdrawal, and academic difficulties may be related to depressive symptoms during childhood and adolescence (APA, 2000; Field & Seligman, 2004). Temper tantrums and behavioral problems may be more apparent in children and adolescents as opposed to young adults (Birmaher, Brent, & Benson, 1998). Symptoms typically found in adult samples such as changes in psychomotor retardation and delusions are less common in younger samples. Although death by suicide in individuals with depression is less common in samples younger than 55 years old, in epilepsy samples, regardless of age, there is an increased risk of suicide (Kanner & Balbanov, 2002; Tellez-Zenteno, Patten, Jette, Williams, & Wiebe, 2007).

The diagnostic criteria for Dysthymic Disorder in children is identical to that of adults with the exception that in children and adolescents it can be diagnosed after symptoms are experienced for one year. According to Birmaher et al. (1996), Dysthymic Disorder occurs in approximately 1 to 2% of children and 2 to 8% of adolescents. Although Dysthymic Disorder occurs at a lower rate than depression in children, those that are affected by it have a high risk for the development of a Major Depressive Episode.

With regard to the prevalence of depressive disorders, no clearly illustrated gender bias in prepubescent males and females exist; however, major depressive disorders (i.e., single-episode and recurrent) are twice as common in adolescent females as adolescent males. The importance of addressing depressive symptomatology during childhood is

underscored by findings that the onset of Major Depressive Disorder in childhood is a strong indicator of the disorder persisting into adulthood (Field & Seligman, 2004). Furthermore, suicide associated with various mood disorders is one of the leading causes of death in young people (Emslie & Mayes, 1999). For example, children diagnosed with a mood disorder experience suicidal ideation at twice the rate compared to children not diagnosed with a mood disorder. Additionally, suicide attempts by those with a diagnosed mood disorder are made at a rate 11 times compared to others without depressive disorders (Kovacs, Goldston, & Gatsonis, 1993).

The importance of addressing depressive symptoms at an early age cannot be emphasized enough. The risk of suicide, deleterious effects on academic performance and social success, and risk for continued symptoms into adulthood all underscore the seriousness of the symptoms and the disorder. Although the DSM-IV-TR conceptualizes the disorders well, it does not explain the etiology in as much depth. Fortunately, progress over the past century has increased understanding of the factors that contribute to the development and persistence of depression.

Theories of Depression

Clinical observations and laboratory-controlled experiments of depression have evaluated the neurobiological underpinnings and cognitive misinterpretations that contribute to the development of depressive symptoms. Animal models of depression have been used in previous research; however, many core symptoms of depression (i.e., depressed mood,

feelings of guilt, suicidality) are difficult to quantify, posing challenges in validating animal models. Many preclinical techniques such as the tail suspension test, forced swim test, and learned helplessness paradigms are used in empirical literature (Nestler et al., 2002). Numerous factors contribute to depressive symptomatology and to conceptualize it solely from one theoretical perspective detracts from understanding the complex, multifactorial nature that accompany it (Field & Seligman, 2004).

Neurobiological Theory

Much like the neurobiological theory of anxiety, some researchers have attempted to study depression from a biological viewpoint (Nestler et al., 2002). Research studies have shown the nervous system structures, various chemicals, hormones and, most recently, genes may be implicated in depressive symptoms.

Several neuroanatomical explanations for depressive symptoms have emerged from a neurobiological perspective. For example, a few studies have shown a decreased amount of tissue in the prefrontal cortex in younger patients with unipolar depression and larger lateral ventricles, implying neuronal tissue loss (Elkis, Friedman, Buckley, & Lee, 1996; Strakowski et al., 2002). As evidenced by fMRI studies, structures such as the prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus have been suggested to play a role in depression (Carlson, 2005; Drevets, 2001). Specifically, as reviewed by Carlson (2005), various studies employing functional imaging have provided support that the activation of the orbitofrontal cortex and amygdala during depressive states reflects patients' attempts to suppress unpleasant thoughts and emotions as they

remember aspects of their life that made them sad. Not all neuroanatomical explanations involve overactivation of areas of the brain as some researchers have suggested that the decreased activation of the subgenual prefrontal cortex is another neuroanatomical correlate of depression (Drevets et al., 1997). This structure plays an inhibitory role in emotional memory and may partially explain the tendency for depressed individuals to ruminate about perceived misfortunes or misgivings.

In addition to the neuroanatomy of depression, chemical hypotheses in adult studies suggest that the monoamine system should be a focus of attention. Various studies have shown lowered concentrations of neurotransmitters and neurotransmitter metabolites as measured in the cerebrospinal fluid and plasma of patients with depression (K. D. Stark, Vaughn, Doxey, & Luss, 1999). These researchers have suggested that there is also an alteration in the number or affinity of serotonin and norepinephrine receptors. This decrease in the number of receptors or effectiveness of receptors poses problems for the functioning of serotonin and norepinephrine, two neurotransmitters implicated in mood disorders.

Approximately 80% of people with depressive symptoms show improvement with various psychotropic drugs (Nestler et al., 2002). Drugs such as tricyclic antidepressants, SSRIs, and monoamine oxidase inhibitors (MAOIs) act on the various monoamines and have antidepressant effects, suggesting there may be neurochemical explanations of depression. The finding that MAOIs and various SSRIs cause a decrease in depressive symptoms lends support to the monoamine hypothesis, which states that depression is

caused by insufficient activity of the monoaminergic neurons (Carlson, 2005). Additionally, depression does not respond to dopamine agonists, therefore the majority of research in depression has been focused on serotonin and norepinephrine.

Notably, one research study employed the tryptophan depletion procedure in order to study the effects of serotonin in depression (Delgado et al., 1990). In the study, the diet consisted of food low in tryptophan, an amino acid that is later synthesized to serotonin. The researchers recruited participants with Major Depressive Disorder who were receiving antidepressant medication, and prescribed the low-tryptophan diet. Over the course of the study, the majority of the participants in the study relapsed into depression, even when taking antidepressant medication. However, the participants recovered after eating a normal diet, strengthening the hypothesis that serotonin plays a role in depressive symptomatology.

The monoamine hypothesis of depression is supported by studies of neurotransmitter metabolite levels in depressed individuals. For example, lower levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite that is a by-product as serotonin is broken down, is indicative of lower levels of serotonin. Previous studies have shown that individuals who have attempted suicide have decreased levels of 5-HIAA (Roy, De Jong, & Linnoila, 1989; Traskmann, Asberg, Bertilsson, & Sjostrand, 1981). The monoamine hypothesis of depression is the most commonly cited biological explanation of depressive symptoms as supported by clinical observations of the efficacy of pharmacological agents and research studies of serotonin, norepinephrine, and 5-HIAA levels.

Much like hormonal theories of anxiety, hormones may also contribute to depressive symptoms. For example, HPA axis dysregulation may contribute to the experience of depressive symptoms (Nestler et al., 2002). Specifically, part of the HPA axis is controlled by the hippocampus, which acts as an inhibitory influence and may cause the hypothalamus to decease corticotropin-releasing hormone. Additionally, the amygdala may direct excitatory influence upon the hypothalamus. This negative feedback loop helps control the amount of cortisol that is released in the body during short bouts of stressors. As previously stated, prolonged exposure to stressful situations, in this case depressive symptoms, causes damage to CA3 pyramidal neurons of the hippocampus, thereby increasing the circulating cortisol levels and the experience of cognitive distortions. Excessive activation of the HPA axis has been found in adults with depression and these abnormalities have been shown to be corrected with antidepressant regimens (Holsboer, 2001). Despite this evidence, speculation still exists as to whether HPA axis abnormalities are a primary cause of depression or a consequence to the disease process. Particularly with regard to children, rates of depression between genders have been found to be roughly equal during early childhood. However, during adolescence, rates of depression in girls are double that found in boys (Birmaher et al., 1996). Although this finding could be due to demand characteristics such as boys' unwillingness to admit to difficulties with sad feelings, some researchers have suggested that the finding may be due to female hormones, particularly estrogen levels, of which increase during adolescence and puberty and into adulthood (K. D. Stark et al., 1999).

Genetic explanations for depressive symptomatology are supported by epidemiological studies showing that 40 to 50% of the risk of depression has a genetic basis, which is at least as heritable as common complex-medical conditions such as type II diabetes and hypertension (Sanders, Detera-Wadleigh, & Gershon, 1999). According to the APA (2000), Major Depressive Disorder is 1.5 to 3 times as likely in first-degree relatives of those who have been diagnosed with a depressive disorder, and is also the case with Dysthymic Disorder. Twin studies have shown that concordance rates for monozygotic twins is higher than that of dizygotic twins (McGuffin & Katz, 1989). Furthermore, higher concordance is typically found in monozygotic twins whether twins were raised together or apart (Price, 1968). These studies suggest genetic involvement in depression despite limited evidence of specific genetic abnormalities being identified to date. Nestler et al. (2002) suggest that genetics are the key to understanding depression from a purely biological perspective. Furthermore, the importance of genetic correlates of depression is highlighted by the fact that as we begin to understand the underlying genetics, more definitive treatments and preventative measures can be taken to address symptoms.

Neurobiological theories of depression continue to expand as technology advances. However, some have criticized this way of conceptualizing depression, as it does not account for the large amount of variance even within each specified disorder. As described, depressive symptoms may be a result from a range of causes ranging from unknown reasons to the bereavement of a close loved one. Learning, cognitive, and behavioral theories may explain to a better extent how depressive symptoms are

maintained. Finally, much like the research in the neurobiology of anxiety, limited research has used child and adolescent samples.

Learning, Cognitive, and Behavioral Theory

The *Theory of Learned Helplessness* (Overmier & Seligman, 1967; Seligman & Maier, 1967) suggests that depression could be related to perceived absences of control over situations. In one of the first animal models of depression, these researchers showed that compared to dogs that had operant control over receiving shocks (i.e., they could press a lever to avoid shock), dogs with no control developed depressive-like behaviors (i.e., laying down passively) over the course of many trials. As the contingencies were changed to allow the latter group of dogs the option of escape in another test of active avoidance, the dogs that previously "learned" that they were unable to control the outcome still were not able to escape the now escapable shocks. This theory has also been tested in human subjects. In multiple studies using a similar methodology, adults performing mental tasks who were exposed to escapable distracting sounds performed better on these tasks versus those with no control (Hiroto & Seligman, 1975; Maier & Seligman, 1976). In fact, these individuals performed much better than individuals with no control regardless of whether they chose to use the control or not. The authors surmised that the mere fact that these individuals believed they had control was strong enough to facilitate mental concentration and attention. The lack of escape-like behavior in later trials across these research studies closely represents the hopelessness often experienced by individuals who are depressed.

Cognitive theories of depression focus on the unique disturbances in cognition that contribute to depressive symptoms. For example, Beck (1976) suggests that the cognitions of a depressed individual reflect the theme of loss. The cognitive triad of depression has been suggested by numerous clinicians and consists of negative views of oneself, the environment, and the future (Young, Weinberger, & Beck, 2001). According to the cognitive model, those who are depressed view themselves as worthless, deficient, and incapable; the world as insurmountable; and the future as gloomy and hopeless. Numerous cognitive distortions such as all-or-nothing thinking, disqualifying the positive, overgeneralization, selective abstraction, and magnification are frequently used by depressed individuals (Beck, Rush, Shaw, & Emery, 1979). According to theorists, much of the cognitive distortions and depressive thoughts come from early maladaptive enduring themes in childhood, or negative schemas.

The cognition of self-blame seems to be intrinsic to individuals who are depressed. Janoff-Bullman (1979) suggested two types of self-blame – behavioral and characterological. The former refers to a modifiable source that can help aid with the future avoidance of negative outcome as individuals who use behavioral self blame attribute causes to different circumstances. However, characterological self-blame is associated with one's character and a belief in the personal deservingness for prior negative transgressions. In the 1979 study, depressed subjects engaged in more characterological self-blame versus nondepressed groups. The depressed individuals also thought that negative events that took place in their life were attributable to chance, suggesting a lower sense of self-efficacy.

A meta-analytic study of depressive symptoms and attributions in children included 28 studies that comprised over 7,500 children (Gladstone & Kaslow, 1995). Results of analyses suggested that depressive symptomatology was consistent with the reformulated theory of learned helplessness (Abramson, Seligman, & Teasdale, 1978). Specifically, internal-stable-global attributions of negative events and external-unstable-specific attributions of positive events were associated with levels of depression. These explanatory styles may contribute to depressive symptoms. However, the author noted that a limitation of the study was the issue of causality: it is difficult to conclude by the results whether depressive symptoms led to the attributional style or vice versa. Nevertheless, the medium to large effect sizes suggested that the attributional style and depressive symptoms go hand in hand.

From a treatment perspective, cognitive-behavioral theories of depression are represented by the efficacy of CBT, typically used in conjunction with pharmacotherapy with depressed children. In CBT, distorted thoughts are challenged to decrease the reliance on childhood schemas, behavioral assignments help target neurovegetative symptoms, and coping skills are taught in order to provide a more diverse way of dealing with difficult ambiguous situations.

Depression and anxiety are important to examine during childhood and adolescence due to the high prevalence and life-changing events that occur at these developmental stages. Although biological models suggest that these disorders occur due to underlying brain

anatomy, chemistry, hormones, or genetics, it may be too atomistic to think that all psychiatric complications stem from nature. Learning, cognitive, and behavioral theorists note that a combination of individual and social perspectives may also contribute to depressive and anxious symptomatology.

As more holistic and eclectic theories of psychopathology gain support, the old dichotomy of "nature versus nurture" seems inappropriate (Erk, 2004). Biological forces have a pervasive influence on our lives; however, they may affect behavior only in how they interact with environmental factors. The "diathesis-stress" model of psychiatric symptomatology may explain this viewpoint by stating that some individuals have a genetic and biological predisposition to experiencing psychiatric symptoms and it is not until and environmental trigger that those symptoms manifest. Biopsychosocial explanations of anxiety and depression may be a more holistic way of addressing the issues in order to develop and implement more appropriate treatment recommendations (Engel, 1977).

Some have criticized neurobiological explanations for the reliance on explaining behavior with biological components and observation that some disorders, such as specific phobias, have no readily identifiable biological cause. Furthermore, neurobiological explanations have been criticized because biological dysfunction may be a product of environmental stress as in the case of the overactivation of the HPA axis. On the other hand, behavioral models have been criticized due to the low importance placed on inner determinants of behavior. Though behavioral perspectives are deeply rooted in animal

models of learning, they neglect the fact that human beings are more dynamic, free-thinking individuals. Nevertheless, these two complementary theories of depression and anxiety have changed over the past century to incorporate more scientific rigor in order to develop more appropriate treatment plans.

Anxiety and Depression in Children: Current Thoughts

In general, anxiety disorders and mood disorders have a high comorbidity with up to 90% of patients diagnosed with an anxiety or depressive disorder experiencing symptoms of both at one point in their life (Gorman, 1997). Furthermore, 20 to 65% of anxious individuals experienced depressive symptoms at some point in their life (APA, 2000). This finding may illustrate a true comorbidity in the population, it may also stimulate a question of whether these are theoretically similar conceptualizations of symptoms. Many researchers have suggested that the diagnoses are two unique entities, whereas others have suggested that they are essentially different variations of the same disturbance. Norvell, Brophy, and Finch (1985) stated, "traditionally anxiety has been one of the most frequently cited symptoms associated with childhood depression and often symptoms related to anxiety are included in symptom lists for depression" (p.150). This diagnostic overlap causes the boundaries and distinction between disorders and symptoms to blur and may complicate diagnosis and treatment.

Numerous researchers have postulated whether it is possible to theoretically differentiate between the anxiety and depression in children. Some have suggested that the large

overlap between depressive and anxious symptoms in children can be best explained by the larger construct of generalized emotional distress (Wolfe et al., 1987). Others believe that negative affect is a generalized construct that encompasses many symptoms that could be classified as symptomatic of depression or anxiety (Watson & Clark, 1984). Much like broadband internalizing scales on measures of psychopathology such as the Child Behavior Checklist (CBCL, Achenbach & Edlebrock, 1983) and the Behavior Assessment for Children-2 (BASC-2, Reynolds & Kamphaus, 2004), negative affectivity describes a general overcontrolled behavior. Other proponents believe in the more traditional model of child psychopathology, which suggests that although there are some symptoms that overlap between depression and anxiety, there are some distinctive symptoms that are unique to each diagnosis (Kashani, Suarez, Jones, & Reid, 1999). According to K.D. Stark and Kaslow (1993), negative affectivity is defined as:

> A stable and global mood-dispositional dimension of personality. It is reflected in a pervasive negative valence to the individual's emotions, thoughts, and self-concept. Individuals who are experiencing elevated levels of negative affectivity are distressed, upset, have a negative view of themselves, and dwell upon and magnify personal mistakes, frustrations, disappointments, and threats. They also focus on negative aspects of others and the world. (p. 150)

In a study by K.D. Stark and Kaslow (1993), children diagnosed as depressed, anxious, or both were compared to a nonclinical group through clinical interview. These researchers found that on self-report measures of depression and anxiety, the symptomatology overlapped, making the distinction between the two groups more difficult. This finding

supported the idea of depression and anxiety in children as a part of the larger construct of negative affectivity.

Laurent and Landau (1993) addressed the confusion in diagnosing depression and anxiety in children by assessing what symptoms or lack of symptoms successfully predicted anxiety or depression. Using a sample of children who were diagnosed with depression or anxiety and a set of control children, they were able to show that feeling unloved, experiencing anhedonia, having excessive guilt, and experiencing depressed mood were efficient inclusion symptoms to diagnose depression. Furthermore, worries, especially those about the future, were the most efficient inclusion criteria for anxiety disorders. Although this finding illustrated that there are ways in which researchers and clinicians can differentiate between pediatric anxiety and depressive disorders, in the researchers' analysis they found that the anxiety symptoms on the self report measure (i.e., Revised Children's Manifest Anxiety Scale (RCMAS)) were more efficient predictors of the depression diagnosis over the anxiety diagnosis. This study provided support that depression and anxiety may represent overlapping internalizing symptoms, which ultimately leads to diagnostic confusion. Despite this finding, the four symptoms found to accurately predict depression were supported by a previous study with adults (Clark & Watson, 1991).

These two briefly reviewed studies provide support that pediatric depression and anxiety are difficult to conceptualize and differentiate; however, other studies that support conceptualizing these two entities as qualitatively separate disorders (Lipman, 1982;

Mullaney, 1984). More recently a study investigated whether anxiety and depressive disorders in adolescents should be described as a general factor or as two separate disorders with merely similar growth processes (Hale, Raaijmakers, Muris, van Hoof, & Meeus, 2009). Over the course of five years, these researchers studied over 1,000 children aged 10 to 20 years to address the risk of developing and document the trajectory of anxiety and depressive disorders through self-report questionnaires. Results suggested that the disorders were distinct entities and although they had similar growth processes, each had unique characteristics of growth across the time span.

Although there have been strides in the last 20 years, no definitive conclusions can be made as to the proper way to conceptualize childhood and adolescent depression and anxiety. Due to the question of interest, pediatric depression and anxiety symptoms were classified as separate entities in the current study. Though symptoms of anxiety and depression can be found in samples of medically-normal children, an understanding of the research on children with epilepsy and anxiety and depression is essential to the current study.

ANXIETY AND DEPRESSION IN EPILEPSY

Psychiatric Symptoms in Individuals with Epilepsy

In individuals diagnosed with epilepsy, seizure emanation has been compared to the tip of the iceberg with an underlying mass of behavioral, emotional, and social factors that need

to be addressed for a comprehensive biopsychosocial conceptualization of the impact (Aicardi, 1999). A great deal of research that examines the sequelae of epilepsy focuses on cognitive and intellectual consequences of repeated seizure emanations (Cormack et al., 2007) and among the relatively few studies that assess the psychological consequences of epilepsy, depression and psychosis have been extensively studied with less research focusing on anxiety (Caplan et al., 1997).

Numerous research studies have shown the comorbidity of epilepsy and psychiatric symptoms. In one of the seminal findings examining psychiatric comorbidity in pediatric epilepsy, Rutter, Graham, and Yule (1970) provided support that children with epilepsy are at an increased risk of experiencing behavioral and emotional disorders. This population-based study, also known as the *Isle of Wight Study*, illustrated that psychological sequelae of chronic illness may be disease-specific, rather than mere chronicity of the condition impacting adjustment of the child (Pless & Pinkerton, 1975). The *Isle of Wight Study* findings illustrated 28% of school-aged children with epilepsy had comorbid psychiatric conditions versus 12% of those with other chronic medical conditions, and 7% of children in the general population. These prevalence rates have been replicated in a recent epidemiological study in which 37% of children with epilepsy had mental health problems versus 11% of those with diabetes and 9% of children in the general population (Davies, 2003). The *Isle of Wight Study* is important as it was the first to suggest that neurological conditions may affect mood and behavior more than chronic medical conditions without neurological dysfunction.

Since the *Isle of Wight Study*, researchers have focused beyond general factors related to pediatric chronic illnesses, such as medication regimen, disruption of the family life, recurrent hospitalizations, and have begun to examine the unique aspects that each chronic illness has on the child's adjustment. Interestingly, the differences in prevalence in psychiatric comorbidity between children with epilepsy and other medical conditions, such as diabetes, exist even when the conditions are newly diagnosed (Hoare, 1984). Although prevalence rates established in the *Isle of Wight Study* have been consistently supported in later research, the theoretical reasons for increased levels of psychopathology have not been extensively studied (Austin & Caplan, 2007).

In 1992, Weiland, Pless, and Roghmann conducted a study of pediatricians of children with health conditions lasting more than three months. They divided the sample based on the seriousness of the child's disorder (i.e., serious disorders versus minor disorders such as hay fever or dermatitis), conducted clinical interviews with the pediatricians to determine if behavioral or emotional symptoms were thought to be present in the child, and asked whether or not the child had been referred to a mental health practitioner. They found that serious chronic illnesses were correlated with higher levels of emotional and behavioral disorders. Moreover, those with serious chronic medical conditions involving the central nervous system had the highest level of behavioral and emotional difficulties compared to those with chronic medical conditions not affecting the central nervous system, much like the suggested results in the earlier *Isle of Wight Study*.

Recently, researchers examined general levels of psychopathology in children affected by epilepsy through a meta analysis of studies dating from the *Isle of Wight Study* through 2003 (Rodenburg, Stams, Meijer, Aldenkamp, & Dekovic, 2005). They included studies involving children between the ages of 4 and 20 years and measured narrowband and broadband scores of several parent-report measures of emotional and behavioral difficulties. They used normative controls, healthy sibling controls, and children with other chronic illnesses as comparison groups for children with epilepsy. The analyses, which included over 2,400 children, revealed that those with epilepsy are prone to more psychological difficulties including somatization and attention problems. Interestingly, it supported the concept that the majority of children with epilepsy have higher levels of internalizing versus externalizing difficulties, which countered previous thought and has been supported in later research (Austin & Caplan, 2007).

In general, it is estimated that 40 to 60% of children with epilepsy have psychiatric or behavioral comorbidities (Beyenberg & Schmidt, 2005; Ott et al., 2003; Pellock, 2004). Prior to examining the contributing factors that are associated with psychiatric symptomatology and reasons that the comorbidity may exist, an in depth discussion of methodological limitations in assessing psychiatric comorbidity will help direct the current study.

Assessing Psychiatric Symptoms in an Epilepsy Population

Since studies carried out in the middle of the twentieth century have revealed higher prevalence of psychiatric conditions in individuals with epilepsy, researchers have sought to clarify this finding and provide definitive conclusions about the level of comorbidity. Methodological issues related to the sample selection and assessment selection pose difficulty in accurately reporting psychiatric comorbidity and symptomatology in epilepsy populations.

Population-Related Issues

Difficulties in assessing psychiatric symptoms in individuals with epilepsy include issues such as the generalizability of findings obtained with certain samples. Many studies that assess the psychiatric sequelae of epilepsy often use a tertiary sample of individuals seen in inpatient settings, EMUs, or those with regular outpatient appointments in neurology clinics (Adewuya & Ola, 2005; Alwash, Hussein, & Matloub, 2000; Austin & Caplan, 2007; Austin et al., 2001; Baki et al., 2004; de Souza & Salgado, 2006; Edeh & Toone, 1987; El Sabbagh et al., 2006; Ettinger et al., 1998; Hopp, Matausch, Zhu, & Krumholz, 2006; Mitchell, Scheier, & Baker, 1994; Oguz, Kurul, & Dirik, 2002; Ott et al., 2001; Piazzini, Canevini, Maggiori, & Canger, 2001; Piazzini & Canger, 2001; Schoenfeld et al., 1999; Shukla, Srivastava, Katiyar, Joshi, & Mohan, 1979; Wagner, Smith, Ferguson, Horton, & Wilson, 2009; Williams et al., 2003). Critics have often suggested that patients sampled from tertiary care settings may not be representative of the more commonly encountered patients with epilepsy in the general population. Those well managed by one

AED may not need to visit tertiary care settings and those who use tertiary services may be on polytherapy or have failed other types of treatments, thereby increasing the likelihood that they will experience psychiatric symptoms (Lambert & Robertson, 1999; B. Scheepers, Clough, & Pickles, 1998; M. Scheepers & Kerr, 2003; Torta & Keller, 1999; Whitman & Hermann, 1986).

To remedy the issue of generalizability of findings, studies that have attempted to assess the comorbidity of epilepsy and psychiatric symptoms using community-based samples (Berg et al., 2004; Blum, Reed, & Metz, 2002; Davies, Heyman, & Goodman, 2003; Ettinger, Reed, & Cramer, 2004; Jacoby, Baker, Steen, Potts, & Chadwick, 1996; Klein & van Passel, 2005; Kobau et al., 2006; Mensah, Beavis, Thapar, & Kerr, 2007; Rutter, Tizard, & Yule, 1970; Tellez-Zenteno et al., 2007). Additionally, studies employ the use of both types of samples in order to assess for differences (Caplan et al., 2004). Despite the generalizability issue, studies employing community-based samples continue to find psychiatric comorbidity at an increased rate versus the general population and other chronic medical conditions.

The population-related matter of sample selection highlights the need to balance obtaining an adequate patient sample size and using samples that are similar to the general population. Critics contend that findings from these studies should not be generalized to individuals with well-controlled epilepsy and may actually overestimate the amount of pathology. Despite this contention, patients in tertiary care clinics are typically more accessible for research purposes and are less prone to attrition than those

who are in the general population when being followed over time. The majority of the studies, including current study, that assess psychiatric symptomatology in children with epilepsy use tertiary care types of samples, which may be perhaps out of convenience.

Assessment-Related Issues

Many methods have been employed to assess the psychiatric and behavioral symptoms in epilepsy samples, ranging from comprehensive clinical interviews directed by licensed mental health providers to self-report inventories. With regard to children, the use of a parent report of the child's behavioral and emotional functioning has been important in conceptualizing psychiatric comorbidity.

In the body of pediatric epilepsy research, comprehensive techniques can be used to assess psychiatric disorders and symptoms. Despite the cost in terms of time and money of using this type of procedure to diagnose psychiatric symptoms, many studies have used full diagnostic interviews in conjunction with other types of measures to be able to make conclusive statements about psychiatric diagnoses and epilepsy (Caplan et al., 2005; Caplan et al., 2004; Davies et al., 2003; Ott et al., 2001; Ott et al., 2003). The use of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, Spitzer, Williams, Gibson, & First, 1992) is another way to accurately diagnose psychiatric conditions. The SCID-I is a semi-structured interview administered by a mental health practitioner or someone trained in clinical interviewing and uses an algorithmic model to arrive at accurate DSM-IV-TR diagnoses. Like clinical interviews, when used with individuals with complex psychiatric history, it can become a time-consuming procedure

and may not be feasible if a large number of subjects to be assessed. Despite these limitations, some studies use similar types of structured interviews to diagnose DSM-IV-TR disorders (Adewuya & Ola, 2005). The use of clinician interviews and structured clinical interviews represents a highly *qualitative* way of assessing for psychiatric sequelae.

In the current body of epilepsy research devoted to describing psychiatric symptoms, an overwhelming reliance on self-report measures exists (Baki et al., 2004; Bilgic, Yilmaz, Tiras, Deda, & Kilic, 2006; Cramer et al., 2005; de Souza & Salgado, 2006; Ettinger et al., 2004; Ettinger et al., 1998; Hopp et al., 2006; Kobau et al., 2006; Mensah et al., 2007; Muris et al., 2003; Oguz et al., 2002; Piazzini et al., 2001; Piazzini & Canger, 2001; Thapar, Kerr, & Harold, 2009; Wagner et al., 2009; Williams et al., 2003). In pediatric epilepsy research, self-report (Baki et al., 2004; Ettinger et al., 1998; Oguz et al., 2002) and parent-report questionnaires (Aldenkamp & Bodde, 2005; Mitchell et al., 1994), such as the CBCL (Achenbach & Edelbrock, 1983), are frequently used to examine psychiatric symptoms (Austin, Dunn, Johnson, & Perkins, 2004; Caplan et al., 2005; El Sabbagh et al., 2006; Freilinger et al., 2006; Ott et al., 2001; Schoenfeld et al., 1999; Williams, Griebel et al., 1998). The CBCL is an empirically-derived scale that has been heavily researched with numerous studies attesting to its reliability and validity. The BASC-2 (Reynolds & Kamphaus, 2004) is another parent-, self-, and teacher-report inventory that quantifies general and specific emotional, behavioral, and social concerns. The BASC-2 has specific features, which is discussed in a later section.

In addition to general measures of behavioral and emotional symptoms used in pediatric epilepsy research, studies also use anxiety-specific and depression-specific measures. For example, the State-Trait Anxiety Inventory for Children (STAIC, Spielberger, 1967) and the RCMAS (Reynolds & Richmond, 1978) are frequently used to assess the levels of anxiety (Baki et al., 2004; Bilgic et al., 2006; Ettinger et al., 1998; Muris et al., 2003; Oguz et al., 2002; Williams et al., 2003). The Children's Depression Inventory (CDI, Kovacs, 1985) is a self report that assesses depressive symptoms in children and has been used in numerous research studies involving children with epilepsy (Baki et al., 2004; Bilgic et al., 2006; Ettinger et al., 1998; Oguz et al., 2002; Wagner et al., 2009).

Similar across most of the parent- and self-report measures is the use of scores compared to normative data. The scores obtained allow clinicians to compare the individuals to others who have taken the exact same measure or survey. Many of the measures also use cutoff scores that allow clinicians to conceptualize the level of dysfunction the patient has on a particular scale. Although some tests use raw scores (e.g., total number of questions answered on a scale), most tests use some type of standard (i.e., deviation) score to quantify how much an individual scores differs from the normative average. The cost-effectiveness and utility of observer-reported measures is evident in the large number of studies that use them and in the quantitative and qualitative data that can be collected with them. Finally, recent studies have shown the importance of parent-report measures as they can accurately describe psychiatric symptomatology due to the cited correlation between parent-report and objective behavior (Aldenkamp & Bodde, 2005; Rodenburg et al., 2005). The current study addressed psychiatric symptoms in children by use of

parent-report measures, the most commonly used measure to address psychiatric symptoms in children with epilepsy in the current body of literature.

Because the majority of research addressing psychiatric symptoms in children with epilepsy use parent-report inventories of behavioral and emotional problems with a tertiary care sample of children, the current study replicated this trend with similar methodology. Despite the identified issues in assessing psychiatric sequelae in pediatric epilepsy, researchers have strived to conceptualize the levels of specific psychiatric symptoms. Furthermore, some have theorized possible contributing factors as well as reasons that psychiatric symptoms may manifest in children with epilepsy.

Anxiety, Depression, and Possible Contributing Factors in Pediatric Epilepsy

As reviewed in a previous section, many child and adolescent studies have addressed anxiety and depression as distinct entities and others have strived to conceptualize them as more general constructs of internalizing distress. However, specific to pediatric epilepsy studies addressing psychiatric symptoms, researchers have noted that anxiety and depression should be addressed separately as they seem to contribute to the quality of life in different ways (Cramer et al., 2005). Most studies involving children with epilepsy have addressed anxiety and depression as separate entities, but with separate measures for anxiety and depression specifically (i.e., STAIC and CDI). Therefore the majority of studies presented address both anxiety and depressive symptoms together with the understanding that they are distinct symptoms. However, methodological difficulties

arise as some research utilizes separate measures that were normed on different samples of children. The current study addressed this issue by using a measure that assesses anxiety and depressive symptoms with the same symptom inventory (i.e., BASC-2). The importance of studying anxiety and depression comorbidity in epilepsy samples is illustrated by the finding that unmanageable psychiatric symptoms tend to inhibit effective seizure control. For example, decreased adherence in a wide variety of chronic medical conditions is often related to anxiety and depressive symptoms and poor psychosocial outcomes of the condition itself (Kyngas, 2000). Furthermore, persistent thoughts of death, plans for suicide, and suicidal gestures are all depressive symptoms that have serious implications for the individual and are four to five times higher in individuals with epilepsy versus the general population (Caplan et al., 2005; Kanner & Balabanov, 2002; Oguz et al., 2002; Tellez-Zenteno et al., 2007). Therefore, the current study addressed anxiety and depression as separate entities.

Despite the effects that anxiety may have on an individual's adjustment to being diagnosed with epilepsy, adherence to medication management, and quality of life, it has not been as exhaustively studied as depression (Beyenberg & Schmidt, 2005; Beyenburg, Mitchell, Schmidt, Elger, & Reuber, 2005; Gilliam et al., 2003; Goldstein & Harden, 2000). The cyclical nature of anxiety and adjustment to epilepsy illustrate why there is a need to address anxiety separately as a serious complication associated with seizures. Comorbid epilepsy and anxiety may lead to lower quality of life, which may contribute to a decrease in seizure control, thus leading to more anxiety. Although comparatively fewer studies address anxiety relative to depression in pediatric epilepsy, some research has

estimated percentages of children affected by the comorbidity. For example, in 1998, Ettinger et al. found that over 16% of children surveyed on the RCMAS endorsed significant anxiety symptomatology. This heightened level was not correlated with gender, epilepsy duration, or age of onset. Additionally, more recently Williams et al. (2003) used the same scale to address variables that could be correlated with heightened levels of anxiety. They found that the 23% of 6 to 16 years olds with epilepsy endorsed mild to moderate levels of anxiety. These findings suggest that the percentage of children with epilepsy who experienced anxiety was much higher than the lifetime prevalence rates for children in the general population (i.e., 10%) cited in an earlier section and was correlated with polytherapy treatment regimen. Generally, previous research estimates the comorbidity of anxiety and epilepsy to be around 10 to 25% in adults and 14 to 25% in children (Jacoby et al., 1996).

Depressive symptomatology has been reported in up to two-thirds of individuals with epilepsy in tertiary care settings and in one-fourth of individuals in community-based settings (Lambert & Robertson, 1999). Rates of interictal depression are lowest in individuals in community samples, higher in patients attending outpatient clinics, and highest in medically-intractable patients being evaluated for epilepsy surgery. This overall rate of depression in individuals with epilepsy is five times as high as in the general population (Kanner & Balabanov, 2002). Regarding pediatric samples, in the Ettinger et al. (1998) study described above, over 26% of children significantly endorsed depressive symptomatology on the CDI which was, as stated, not associated with gender, epilepsy duration, or age of onset. Depressive comorbidity with epilepsy is an important

topic to address due to the high percentages of individuals affected, lost productivity, strained interpersonal relationships, and thoughts or acts of suicide that accompany depression. Numerous studies have supported the finding that depression is the most common interictal disorder (Alwash et al., 2000; Caplan et al., 2005; Ettinger et al., 1998; Gilliam et al., 2003; Kanner, 2005; Kanner & Balabanov, 2002; Lambert & Robertson, 1999; Oguz et al., 2002; Pellock, 2004).

Researchers have been able to pinpoint a specified range of anxiety and depressive symptoms in children with epilepsy and others have addressed possible contributing factors that may increase the likelihood of experiencing these symptoms. An early study in this line of research addressed both the behavioral problems and cognitive difficulties of children with various types of seizures. For example, researchers addressed whether children with complex partial seizures were higher than a control group on behavioral and emotional difficulties as measured by the CBCL and poorer than a control group on neuropsychological status according to a variety of neuropsychological measures (Schoenfeld et al., 1999). They found that children with epilepsy had higher levels of internalizing difficulties, which was related to seizure frequency. Though age of onset was not related to internalizing difficulties, the researchers found that an early age of onset was associated with poorer cognitive status. Though this was one of the first studies to address the contributing factors that may affect behavioral and psychiatric adjustment in children with epilepsy, it did not specifically address anxiety and depressive symptoms, nor did it address secondary generalized seizures, the primary focus of the current study.

Austin et al. (2001) addressed the rates of behavior problems in children prior to their first recognized seizure and identified the variables that were associated with the behavior problems. They used the CBCL with a sample of 224 children and found that even prior to children experiencing their first seizure, 32.1% of children were rated as at-risk for experiencing internalizing, attention, thought, and somatic complaints. Furthermore, their scores were higher than those of nearest-in-age sibling controls. The higher level of behavior problems was associated with socioeconomic status (SES), seizure type, and gender. Specifically, they found that males and children with partial seizures had the highest level of parent-reported complaints. However, as with most previous studies, and different than the current study, the research did not examine partial seizures with secondary generalization as a separate subtype of seizure. Anxiety and depression on the CBCL are grouped together to yield one factor score, which makes it difficult to interpret anxiety and depressive symptoms separately. The objective of the current study was to conceptualize anxiety and depression as distinct entities in the hope that more definitive statements about anxiety and depression in pediatric epilepsy could be made.

Ott et al. (2001) examined psychopathology of children with complex partial seizures or primary generalized seizures versus a control group of nonepileptic children using the CBCL and the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). They found that although there were no major differences in level of pathology according to seizure type, the CBCL identified psychopathology in 26% of the sample and the K-SADS identified it in over 50%. The percentage of children

with epilepsy with psychopathology was significantly higher than that of control children. Although this study seems to counter the intended purpose of the current study in their finding that seizure type did not contribute to distinct levels of psychiatric symptoms, it should be noted that seizures with secondary generalization were not grouped as a specific subtype of seizure.

In a study employing children with epilepsy ranging from 9 to 18 years old, researchers addressed the relationship of epilepsy-related factors to self-reported anxiety and depression scores (Oguz et al., 2002). They used anxiety- and depression-specific measures (i.e., STAIC and CDI) and were able to provide support that 28.6% of children with epilepsy endorsed higher levels of self-reported anxiety and depressive symptoms versus a control group. With regard to epilepsy-related variables, epilepsy duration (i.e., years since diagnosis of epilepsy), seizure frequency, and polytherapy were all associated with higher levels of anxiety and depressive symptoms. However, age of seizure onset and seizure type were not associated with levels of anxiety or depression. The finding that seizure type did not affect the level of anxiety or depressive symptoms seems to counter the rationale for the current study; however, the described research grouped seizure type into generalized tonic-clonic seizures, simple partial seizures, complex partial seizures, and absence seizures, with limited explanation of the role of secondary generalization. Furthermore, the great majority of the research reviewed has not included partial seizures with secondary generalization as a subtype of seizures and may have missed the nuances of anxiety and depressive correlations in this type of seizure.

Caplan et al. (2004) studied children with complex partial seizures and attempted to account for the medically- and epilepsy-related variables that were associated with heightened levels of psychopathology. Using a structured clinical interview and the CBCL, they found that compared to controls, significantly more children with complex partial seizures had a psychiatric diagnosis. As they addressed medically- and epilepsy-related variables (e.g., AED effect and seizure frequency), they found that these were unrelated to psychopathology. This study replicated earlier studies' findings of higher levels of psychopathology in children diagnosed with epilepsy, but the study did not include children with generalized seizures or children with seizures that secondarily generalize, which may have skewed the research findings. In addition, the research did not conceptualize on anxiety and depression as separate sets of symptoms, but instead grouped psychiatric symptoms as a whole, which is qualitatively different than the current study.

The researchers extended the previous study to more specifically assess the level of anxiety and affective disorder diagnoses in children with complex partial seizures and childhood absence epilepsy (Caplan et al., 2005). They used similar methodology in addressing these symptoms and were able to provide support that as a whole, 33% of children diagnosed with epilepsy had either a diagnosed mood disorder or anxiety disorder. Of the 33% of the children who were diagnosed with either a mood or anxiety disorder, approximately two-thirds also had some type of anxiety disorder, suggesting that anxiety disorders may be higher in prevalence relative to affective disorders in children diagnosed with epilepsy. This study was more precise than their previous study

as they addressed specific psychiatric symptomatology and included two separate seizure types. Although the researchers included these two separate types of seizures (e.g., generalized and partial), the study did not address the role the seizure type may have had with regard to the level of psychiatric symptoms. Furthermore, as with most of the reviewed research and unlike the current study, the study did not include secondary generalized seizures as a separate subtype, which the current study examined.

Freilinger et al. (2006) addressed the specific medically- and epilepsy-related factors they believed to be associated with emotional problems. They used the CBCL with 5- to 18-year-old children to investigate how contributing factors such as etiology, age of onset, AEDs, and EEG findings may be associated with levels of emotional problems. In general, they found that 22% of children endorsed moderate to severe behavioral or emotional problems. Higher scores were associated with symptomatic etiology, later age of onset, and polytherapy. Though this study illustrates that certain medically- and epilepsy-related factors may be associated with emotional problems, it did not specifically address anxiety and depression separately and merely found results for a broadband score representing total emotional and behavioral problems. Unlike the main concern of the current study, this research did not specify the differences amongst seizure types.

Researchers have recently assessed the differences in levels of anxiety and depression in a tertiary-care sample of children with epilepsy ranging from 8 to 16 years old (Bilgic et al., 2006). With the STAIC and the CDI, they compared these children to a control group.

Results supported that state anxiety and suicidality were all at significantly higher levels in children with epilepsy. They found that, as a whole, 26.7% of children with epilepsy were diagnosed with some type of psychiatric disorder according to the Mini-International Neuropsychiatric Interview, which the researchers also employed. The heightened levels of anxiety and depression did not correlate with epilepsy-related variables such as symptom severity, duration of epilepsy, and age of seizure onset. However, researchers found that boys had higher levels of psychiatric symptoms compared to girls. Although these findings illustrates that certain demographic attributes of children with epilepsy are associated with a heightened risk of experiencing psychiatric symptoms, it does not support the notion that epilepsy-related variables contribute to psychiatric symptoms. However, limitations of the study included not separating seizures by the different subtypes and a small sample size (i.e., n=30). The current study addressed these limitations by separating seizures by the subtypes and using a larger sample size.

In a recent study researchers addressed the psychiatric comorbidity of children with partial seizures due to mesial temporal sclerosis or juvenile myoclonic epilepsy (i.e., generalized seizures) using the SCID-I (de Araujo Filho et al., 2008). They found that in the sample of children with partial seizures, approximately 26% had a mood disorder and 14% had an anxiety disorder. Among the children with juvenile myoclonic epilepsy, 19% had a mood disorder and 23% had an anxiety disorder. These findings support the general prevalence levels of anxiety and depressive symptoms found in previous studies of children with epilepsy, although the researchers did not find that the higher levels of

psychiatric symptoms were associated with the number or type of AED, seizure frequency, or epilepsy duration.

As reviewed, anxiety and depressive symptoms have been found to be prevalent in individuals with epilepsy regardless of the methodology or assessment measure used. This pattern of heightened anxiety and depressive symptoms has been found across cultures (Adewuya & Ola, 2005; Alwash et al., 2000). Although one can make conclusive statements regarding the high levels of anxiety and depressive symptoms in children with epilepsy compared to normative controls, researchers and clinicians have sought to understand contributing factors that increase the likelihood of a child with epilepsy experiencing anxiety and depressive symptoms. Factors related to the treatment of seizures and medically- and epilepsy-related variables have been examined. A review of the contributing factors are emphasized in the following section in order to more clearly address these possible contributing factors in the current study.

Iatrogenic Effects Related to Treatment

Although reviewed in depth in the treatment section of this work, anxiety and depressive symptoms may be affected by iatrogenic effects of epilepsy treatment, such as in AEDs and surgical interventions. Numerous variables related to AEDs have been studied such as the number of medications taken and side effects of specific medications; however, polytherapy is the only variable which has been consistently backed in research as being associated with higher levels of anxiety and depressive symptoms in individuals with

epilepsy (Adewuya & Ola, 2005; Freilinger et al., 2006; Mendez et al., 1993; Oguz et al., 2002).

Findings have suggested that children who are prescribed a polytherapy regimen are referred to specialized schools (El Sabbagh et al., 2006) and seek mental health treatment at a higher rate than those with monotherapy regimens (Ott et al., 2003). In addition, phenobarbital, levetiracetam, topiramate, and zonisamide have all been associated with psychiatric side effects. AEDs directly affect an individual's mood through psychiatric side effects and may also inadvertently affect the mood of children through unwanted side effects that interfere with the child's social life such as oxcarbazepine exacerbating acne symptoms and valproic acid leading to weight gain. These unwanted side effects could obviously impact adolescents during times of increased self-awareness of body image. In addition to AEDs' effects on mood, surgery outcomes have also been shown to lead to increases and decreases in depressive symptomatology (Jambaque et al., 2007; Lendt et al., 2000; R. E. Stark et al., 1995; Vining et al., 1997).

Medically- and Epilepsy-Related Variables

Medically-related variables such as handedness, gender, and the presence of other neurological conditions and epilepsy-related variables such as age of onset, lateralization, seizure duration, and seizure type have been proposed to contribute to the experience of anxiety and depressive symptoms in children diagnosed with epilepsy.

Regarding medically-related variables, although there are bodies of research that suggest individuals with left-handedness, males, and those with other complicating neurological conditions are at a higher risk for psychiatric symptoms, there are numerous other studies that provide evidence to the contrary (Ettinger et al., 2004; Mensah et al., 2007). At this time, it is difficult to make conclusive statements about medically-related variables; however, it is important to address these factors in the current study to add to the body of research. Adding to the difficulty in addressing medically-related variables is that most studies that research anxiety and depressive symptoms and possible contributing factors focus mainly on epilepsy-related variables such as age of onset, lateralization, seizure duration, and seizure type.

The age of onset in epilepsy is typically quantified by parent report of children with epilepsy in pediatric literature or the individual with epilepsy in adult literature. In the literature, age of onset has had mixed results, with some research studies indicating no relationship (Bilgic et al., 2006; Ettinger et al., 1998; Oguz et al., 2002; Piazzini & Canger, 2001) and some indicating higher level of depressive symptomatology with later age of onset (El Sabbagh et al., 2006; Meador et al., 2001; Schoenfeld et al., 1999). Additionally, research exists stating that an earlier age of onset is correlated with higher levels of anxiety (Mensah et al., 2007). What seems to complicate matters in addressing age of onset as a contributing variable is that it has also been conceptualized as a proxy for the chronicity of the condition, possibly creating difficulty in accurately assessing the effect of the age of onset (Beyenburg et al., 2005; Zeber et al., 2007). Another complication is that subclinical epileptic semiology may present years prior to children

having a first seizure. Even so, early age of onset is thought to affect cognitive functioning to a higher degree than behavioral adjustment (Schoenfeld et al., 1999). Because of the mixed results regarding age of onset, the current study addressed this variable in order to add to the body of current research.

Among individuals with partial seizures, studies have also attempted to address whether seizures emanating from the left or right cerebral hemisphere are predictive of psychiatric symptomatology. There are occasional studies that support no relationship between seizure lateralization and anxiety and depression; however, the great majority of findings suggest that individuals with left-hemisphere pathology tend to exhibit more depressive symptoms (Altshuler, Devinsky, Post, & Theodore, 1990; Mendez, Cummings, & Benson, 1986; Mendez et al., 1993; Piazzini et al., 2001; Piazzini & Canger, 2001; Robertson, 1998; Robertson, Trimble, & Townsend, 1987; Septien et al., 1993). Despite the overwhelming evidence supporting increased depressive symptoms with left-sided foci, other researchers have explained those with left-sided foci tend to be more self-critical than those with right-sided foci. Simply put, these researchers suggest that individuals with right-sided pathology generally present with higher levels of impression management, thus minimizing or denying depressive symptoms and affecting the results of studies (Bear & Fedio, 1977). Regarding lateralization, the majority of the studies that support the findings come from studies using adult samples, perhaps due to the neuronal plasticity found in children of a young age. Therefore, it is difficult to make definitive statements about the lateralization of seizures and the role that it may play in the

psychiatric symptoms in children diagnosed with epilepsy. The current study aimed to add to the current body of literature regarding lateralization in partial seizures.

The time that has elapsed since the initial diagnosis, typically defined as the duration of epilepsy, is another variable thought to contribute to psychiatric symptoms in pediatric epilepsy that has been studied in previous research. Some studies find that there is a positive correlation with duration of epilepsy (Oguz et al., 2002) while other studies find no correlation between the duration of epilepsy and psychiatric symptoms in pediatric epilepsy (Bilgic et al., 2006; de Araujo Filho et al., 2008; Ettinger et al., 1998). Definitive statements characterizing the relationship between this variable and psychiatric symptoms in pediatric epilepsy cannot be made at this time.

Conventional thinking typically postulated that children who experience generalized seizures have more internalizing (e.g., anxiety and depression) symptoms versus children who experience partial seizures (Ott et al., 2001; Ott et al., 2003). However, regarding seizure type, there have been consistent studies illustrating that individuals with complex partial seizures have higher prevalence of anxiety (Goldstein & Harden, 2000; Marsh & Rao, 2002; Piazzini et al., 2001; Vazquez & Devinsky, 2003) and depressive symptoms (Berg et al., 2004; Caplan et al., 2004; Edeh & Toone, 1987; Kanner & Balabanov, 2002; Mintzer & Lopez, 2002; Piazzini et al., 2001; Piazzini & Canger, 2001; Rutter, Graham, & Yule, 1970; Schmitz et al., 1997; Shukla et al., 1979) compared to those with generalized seizures. Furthermore, numerous studies have provided support that individuals with epilepsy who are affected by complex partial seizures evidence higher

levels of psychiatric symptoms in general compared with those with generalized epilepsy (Berg et al., 2004; Caplan et al., 2004; Cockrell, Moriarty, Trimble, Sander, & Shorvon, 1996; Piazzini et al., 2001; Piazzini & Canger, 2001; Shukla et al., 1979). Some researchers suggest that the involvement of the temporal lobes, often compromised in individuals with complex partial seizures, contribute to the higher levels of psychopathology perhaps due to the involvement of the limbic system (Edeh & Toone, 1987; Gaitatzis, Trimble, & Sander, 2004; Kanner & Balabanov, 2002; Mintzer & Lopez, 2002; Schmitz et al., 1997; Shukla et al., 1979).

A few studies have refuted the claim that seizure type does not affect levels of psychiatric symptomatology, but methodological difficulties found in these studies do not allow for a definitive statement of results (Lambert & Robertson, 1999; Robertson et al., 1987; Weintraub et al., 2007). For example, in the Williams et al. (2003) study, the level of anxiety experienced by the individuals with epilepsy was correlated with behavioral difficulties, ethnicity, and polytherapy. More specifically, by using a stepwise regression analysis they were able to provide support that Caucasian children with comorbid learning disorders or behavioral problems on polytherapy were at the highest risk of experiencing anxiety symptoms. However, gender, age, epilepsy duration, or seizure type did not contribute to the levels of anxiety. Although the finding that anxiety was no different in the various seizure types seems to counter the purpose of the current study, the previous research did not differentiate the secondary generalized subtype, which the current study did.

Only a couple of studies have addressed secondary generalized seizures as a separate subtype, only one of which is published (de Araujo Filho et al., 2008). An important point to emphasize is that most studies addressing psychiatric symptoms in children with epilepsy include partial seizures with secondary generalization in their samples; however, the way that these seizures are grouped in a diagnostic scheme is not consistent across studies. For example, some studies group partial seizures with secondary generalization with other non-generalizing partial seizures (e.g., simple partial seizures without secondary generalization) and others group them with generalized seizures (e.g., generalized tonic-clonic seizures). The purpose of the current study was to address whether children affected by partial seizures with secondary generalization present with higher levels of psychiatric symptoms due to the unique experiential component of seizure semiology they encounter compared to children that have only partial or generalized seizures.

In the de Araujo Filho et al. (2008) study described earlier, researchers found that children with secondary generalized seizures did not endorse higher levels of psychiatric disorders compared to children with other types of seizures. However, this research only included of children affected by mesial temporal sclerosis unlike the current study that included all types of etiologies of partial seizures.

In addition to the de Araujo Filho et al. (2008) study, only one other study (Suli Moci, 2007) has addressed the behavioral and emotional effects of pediatric epilepsy specifically designating partial seizures with secondary generalization as a separate

subtype. This study used a retrospective design and a parent-report measure (i.e., CBCL) to address which epilepsy-related variables were associated with higher levels of behavioral and internalizing difficulties. The researcher found, as a whole, that most children showed internalizing as opposed to externalizing behavioral difficulties. Furthermore, results suggested that children who experienced secondary generalized seizures or generalized seizures had more internalizing symptoms than those with simple partial or complex partial seizures. Additionally, the higher level of internalizing difficulties was associated with lower intellectual functioning. It was concluded that those who are affected by seizures that spread to multiple lobes had the highest level of behavioral difficulties. Although this study did not find a difference in psychiatric symptomatology between children with secondary generalized seizures and generalized seizures, the current study hoped to add to the body of research with a larger sample size as the previous study used a small number of individuals (i.e., n=57). The study used the CBCL, which groups anxiety and depressive symptoms together in one factor score, making it difficult to address these two qualitatively different psychiatric symptoms separately. The current study used a measure that has separate anxiety and depressive symptom factor scores.

In addition to the two previous studies that addressed partial seizures with secondary generalization, a recent presentation used a pilot sample of children diagnosed with epilepsy. Findings suggested that parents of children with secondary generalized seizures perceived their children to have more anxiety symptoms relative to those with partial seizures without secondary generalization or generalized seizures (Benitez, Castillo,

Begyn, Hagar, & Stavinoha, 2008). Though this research was a pilot study, it seems promising given that children with secondary generalized seizures experienced anxiety symptoms in the "at-risk" range on the BASC-2 compared to the others who were within normal limits on the measure.

Mixed results regarding the relationship between medically- and epilepsy-related variables and anxiety and depressive symptoms are often related on the measures and samples used. Although some studies suggest that epilepsy-related variables are unrelated to psychiatric symptoms (Caplan et al., 2004; Weintraub et al., 2007; Williams, Griebel et al., 1998), few studies suggest otherwise. However, it is important to note that the overwhelming majority of studies have not addressed partial seizures with secondary generalization as a separate subtype of seizure, which was a main concern of the current study. There are a variety of factors that may contribute to the experience of anxiety and depressive symptoms in children diagnosed with epilepsy such as iatrogenic effects related to the medication and surgical treatment of seizures and medically- and epilepsy-related factors. Beyond the purview of the current study, there have been theories as to why anxiety (Ekinci, Titus, Rodopman, Berkem, & Trevathan, 2009; Gaitatzis et al., 2004; Kanner, 2009; Kanner & Balabanov, 2002; Manchanda, 2002; Tellez-Zenteno et al., 2007; Torta & Keller, 1999) and depression (Kanner & Balabanov, 2002; Lambert & Robertson, 1999; Tellez-Zenteno et al., 2007) may occur in pediatric epileptic conditions. These theories have suggested that epilepsy is typically comorbid with anxiety and depression by addressing the biological underpinnings (e.g. shared neuronal pathology) and psychosocial factors (e.g., stigma of having the disorder) that accompany epileptic

disorders. Though it is possible that with each individual the psychiatric symptoms and recurrent seizure emanation are completely unrelated, the high percentage of psychiatric symptoms found in epilepsy samples typically provides evidence against this explanation.

Secondary Generalized Seizures and Anxiety and Depression

The primary seizure type that the current study proposed to examine was partial seizures with secondary generalization. Seizures that secondarily generalize are those with paroxysmal activity beginning on one side of the brain and subsequent generalized spread across both cerebral hemispheres. Pertinent to the current study, a variety of issues unique to secondary generalized seizures may explain the heightened levels of anxiety and depression. The current study examined possible differences in anxiety and depressive symptoms experienced by children with secondary generalized seizures as compared with other seizure types with hopes that in the future specific theories may articulate why this pattern may occur. Some underlying theories may be addressed briefly to explain the possibility of hypothesized differences in anxiety and depressive symptomatology in children with secondary generalized seizures.

The onset of a partial seizure may serve as a cueing system, which signals the child to an impending tonic-clonic seizure. Learning theory, as reviewed in an earlier section, may be directly applicable to partial seizures with secondary generalization and subsequent anxiety and depressive symptoms. For example, simple or complex partial seizures or secondary generalized seizures may serve as an unconditioned stimulus during an

individual's first seizure experience in that they lead to innate responses (i.e., semiology). However, with repeated seizure experiences and the temporal cueing that takes place (i.e., partial seizure emanation occurs first and secondary tonic-clonic seizures follow), the partial seizure and any initial semiology (e.g., auras) may become repeatedly paired with the postictal effects of the tonic-clonic seizure (e.g., confusion, depression, anxiety) and as a result, a cueing system is created by which tonic-clonic seizures may be predicted.

The initial symptoms may cue the individual to the impending occurrence of a tonic-clonic seizure. It is easy to fathom that the cue may cause fear in the person affected as certain symptoms alert one of the possibility of an impending loss of consciousness with a tonic-clonic seizure. Furthermore, some children are affected by partial seizures with and without secondary generalized seizures, which may foster more anxiety as occurrence of secondary generalized seizures may be inconsistent. It is plausible to assume that children who are affected by secondary generalized seizures have preictal, ictal, postictal, and interictal anxiety in addition to the proposed fear and anxiety-cueing mechanism. The proposed mechanism of learning to anticipate a tonic-clonic seizure experienced by children with secondary generalized seizures can be found in Figure 1.

Children affected by partial seizures with secondary generalization experience the same loss of control and hopelessness as those with other types of partial and generalized seizures and may have similar levels of depression than children with other types of seizures. Through an understanding of learning principles, the cue experienced may predispose the individual to feeling anxious about the impending generalized seizure that

they may or may not experience. Specifically with regard to individuals experiencing recurrent seizures, the fear of the unpredictable nature of seizures themselves and perceived inability to control certain aspects of ictal semiology may predispose individuals to experiencing anxiety (Goldstein & Harden, 2000; Mensah et al., 2007).

Although psychosocial factors proposed may explain why children with secondary generalized seizures may have higher levels of anxiety, there may be underlying biological reason as well. Higher levels of anxiety may occur due to the involvement of the limbic system and subsequent neuronal spread possibly affecting various monoamines. A biological explanation is countered by the observation that most AEDs targeted at reducing secondary generalized seizures are also used to decrease the occurrence of other types of seizures. Since medications target secondary generalized seizures in a similar fashion as other types of seizures, any differences in anxiety or depressive symptoms in children affected by partial seizures with secondary generalization may be not be explained comprehensively by biological theories.

RATIONALE SUMMARY

Pediatric epilepsy is a prevalent medical condition that has far reaching effects on a child's daily life, cognitive abilities, and well-being. Various treatments aimed to reduce seizures cause side effects that can be more debilitating than the seizures themselves. In addition to effects related to seizure emanation and treatment, children with epilepsy also have to manage the stigma associated with it, the relative lack of knowledge of their peers

of the condition compared to other chronic diseases, and the loss of control related to seizure management. Children with epilepsy have been shown to be at an increased risk of experiencing psychiatric symptoms, namely anxiety and depression, versus healthy children and even children with other chronic medical conditions. Despite criticism, most research has used parent-report inventories to assess for psychiatric symptom levels in pediatric epilepsy as this is a convenient and generally valid way of assessing symptomatology. Most research has used tertiary care samples, possibly related to the decreased rate of attrition and large availability of samples. Most research using pediatric samples shows differences in anxiety and depression depending on the main type of seizures experienced; however, secondary generalized seizures have not been uniquely studied as a separate subtype of seizure. The temporal cueing that takes place over repeated seizure emanations in children presenting with this type of seizure may serve to create a system in which tonic-clonic seizures may be predicted. Though the cueing may give these children a sense of control, it may also lead to higher levels of anxiety as anticipating a tonic-clonic seizure may be particularly anxiety provoking. The current study addressed these possible heightened levels of anxiety in children affected by partial seizures with secondary generalization.

CHAPTER THREE
Methodology

OVERVIEW

Current models of conceptualizing sequelae in children with epilepsy tend to focus on cognitive outcomes. Although a body of research is devoted to addressing general psychiatric comorbidity and pediatric epilepsy, less research is devoted to addressing anxiety and depression. Finally, within the body of literature focusing on psychiatric sequelae of pediatric epilepsy, virtually no studies have included partial seizures with secondary generalization separate from generalized and partial seizures.

The current study evaluated the possibility of increased levels of parent-reported anxiety and depression symptomatology in children between the ages of 4 and 17 years diagnosed with epilepsy compared to the normative population. The study considered children who have partial seizures with secondary generalization as a separate entity due to the unique clinical features within this subgroup that may predispose these children to a different level of psychiatric comorbidity. Analyses were conducted to characterize the varying levels of depression and anxiety in the three subtypes of seizures (i.e., partial, generalized, and partial with secondary generalization) and to discern whether the differences can be accounted for by other variables (e.g., demographic, cognitive, medication-related, and seizure-related). Based on these analyses, the aim of this study was to address whether those with secondary generalized seizures have different levels of anxiety and depressive symptoms compared to children with solely partial or generalized seizures with a primary focus on anxiety, which is less studied than depression.

The current study used medical record review to obtain demographic, neuropsychological, and health information from children diagnosed with epilepsy seen in either the outpatient neuropsychology clinic or the EMU at Children's Medical Center Dallas (CMCD). The following section describes the participants, materials, and procedures relevant to the current study.

PARTICIPANTS

The specific inclusion criteria for the current study consisted of children between the ages of 4 years 0 months and 17 years 11 months on the date they were seen at either the outpatient neuropsychology clinic or EMU. Neuropsychological evaluations occurred between 2004 (i.e., the year the instrument containing the primary dependent variable was released) and present. These subjects were diagnosed with epilepsy by a neurologist according to ILAE standards.

Subjects with incomplete medical records (e.g., lack of medication information) or whose information was not accessible through the electronic charting system of CMCD were excluded from the study. In accordance with previous studies assessing emotional and behavioral sequelae of pediatric epilepsy, subjects who received surgical intervention (e.g., corpus callosotomy, hemispherectomy) were not included in the study due to the possible relationship between the resected areas of the brain (e.g., the limbic system in the temporal lobe) and mood and anxiety symptoms, which is documented in previous

research (Jambaque et al., 2007; Lendt et al., 2000; R. E. Stark et al., 1995; Vining et al., 1997).

MATERIALS

The current study used a variety of measures and variables in order to address the effect the type of seizure has on the level of parent-reported anxiety and depression. Measured variables included anxiety, depression, and intelligence. Demographic variables collected included age, gender, ethnicity, handedness, and median household income. Medical-related variables collected include the type of seizure experienced, age of onset, lateralization, functional etiology, EEG findings, and MRI findings. Finally, medication-related variables collected include the number of AEDs taken, the side-effect profile of the medication, and therapy regimen. These variables are described in more detail below.

Behavior Assessment System for Children, Second Edition (BASC-2)

The Behavior Assessment System for Children, Second Edition (Reynolds & Kamphaus, 2004) was used as the primary measure of anxiety and depressive symptoms in this study. The BASC-2 is a collection of self-report, parent-report, and teacher-report questionnaires used to assess a "child's adaptive and problem behaviors in community and home settings" (Reynolds & Kamphaus, 2004 , p. 4) and is a revision of the Behavior Assessment System for Children (Reynolds & Kamphaus, 1992). The parent-report instrument is a questionnaire that assesses a wide variety of emotional, behavioral, and

adaptive skill domains, including anxiety and depressive symptomatology. Three forms of the parent-rating scales can be used (e.g., preschool, child, and adolescent) and are comparable across the different types of forms. The items on the report were derived in a rational approach, unlike the more widely used CBCL, which was derived using empirical methods. More specifically, during the development of the original BASC, Reynolds and Kamphaus based the measure on a comprehensive review of multiple behavior-rating and self-report inventories. They included the input of teachers and students during the item-generation process. Like most other parent-report measures of behavior problems, they relied on numerous clinicians with experience with children to provide expert consultation. The result is a clearly-defined measure with nonoverlapping scales, illustrated by Covariance Structure Analysis (i.e., confirmatory factor analysis) (Reynolds & Kamphaus, 2004). A recent study suggested that there are qualitative differences in what this instrument detects with regard to a pediatric epilepsy population (Titus, Kanive, Sanders, & Blackburn, 2008). For instance, although the CBCL was derived using a more empirical approach, the overlap in items among various scales presents methodological difficulties in research.

The BASC-2 has validity scales to address the qualitative aspect in which an individual responded to the questions. Specifically, the *F* index is designed to detect a negative response set by addressing whether the respondent was excessively negative about the child's behaviors. If this raw score is in the "Caution" range, it is indicative of a negative response set obtained in less than 5% of the population and if the score is in the "Extreme Caution" range, it is indicative of an extremely negative response set obtained in less than

1% of the population. The Response Pattern Index helps identify invalid forms by assessing whether the parent was inattentive to the content of the items. Although it was anticipated and found that most Response Pattern Scores would fall in the "Acceptable" range, the authors use the terms "Caution-Low" to describe very few changes in the responses and "Caution-High" to describe considerable variation in the responses. Finally, the Consistency Index helps identify forms with inconsistent responding by assessing whether the respondent answers two similar questions differently.

Unique to each type of measure (e.g., self-, parent-, and teacher-report) are narrowband scales, which contribute to the broadband scores. Within the parent-report measure that was used in the current study, narrowband scales contribute to Externalizing Problems, Internalizing Problems, and Adaptive Skills broadband scores, respectively. Included is the Behavioral Symptoms Index, an assessment of the overall level of behavioral and emotional well-being. Individual items consist of statements or descriptions of behavior on a four-point likert scale ranging from *Never* to *Almost Always*.

The BASC-2 has been correlated with the CBCL in a few studies; however, it has not been used frequently in the pediatric epilepsy body of research. Like other parent-report questionnaires, the BASC-2 scores are represented as T-scores with a mean of 50 and a standard deviation of 10. Elevated scores of the Internalizing, Externalizing, and Behavioral Symptoms Index suggest behavioral and emotional dysfunction whereas lower scores in the Adaptive Skills domain suggest dysfunction related to the child's social well-being. The general cutoffs for the BASC-2 suggest that a T-score from 60

through 69 on clinical scales and 31 through 40 on adaptive scales are considered "At Risk." If individuals endorse scores in this range, the child should be closely monitored for any symptoms that the scale may suggest. BASC-2 scores that elevate above a T-score of 69 on clinical scales and below 31 on adaptive scales are in the "Clinically Significant" range and suggests that it is likely that the individual is experiencing significant symptoms related to the scale, which interferes with daily functioning.

A recent meta-analysis reviewing multiple non-overlapping studies showed that accurate research findings can be obtained by means of parent report (Rodenburg et al., 2005). Furthermore, some have suggested the importance of parent report because of the mismatch between self-reported behavioral problems and objectively-determined behavioral and emotional problems (Aldenkamp & Bodde, 2005). This measure was not developed for specific use with a pediatric epilepsy population, which was taken into consideration during interpretation of the results. However, previous research has shown that even when parents were asked to assess their children on behaviors unrelated to seizure activity, they still reported higher levels of psychopathology in children with epilepsy versus the general population (Austin et al., 2001). To date, only one study has used the BASC-2 with a pediatric epilepsy population (Titus et al., 2008).

In the current study, the variable of anxiety symptoms was obtained from the BASC-2 parent report and defined as the T-score on the Anxiety scale. Reynolds and Kamphaus (2004) define the Anxiety factor as "the tendency to be nervous, fearful, or worried about real or imagined problems" (p. 60). Furthermore, the variable of depressive symptoms

was obtained from the BASC-2 parent report and is defined as the T-score on the Depression scale described as "feelings of unhappiness, sadness, and stress that may result from an inability to carry out everyday activities or may bring on thoughts of suicide" (Reynolds & Kamphaus, 2004, p. 60). The use of the anxiety and depressive scores were contingent on the three measures of validity, the *F* Index, Response Pattern Index and Consistency Index. Scores in the "Extreme Caution" range on any of the validity scales were not used for anxiety and depression analyses.

Cognitive Variable

In the current study, intelligence estimates were obtained. A review of measured variables collected for the study can be found in Table 2.

Intelligence Estimate

The Wechsler tests (Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III, Wechsler, 2002); Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV, Wechsler, 2003); Wechsler Adult Intelligence Scale, Third Edition (WAIS-III, Wechsler, 1997); and Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999)) are standardized norm-referenced tests of intelligence. Long considered the "gold standard" of intelligence testing, each Wechsler test provides verbal, nonverbal, and full-scale intelligence estimates on a standard scale with a mean of 100 and a standard deviation of 15. Qualitative groupings that may be used to characterize an individual's intellectual abilities range from Extremely Low (i.e., Full Scale IQ (FSIQ) below 70) to

Very Superior (i.e., FSIQ above 129). Comparison across test forms has been used in prior research (Caplan et al., 2005; Caplan et al., 2004).

Numerous studies assessing the behavioral and emotional sequelae of epilepsy have indicated inclusion criteria of children with full-scale intelligence quotients greater than 69 (Ettinger et al., 1998; Rodenburg et al., 2005; Steffemberg, Gillberg, & Steffemberg, 1996; Weiland, Pless, & Roghmann, 1992; Williams et al., 2003). Behavioral disorders are more common in individuals with intellectual disability, with reports suggesting prevalence as high as 31% (Molteno, Molteno, Finchelescu, & Dawes, 2001). Shinnar and Pellock (2002) conducted an epidemiological study that revealed that over 30% of individuals with childhood-onset epilepsy met criteria for mental retardation, therefore it was anticipated that at least one-quarter of the individuals in the current study may have met the intelligence criteria for mental retardation. Intelligence estimates below a full scale estimated IQ of 70 were documented and were reported in the description of the demographics of the sample. Specifically, intelligence was addressed as a possible covariate of anxiety to evaluate whether seizure types are associated with different levels of parent-reported symptoms.

Regarding the current study, the variable for the subject's intelligence estimate was defined as the FSIQ on the WPPSI-III, WISC-IV, or WAIS-III depending on the intelligence test administered to the subject. There were two possibilities of full scale intelligence estimates for subjects who have received the WASI as a primary test of intelligence. Full scale intelligence can be derived with either two or four of the four

subtests. If subjects were tested with only two subtests, the variable for intelligence was defined as the FSIQ estimated from the two subtests (i.e., Vocabulary and Matrix Reasoning). However, if subjects were administered all four subtests (i.e., Vocabulary, Similarities, Block Design, and Matrix Reasoning), the FSIQ was estimated from all four tests given that estimates derived from four subtests are more highly correlated with full tests of intelligence. For nonparametric tests of interaction, efforts were made to address intelligence using proper statistical tests. Intelligence was also coded according to the Wechsler IQ range into which the specific IQ falls (i.e., Extremely Low, Borderline, Low Average, Average, High Average, Superior, Very Superior).

Demographic Data

In addition to the measured variables, a variety of demographic variables were collected to address the effect that they may have had on the primary outcome variables. Efforts were made to use interval/ ratio data when appropriate and nonparametric data to assess for differences in the outcome variables among groups. A review of demographic variables collected for the current study can be found in Table 3.

Age

Anxiety and depressive symptoms vary across the lifespan. What may be described as anxious worries in a 15-year-old may be developmentally appropriate thoughts in a 5-year-old. The variable of age was defined as the age, in months, when the subject underwent neuropsychological evaluation. Age was reported in the description of the

demographic characteristics of the sample. Furthermore, in the analyses addressing seizure type and level of anxiety symptoms, age was analyzed as a covariate to address whether it may impact the relationship that seizure type has on anxiety and depressive symptoms.

Gender

Numerous studies have provided support to show that mood and anxiety symptoms may be differentially distributed between the two genders. Gender was defined as either male or female and was reported in the description of the demographic characteristics of the sample. During analysis, gender was explored to address whether it has an interacting effect with the type of seizure or as a main effect by itself in explaining the levels of heightened anxiety and depressive symptoms.

Ethnicity

Although multiple studies addressed ethnicity as one of interest in explaining levels of psychiatric symptoms, no findings suggest that ethnicity is associated with the degree of anxiety or depressive symptoms in epilepsy samples. Ethnicity was defined as Caucasian, African-American, Latino, or Asian and was determined by the race identified in the patient's medical chart. Ethnicity was reported in the description of the demographic characteristics of the sample collected and was addressed in an exploratory nature as to whether certain children of different ethnicities with epilepsy have higher levels of parent-reported anxiety.

Handedness

Handedness may be a proxy for central nervous system lateralization (Cherbuin & Brinkman, 2006). For example, some research has shown that left-handedness may be a proxy for left-hemisphere brain damage (Gleissner et al., 2003; Lansdell, 1969; Nelson & Fischer, 2007; Strauss & Satz, 1990). The theory posits that early insults to the dominant hemisphere during childhood may cause functional reorganization of the cortex, thus leading the child to rely on the left hand as the primary source for fine motor coordination. Handedness was defined as left-handed, right-handed, or ambidextrous as identified in the neuropsychological report or as documented in the EEG findings. Given the current state of research on handedness in pediatric epilepsy samples, it is unclear whether handedness could be a potential predictor of hemispheric dysfunction and whether it may be predictive of anxiety and depressive symptoms. Handedness was documented and reported in the description of the samples, was explored as an ancillary variable to address whether each respective handedness is associated with different levels of psychiatric symptoms (i.e., only left-handedness and right-handedness was used in analysis), and was not used in the primary statistical analyses.

Median Household Income

Previous research has shown that those born into lower SES groups experience more intense stressors, which certainly have an impact on chronic illnesses (Steinbrook, 2004). Proximity to violence, lack of vital goods, and inadequate medical facilities are just a few challenges experienced by those with lower SES. Because of the retrospective nature of

this study, respondent-reported SES could not be obtained. Estimates of SES have been found to be an adequate proxy for SES (Krieger, 1992). Socioeconomic status of the child's family has been estimated in numerous ways, some of which include the provision of federally-funded health insurance (e.g., Medicaid) as a proxy for low SES (Weiland et al., 1992). Additional methods for estimating SES have included the median household income within neighborhoods and parental education. Socioeconomic status of the child's family was estimated using the median household income with public data (i.e., zip code and street level), which appears to be a valid measure of SES (Chen & Paterson, 2006). Furthermore, median household income was reported in the description of the demographic characteristics of the sample and in the final analysis on seizure type and level of anxiety symptoms, median household income was analyzed as a potential covariate to address whether it may impact the relationship that seizure type has on anxiety and depressive symptoms.

Medically-Related Variables

This current study also examined a variety of medically-related variables to address the role they may play in the reported anxiety and depressive symptoms. Research shows that medically-related variables such as seizure type and laterality of epileptogenesis have inconsistent findings as they relate to psychopathology (Gaitatzis et al., 2004). The current research is fundamentally different in that secondary generalized seizures were included as a separate subtype. A review of the medically-related variables collected for the current study can be found in Table 4.

Type of Seizure Experienced

The type of seizure experienced was used as the primary grouping variable and consisted of one of the following: partial seizures (e.g., complex partial, simple partial), generalized seizures (e.g., myoclonic, absence), or partial seizures with secondary generalization. Because the primary hypothesis sought to study the emotional sequelae of secondary generalized seizures, the individuals classified as having partial seizures with secondary generalization had at least one prior episode of secondary generalization. There were a few children who experienced partial seizures with and without secondary generalization. For the purpose of the current study, and because of the research hypothesis described, any child with at least one instance of secondary generalization was defined as experiencing partial seizures with secondary generalization. Although equal sample sizes for each type of seizure would yield more statistically powerful results, it was anticipated that the various levels of prevalence among the three types may lead to unequal distribution among seizure types. In the Williams et al. (2003) study, over 61% of the sample consisted of children with complex partial seizures; generalized tonic-clonic seizures accounted for 13% and absence seizures accounted for 25%. The type of seizure experienced was obtained from neurology progress notes closest to the date of neuropsychological testing. By examining the type of seizure experienced and the level of anxiety or depressive symptoms experienced, it allowed for preliminary statements to be made about the level of psychiatric symptoms in children who experience secondary generalized seizures, an often overlooked seizure type in the current body of pediatric epilepsy research.

Age of Onset

Previous research has suggested that age of onset of seizures is a proxy for chronicity (Beyenburg et al., 2005; Zeber et al., 2007). Some research shows that first-onset epilepsy later in life may be linked with increased levels of anxiety (Baker et al., 2001; Mensah et al., 2007); others have provided support to show that adults who were diagnosed with epilepsy in childhood versus adulthood had higher CBCL scores (Austin et al., 2001). Some research has suggested that individuals with newly diagnosed epilepsy and chronic epilepsy have similar levels of behavioral disturbance after controlling for the age of onset (Hoare, 1984). Although this body of literature seems to have mixed results, including age of onset in the present study added to the growing body of research addressing this variable of interest. Age of onset was obtained from the neurology progress notes or neuropsychological evaluation in the subject's medical chart and was defined in months.

Lateralization

In previous sections the influence that lateralization may have on anxiety and depressive symptoms have been reviewed. Left-hemisphere dysfunction correlates with depressive symptomatology (Menkes, Bodnar, Ballesteros, & Swenson, 1999). When addressed statistically, the lateralization may clarify the relationship between the type of seizure experienced and parent-reported anxiety and depressive symptoms. Lateralization was only applicable to children with partial seizures or partial seizures with secondary generalization. It was defined as left-hemisphere or right-hemisphere seizure emanation

according to the subject's medical chart. Efforts were made to address whether lateralization interacted with the type of seizure to affect parent-reported anxiety.

Functional Etiology

The effect that etiology has on outcome variables was also assessed. Although not directly addressed by previous studies, it is plausible that disorders of unknown origin may be more anxiety-provoking as compared to those with clearly identified causes (i.e., genetic, neurological insult). Functional etiology was classified as symptomatic, cryptogenic, or idiopathic and were obtained from the patient's medical chart. Because etiology is not heavily researched in addressing the presence of anxiety and depressive symptoms in pediatric epilepsy samples, this variable was reported in the description of the demographic characteristics of the sample and was more exploratory in nature.

Imaging Findings

It was anticipated that the majority of the children who comprised the current study's sample received at least one EEG and MRI. Previous research has not assessed these variables as much as other medically-related variables. The current study assessed EEG and MRI findings in an exploratory manner to address whether certain types of seizures may have interacting effects with negative or positive signs of dysfunction on EEG or MRI in parent-reported anxiety. Imaging findings were obtained from the patient's medical record and consisted of brain EEG and MRI findings closest to the date of neuropsychological evaluation that were either normal or abnormal.

Medication-Related Variables

Previous studies (Baki et al., 2004; Davies et al., 2003; Rodenburg et al., 2005; Shukla et al., 1979; Zeber et al., 2007) have not included AEDs as a variable of interest, which is unfortunate given the wide range of cognitive and behavioral side effects that the medication may have. The presence of anxiety and depressive symptoms is affected by a few medication-related variables that were investigated in the current study. A review of the medication-related variables collected for the current study can be found in Table 4.

Number of AEDs Prescribed and Therapy Regimen

The number of AEDs prescribed to the subject was included in analysis due to the differential cognitive and behavioral side effects that a number of drugs have on children. Several studies have provided support to show that children with polytherapy regimens have higher levels of behavioral and emotional disturbances (Adewuya & Ola, 2005; Freilinger et al., 2006; Mendez et al., 1993; Oguz et al., 2002; Williams et al., 2003). The number of AEDs taken were obtained through medical records, closest in date to the neuropsychological evaluation, and allowed for more definitive statements about the relationship between type of seizure experienced and anxiety and depressive symptoms when used as a covariate in the final analysis. The variable of therapy regimen was created based on the number of antiepileptic drugs taken and was coded as follows: children prescribed one AED during the time of neuropsychological evaluation were coded as having a monotherapy AED regimen and children prescribed two or more AEDs

at the time of neuropsychological evaluation were coded as having a polytherapy AED regimen.

Side-Effect Profile

Many AEDs have side-effect profiles that include detrimental cognitive effects (e.g., slower processing speed) and others have behavioral side effects (i.e., anxiety). By considering this variable in analysis, more definitive statements about the effect of seizure type on depression and anxiety symptoms were made. Certain drugs have been associated with cognitive effects (e.g., valproic acid, carbamazepine, and phenytoin), others with behavioral/ psychiatric effects (e.g., levetiracetam, zonisamide), and others with both side effects (e.g., phenobarbital and topiramate). These data were obtained in the same fashion as the number of AEDs prescribed and were defined according to the AED taken around the time of the neuropsychological evaluation. Though it was anticipated that very few children in the sample would not be prescribed an AED, those that were not currently on AED treatment regimen were not included in this analysis. Regarding the specific drugs and their effects, previous research has shown mixed results with specific AEDs, especially in pediatric samples. Because of the main hypotheses of the study include behavioral and emotional outcome variables, AEDs were coded as either having a behavioral/ psychiatric side-effect profile or nonbehavioral/ psychiatric side-effect profile. Children who were prescribed phenobarbital, topiramate, levetiracetam, and/ or zonisamide were coded as having a behavioral/ psychiatric side-effect medication profile. Children who were prescribed valproic acid, carbamazepine, phenytoin, lamotrigine, oxcarbazepine, or gabapentin during the time of their

neuropsychological evaluation were coded as having a nonbehavioral/ psychiatric side-effect profile. These codings allowed for more clear statements about whether the type of seizure experienced is indicative of varying levels of anxiety symptoms or if the effects are related to interacting effects of certain AEDs. A summary of the cognitive and behavioral side effects of the ten most commonly prescribed AEDs for children can be found in Table 1.

PROCEDURE

Medical charts of patients seen in the neuropsychology clinic or EMU at CMCD and who had at least one session of neuropsychological evaluation were retrospectively reviewed. The CMCD neuropsychology outpatient clinic provided a list of subjects diagnosed with epilepsy and data were collected, within the confines of the inclusion criteria, from that sample of children. Because of the chronic nature of epilepsy, a number of subjects had several rounds of neuropsychological testing (e.g., patient seen in the EMU and the same patient seen as an outpatient for follow-up). If subjects had numerous rounds of neuropsychological testing over the past few years, the most current data, within the parameters of the inclusion/exclusion criteria, were used. All hypotheses were tested statistically with Predictive Analytics SoftWare (PASW) version 18.0.1.

STUDY AIMS AND HYPOTHESES

Aim I Rationale

To date, the majority of research citing psychiatric sequelae of epilepsy has used parent report of emotional and behavioral functioning to document levels of depression and anxiety in a pediatric epilepsy sample. Those experiencing a heightened level of mood or anxiety disturbance have additional concerns compared to those who are not affected with these psychiatric symptoms.

Aim I

The current study aimed to replicate the current body of research that suggests that children and adolescents with epilepsy have heightened levels of parent-reported anxiety and depression versus the general (i.e., normative) population.

Aim I Hypothesis

Compared to the general population, children with epilepsy will exhibit greater levels of parent-reported symptoms of anxiety and depression.

Aim II Rationale

Current research provides very limited information on the specific psychiatric sequelae of partial seizures with secondary generalization as a unique subtype of pediatric seizures. The lack of research is unfortunate given that aspects of partial seizures may

serve as cues for the later occurrence of generalized seizures and may induce higher levels of anxiety. As a result, the second aim of the current study was to characterize and compare the different levels of depression and anxiety symptomatology between children with different types of seizures.

Aim II

The current study aimed to determine if children with partial seizures, generalized seizures, or partial seizures with secondary generalization have different levels of parent-reported symptoms of anxiety and depression.

Aim II Hypothesis

Compared to children with generalized or partial seizures, children with partial seizures with secondary generalization will evidence similar levels of depression, but significantly higher levels of parent-reported anxiety.

Aim III Rationale

A variety of variables correlate with psychiatric symptoms such as age, seizure-related variables (e.g., age of seizure onset), and the amount of medications prescribed to an individual. Furthermore, it is plausible that some variables may have an interactive effect with the type of seizure experienced that may affect the level of psychiatric symptoms in children with epilepsy.

Aim III

The current study aimed to examine whether differences in parent-reported anxiety occur independently of identified demographic, medically-related, and medication-related variables.

Aim III Hypothesis

Compared to children with generalized or partial seizures, and when taking other variables into account, children who experience secondary generalized seizures will evidence higher levels of parent-reported anxiety.

STATISTICAL CONSIDERATIONS

Prior to statistical analysis, all data were preliminarily evaluated for violations of statistical assumptions and outliers that may have impacted statistical analysis were addressed. Distributional characteristics of all the variables were obtained to ensure that they were normally distributed. Furthermore, chi-square analyses for nominal level variables and ANOVAS for continuous variables were conducted to identify any differences in the demographic, medically-related, and medication-related variables for children with each type of seizure.

Using means and standard deviations from a previous study's anxiety outcome (Generalized M = 48.00, Partial M = 54.04, Partial with Secondary Generalization M = 64.14 with the most conservative standard deviation (SD =14.80)), a priori power

analysis indicated that a total sample size of 87 was needed to detect a difference of a medium to large effect size (i.e., effect size f = .39) with .90 power. At the time of analysis, a sample size of 119 children with epilepsy was used in analysis.

For Aim I, a one-sample *t* test was used in order to address whether children with epilepsy have different levels of parent-reported anxiety and depression compared to the normative population. For Aim II, parent-reported symptoms of anxiety and depression were compared across the three different seizure types. Two separate Analyses of Variance (ANOVA) were conducted to assess the differences among the three types of seizures for each variable of interest (i.e., anxiety and depression). Kruskal-Wallis ANOVAs were also used to analyze any differences in the parent-reported anxiety and depression among the three seizure types. For Aim III, multifactorial ANOVAs were used to address the potential main effects and interactive effects of various nominal-level variables and types of seizures, and ANCOVAs were used to address any potential covarying factors between outcome variables among the different seizure types. The .05 level of significance was used in the current study and is consistent with previous research that uses similar methodology. Setting alpha significance at .05 allowed for reasonable protection against Type I errors and a reasonable level of power for most analyses. These analyses helped address whether the type of seizure experienced in children with epilepsy is associated with different levels of parent-reported anxiety and depressive symptoms. Each specific aim is described below.

Aim I

The current study aimed to replicate the current body of research that suggests that children and adolescents with epilepsy have heightened levels of parent-reported anxiety and depression versus the general (i.e., normative) population.

To address whether children with epilepsy have different levels of parent-reported anxiety and depression compared with the normative population, descriptive analyses were used to obtain measures of central tendency as well as measures of variance. Prior to analyzing the differences in parent-reported anxiety and depression, Normal P-P plots, skewness statistics, and frequency histograms were analyzed to address normality assumptions. Two separate one-sample *t* tests were used to evaluate the hypothesis that parent-reported anxiety and depression are higher in children with epilepsy versus those in the normative population. A constant T-score mean of 50 was used to represent the mean anxiety and depression in the normative population.

Aim II

The current study aimed to determine if children with partial seizures, generalized seizures, or partial seizures with secondary generalization have different levels of parent-reported symptoms of anxiety and depression.

Two separate Single Factor ANOVAs were used to address differences in parent-reported anxiety and depression among children presenting with different seizure types. Data were inspected to assure that assumptions were met and that all statistical analyses were appropriate. Normal P-P plots, skewness statistics, and frequency histograms were analyzed to address normality assumptions. To evaluate whether the variances of the dependent variables are equal among the three seizure types, the Levene's Test of Error Variances was inspected. Finally, the third assumption of independent of test variable independence was met in that there was no categorical overlap among scores of the dependent variables for each of the three seizure types. When appropriate, post-hoc analyses were used to identify which of the types of seizures experienced by the children were significantly different from each other. The Dunnet's C post-hoc analysis was used as it is a conservative method which does not assume equality of variances and is the most preferred method to use when sample sizes are much different from one another. Separate ANOVAs were run instead of a Multivariate Analysis of Variance (MANOVA). Because the analysis was hypothesis driven for each outcome variable (i.e., anxiety and depression), it was unnecessary to correct for multiple tests and is in accordance with previous literature (Caplan et al., 2004).

Median Tests and Kruskal-Wallis ANOVAs were also used to illustrate whether nonparametric results would mirror results found in parametric analyses. Nonparametric analyses are not as statistically powerful as parametric statistics, but they can still identify differences among different groups on a dependent measure. Post-hoc analyses of each pairwise comparison with Bonferroni correction addressed which seizures had higher

median levels of parent-reported anxiety and depressive symptoms, if any differences in the measure existed. The .05 level of significance was divided by the number of pairwise comparisons made (i.e., .05/3 = .017) and used in nonparametric analyses.

Aim III

The current study aimed to examine whether differences in parent-reported anxiety occur independently of demographic, cognitive, medically-related, and medication-related variables.

To evaluate whether group differences in parent-reported anxiety are due to seizure type and occur independently of identified demographic, cognitive, medically-related, and medication-related variables, two distinct analyses were conducted depending on the level of measurement. For nominal-level variables, Two-Factor Between Subjects Factorial ANOVAs were used, and for continuous variables, Analyses of Covariance (ANCOVA) were used. These analyses are important for clarifying the role of secondary generalized seizures and the proposed presence of higher anxiety levels.

Nominal Variables

Previous research has suggested a variety of nominal-level variables such as gender, lateralization of neuronal pathology, side-effect profile of certain medications, and therapy regimen may contribute to psychiatric symptoms. To address the main effects these variables may have with parent-reported anxiety and depression as well as the

possible interactive effects that these variables may have with different types of seizures, each nominal-level variable was examined along with the type of seizure experienced in a Two-Factor Between Subjects Factorial ANOVA for anxiety.

Prior to analyzing the potential interactive effect between nominal-level variables and type of seizure experienced, data was inspected to ensure assumptions of a Factorial ANOVA were met and that statistical analyses were appropriate. Assumptions of a Factorial ANOVA include: (1) the dependent variable is normally distributed for each of the populations, (2) the population variances are the same for all cells, and (3) the cases are random samples from the population and scores of the dependent variable are independent of each other (Green & Salkind, 2005).

Multiple Factorial ANOVAs were used to examine the possible interactive and main effects that nominal-level variables may play in explaining the relationship between the type of seizure experienced and parent-reported anxiety and depression. For gender a 3x2 Factorial ANOVA (e.g., male, female) was used, for lateralization a 2x2 Factorial ANOVA was used only including children with partial seizures or partial seizures with secondary generalization (e.g., right or left), for the side-effect profile of medication, a 3x2 Factorial ANOVA was used (e.g., behavioral/ psychiatric effect or nonbehavioral/ nonpsychiatric effect), and for therapy regimen, a 3x2 Factorial ANOVA was used (e.g., monotherapy or polytherapy). Appropriate follow-up analyses of simple main effects and pairwise comparisons addressed specific findings.

Continuous Variables

In addition to nominal-level variables that may have an interactive effect with the type of seizure experienced, there were five continuous-level variables that may have been covariates with parent-reported anxiety. The potential covariates included age of the child, age of onset of seizures, the number of AEDs prescribed, median household income, and intelligence. To address the possible effect the type of seizure a child with epilepsy experiences has on parent-reported anxiety, taking possible covariates into account, multiple ANCOVAs were used.

Prior to addressing the possible covarying effects of continuous-level variables, data was inspected to evaluate whether the assumptions of an ANCOVA were met. The assumptions of the ANCOVA include: (1) the test variable is normally distributed in the population for any specific value of the covariate and any one level of the independent variable, (2) the variances of the dependent variable for each group of the independent variable are equal, (3) the cases represent a random sample from the population, and scores on the dependent variable are independent of each other, and (4) the covariate is linearly related to the dependent variable within all levels of the factor, and the weights or slopes relating the covariate to the dependent variable are equal across all levels of the factor (Green & Salkind, 2005). The first three assumptions are similar to the assumptions of the previous analyses explained above and have been described in detail. However, the fourth assumption is unique to the ANCOVA analysis. In order to meet this assumption, bivariate correlations for each of the five continuous variables described above were used to determine if there a linear relationship exists among the continuous

variables and parent-reported anxiety. Furthermore, the homogeneity of slopes aspect of the fourth assumption was checked using statistical software in order to address the possible interaction between the covariate and the factor.

For variables meeting all the assumptions of a One-Way ANCOVA, separate ANCOVAs were used to assess the role that seizure type may play in parent-reported anxiety while simultaneously controlling for the effects of covariates. Pairwise comparisons addressed findings of significant main effects.

Exploratory Variables

As reviewed, a variety of variables have an unclear relationship with how they may be related to anxiety. In the current study, there were a variety of documented nominal-level variables that may have interacted with different types of seizures to affect levels of parent-reported anxiety as well as continuous-level variables that may have covaried with anxiety symptoms. These variables have not been addressed in previous research and were addressed in the current study in an exploratory manner. Nominal-level variables such as ethnicity, handedness, etiology, EEG findings, and MRI findings are all variables that the current study addressed in an exploratory nature.

CHAPTER FOUR
Results
GENERAL FINDINGS

In the current study, 143 patients were identified as children seen on an outpatient or inpatient basis for neuropsychological evaluation between 2004 and the present with a diagnosis of epilepsy. The breakdown of children excluded and included in the current study's analyses can be found in Figure 2. Twenty-four subjects of the 143 met some form of exclusion criteria (e.g., 13 were missing some scores required for analysis, three were evaluated in 2004, but with an earlier edition of the BASC-2, three were status/ post cerebral resection, two had epilepsy secondary to brain tumors, two were younger than 48 months, and one had an "extreme caution" F Score on the BASC-2). Of the 119 children who met all criteria for inclusion, approximately half of them were girls (N = 58) and the rest were boys (N = 61). Approximately 38.7% of the sample was Caucasian, 22.7% was African-American, 37.8% was Latino, and 0.8% was Asian. Finally, 82.4% of the sample was right handed, 14.3% of the sample was left handed, and 3.4% were ambidextrous. Demographic characteristics of all the children included in the study by seizure type and as a whole are presented in Table 5. Chi-square analyses reveal that there are no significant differences in gender or ethnicity among children with the three different seizure types. As anticipated due to the prevalence of various types of seizures found in previous pediatric epilepsy literature, the sample of children obtained for the current study was comprised of 60.5% children with partial seizures, 19.3% children with generalized seizures, and 20.2% children with partial seizures with secondary

generalization. Of the 119 subjects included in the study, approximately two-thirds were seen on an outpatient basis and one-third were seen in the EMU.

Table 6 illustrates seizure-related variables of the sample collected for the current study. Of the 119 children comprising the sample, 50% had symptomatic etiology, 27.1% had idiopathic etiology, and 22.9% had cryptogenic etiology. Chi-square analysis reveals significantly different frequencies of etiology according to seizure type. Furthermore, of children affected by partial seizures or partial seizures with secondary generalization, 54.7% had left-hemisphere pathology and 45.3% had right-hemisphere pathology on imaging findings. Lab-related findings are presented in Table 7, and were intended to be addressed in an exploratory manner. In the obtained sample, 118 children had documented EEGs. Findings reveal that, as a whole, 85.6% of children had abnormal EEGs and the remaining percentage of children had normal findings. Only 113 of the 119 children comprising the final sample used for analyses received MRIs as part of their diagnostic workup, 59.3% of which were abnormal. Though initial chi-square analysis revealed that there are no significant differences in EEG results among children with different seizure types, similar analyses suggest that the frequency of MRI abnormality and normality differ according to the child's seizure type.

Table 8 illustrates medication-related variables collected in the current study. Approximately 95% of children who comprise the final sample were on at least one AED during the time of their neuropsychological evaluation. Of the children in the sample who were prescribed AEDs, 48.7% were prescribed monotherapy regimens and 51.3% were

on polytherapy AED regimens during the time of the neuropsychological evaluation. It was anticipated that the current study would find that most children would be prescribed AEDs from the list of the ten most commonly used AEDs with children as described by Meador (2005). It was found that most children were prescribed at least one of the AEDs from that list, with the exception of gabapentin, which no children were prescribed at the time of their neuropsychological evaluation. Furthermore, some children were prescribed ethosuximide, an AED which was not anticipated to be prescribed as it was not described as one of the most commonly prescribed AEDs for children in previous literature. Similar to other AEDs, ethosuximide was classified as a drug with nonbehavioral/ psychiatric side effects, as described by previous studies showing that it has a relatively safe side-effect profile with most effects being transient (Glauser et al., 2010). Of the children on some form of AED treatment, 53.1% had a regimen that consisted of AEDs with behavioral/ psychiatric effects and 46.9 were on AED medication with nonbehavioral/ psychiatric effects. The percentages of drugs prescribed in the current study can also be found in Table 8.

The current study also addressed a variety of variables, found in Table 9. The average age at neuropsychological evaluation was about 11 years 3 months and the average age of onset around 5 years. Median household income was approximately $42,322.99 per year. As anticipated, the average intelligence estimate in the obtained sample was in the Borderline range of intelligence, with a standard score of approximately 79. Additionally, approximately 29.5% of the sample obtained an FSIQ below 70, thereby meeting the intelligence criteria for mental retardation, a finding that was anticipated and documented

in previous literature. Especially pertinent to the current study, the mean anxiety T-score was 53.85 and depression T-score was 58.13. Preliminary analyses of normal P-P plots, skewness statistics, and frequency histograms suggest that all continuous variables were normally distributed, with the exception of median household income, which was moderately positively skewed. The median household income was transformed with statistical software by using a Log10 command and subsequent results presented will describe a Log10 transformed median household income, which is normally distributed.

Preliminary ANOVAs suggest that there are no differences among the three seizure types for age, $F(2, 116) = 1.47$, $p = .23$; age of onset, $F(2, 116) = 0.69$, $p = .504$; median household income, $F(2, 116) = 0.03$, $p = .22$; and intelligence, $F(2, 107) = 1.45$, $p = .240$. However, results suggest that children with different seizure types differ on the number of AEDs prescribed, $F(2, 116) = 4.74$, $p = .01$. Pairwise comparisons suggest that children with partial seizures are prescribed more AEDs than children with generalized seizures. Furthermore, findings suggest children with secondary generalized seizures are prescribed more AEDs than children with generalized seizures. However, it is important to note that this finding is one of statistical significance as the mean number of AEDs prescribed to children with partial seizures, generalized seizures, and partial seizures with secondary generalization were 1.63, 1.13, and 1.79, all nearly identical.

AIM I FINDINGS

Aim I of the current study sought to address the level of parent-reported anxiety and depression in children with all types of seizures. As stated, descriptive statistics show that the mean parent-reported anxiety was 53.85 (*SD* = 13.30). Furthermore, parent-reported depression was a T-score mean of 58.13 (*SD* = 13.51). On the BASC-2, these means are not considered to be in the "At-Risk" range or clinically significant.

Analysis of normal P-P plots, skewness statistics, and frequency histograms revealed that parent-reported anxiety and depression were approximately normally distributed with no major outliers affecting the dataset. The current study also employed a large sample to ensure normality for each distribution of dependent variables. Parent-reported anxiety and depression were compared to the mean of the normative population (i.e., T-score of 50) with two separate one-sample *t* tests. A one-sample *t* test was conducted on the parent-reported anxiety scores to evaluate whether their mean was significantly different from 50, the average T-score of parent-reported anxiety in the normative population. With alpha set at .05, the mean for the sample was significantly different from 50, $t(118) = 3.16$, $p = .002$. The effect size *d* of .29 indicates a small effect. Furthermore, a one-sample *t* test was conducted on parent-reported depression to evaluate whether their mean was significantly different from 50. With alpha set at .05, the mean for the sample was significantly different from 50, $t(118) = 6.57$, $p < .001$. The effect size *d* of .60 indicates a medium effect. The results support the hypothesis that parent-reported anxiety and depression is significantly different than the mean of the normative population. Given the

results, a post-hoc Paired-Samples *t* test was conducted in order to evaluate whether parent-reported depression was higher than parent-reported anxiety. The results indicated that the average parent-reported depression score (M=58.13, SD = 13.51) was significantly greater than the average parent-reported anxiety score (M = 53.85, SD = 13.30), $t(118) = -3.52$, $p = .001$.

AIM II FINDINGS

Aim II of the current study sought to address whether the levels of parent-reported anxiety and depression in children with epilepsy are different across three separate seizure types. Two separate ANOVAs were used to address whether these parent-reported psychiatric symptoms were different in children with partial seizures, generalized seizures, or partial seizures with secondary generalization. Analyses of normal P-P plots of the distribution, skewness statistic, and frequency histogram, nonsignifcant Levene's tests for the homogeneity of variance, and independence of parent-reported anxiety and depression T-scores across the three types of seizures suggested that all appropriate assumptions were met for both ANOVAs. As anticipated, due to the retrospective nature of the current study and different prevalence rates of the three types of seizures in the general population, group sizes for each type of seizure experienced were uneven.

Parametric Analyses

Anxiety

A one-way ANOVA was conducted to evaluate the relationship between seizure type and the level of parent-reported anxiety. The independent variable, seizure type, included three types: partial seizures, generalized seizures, and partial seizures with secondary generalization. The dependent variable was the T-score of anxiety on the BASC-2 Parent Rating Scale. The ANOVA was significant, $F(2, 116) = 4.79$, $p = .01$. The strength of the relationship between the seizure type and the parent-reported anxiety, as assessed by η^2, was moderate, with seizure type accounting for 8% of the variance of parent-reported anxiety.

Follow-up tests were conducted to evaluate pairwise differences among the means. Because the variances among the three groups ranged from 140.23 to 250.30, there was no assumption that the variances were homogeneous and post hoc comparisons were made with the Dunnett's C test, a test that does not assume equal variances among the three groups. There was a significant difference between the means for children with partial seizures with secondary generalization and those with generalized seizures; however, there was not a significant difference between the means for children with partial seizures and those with generalized seizures or the means for children with partial seizures and those with partial seizures with secondary generalization. Children with partial seizures with secondary generalization showed the highest level of parent-reported anxiety ($M = 60.71$). An illustration of the means of parent-reported anxiety by seizure

type can be found in Figure 3, and 95% confidence intervals for the pairwise differences as well as the means and standard deviations for the three seizure types are reported in Table 10.

Depression

A one-way ANOVA was conducted to evaluate the relationship between seizure type and the level of parent-reported depression, as well. The independent variable, seizure type, included three types: partial seizures, generalized seizures, and partial seizures with secondary generalization. The dependent variable was the T-score of depression on the BASC-2 Parent Rating Scale. The ANOVA was not significant, $F(2, 16) = 2.13$, $p = .12$, indicating that parent-reported depression does not differ according to seizure type. An illustration of the means of parent-reported anxiety by seizure type can be found in Figure 4, which are 56.88, 56.83, and 63.17 for children with partial, generalized, and secondary generalized seizures, respectively.

These results partially support the hypotheses that compared to children with generalized or partial seizures, children with partial seizures with secondary generalization evidence similar levels of depression, but significantly higher levels of parent-reported anxiety.

AIM III FINDINGS

Aim III of the current study sought to expand upon the findings from Aim II to address whether the finding of different levels of parent-reported anxiety occur exclusive of other

contributing factors or covariates. Discrete variables thought to interact with seizure types were addressed with separate two-factor ANOVAs. Furthermore, continuous variables thought to covary with parent-reported anxiety were addressed with separate ANCOVAs.

Nominal Variables

Nominal variables suspected to have an interactive effect with seizure type were addressed with separate two-factor ANOVAs. Specifically, the nominal variables of gender, seizure lateralization, side effect-profile of medication, and therapy regimen, were addressed to identify whether they contributed to parent-reported anxiety exclusively, or interacted with seizure type. Due to the retrospective nature of the current study, equal cell sizes were not obtained for most analyses, therefore each design could be considered unbalanced. Because of this notion, weighted means are reported in each respective section. Furthermore, upon analyses in PASW, Type III and Type IV sums of squares were each calculated to evaluate for any differences in the results of *F* tests. Regardless of the specific type of sums of squares, results of the *F* test for Type III sums of squares agreed with Type IV sums of squares, much like in previous research addressing unequal sample sizes (Tanguma & Speed, 2000). Prior to each analysis, initial analyses of normal P-P plots of each of the distributions, skewness statistics, and frequency histograms, nonsignifcant Levene's tests for the homogeneity of variance, and independence of parent-reported anxiety across the three types of seizures suggested that all appropriate assumptions were met for factorial ANOVAs. Each computation will be described separately below.

Gender

A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and gender on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 11. The results of the ANOVA indicated a significant main effect for seizure type, $F(2, 113) = 4.01$, $p = .02$, partial $\eta^2 = .07$, no main effect for gender $F(1, 113) = .21$, $p = .64$, partial $\eta^2 = .02$, and a significant interaction between seizure type and gender $F(2, 113) = 4.02$, $p = .02$, partial $\eta^2 = .07$.

Because the interaction between seizure type and gender was significant, method main effects were ignored and method simple main effects were examined; (i.e., the differences among seizure types for boys and girls separately). To control for Type I error across the two simple main effects, alpha was set at .025. There were significant differences for boys, $F(2, 113) = 5.26$, $p = .007$, and girls, $F(2, 113) = 3.88$, $p = .02$.

Follow-up tests were conducted to evaluate the three pairwise differences among the means for boys and girls, with alpha set at .008 (.025 / 3 = .008) to control for Type I error over the three pairwise comparisons. Boys affected by partial seizures with secondary generalization had significantly higher parent-reported anxiety than boys with generalized seizures. There were no significant differences between boys with partial seizures and those with generalized seizures and no significant differences between boys with partial seizures and those with partial seizures with secondary generalization.

Follow-up tests with girls did not evidence any statistically significant differences among the three seizure types, after controlling for pairwise comparisons. A visual of estimated means of anxiety by gender can be found in Figure 5.

Lateralization

A 2 x 2 factorial ANOVA was conducted to evaluate the effects of two seizure types (e.g., partial seizures and partial seizures with secondary generalization) and lateralization on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 12 and an illustration of the means can be found in Figure 6. The results of the ANOVA indicated no main effect for seizure type, $F(1, 82) = 3.16$, $p = .08$, partial $\eta^2 = .04$, no main effect for lateralization $F(1, 82) = 2.40$, $p = .64$, partial $\eta^2 = .03$, and no interaction between seizure type and lateralization $F(1, 82) = 7.32$, $p = .84$, partial $\eta^2 = .001$.

Side-Effect Profile

A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and side-effect profile of medication on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 13 and an illustration of the means can be found in Figure 7. The results of the ANOVA indicated a significant main effect for seizure type $F(2, 107) = 4.82$, $p = .01$, partial $\eta^2 = .08$, no main effect for side-effect profile of medication, $F(1, 107) = 0.64$, $p = .43$, partial $\eta^2 = .01$, and no interaction between seizure type and side-effect profile of medication, $F(2, 107) = 2.52$, $p = .09$, partial $\eta^2 = .05$.

Therapy Regimen

A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and therapy regimen on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the therapy regimen factor are presented in Table 14, and an illustration of the means can be found in Figure 8. The results of the ANOVA indicated a significant main effect for seizure type $F(2, 107) = 3.41$, $p = .04$, partial $\eta^2 = .06$, no main effect for therapy regimen, $F(1, 107) = 0.05$, $p = .83$, partial $\eta^2 = .00$, and no interaction between seizure type and therapy regimen, $F(2, 107) = 0.49$, $p = .62$, partial $\eta^2 = .01$.

The primary purpose of the study was to determine which seizure type was associated with the highest level of parent-reported anxiety. Follow-up analyses to the main effect for seizure type for side-effect profile of medication and therapy regimen examined this finding. The follow-up tests consisted of all pairwise comparisons among the three types of seizures. The Dunnet's C procedure was used due to the variances not being completely homogeneous as well as the differences in sample sizes. The results of this analysis indicate that children affected by partial seizures with secondary generalization had the highest levels of parent-reported anxiety, which was significantly higher than those with generalized seizures. However, there was no significant difference between the children with partial seizures with secondary generalization and those with partial seizures or between the children with generalized seizures and those with partial seizures. Overall, the 3 x 2 ANOVA for side-effect profile of medication and therapy regimen

indicated that children affected by partial seizures with secondary generalization have the highest level of parent-reported anxiety.

After taking into account lateralization, side-effect profile of medication, and therapy regimen, the type of seizure that the child experiences still substantiates the results found in Aim II. However, when gender is considered, the group differences found in Aim II only apply to boys, suggesting that gender accounts for some of the variance in the relationship between seizure type and parent-reported anxiety.

Continuous Variables

Continuous variables that were anticipated to correlate with parent-reported anxiety were age, age of onset, the number of AEDs prescribed, median household income, and intelligence. Prior to analyzing data using an ANCOVA, correlation coefficients were computed between these variables and parent-reported anxiety to assess whether the variables were linearly related to anxiety across all levels of the factor, one of the assumptions of an ANCOVA. The results of the correlational analyses are presented in Table 15 and show that age (r = .30, p = .001), age of onset (r = .25, p = .006), and number of AEDs (r = .21, p = .02) were significantly linearly correlated with anxiety. In general, the results suggest that children with later age at the time of evaluation, later age of onset, and those on multiple AEDs have higher levels of parent-reported anxiety. Because these three variables were linearly correlated with parent-reported anxiety, they were each used as covariates in separate ANCOVAs to address the role that seizure type

has on parent-reported anxiety, while holding these covariates constant. Upon scatterplot, neither median household income nor intelligence showed any kind of relationship to parent-reported anxiety (e.g., linear or curvilinear); however, they were addressed in an ANCOVA model to address how much variance in anxiety could be accounted for by seizure type when statistically controlling for each covariate's effect.

Multiple one-way ANCOVAs were conducted to address covariates. The independent variable, seizure type, included three types: partial seizures, generalized seizures, and partial seizures with secondary generalization. The dependent variable was the T-score of parent-reported anxiety on the BASC-2 and the covariates were age, age of seizure onset, and the number of AEDs prescribed.

Age

A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between the age and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 113) = .10$, $MSE = 151.19$, $p = .10$, partial $\eta^2 = .04$. The ANCOVA was significant $F(2, 115) = 3.64$, $MSE = 154.89$, $p = .03$. The strength of the relationship between the seizure type factor and anxiety was moderate, as assessed by the partial η^2, with the seizure type accounting for 6% of the variance of parent-reported anxiety, holding constant the age of the child at evaluation.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with

secondary generalization had the highest adjusted mean (*M* = 59.61), children with partial seizures had a lower adjusted mean (*M* = 53.12), and children with generalized seizures had the lowest adjusted mean (*M* = 50.13). The Holm's sequential Bonferroni procedure was used to control for Type I error across the three pairwise comparisons. There were significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures; however, there were no other pairwise differences amongst the rest of the seizure types.

Age of Onset

A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between the age of onset and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 113) = .69$, $MSE = 156.44$, $p = .50$, partial $\eta^2 = .01$. The ANCOVA was significant $F(2, 115) = 5.13$, $MSE = 155.61$, $p = .006$. The strength of the relationship between the seizure type factor and anxiety was moderate, as assessed by the partial η^2, with the seizure type accounting for 7.2% of the variance of parent-reported anxiety, holding constant the age of seizure onset.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with secondary generalization had the highest adjusted mean (*M* = 60.56), children with partial seizures had a lower adjusted mean (*M* = 53.16), and children with generalized seizures had the lowest adjusted mean (*M* = 49.01). The Holm's sequential Bonferroni procedure was used to control for Type I error across the three pairwise comparisons. There were

significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures as well as between the children with partial seizures with secondary generalization and those with partial seizures; however, there were no differences between children with partial seizures and children with generalized seizures.

Number of AEDs Prescribed

A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between the number of AEDs prescribed and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 113) = 1.73$, $MSE = 161.22$, $p = .18$, partial $\eta^2 = .03$. The ANCOVA was significant $F(2, 115) = 3.65$, $MSE = 163.27$, $p = .03$. The strength of the relationship between the seizure type factor and anxiety was moderate, as assessed by the partial η^2, with the seizure type accounting for 6% of the variance of parent-reported anxiety, holding constant the number of AEDs prescribed.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with secondary generalization had the highest adjusted mean ($M = 60.10$), children with partial seizures had a lower adjusted mean ($M = 52.73$), and children with generalized seizures had the lowest adjusted mean ($M = 50.84$). The Holm's sequential Bonferroni procedure was used to control for Type I error across the three pairwise comparisons. There were significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures as well as between the

children with partial seizures with secondary generalization and the children with partial seizures; however, there were no differences between children with partial seizures and children with generalized seizures.

Median Household Income

Though the assumption of linear correlation between median household income and reported anxiety was not met, an ANCOVA was used to determine the role that seizure type has on parent-reported anxiety when taking variability due to median household income into account. A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between the median household income and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 113) = .83$, $MSE = 167.32$, $p = .44$, partial $\eta^2 = .014$. The ANCOVA was significant $F(2, 115) = 4.74$, $MSE = 166.81$, $p = .01$. The strength of the relationship between the seizure type factor and anxiety was moderate, as assessed by the partial η^2, with the seizure type accounting for 7.6% of the variance of parent-reported anxiety, holding constant the median household income.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with secondary generalization had the highest adjusted mean ($M = 60.77$), children with partial seizures had a lower adjusted mean ($M = 52.78$), and children with generalized seizures had the lowest adjusted mean ($M = 49.96$). The Holm's sequential Bonferroni procedure was used to control for Type I error across the three pairwise comparisons. There were

significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures as well as between the children with partial seizures with secondary generalization and the children with partial seizures; however, there were no differences between children with partial seizures and children with generalized seizures.

Intelligence

Though the assumption of linear correlation between intelligence and reported anxiety was not met, an ANCOVA was used to determine the role that seizure type has on parent-reported anxiety adjusted for the variability due to intelligence. A preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between intelligence and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 104) = .15$, $MSE = 174.21$, $p = .86$, partial $\eta^2 = .003$. The ANCOVA was significant $F(2, 106) = 4.25$, $MSE = 171.40$, $p = .02$. The strength of the relationship between the seizure type factor and anxiety was moderate, as assessed by the partial η^2, with the seizure type accounting for 7.4% of the variance of parent-reported anxiety, holding constant intelligence.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with secondary generalization had the highest adjusted mean ($M = 60.43$), children with partial seizures had a lower adjusted mean ($M = 53.11$), and children with generalized seizures had the lowest adjusted mean ($M = 49.12$). The Holm's sequential Bonferroni procedure

was used to control for Type I error across the three pairwise comparisons. There were significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures; however, there were no other pairwise differences.

All Linearly-Related Continuous Variables Addressed Together

The final analysis was comprised of an ANCOVA using three continuous variables (i.e., age, age of onset, and the number of medications prescribed) that were linearly correlated with anxiety as covariates to address whether differences in parent-reported anxiety among children with different seizure types still exist when taking into account these possible covariates simultaneously.

When including the three correlated covariates in the model, a preliminary analysis evaluating the homogeneity-of-slopes assumption indicated that the relationship between age and parent-reported anxiety differed significantly as a function of seizure type, $F(2, 104) = 4.26$, $MSE = 142.73$, $p = .02$, partial $\eta^2 = .08$. However, the relationship between age of onset and parent reported anxiety did not differ significantly as a function of seizure type, $F(2, 104) = .16$, $MSE = 142.73$, $p = .85$, partial $\eta^2 = .003$ and the relationship between the number of AEDs prescribed and parent-reported anxiety did not differ significantly as a function of seizure type, $F(2, 104) = .65$, $MSE = 142.73$, $p = .53$, partial $\eta^2 = .01$. Although the homogeneity of slopes assumption was violated for the age of onset, it should be noted that when these covariates were addressed separately, all distributions had homogeneous slopes. When addressing multiple ANCOVAs, as in this

statistical model, there is a decrease in error variance, likely contributing to the significance of the interaction between age and seizure type, therefore it is assumed that all slopes are homogeneous. The ANCOVA was significant $F(2, 113) = 3.40$, $MSE = 151.46$, $p = .04$. The strength of the relationship between the seizure type factor and dependent variable was moderate, as assessed by the partial η^2, with the seizure type accounting for 6% of the variance of parent-reported anxiety, holding constant the age, age of onset, and number of AEDs prescribed.

The means of the parent-reported anxiety adjusted for the initial differences were ordered as expected across the three types of seizures. Children with partial seizures with secondary generalization had the highest adjusted mean ($M = 59.52$), children with partial seizures had a lower adjusted mean ($M = 53.09$), and children with generalized seizures had the lowest adjusted mean ($M = 50.29$), which is illustrated in Figure 9. The Holm's sequential Bonferroni procedure was used to control for Type I error across the three pairwise comparisons. There were significant differences in the adjusted means between children with partial seizures with secondary generalization and children with generalized seizures; however, there were no other pairwise differences.

EXPLORATORY FINDINGS

In the current study, multiple variables were collected and addressed in an exploratory manner. Exploratory nominal variables included ethnicity, handedness, etiology, MRI findings, and EEG findings. Variables were addressed similar to those addressed above in

the main statistical analyses of Aim III. Prior to each analyses, initial analyses of normal P-P plots of each of the distributions, skewness statistics, frequency histograms, nonsignifcant Levene's tests for the homogeneity of variance, and independence of parent-reported anxiety across the three types of seizures suggested that all appropriate assumptions were met for factorial ANOVAs, unless otherwise noted. Each computation will be described separately below.

Ethnicity

As stated earlier, the demographics of the sample obtained included 38.7% Caucasian, 22.7% African-American, 37.8% Latino, and .8% Asian. For the purpose of the exploratory analyses involving ethnicity, only Caucasian, African-American, and Latino children were included as .8% of the sample (i.e., one individual) was of Asian descent. Therefore, the total sample size used in analyses of ethnicity was 118. A 3 x 3 factorial ANOVA was conducted to evaluate the effects of the three seizure types and ethnicity on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 16 and an illustration of the means can be found in Figure 10. The results of the ANOVA indicated no main effect for seizure type $F(2, 109) = 2.93$, $p = .06$, partial $\eta^2 = .05$, no main effect for ethnicity, $F(2, 109) = 2.11$, $p = .13$, partial $\eta^2 = .04$, and no interaction between seizure type and ethnicity, $F(4, 109) = .73$, $p = .57$, partial $\eta^2 = .03$.

Handedness

Inspection of the data revealed that no children with generalized seizures were left-handed; therefore, a factorial ANOVA could not be used with children grouped into three different seizure types. Because the current study hoped to address children with partial seizures with secondary generalization, children with partial seizures and generalized seizures solely were grouped together and compared in a factorial ANOVA model to children experiencing secondary generalized seizures. A 2 x 2 factorial ANOVA was conducted to evaluate the effects of the two groups of seizure types (i.e., children with partial or generalized seizures versus those with partial seizures with secondary generalization) and handedness on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 17 and an illustration of the means can be found in Figure 11. The results of the ANOVA indicated a significant main effect for seizure type, $F(1, 111) = 19$, $p < .001$, partial $\eta^2 = .15$, no main effect for handedness $F(1, 111) = 3.09$, $p = .08$, partial $\eta^2 = .03$, and a significant interaction between seizure type and handedness $F(1, 111) = 10.45$, $p = .002$, partial $\eta^2 = .09$.

Because the interaction between seizure type and handedness was significant, method main effects were ignored and method simple main effects were examined, that is, the differences among seizure types for left- and right-handed children separately. To control for Type I error across the two simple main effects, alpha was set at .025. There were no differences for right-handed children, $F(1, 111) = 1.97$, $p = .16$, and significant

differences for left-handed children, $F(1, 111) = 17.18$, $p < .001$. Findings suggested that left-handed children with partial seizures with secondary generalization had higher levels of parent-reported anxiety compared to children with only partial or generalized seizures.

Etiology

Inspection of the data revealed that only one child with generalized seizures had symptomatic etiology, therefore a factorial ANOVA could not be completed using children grouped into three different seizure types due to the lack of variance in the described cell. Initial coding of etiology included idiopathic, symptomatic, and cryptogenic and because symptomatic etiology is theoretically and clinically closer to cryptogenic etiology, the two groups were combined and compared to children with idiopathic etiology. A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and functional etiology on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 18 and an illustration of the means can be found in Figure 12. The results of the ANOVA indicated a significant main effect for seizure type $F(2, 112) = 4.47$, $p = .01$, partial $\eta^2 = .07$, no main effect for etiology, $F(1, 112) = .14$, $p = .71$, partial $\eta^2 = .001$, and no interaction between seizure type and etiology, $F(2, 112) = .44$, $p = .64$, partial $\eta^2 = .01$.

MRI Findings

A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and MRI findings on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 19 with an illustration of the means found in Figure 13. The results of the ANOVA indicated a significant main effect for seizure type $F(2, 107) = 3.63$, $p = .03$, partial $\eta^2 = .06$, no main effect for MRI findings, $F(1, 107) = .04$, $p = .83$, partial $\eta^2 = .000$, and no interaction between seizure type and MRI findings, $F(2, 107) = 1.33$, $p = .27$, partial $\eta^2 = .02$.

The primary purpose of the study was to determine children with which seizure type exhibit the highest level of parent-reported anxiety. Follow-up analyses to the main effect for seizure type for etiology and MRI findings examined this finding. The follow-up tests consisted of all pairwise comparisons among the three types of seizures. The Dunnet's C procedure was used due to the variances not being completely homogeneous as well as the differences in sample sizes. The results of this analysis indicated that children affected by partial seizures with secondary generalization had the highest levels of parent-reported anxiety, which was significantly higher than those with generalized seizures. However, there was no significant difference between the children with partial seizures with secondary generalization and those with partial seizures or between children with generalized seizures and those with partial seizures. Overall, the 3 x 2

ANOVAs for etiology and MRI findings indicated that children affected by partial seizures with secondary generalization have the highest level of parent-reported anxiety.

EEG Findings

Upon preliminary review of the frequency histograms, normal P-P plots, and skewness statistics data for EEG findings, it was found that the distribution of anxiety scores for children with abnormal EEGs was normally distributed; however, the distribution of anxiety scores for children with normal EEGs was mildly positively skewed. One score was significantly higher than the average in the distribution, which violated one of the assumptions of a factorial ANOVA; however, it was a clinically valid score. Therefore, the distribution of anxiety T-scores was transformed using a Log10 command to ensure normality. Upon transformation, the scores for normal and abnormal EEG findings were normally distributed and the results below describe findings with a Log10 transformed anxiety score.

A 3 x 2 factorial ANOVA was conducted to evaluate the effects of the three seizure types and EEG findings on the level of parent-reported anxiety. The means and standard deviations for parent-reported anxiety as a function of the two factors are presented in Table 20 and an illustration of the means can be found in Figure 14. The results of the ANOVA indicated no main effect for seizure type $F(2, 112) = 2.65$, $p = .08$, partial $\eta^2 = .05$, no main effect for EEG findings, $F(1, 112) = .09$, $p = .77$, partial $\eta^2 = .001$, and no

interaction between seizure type and EEG findings, $F(2, 112) = .57$, $p = .57$, partial $\eta^2 = .01$.

After taking into account etiology and MRI findings, the type of seizure that the child experiences still substantiates the results found in Aim II. However, when handedness is taken into account, the group differences found in Aim II only apply to children who are left-handed, suggesting that handedness accounts for some of the variance in the relationship between seizure type and parent-reported anxiety. Finally, when ethnicity or EEG findings are taken into account, the results found in Aim II are no longer substantiated. However, these results should be interpreted cautiously as EEG findings were found using a Log10-transformed parent-reported anxiety T-score.

CHAPTER FIVE

Conclusions and Recommendations

This study sought to address the level of parent-reported internalizing symptoms in children, with a specific emphasis on anxiety in children affected by partial seizures with secondary generalization. The primary goal of this study was to expand on previous literature by addressing children with secondary generalized seizures as separate from those with partial and generalized seizures. General results reveal that children affected by partial seizures with secondary generalization have higher levels of parent-reported anxiety compared to children with generalized seizures, regardless of a variety of demographic, medically-related, and medication-related variables.

DESCRIPTION OF RESULTS

Aim I Findings

The hypothesis related to Aim I proposed that children with epilepsy have higher levels of parent-reported anxiety and depression compared to the normative population. Results of analyses relevant to Aim I suggested that children with epilepsy have statistically higher T-scores on parent-reported anxiety and depression compared to the means of the normative population, regardless of seizure type. The finding also suggested that, on average, parent-reported depression is higher than parent-reported anxiety. Neither mean

scores for anxiety nor depression were in the clinical range; rather, the BASC-2 labels these scores as within normal limits.

Aim II Findings

The hypothesis related to Aim II stated that, compared to children with generalized or partial seizures, children with partial seizures with secondary generalization would evidence similar levels of depression, but significantly higher levels of parent-reported anxiety. Results of analyses relevant to Aim II supported the notion that children with three different types of seizures (i.e., partial seizures, generalized seizures, and partial seizures with secondary generalization) had similar levels of depression, but different levels of anxiety. Specifically, children experiencing partial seizures with secondary generalization had higher levels of parent-reported anxiety compared to children with generalized seizures. The level of parent-reported anxiety was similar among children with secondary generalized seizures and children with partial seizures. Finally, the level of parent-reported anxiety was similar among children with partial seizures and children with generalized seizures. The level of parent-reported anxiety in children with secondary generalized seizures fell in the "At-Risk" range on the BASC-2, a range that denotes a level bordering on clinical significance, suggesting that this may be a qualitatively important finding for this group of children to monitor from an evaluation and treatment perspective.

Aim III Findings

The purpose of Aim III was to expand upon findings from Aim II that suggested that children with secondary generalized seizures have higher levels of parent-reported anxiety versus those with generalized seizures. The hypothesis related to Aim III suggested that compared to children with generalized or partial seizures, and when taking other variables into account, children who experience secondary generalized seizures would continue to evidence higher levels of parent-reported anxiety. A variety of demographic, medically-related, and medication-related variables thought to potentially have interacting effects with seizure type and covarying effects with parent-reported anxiety were addressed to determine whether seizure type was still associated with variable levels of anxiety when taking these other variables into account.

Regarding medication-related variables, it was found that the three seizure types were associated with different levels of parent-reported anxiety, even when accounting for the side-effect profile of medication, as well as the medication regimen (i.e., monotherapy versus polytherapy). Both findings suggested a similar pattern as found in Aim II in which children with secondary generalized seizures had a higher level of parent-reported anxiety compared to children with generalized seizures.

Gender interacted with seizure type, suggesting that boys with secondary generalized seizures have statistically significant higher levels of anxiety compared to boys with generalized seizures; however, there were no significant differences among seizure types

for girls. Despite that finding, among girls and boys combined, those with secondary generalized seizures had the highest parent rating of anxiety among the three seizure types.

There were no significant interaction effects between seizure type (i.e., partial seizures and partial seizures with secondary generalization) and lateralization of seizure onset, suggesting that children with partial seizures and children with secondary generalized seizures have similar levels of anxiety regardless of lateralization.

Variables that were correlated with parent-reported anxiety included age, age of onset, and the number of AEDs prescribed, while intelligence estimates and median household income did not correlate with anxiety. Each correlated variable was addressed separately, as well as together in one model to see if the finding that children with secondary generalized seizures had a higher level of parent-reported anxiety remained after taking the other correlated variables into account. When age was addressed separately, children with secondary generalized seizures had higher levels of anxiety compared to those with generalized seizures, regardless of the age. Furthermore, when taking the age of onset into account, children with partial seizures with secondary generalization had higher levels of parent-reported anxiety compared to those with generalized seizures as well as those with partial seizures. Similar results were found when taking the number of AEDs prescribed into account.

When entering age, age of onset, and number of AEDs prescribed into one statistical model, results were similar to those found in Aim II, suggesting that children with partial seizures with secondary generalization have higher levels of anxiety compared to those with generalized seizures regardless of these variables.

Exploratory Findings

Exploratory aims were meant to address variables that are not as strongly backed in research as having an impact on anxiety. These variables included ethnicity, etiology, handedness, EEG findings, and MRI findings.

Results related to etiology (i.e., symptomatic/ cryptogenic or idiopathic) and MRI (i.e., normal or abnormal) suggested no interaction effect with seizure types and these variables. These results were similar to those found in Aim II analyses, suggesting that children with partial seizures with secondary generalization have higher levels of parent-reported anxiety compared to children with generalized seizures after taking into account the possible interacting effects of etiology and MRI findings.

Handedness was also addressed as having possible interacting effects with seizure type. After combining children with partial seizures and generalized seizures, findings suggested an interaction effect between handedness and the two seizures types (i.e., secondary generalized and non-secondary generalized). Specifically, it suggested that only left-handed children affected by partial seizures with secondary generalization had

higher levels of parent-reported anxiety compared to those with either generalized or partial seizures.

The findings suggested that when taking the EEG results (i.e., normal or abnormal) into account, the aforementioned relationship of children with secondary generalized seizures having higher levels of parent-reported anxiety was not supported. Furthermore, similar results were found when taking ethnicity into account, as the different seizure types were no longer associated with different levels of parent-reported anxiety. However, the finding for ethnicity may be a product of methodological issues as there seemed to be a trend toward significance for seizure type main effects, which should be followed up on in future research.

Overall, the findings of the current study, with few exceptions, suggest that children with partial seizures with secondary generalization have higher levels of parent-reported anxiety compared to children with generalized seizures. However, gender, handedness, EEG findings, and ethnicity appear to influence this relationship.

IMPLICATIONS OF THE STUDY

The level of symptoms that parents reported in the current study indicates that the average parent-reported anxiety and depression scores in children with epilepsy are above the average score for the normative population. Although depression has been the most commonly studied psychiatric comorbidity in individuals with epilepsy, the research

regarding epilepsy and anxiety has expanded in the recent past, including the development of a flowchart as a clinical guide for the assessment of anxiety in individuals with epilepsy (Beyenburg et al., 2005). The current study's finding of higher levels of depression and anxiety in children with epilepsy is supported by previous research (Adewuya & Ola, 2004; Austin & Caplan, 2007; Beyenburg & Schmidt, 2005; Caplan et al., 2005; Oguz, Kurul, & Dirik, 2002; Ott et al., 2003; Pellock, 2004; Rodenburg et al., 2005; Rutter et al., 1970; Weiland, Pless, & Roghmann, 1992). As stated, the research supporting this finding dates back to the *Isle of Wight Study* and indicates that children with epilepsy are at an increased risk for experiencing a wide range of psychiatric symptoms compared to normal controls and even children with other chronic illnesses with no central nervous system involvement.

Expanding upon the previous research that has addressed psychiatric symptoms in children with different types of seizures, results of the present study indicated that children with partial seizures or generalized seizures have similar levels of anxiety and depression, which counters previous research suggesting children with partial seizures have higher levels of psychiatric symptoms compared to children with generalized seizures (Berg et al., 2004; Caplan et al., 2006; Piazzini et al., 2001; Piazzini & Canger, 2001; Shukla et al., 1979). The current study also found higher levels of anxiety in children with secondary generalized seizures, compared to children with generalized seizures, which almost no research has included as a unique subtype of seizure. Though a few studies that included secondary generalized seizures as a separate subtype found no differences in psychiatric symptoms, these participants were limited to children with

temporal lobe epilepsy (de Araujo Filho et al., 2008), and the methods and instruments used did not allow for conclusive statements about anxiety and depression separately (Suli Moci, 2007). To date, the current study is the first one in which children with secondary generalized seizures were addressed separately from children with partial or generalized seizures.

The current finding that there are similar levels of depression among children with partial seizures, generalized seizures, or partial seizures with secondary generalization is not congruent with previous research which has tended to find a higher level of depression among children with partial seizures (Berg, Smith, & Frobish, 2004). Separating out children with secondary generalized seizures may have factored into the finding of no difference in parent-reported depression among children with different types of seizures. In other words, the finding may be related to the inherent difference in grouping the children into three distinct groups rather than two (i.e., children with partial seizures or generalized seizures), which seems to have been the most standard way of addressing differences in psychiatric symptoms among children with different types of seizures in previous research. However, two statistical analyses using Independent Sample *t* tests comparing children with partial or generalized seizures (i.e., children with secondary generalized seizures were first grouped with those who had partial seizures and subsequent analyses grouped them with those who had generalized seizures), suggested that there were still no differences between the two subtypes. Therefore, the current study's finding of similar levels of depression among the three seizure types is unique within the current body of literature. Furthermore, in the context of the current study, this

finding may be explained from a psychosocial perspective by a perceived loss of control among all children with any type of recurrent seizure (Goldstein & Harden, 2000); this may impact their ability to feel as if they have any type of efficacy in managing their health condition. As reviewed, children who experience a loss of control are at risk for developing depressive symptomatology (Goldstein & Harden, 2000). This psychological explanation and common thread among children with three different types of seizures counters previous research that takes a lone biological point of view, suggesting that it is typically the involvement of the limbic system in children with partial seizures that explains the psychiatric comorbidity.

To expand upon the findings that children with secondary generalized seizures have more parent-reported anxiety compared to children with generalized seizures, a variety of possible contributing and interacting factors were taken into account. The current study found a positive linear relationship between age and levels of anxiety, suggesting that older children have higher levels of anxiety. Age at evaluation has not been extensively studied in previous pediatric epilepsy studies, which the current study addressed. This finding could be explained by the general finding that certain anxiety disorders develop in early adolescence compared to early childhood (APA, 2000). Furthermore, younger children may exhibit anxiety through a variety of somatic complaints which may not be as readily identifiable as other expressions of anxiety, as reviewed (Ginsberg, Riddle, & Davies, 2006). Finally, it may be possible that the parents of younger children construed anxiety symptoms as “developmentally-appropriate” and underreported the symptoms on the BASC-2. Though this may represent a relative risk of experiencing psychiatric

symptoms in older children, it may also be that anxiety and depressive symptomatology are more difficult to identify in younger children (i.e., children with difficulty expressing things verbally).

Those with a later age of onset were at higher risk for experiencing anxiety, regardless of seizure type. The current study's findings on age of onset countered previous research, which suggested that children with an earlier age of onset have higher levels of anxiety (Mensah et al., 2007). This finding may have occurred in that children with a later age of onset of seizures may have been accustomed to life without seizures. Perhaps the later age of onset of seizures fosters anxiety, as this may be a stark contrast in their daily life compared to children who had been living with seizures since they were very young.

Additionally, just as most studies have suggested a positive relationship between the number of AEDs prescribed and level of psychiatric symptoms, this study also found a relationship between the number of AEDs prescribed and anxiety (Dodrill, 1992). As previously reviewed, the finding that there is a positive relationship between the number of AEDs prescribed and the level of psychiatric symptoms may be due to a variety of reasons. For instance, the findings could be due to a higher number of AEDs being a proxy for seizure intractability. For example, children with more recurrent or debilitating seizures may be prescribed a higher number of AEDs; thus, it may be seizure frequency that is truly driving anxiety. On the other hand, it could also be related to a higher number of psychiatric side effects with multiple AEDs. Lastly, it may be possible that parents who have children that are prescribed multiple medications may perceive their child as

more anxious simply because the parents are anxious themselves. Though in the context of the current study it is difficult to identify the mechanism that accounts for the positive relationship between the number of AEDs prescribed and level of parent-reported anxiety, it nevertheless illustrates that children prescribed more AEDs are at a higher risk of experiencing psychiatric symptoms.

Additional concurrent analysis involving age, age of onset, and the number of AEDs together suggested that even when taking these variables into account, children with secondary generalized seizures still evidenced a higher level of parent-reported anxiety compared to children with generalized seizures. Perhaps children with secondary generalized seizures have a unique seizure-related experience that contributes to this relative risk, which explains higher levels of anxiety beyond the identified demographic, medically-related, and medication-related variables that correlate with anxiety.

In addition to age, age of onset, and the number of AEDs prescribed, the current research also addressed gender, lateralization of seizure onset, AED side-effect profile, and therapy regimen to determine if those variables had unique effects on anxiety or if they interacted with seizure type to affect anxiety. There were no differences in parent-reported anxiety between the genders, as boys were rated as exhibiting the same level of anxiety symptoms as girls. This finding replicated studies using similar methodology in which gender was not associated with different levels of anxiety symptoms (Ettinger et al., 1998, Williams et al., 2003). It is likely that the general increased risk of anxiety in children with epilepsy, regardless of gender, could override the findings routinely found

in the general population. Despite this finding, when gender was taken into account with seizure types, there was an interaction suggesting that boys with secondary generalized seizures had higher levels of anxiety compared to boys with generalized seizures. This was not the case with girls as there were no significant differences among the three seizure types. Because the current research was the first to focus exclusively on secondary generalized seizures as a unique subtype, there is limited research addressing gender and seizure type together in one statistical model. Notably, the current results suggest that parents of boys with secondary generalized seizures reported, on average, a level of anxiety above the mean of the normative population (M=60.46), thereby contributing to the significant difference in parent-reported anxiety among boys with secondary generalized seizures versus generalized seizures. This finding was not anticipated and future research should focus on addressing what may be the underlying cause for the interaction.

Regarding lateralization, the current study found no differences in parent-reported anxiety among children with seizures (e.g., partial and secondary generalized seizures) emanating from the left or right hemisphere. This finding is inconsistent with previous research, which suggests that individuals with left-hemisphere dysfunction have higher levels of psychiatric symptoms in general (Rutter et al., 1970). However, it is important to note that previous research focused mainly on psychiatric symptoms in general, such as externalizing behaviors, and did not have an exclusive focus on anxiety like the current study. Again, minimal studies address anxiety symptoms in children with epilepsy compared to depressive symptoms and in the few studies that do, lateralization has not

been a variable addressed. Furthermore, the findings suggest that when taking lateralization into account, children with partial seizures or secondary generalized seizures have similar levels of anxiety. This finding was congruent with results from Aim II and may be explained by a similar underlying biological diathesis of partial seizures in general. Specifically, because children with partial seizures have similar levels of parent-reported anxiety compared to children with secondary generalized seizures, these two seizure types may share similar pathophysiology compared to those with generalized seizures. Though the finding of no difference in parent-reported anxiety among children with either left- or right-sided seizure emanation was not anticipated, it is important to keep in mind that the previous findings that have supported the relative risk of psychiatric symptoms in those with left-sided pathology are based on research with adult subjects (Altshuler, Devinsky, Post, & Theodore, 1990; Mendez, Cummings, & Benson, 1986; Mendez et al., 1993; Piazzini et al., 2001; Piazzini & Canger, 2001; Robertson, 1998; Robertson, Trimble, & Townsend, 1987; Septien et al., 1993). In the current study, the findings regarding lateralization and anxiety may be related to the relative neuronal plasticity of the sample of children compared to the previous literature's reliance on adults with presumably less neuronal plasticity.

Medication effects were addressed in the current study in terms of side-effect profile and therapy regimen (i.e., monotherapy compared to polytherapy). Findings suggested that the side-effect profile and therapy regimen were not associated with different levels of anxiety, unlike previous research that indicated that children on polytherapy regimens have higher levels of anxiety (Adewuya & Ola, 2005; Freilinger et al., 2006; Oguz,

Kurul, & Dirik, 2002; Williams et al., 2003). Much like other results in the current study that are not congruent with previous research, the findings related to medication effects were not anticipated. However, regarding side-effect profile and therapy regimen, the findings of a higher level of anxiety among the whole group of children with epileptic seizures may be explained by variables unrelated to medication effects. However, as reviewed, a positive relationship between anxiety symptoms and number of AEDs prescribed was found and perhaps the dichotomy between monotherapy and polytherapy was too broad of a construct or classification in the current study. In other words, the effects of three or four AEDs may contribute to anxiety symptoms incrementally more compared to those with merely two AEDs. The grouping of children into one group including all AEDs prescribed other than monotherapeutic regimens may not have been sensitive to this finding. When taking these medication-related variables into account alongside seizure type, the results still suggested that children with secondary generalized seizures had higher levels of parent-reported anxiety compared to those with generalized seizures. Again, previous research has not consistently grouped children with secondary generalized seizures as a separate subtype; therefore, it is difficult to make conclusive statements about whether this finding supports or refutes previous research. This finding suggests that even when taking medication-related variables into account, children with secondary generalized seizures have a relatively higher risk of experiencing anxiety symptoms compared to those with generalized seizures. The finding also may be indicative of psychological, rather than biological, reasons for higher levels of anxiety.

The exploratory variables of ethnicity, etiology, handedness, EEG, and MRI findings have not been as extensively studied as other demographic and medically-related variables. Results of the present study suggested that for each of these variables, the three seizure groups were not different from one another (e.g., within each respective variable) in parent-reported anxiety. The current study's finding of no differences among ethnic groups differs from previous research suggesting Caucasian children are more likely to experience parent-reported anxiety symptoms compared to African-American and Latino children (Williams et al., 2003). However, when addressing ethnicity and seizure type together, the finding that children with secondary generalized seizures have higher levels of parent-reported anxiety compared to children with partial seizures no longer exists. This finding may illustrate that though anxiety is not statistically significantly different among different ethnicity groups, ethnicity may account for some variability in the relationship among seizure type and parent-reported anxiety.

The current study's findings on etiology are also different from previous research, which found that individuals with symptomatic etiology are at higher risk for experiencing psychiatric symptoms (Freilinger, 2006). The current study's findings may be attributed to the combining of children with symptomatic etiology and children with cryptogenic etiology, which was necessary given the assumptions for statistical analyses (i.e., only one child with generalized seizures had symptomatic etiology, which prompted the combining of children with symptomatic and cryptogenic etiology). In spite of this finding, after taking etiology into account when assessing the relationship between seizure type and parent-reported anxiety, children with secondary generalized seizures

still evidence higher levels of anxiety compared to children with generalized seizures. Again, this was an exploratory finding as the few studies that address etiology as a factor in understanding psychiatric symptoms address the symptoms as a whole rather than specifically, as anxiety was addressed in the current study.

Handedness has been studied the least as it relates to psychiatric symptoms in the epilepsy population; therefore, the finding of no differences in parent-reported anxiety among children with epilepsy who are left- and right-handed is preliminary. Furthermore, no studies exist that specifically address handedness as a possible interacting factor with seizure type; therefore, the interactive relationship that suggests only left-handed children with secondary generalized seizures have higher levels of anxiety compared to children with generalized seizures is unique among the current corpus of literature and should be addressed in future research. A speculative explanation of the findings on handedness may be related to left-handedness syndrome, which may represent an underlying damage to the left hemisphere, a clearly biological explanation. However, the current study did not use prospective means to obtain the familial patterns of left-handedness and combined children with partial seizures and generalized seizures for the purpose of statistical analysis.

Finally, neither EEG nor MRI (i.e., normal and abnormal findings) were associated with different levels of anxiety, which adds to the body of literature as these variables have not been extensively studied in previous research. Perhaps the general construct of EEG and MRI findings in the current study (i.e., normal and abnormal findings) was too general of

a dichotomy that is not sensitive to differences in parent-reported anxiety. Findings also suggested that after accounting for EEG findings, the relationship between seizure type and parent-reported anxiety found in Aim II analyses (i.e., children with secondary generalized seizures have significantly higher parent-reported anxiety than children with generalized seizures) no longer exists. This suggested that some variance in parent-reported anxiety can be attributed to EEG findings, although not to the extent that there are statistically significant differences between EEG normality and abnormality. Additionally, as stated, these results should be interpreted with caution as the parent-reported anxiety in EEG analyses was transformed using a Log10 command to ensure normality of the distribution.

The findings from the current study are unique as they expand upon previous research that has not specified children with partial seizures with secondary generalization as a separate subgroup. This finding that children with secondary generalized seizures have a higher level of parent-reported anxiety compared to children with generalized seizures was supported with multiple statistical analyses that took into account possible influences like age and AEDs with the finding still remaining. Though the current study clearly illustrates the relative risk of experiencing anxiety in children with secondary generalized seizures, a theoretical understanding of the mechanism of why this may be occurring has not been elucidated and is more speculative in nature. In previous literature, a few hypotheses have been made to explain the comorbidity between seizures and psychiatric symptoms, including biological and psychosocial explanations, which will be expanded upon.

Possible Explanations for the Comorbidity of Psychiatric Symptoms and Epilepsy

Most researchers offer biological or psychosocial explanations for psychiatric comorbidity within children with epilepsy. Though biological explanations of the comorbidity have been offered, the prevailing research that exists suggests that these variables are limited in explaining all of the variance in symptoms. Psychosocial variables have also been offered to explain the presence of psychiatric symptoms in children with epilepsy, and better explain both the development of and maintenance of symptoms. Nevertheless, the relationship between psychiatric symptoms and epilepsy may be related to a multitude of biopsychosocial factors. Especially pertinent to the current study's finding of increased parent-reported anxiety in children with secondary generalized seizures, a variety of theories may used to explain the higher levels.

Biological Factors

The mere presence of neurological dysfunction in epilepsy has been suggested as causing higher levels of anxiety and depressive symptoms (Rodenburg, Stams, Meijer, Dekovic, & Aldenkamp, 2005). As reviewed previously, researchers have consistently found that children with epilepsy have higher rates of psychiatric comorbidity when compared to children with other chronic medical conditions that do not involve the central nervous system, such as diabetes mellitus type I and asthma (Austin, Smith, Risinger, & McNelis,

1994; Blum et al., 2002; Schiffer & Babigian, 1984; Torta & Keller, 1999; Weiland, Pless, & Roghmann, 1992).

The current study's finding that children with secondary generalized seizures experience higher levels of parent-reported anxiety compared to children with generalized seizures may be related to underlying neurological diathesis that is associated with partial seizures (i.e., partial seizures and secondary generalized seizures were not significantly different). On the other hand, it should be noted that children with secondary generalized seizures approached the clinical range (i.e., "At-Risk") on the BASC-2, unlike children with partial seizures solely. Neurochemical explanations may not entirely explain the current study's findings either, as children with secondary generalized seizures still had the highest level of psychiatric symptoms, even when factoring in the number of AEDs prescribed, side-effect profile of medication, and therapy regimen. Therefore, it may be pertinent to address a few psychosocial explanations of the current study's findings.

Psychosocial Factors

Anxiety and depressive symptoms in epilepsy may occur due to a variety of psychosocial reasons, as well. From a psychosocial perspective, individuals with epilepsy are faced with a loss of control and stigma of the diagnosis. For children with epilepsy, successfully managing the reactions and misconceptions of others as well as understanding their own self-efficacy may increase quality of life and possibly combat depressive and anxious symptoms.

Locus of control describes what a person believes causes the good and bad events in his or her life to happen (Rotter, 1966), and has been used to describe the belief an individual has about his or her ability to manage their illness. This concept is highly related to attributional style in which people determine if successes or failures are due to internal or external events. Often, a loss of control over one's life events may lead to depressive symptomatology (Goldstein & Harden, 2000). The unpredictability in some types of seizures (e.g., sudden unexpected seizures without auras) and perceived loss of control may explain the level of depression found in the current study. It has been suggested that the unpredictable nature and recurrent pattern of seizures focuses the individual on the amount of control, or lack of control, he or she possess in a situation (Hermann, 1979).

It is plausible that the finding in the current study of similar levels of depression among children with three types of seizures may be related to the similarities in the external locus of control and/ or loss of control that children with epilepsy seem to have. The source of the difference in levels of parent-reported anxiety may be that children with secondary generalized seizures have a cue to alert them that a generalized seizure is imminent (i.e., anxiogenic), yet they still have no ability to control the generalized seizure that follows (i.e., depressogenic).

Children with seizures also may experience anxiety and depressive symptoms because of the shame of having a stigmatized condition as well as the fear of becoming a victim of discrimination (Lambert & Robertson, 1999). Kale (1997) states, “The history of epilepsy, can be summarized as 4,000 years of ignorance, superstition and stigma,

followed by 100 years of knowledge, superstition and stigma" (p. 2). Children with epilepsy that have negative views of their condition often develop those views from the early perceptions of their parents. Children may construe their condition as something to worry about if a parent's self-reported anxiety about their child's epilepsy is high (Williams et al., 2003).

Stigma may occur in peer groups and also be evident in parental perceptions of seizures. Compared to other chronic medical conditions such as diabetes or asthma, more people hold negative associations with epilepsy, with up to one-fifth of teenagers attributing the cause of epilepsy to a mental handicap (Wirrell, Cheung, & Spier, 2006). Most studies suggest that children and teens have less knowledge of epilepsy versus other disorders, view individuals with epilepsy as less socially adept, and befriend individuals with epilepsy at a significantly lesser rate than those with other chronic health problems due to the fear of "catching" epilepsy and burdens of excessive responsibility (Cheung & Wirrell, 2005; Wirrell, Cheung, & Spier, 2006). The difficulty with peer relations may lie in the finding that compared to children with asthma or diabetes, children with epilepsy typically have less knowledge of their medical condition (e.g., psychological effects, medications, etiology, and restriction of lifestyle) (Houston, Cunningham, Metcalfe, & Newton, 2000). The child's relative lack of knowledge of their condition has been proposed to contribute to the child feeling stigmatized and their reluctance to tell their friends about their diagnosis.

In previous research, psychosocial factors, medically- and epilepsy-related variables, and medication-related effects all seem to contribute to anxiety and depressive symptoms experienced by those with epilepsy. However the continued finding of individuals with epilepsy having higher levels of psychiatric symptoms compared to those with other chronic medical conditions without neurological impairment lends support to the underlying biological impact. Nevertheless, it is an incomplete theory of explaining psychiatric symptoms as variance exists in psychiatric symptoms of children with epilepsy that have the same biological or neurological abnormalities. It is also possible that the pattern found could occur due to the underlying biology of anxiety in partial seizures as well as the proposed cueing mechanism that may occur with secondary generalized seizures. This notion could explain the lack of significant differences in parent-reported anxiety among the children with secondary generalized seizures versus those with partial seizures.

Although it may be difficult to say whether the findings of higher levels of parent-reported anxiety in children with partial seizures with secondary generalization found in the current study reflect an underlying biological substrate or a psychosocial reaction to the unique aspects of seizure emanation, the consistent finding of this higher level of parent-reported anxiety, despite taking into account a variety of other variables, suggests that this may be a topic worthy of future research.

CLINICAL IMPLICATIONS

There are a variety of clinical implications that could be derived from the current study. Special emphasis should be placed on medical teams evaluating for the relatively higher risk of anxiety symptoms in children who experience partial seizures with secondary generalization. Furthermore, treatment teams should take note of the risk and integrate it into the treatment of children with secondary generalized seizures as well as strive to prevent such symptoms from developing.

Evaluation and the Need for Mental Health

The findings from this study are similar to previous studies that illustrate children with epilepsy are at an increased risk of experiencing psychiatric symptoms. However, very few children in this sample were formally diagnosed with a mood or anxiety disorder, as illustrated in Table 21. Specifically, in the whole sample of children, only 5% were diagnosed with a depressive disorder and 4.2% were diagnosed with an anxiety disorder. This low percentage is likely due to the primary goal of neuropsychological evaluations relating to the documentation of neurocognitive functioning with less emphasis on investigating psychiatric functioning. Though this finding has been documented in previous research, referral patterns to mental health practitioners typically do not correlate with higher levels of psychiatric symptoms (Ettinger, Reed, & Cramer, 2004; Weiland, Pless, & Roghmann, 1992). Needs go unmet and quite often, there may be a

tendency to attribute psychiatric comorbidity to seizure-related variables such as drug side effects despite past literature suggesting that this may not be the case.

Especially pertinent to this study, children with secondary generalized seizures seem to be at an increased risk of experiencing anxiety symptoms and children with epilepsy as a whole are at risk for experiencing depressive symptoms. This finding provides a rationale for the recommendation that providers should routinely screen for psychiatric symptoms due to the high comorbidity rates between these symptoms and epilepsy, especially with regard to anxiety in children with secondary generalized seizures. Routine assessment is especially important to address during formative years as there are a wide variety of negative implications of untreated psychiatric symptoms, as reviewed. Additionally, the need for interdisciplinary approaches among pediatric neurology services within hospital settings would be highly beneficial to allow mental health professionals the opportunity to educate the family on appropriate ways to acknowledge the medical condition. Mental health professionals can be instrumental in taking the time to address the concerns of the child, which is often difficult for physicians to do given the medical needs they need to address in a limited amount of time.

The primary aim of the current study was not to address referral patterns, but to discern patterns of anxiety in children with secondary generalized seizures. The findings can be used to extend the current efforts to screen for psychiatric symptoms in children with epilepsy, especially in children with secondary generalized seizures. Results from the current study should result in clinicians anticipating ways to better screen for psychiatric

symptoms and increase appropriate referrals to licensed mental health providers. The current study found that children with partial seizures and generalized seizures may have parent-reported anxiety within normal limits. Clinicians may not expect anxiety to be high in children with secondary generalized seizures because of that finding; however, this is not the case.

Treatment of Anxiety and Depression

As reviewed, epilepsy often has a chronic course with a variety of biological, psychological, and social effects. Because of the wide range of difficulties that children with epilepsy may encounter, a biopsychosocial framework for treatment should be used in which seizures are reduced (i.e., biological), coping resources are bolstered (i.e., psychological), and social support is encouraged (e.g., social). Though the current study focused on identifying the level of anxiety symptoms in children with epilepsy, especially regarding those with secondary generalized seizures, findings could be extrapolated to treating these symptoms. Furthermore, if there is a true learning mechanism that contributes to the symptoms, treatment can be focused on alleviating the symptoms associated with the cueing involved in children who experience secondary generalized seizures.

Future research should focus on developing appropriate plans of treatment to address the higher rate of anxiety symptoms in children with secondary generalized seizures as found in the current study. If there is a true learning mechanism that contributes to anxiety in

children with secondary generalized seizures, treatment should be focused on teaching children new ways of coping with the occurrence of an impending tonic-clonic seizure. For example, with vagal nerve stimulation (VNS), a special magnet can activate the stimulator when held nearby, thereby decreasing the likelihood of a seizure. This may be beneficial for those who have auras, and is especially relevant to children with secondary generalized seizures. The use of this treatment modality may allow children to feel as if they have more self-efficacy in reducing the likelihood of secondary generalized seizures, which may thereby reduce depressive symptoms. Additionally, because the association between partial seizures and secondary generalized seizures may decrease with repeated intervention involving VNS, anxiety levels may drop. Finally, VNS has been shown to have a psychotropic effect as well, occasionally used in the treatment of depression (Marangell et al., 2002).

There are a variety of treatments to which anxiety is amenable including anxiolytic medication, psychotherapy, and behavioral medicine. Behavioral medicine encompasses a wide variety of interventions aimed at decreasing stressful reactions to physical health conditions. These types of treatments may include biofeedback training, CBT, and relaxation training. Previous research has shown that children with various types of epilepsy can benefit from these treatment modalities, though more sophisticated research is needed in the future (Wagner & Smith, 2006). The mechanism of action that may be at work with these types of modalities may be in helping individuals gain a sense of control over their bodily function. Regarding the treatment of anxiety in children with secondary generalized seizures from a cognitive-behavioral perspective, it may also be helpful for

individuals to practice mental techniques to decrease anxiety-provoking thoughts that accompany the possible learning paradigm. Furthermore, these types of interventions can also help with increasing a person's self-efficacy and control and may in turn combat depressive symptoms.

Psychoeducational programs can inform children of their condition, and systematic efforts to educate children and parents about the nuances of epilepsy may be helpful in curbing anxiety revolving around being uninformed or misinformed. Families should be encouraged to learn appropriate reactions to seizures and ways of promoting their child's self-efficacy as well. Because a large majority of time for children with epilepsy is spent in school, interventions should be aimed at appropriately managing others' expectations and misconceptions of the illness. For example, mental health professionals can help children with epilepsy develop a script explaining their condition to peers who do not have as sophisticated an understanding of seizures and epilepsy as they do. This may help decrease the stigma associated with epilepsy as well as increase the child's self-efficacy and self-esteem in taking active efforts to educate others. Not all psychosocial treatments need to be addressed on an individual basis. Many children with pediatric chronic health conditions obtain benefit from participation in support groups alongside children with similar conditions, and children with epilepsy are no exception. Self-help groups have been shown to decrease the stigma of the disorder and help participants make sense of societal reactions to their condition (Droge, Arntson, & Norton, 1986).

If depression and anxiety symptoms are very debilitating to an individual, pharmacological and psychosocial interventions can be prescribed together. Numerous studies have shown the efficacy of using both antidepressants and CBT as treatment for children with major depressive disorder (March et al., 2004) and preventing relapse (Kennard et al., 2008); therefore, it may be beneficial to take this type of approach with children who have epilepsy. Despite the promising treatment implications of concurrent pharmacology and behavioral medicine with children who have epilepsy, research on this approach is not extensive.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

Although the findings of this study are unique when compared to the current body of literature, there are some methodological limitations that need to be addressed, such as the use of a parent-report measure, retrospective design, sample characteristics, and difficulty in addressing current psychiatric symptomatology.

The current study used a parent-report measure of their child's emotional functioning to derive the main dependent measures. A clear disadvantage to this method of assessing for psychiatric symptoms is the inability to diagnose a clinical anxiety or mood disorder. Additionally, this measure may underestimate psychiatric symptoms, as Ettinger et al. (1998) found by self-report that over 15% of children with epilepsy had significant levels of anxiety despite previous caregiver notions that they were not anxious. However, much

like the tertiary care sample used in the current study, previous studies have used similar ways of assessing for psychiatric symptoms.

The current study also used a retrospective chart review as a main source of data. Because of the retrospective nature of the study, there were some subjects in the pooled sample that did not have the full amount of data available. Data were collected from children seen on an outpatient basis or during stays at the EMU and it is plausible that children who have adequate seizure control and do not need frequent contact with a neurologist may not be represented in the current study. Nevertheless, the demographic make-up of the sample is similar to previous seminal research studies. Furthermore, as reviewed in previous research studies, children with epilepsy sampled from community settings typically evidence similar amounts of psychiatric symptoms as children with epilepsy sampled from tertiary care settings.

The absence of a systematic, prospective way to address the presence of psychiatric illnesses in this population is another issue that may have posed a difficulty in the current study. This was due to the unavailability of referral information in the sample and the limited time clinicians typically have in assessing neuropsychological functioning, especially in inpatient settings. Consequently, full diagnostic psychiatric interviews were not typically a part of the evaluation process and an accurate statement regarding the psychiatric diagnostic profile of the current sample could not be made. Nevertheless, the psychiatric disorders diagnosed in the current study were significantly lower than previous research studies on children with epilepsy.

Future studies should strive to examine secondary generalized seizures as a specific subtype as there seems to be a unique experience that affects children with this type of seizure that may contribute to higher levels of anxiety. Future studies should use more methodologically-sophisticated measures such as a prospective design and ideally include community and hospital samples. Though self- and parent-report measures have been used in previous studies, efforts could be made to assess for levels of psychiatric symptoms using finer tuned, more accurate, gold standard assessment measures such as structured diagnostic interviews, which are more thorough in nature.

Beyond issues pertaining to studying partial seizures that secondarily generalize, and because children with epilepsy may exhibit psychiatric symptoms due to a variety of reasons (e.g., before a seizure, during a seizure, as a reaction to having a seizure), future research could be devoted to developing specific measures of psychiatric symptoms in children with epilepsy. There are a variety of epilepsy-specific measures that already exist for adults and children with epilepsy, which primarily focus on quality of life and are frequently used in research. Due to the high prevalence of psychiatric symptoms in children with epilepsy, developing epilepsy-specific measures should become a priority. The current study used a retrospective, cross-sectional design of children who received neuropsychological testing, and future studies should focus on obtaining measures of depression and anxiety across time to gauge whether patterns can be explained in a developmental context. Furthermore, to expand upon the finding that children with secondary generalized seizures have a higher level of parent-reported anxiety compared

to children with generalized seizures, efforts should be made in future research to ascertain whether this is related to a possible cueing mechanism through clinical interviews with children affected by secondary generalized seizures. Lastly, the current study's findings on the interactive effects of gender and handedness were not anticipated. Future studies should strive to add to the body of literature by addressing these two variables as possible interactive factors with seizure type in affecting anxiety symptomatology.

Despite the limitations, the current study has unique aspects and findings compared to previous studies and sought to develop the current body of literature in a few distinct ways. Previous studies have included children with partial seizures with secondary generalization in research addressing psychiatric symptomatology; however, the researchers have not consistently grouped secondary generalized seizures as a separate subtype, unlike in the current study. Additionally, anxiety comorbidity is not researched in pediatric epilepsy to the same extent as depression, and the current study helped expand upon the literature addressing anxiety as a common comorbidity in children with epilepsy. Finally, the current study is very clinically relevant given the range of children who are affected by secondary generalized seizures. As future research continues to expand upon the subject area of the current study, many disciplines that treat pediatric epilepsy may benefit from more thoroughly evaluating and treating comorbid psychiatric symptoms.

Because of the qualitative aspects of seizure emanation that children with secondary generalized seizures experience, the current study sought to address psychiatric symptoms, namely anxiety, in these children as a unique subtype. Results suggest that children with secondary generalized seizures have higher level of parent-reported anxiety compared to children with generalized seizures despite a multitude of covariates and possible interacting factors. Future research should continue to expand upon this line of research with more methodologically-sophisticated designs, as many children have this type of seizure and could benefit from an evaluation and treatment perspective.

APPENDIX A

Figure 1.

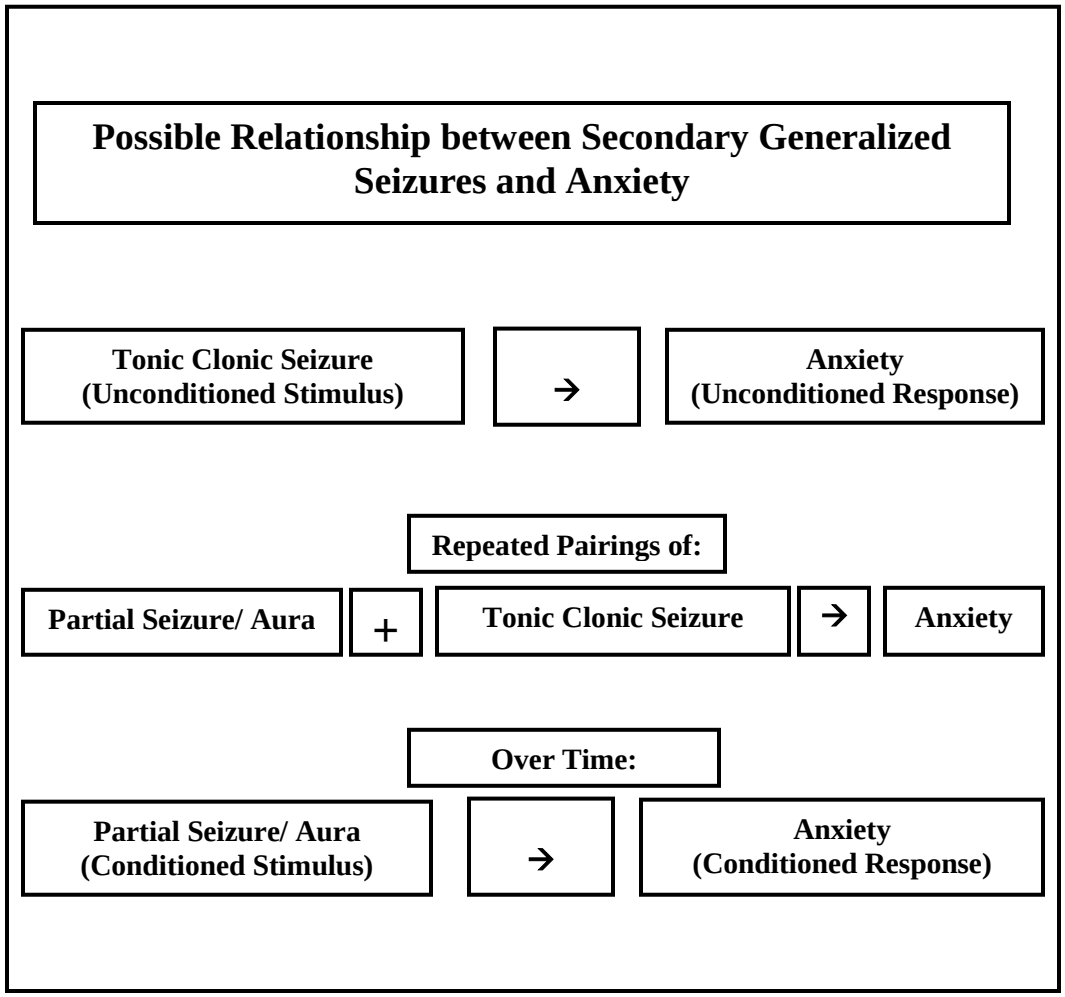


Figure 2.

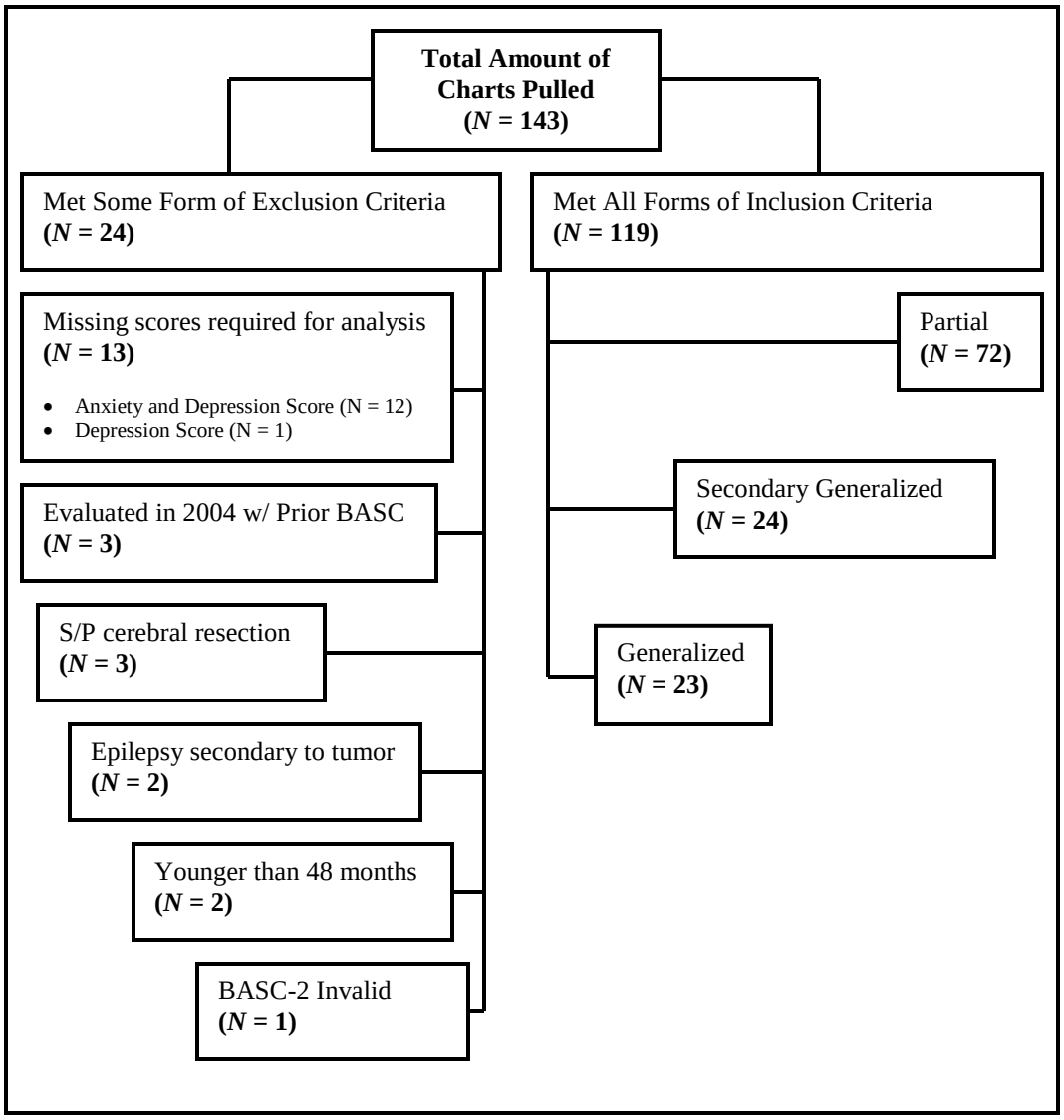

Total Amount of Charts Pulled (N = 143)
Met Some Form of Exclusion Criteria (N = 24)
Met All Forms of Inclusion Criteria (N = 119)
Missing scores required for analysis (N = 13)
Anxiety and Depression Score (N = 12)
Depression Score (N = 1)
Evaluated in 2004 w/ Prior BASC (N = 3)
S/P cerebral resection (N = 3)
Epilepsy secondary to tumor (N = 2)
Younger than 48 months (N = 2)
BASC-2 Invalid (N = 1)
Partial (N = 72)
Secondary Generalized (N = 24)
Generalized (N = 23)

Figure 3.

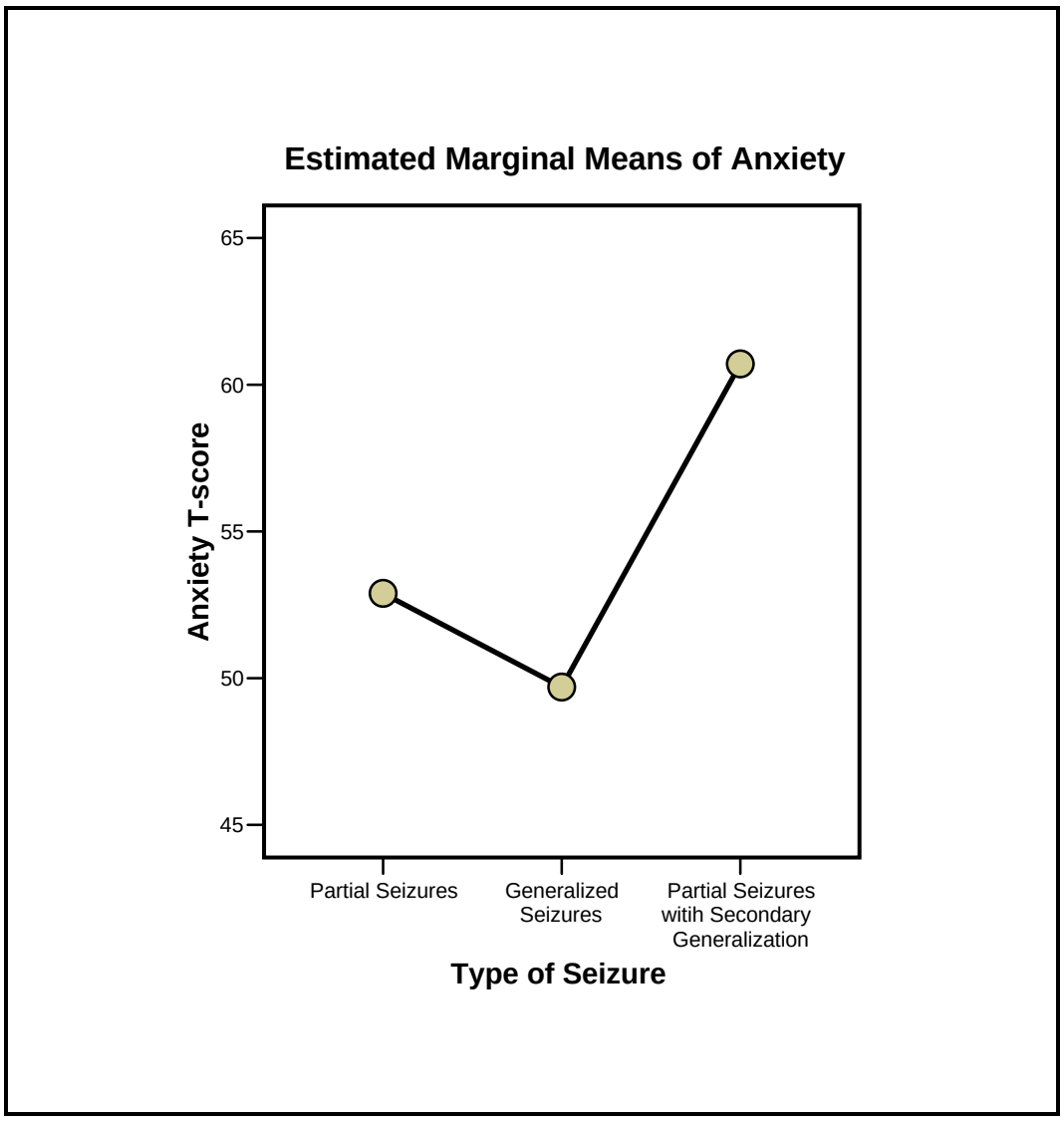

Estimated Marginal Means of Anxiety
Anxiety T-score
65
60
55
50
45
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 4.

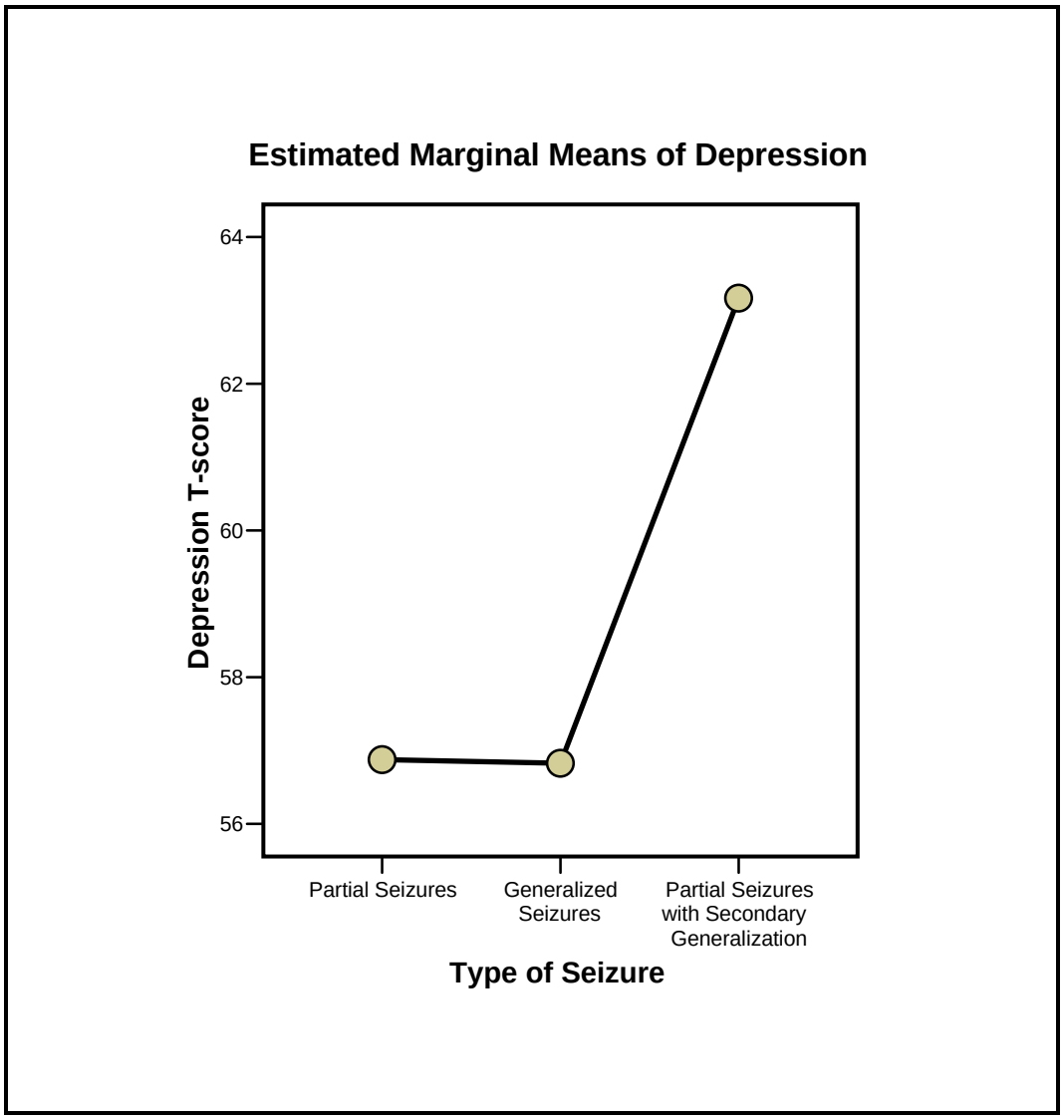

Estimated Marginal Means of Depression
Depression T-score
64
62
60
58
56
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 5.

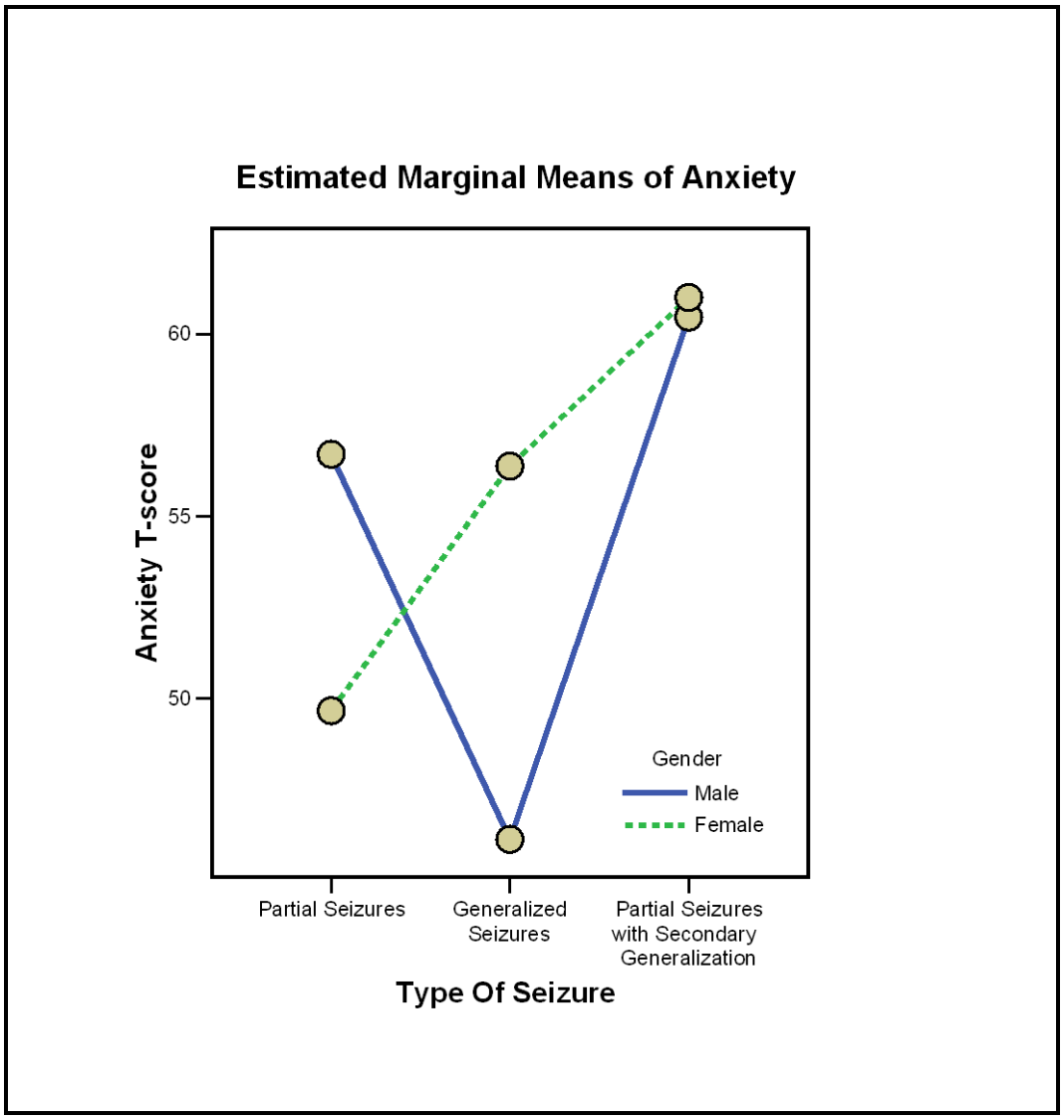

Estimated Marginal Means of Anxiety
Anxiety T-score
60
55
50
Gender
Male
Female
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type Of Seizure

Figure 6.

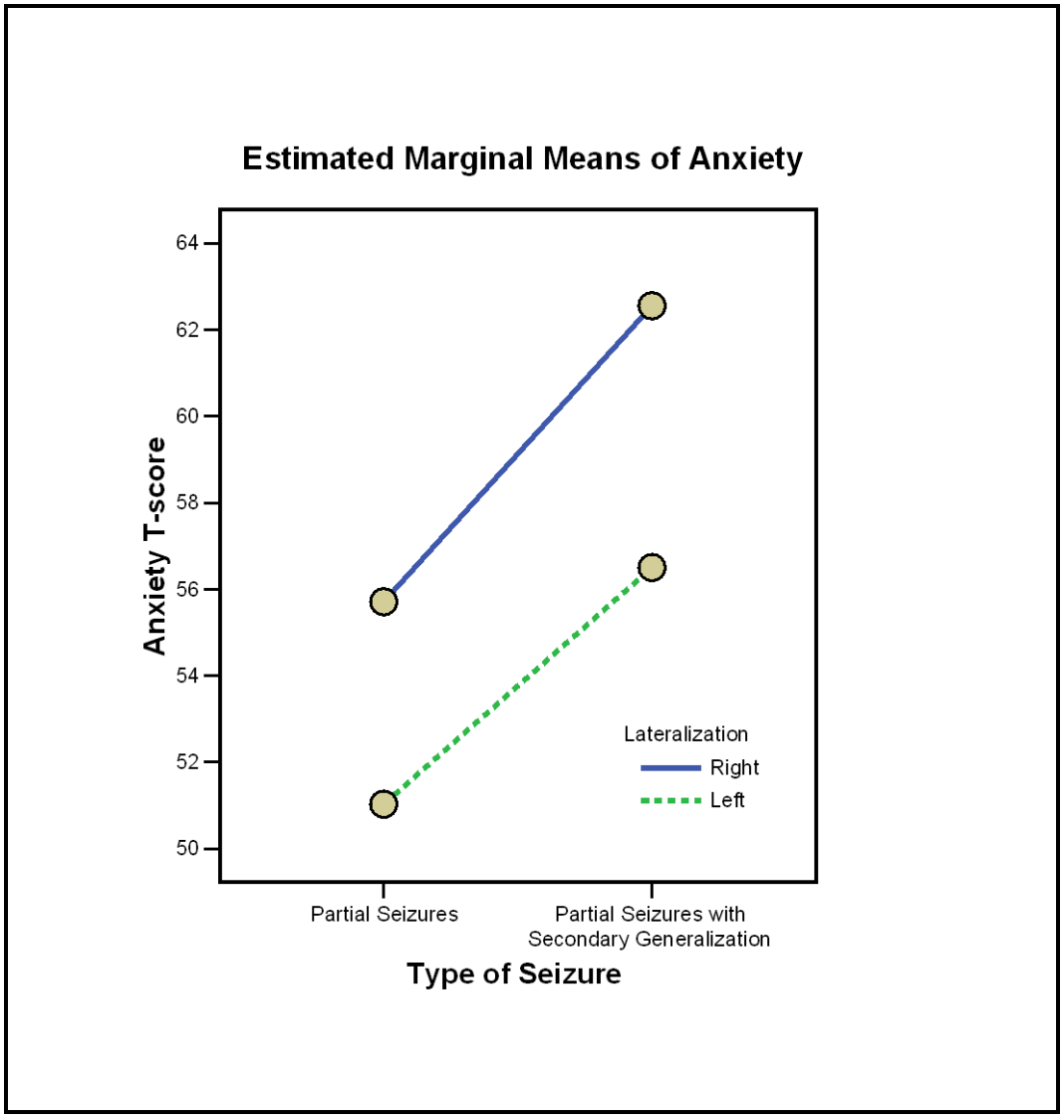

Estimated Marginal Means of Anxiety
Anxiety T-score
64
62
60
58
56
54
52
50
Lateralization
Right
Left
Partial Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 7.

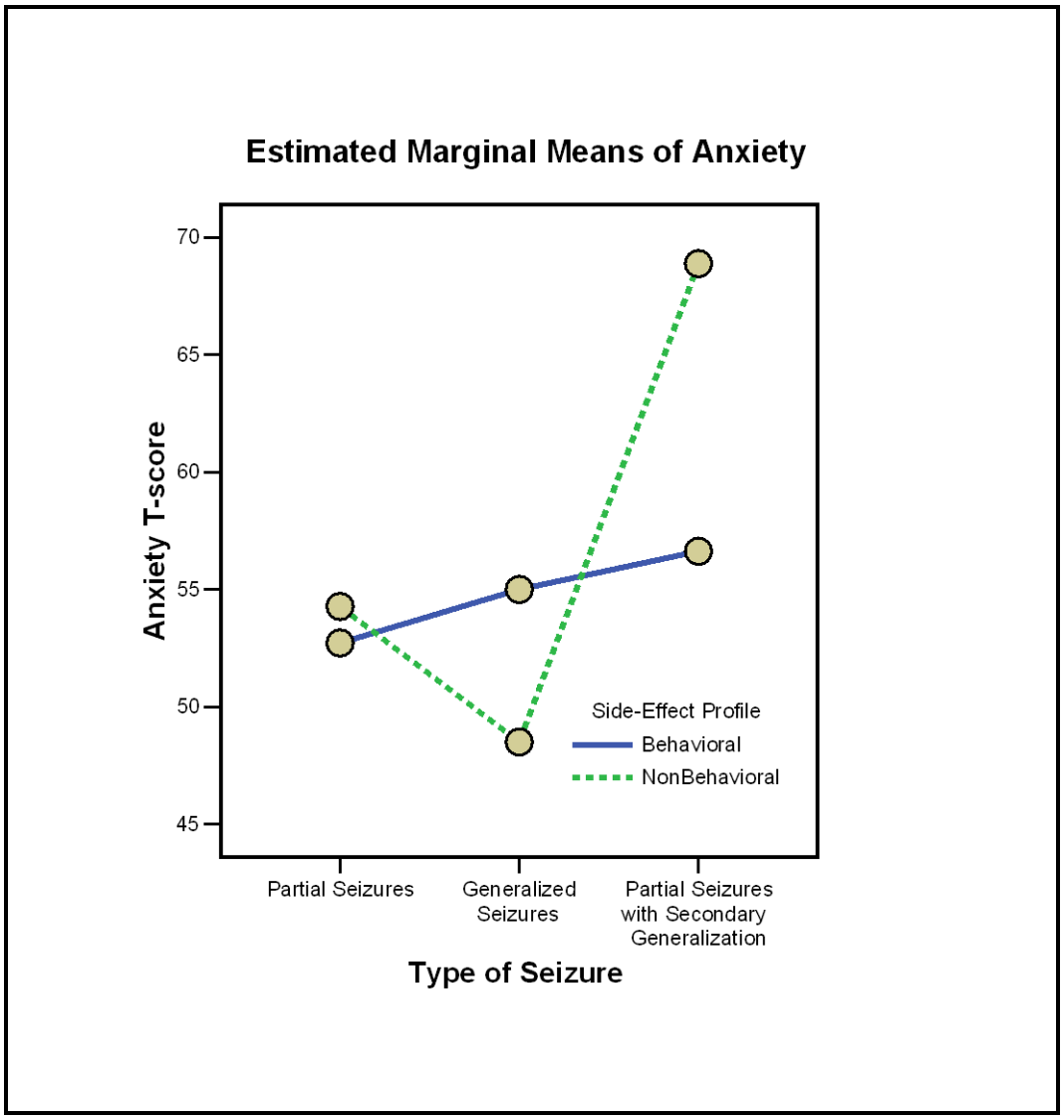

Estimated Marginal Means of Anxiety
Anxiety T-score
70
65
60
55
50
45
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure
Side-Effect Profile
Behavioral
NonBehavioral

Figure 8.

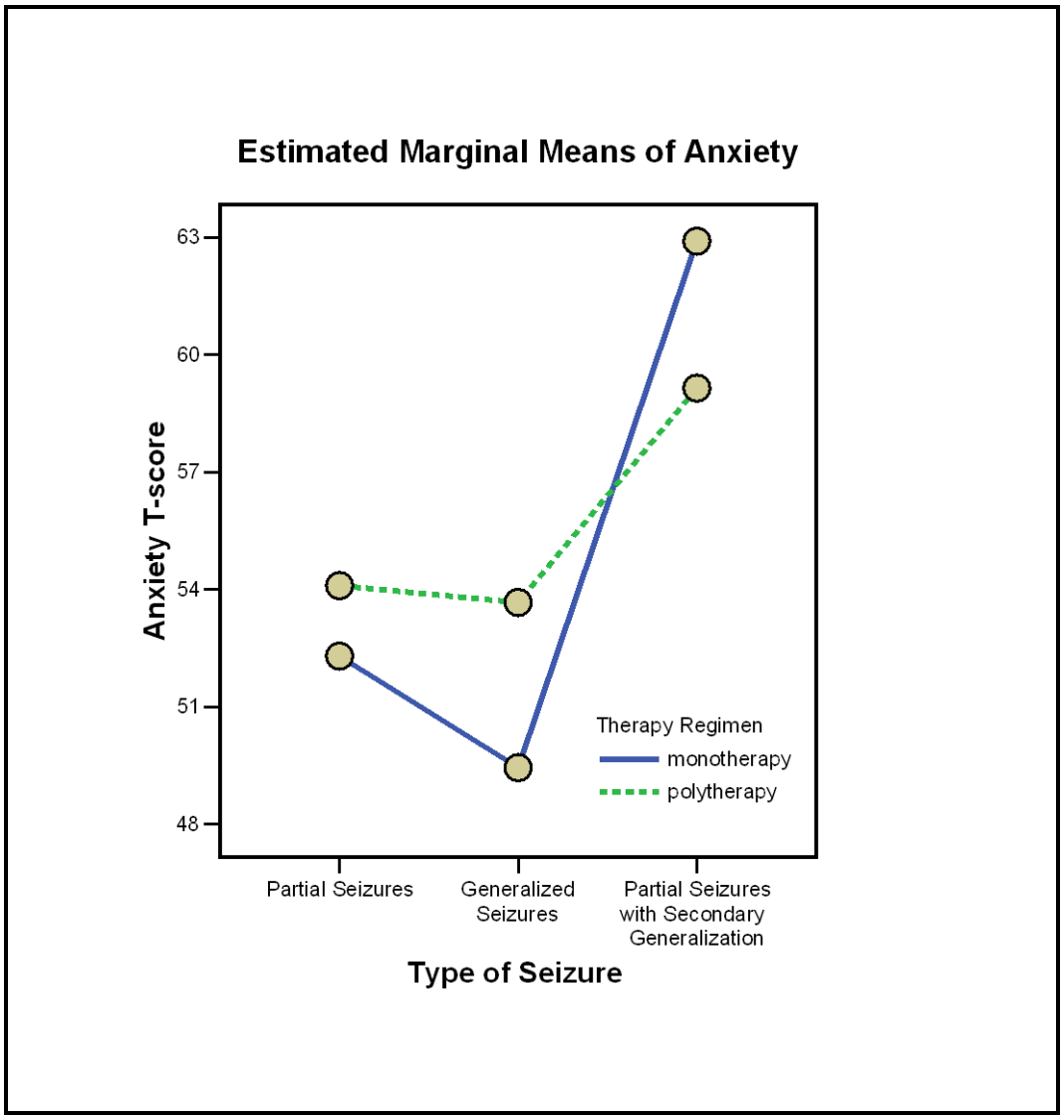

Estimated Marginal Means of Anxiety
Anxiety T-score
63
60
57
54
51
48
Therapy Regimen
monotherapy
polytherapy
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 9.

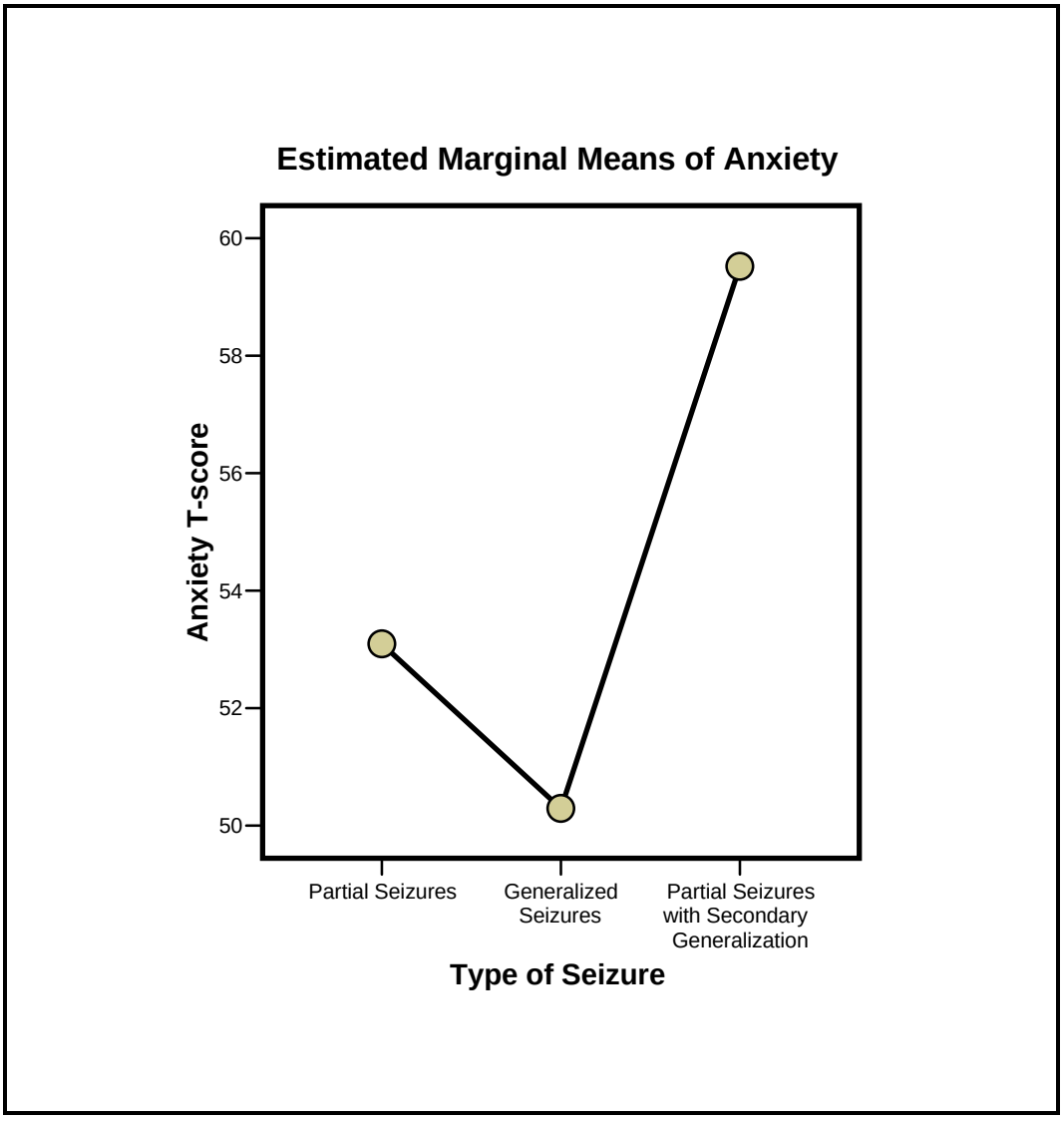

Estimated Marginal Means of Anxiety
Anxiety T-score
60
58
56
54
52
50
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 10.

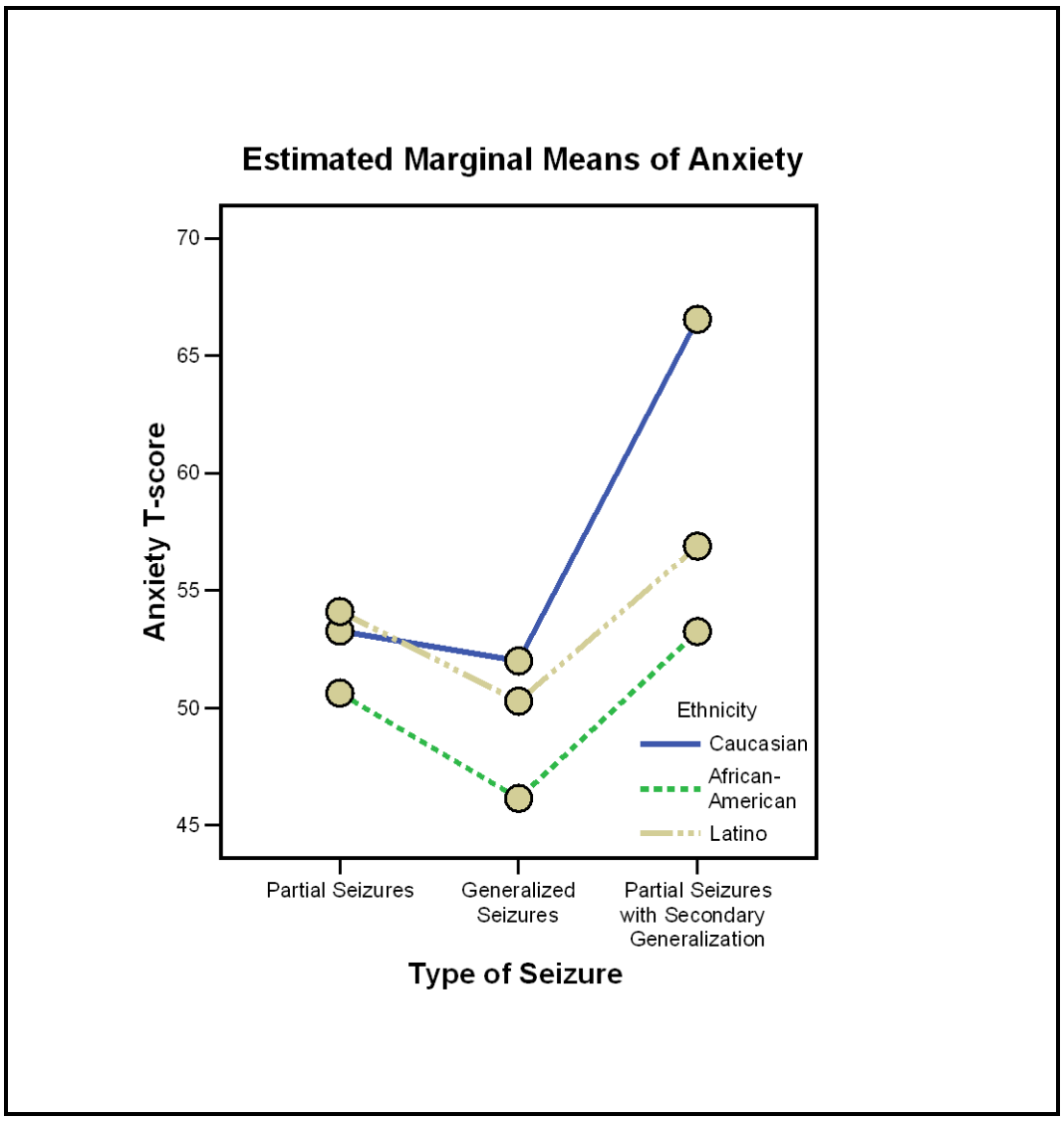

Estimated Marginal Means of Anxiety
Anxiety T-score
70
65
60
55
50
45
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure
Ethnicity
Caucasian
African-American
Latino

Figure 11.

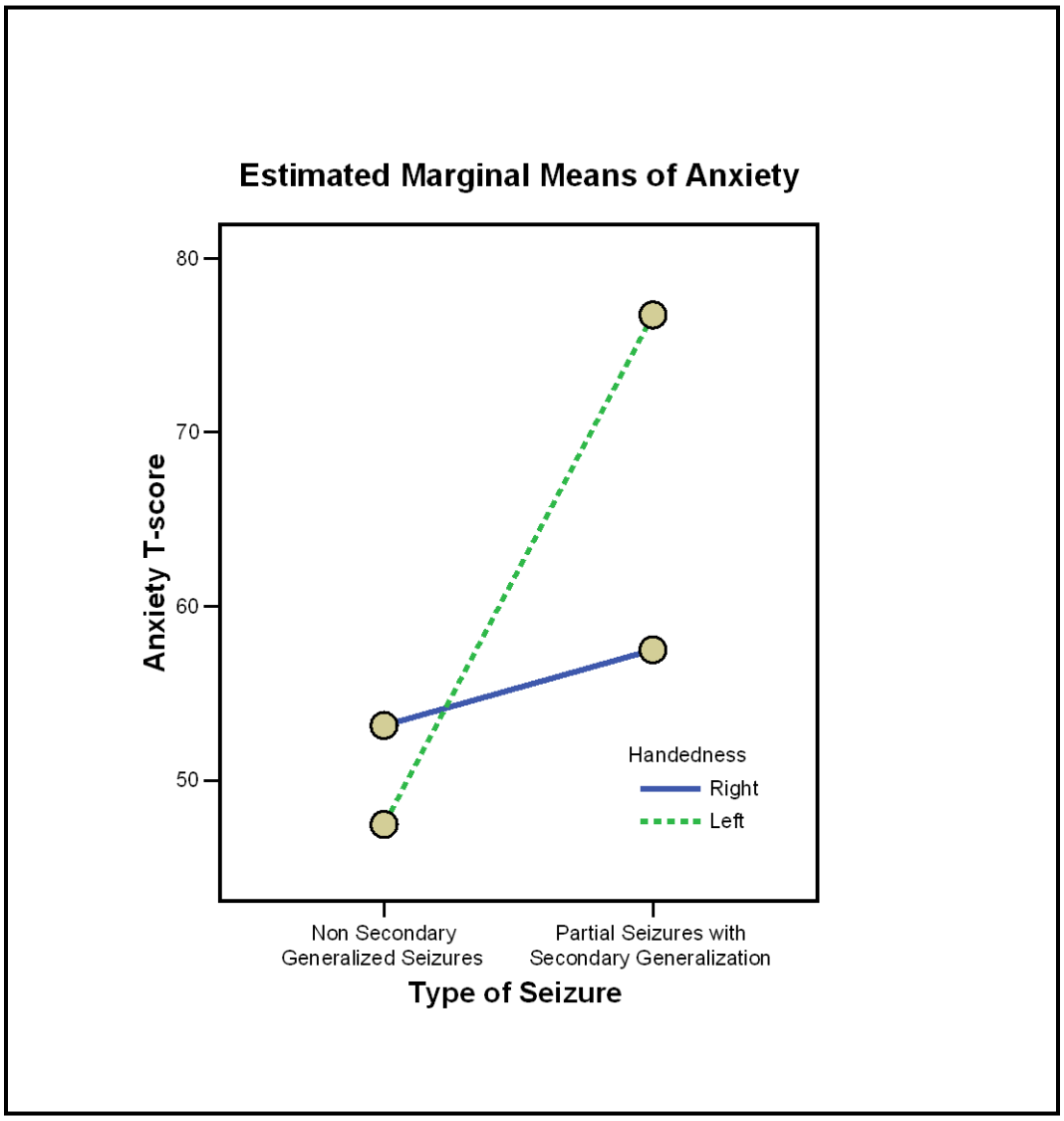

Estimated Marginal Means of Anxiety
Anxiety T-score
80
70
60
50
Handedness
Right
Left
Non Secondary Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure

Figure 12.

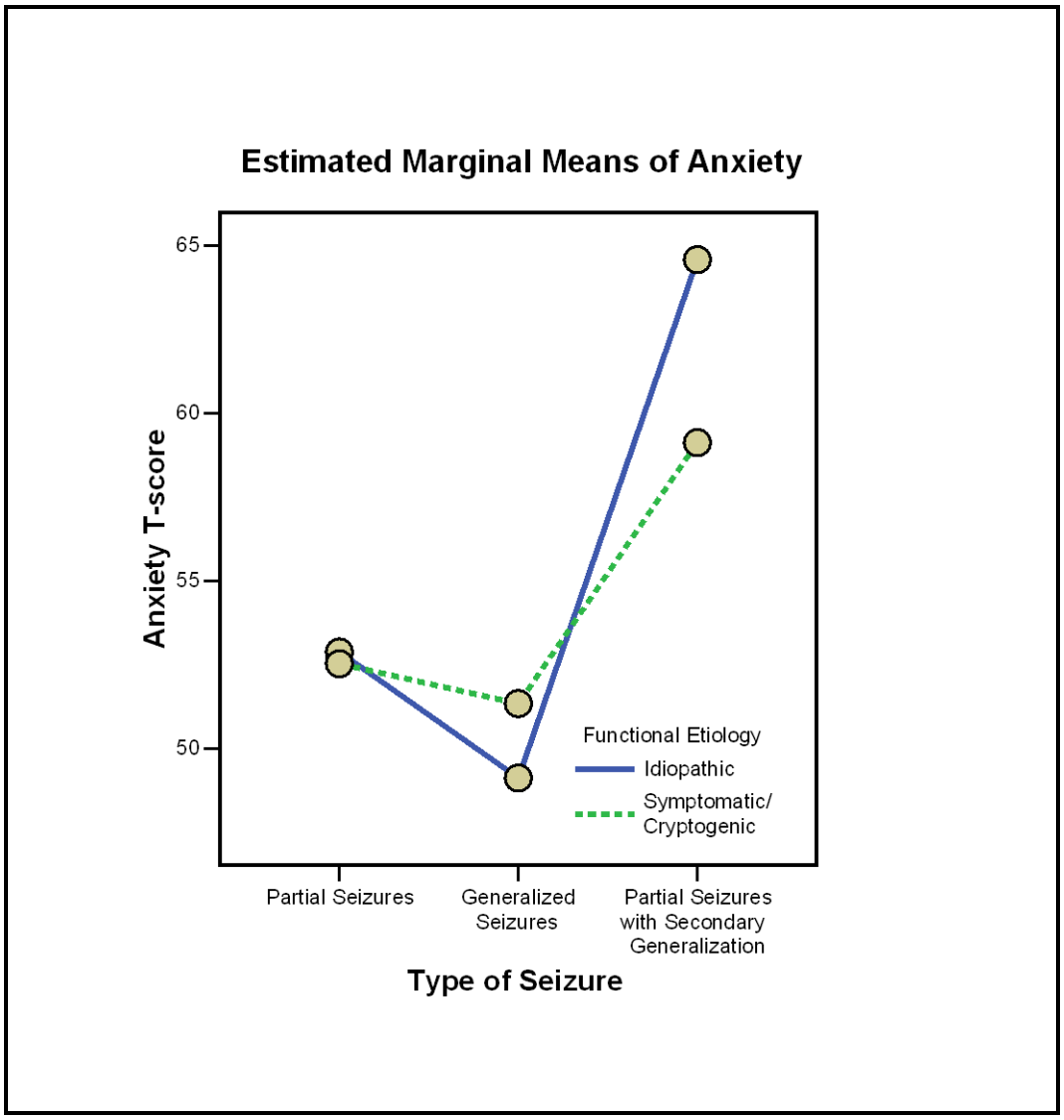

Estimated Marginal Means of Anxiety
Anxiety T-score
65
60
55
50
Functional Etiology
Idiopathic
Symptomatic/
Cryptogenic
Partial Seizures
Generalized
Seizures
Partial Seizures
with Secondary
Generalization
Type of Seizure

Figure 13.

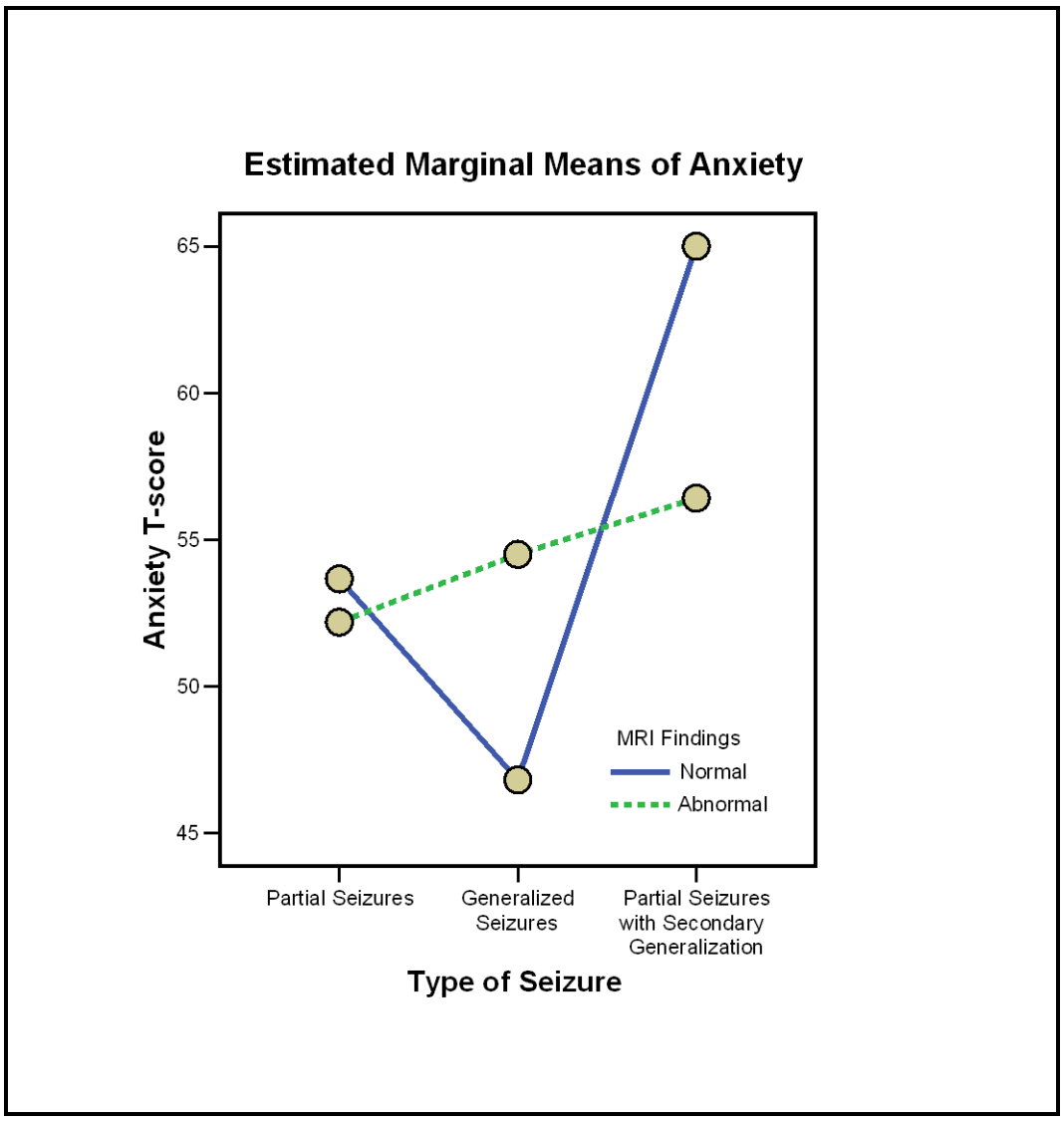
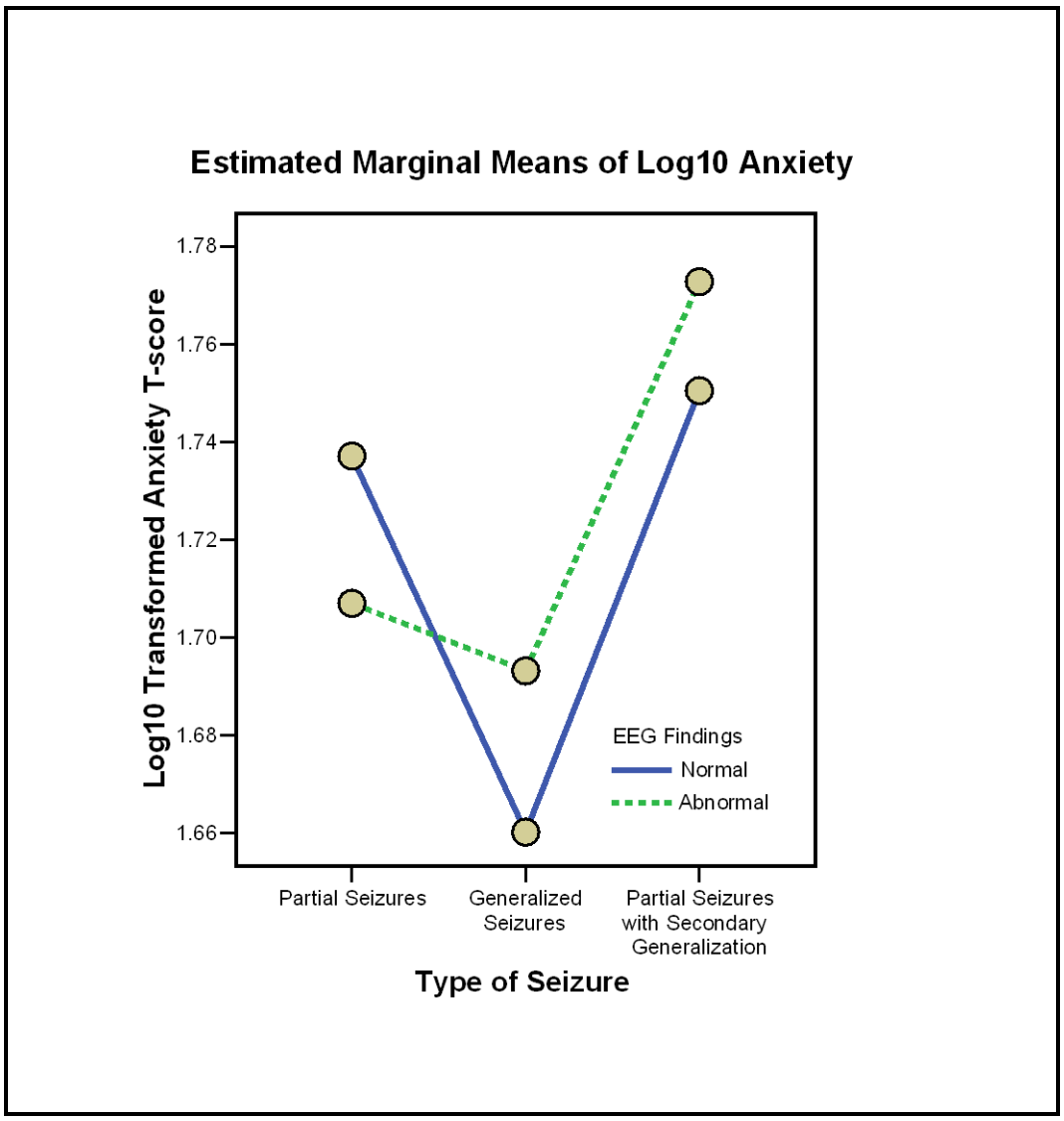

Estimated Marginal Means of Anxiety
Anxiety T-score
65
60
55
50
45
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure
MRI Findings
Normal
Abnormal

Figure 14.


Estimated Marginal Means of Log10 Anxiety
Log10 Transformed Anxiety T-score
1.78
1.76
1.74
1.72
1.70
1.68
1.66
Partial Seizures
Generalized Seizures
Partial Seizures with Secondary Generalization
Type of Seizure
EEG Findings
Normal
Abnormal

APPENDIX B

Table 1

Negative Cognitive and Behavioral Effects of Common Antiepileptic Drugs for Children

Antiepileptic drug	Cognitive Effect	Behavioral Effect
Valproic Acid	Decreases in attention and memory, somnolence	Minimal
Carbamazepine	Psychomotor slowing, decreases in attention and memory	Minimal
Phenobarbital	Declines in intelligence, slowed mental growth	Depressive symptoms
Lamotrigine	Minimal	Minimal
Phenytoin	Decreases in attention and memory, psychomotor slowing, confusion	Minimal
Levetiracetam	Minimal	Irritability, aggression
Oxcarbazepine	Minimal	Minimal
Topiramate	Deficits in memory, speech, attention, and concentration; psychomotor slowing	Endogenous depression
Zonisamide	Minimal	Psychotic symptoms, OCD symptoms
Gabapentin	Minimal	Minimal

Note. From (Bourgeois, 2004; Glauser, 2004a; Glauser 2004b; Loring & Meador, 2004).

Table 2

Measured Variables Collected and Reviewed

Variable	Instrument used	Definition of Score
Anxiety	Behavior Assessment System for Children, Second Edition[a]	Parent-Report Anxiety Score (T-score)
Depression	Behavior Assessment System for Children, Second Edition[a]	Parent-Report Depression Score (T-score)
Intelligence estimate	Wechsler Preschool and Primary Scale of Intelligence, Third Edition[b]	Full Scale Intelligence Quotient (Standard Score)
	Wechsler Intelligence Scale for Children, Fourth Edition[c]	Full Scale Intelligence Quotient (Standard Score)
	Wechsler Adult Intelligence Scale, Third Edition[d]	Full Scale Intelligence Quotient (Standard Score)
	Wechsler Abbreviated Scale of Intelligence[e]	Full Scale Intelligence Quotient (Two or four subtest standard score)

[a]Reynolds & Kamphaus, 2004 [b]Wechsler, 2002 [c]Wechsler,2003 [d]Wechsler,1997

[e]Wechsler,1999

Table 3

Demographic Variables Collected and Reviewed

Variable	How the variable was defined
Age	Age, in months, at the time of the neuropsychological evaluation
Gender	Female or Male
Ethnicity	Caucasian, African-American, Latino, or Asian
Handedness	Left-handed, Right-handed, or Ambidextrous
Median Household Income	Median neighborhood income of address at the time of evaluation as estimated from the respondent's zip code

Table 4

Medically- and Medication-Related Variables Collected and Reviewed

Medically-related variables	How the variable was defined
Type of seizures experienced	Partial seizures, generalized seizures, or partial seizures with secondary generalization
Age of onset	Age, in months, when first seizure was experienced
Lateralization	Left, right
Functional etiology	Symptomatic, cryptogenic, or idiopathic
EEG findings	EEG normal, EEG abnormal,
MRI findings	MRI normal, MRI abnormal

Medication-related variables	How the variable was defined
Number of AEDs taken	Number of AEDs taken during the time of the neuropsychological evaluation
Therapy regimen	Monotherapy, polytherapy
Side-effect profile	Behavioral Effects, nonbehavioral effects

Table 5

Demographic Variables Percentages of the Sample

Characteristic	All (*n*=119)	Partial (*n*=72)	Gen[a] (*n*=23)	2° Gen[b] (*n*=24)	χ^2	*df*	*p*
Gender					2.72	2	.26
Male	51.3	45.8	65.2	54.2			
Female	48.7	54.8	34.8	45.8			
Ethnicity					1.87	4	.76
Caucasian	38.7	36.1	39.1	45.8			
African-American	22.7	22.2	30.4	16.7			
Latino	37.8	40.3	30.4	37.5			
Asian	0.8	1.4	0.0	0.0			

Note. Gen = Generalized; 2° Gen = Partial Seizures with Secondary Generalization.

Table 6

Seizure-Related Variables Percentages of the Sample

Characteristic	All	Partial	Gen	2° Gen	χ^2	*df*	*p*
Lateralization	(*n*=86)	(*n*=68)		(*n*=18)	.01	4	.215
Right	45.3	45.6	NA	44.4			
Left	54.7	54.4	NA	55.6			
Functional etiology	(*n*=118)	(*n*=71)	(*n*=23)	(*n*=24)	44.93	4	.000
Idiopathic	27.1	11.3	73.9	29.2			
Symptomatic	50.0	70.4	4.3	33.3			
Cryptogenic	22.9	18.3	21.7	37.5			

Note. Gen = Generalized; 2° Gen = Partial Seizures with Secondary Generalization.

Table 7

Lab-Related Variables Percentages of the Sample

Findings	All	Partial	Gen	2° Gen	χ^2	*df*	*p*
EEG	(*n*=118)	(*n*=71)	(*n*=23)	(*n*=24)	3.84	2	.147
Normal	14.4	9.9	26.1	16.7			
Abnormal	85.6	90.1	73.9	83.3			
MRI	(*n*=113)	(*n*=71)	(*n*=18)	(*n*=24)	25.11	2	.000
Normal	40.7	25.4	88.9	50.0			
Abnormal	59.3	74.6	11.1	50.0			

Note. Gen = Generalized; 2° Gen = Partial Seizures with Secondary Generalization.

Table 8

Medication-Related Variables Percentages of the Sample

Characteristic	All	Partial	Gen	2° Gen
AED Prescribed	(*n*=119)	(*n*=72)	(*n*=23)	(*n*=24)
Valproic Acid	28.6	25.0	47.8	20.8
Carbamazepine	26.9	29.2	13.0	33.7
Phenobarbital	2.5	2.8	0.0	4.2
Lamotrigine	5.9	1.4	17.4	8.3
Phenytoin	8.4	9.7	4.3	8.3
Levetiracetam	34.5	40.3	4.3	45.8
Oxcarbazepine	27.7	33.3	4.3	33.3
Topiramate	10.1	8.3	8.7	16.7
Zonisamide	10.1	11.1	8.7	8.3
Ethosuximide	1.7	1.4	4.3	0.0
No AED	5.0	5.6	8.7	0.0
Therapy Regimen	(*n*=119)	(*n*=72)	(*n*=23)	(*n*=24)
No AED	5.0	5.6	8.7	0.0
Monotherapy	46.2	37.5	78.3	41.7
Polytherapy	48.7	56.9	13.0	58.3
Side-effect profile	(*n*=113)	(*n*=68)	(*n*=21)	(*n*=24)
Behavioral	53.1	57.4	23.8	66.7
Nonbehavioral	46.9	42.6	76.2	33.3

Note. Gen = Generalized; 2° Gen = Partial Seizures with Secondary Generalization.

Table 9

Means of Measured Variables of the Sample

Characteristic	All (*n*=119)	Partial (*n*=72)	Generalized (*n*=23)	2° Generalized (*n*=24)
Age	135.33 (44.30)	132.47 (47.08)	130.00 (40.08)	149.00 (37.92)
Age of onset	61.93 (45.22)	58.42 (45.04)	70.91 (47.01)	63.88 (44.62)
Median HH income	42322.99 (14825.39)	41046.72 (15438.06)	45280.61 (11122.13)	43317.42 (16084.24)
Anxiety T-score	53.85 (13.31)	52.89 (12.12)	49.70 (11.84)	60.71 (15.82)
Depression T-score	58.13 (13.51)	56.88 (12.85)	56.83 (14.91)	63.17 (13.47)
Intelligence estimate	78.98 (15.15)	80.79 (15.52)	74.62 (13.10)	77.64 (15.49)

Note. HH = Household. Standard deviations in parenthesis.

Table 10

95% Confidence Intervals of Pairwise Differences in Parent-Reported Anxiety

Seizure Type	M	SD	Partial	Generalized
Partial	52.89	12.12		
Generalized	49.70	11.84	-3.89 to 10.27	
2° Gen	60.71	15.82	-16.60 to 0.96	-21.20 to -0.82

Note. 2° Gen = Partial Seizures with Secondary Generalization.

Table 11

Parent-Reported Anxiety by Gender

	Male			Female		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	33	56.70 (12.72)	[52.36, 61.03]	39	49.67 (10.73)	[45.68, 61.03]
Generalized	15	46.13 (11.34)	[39.71, 52.56]	8	56.38 (10.25)	[47.57, 65.18]
2° Gen	13	60.46 (18.74)	[53.56, 67.37]	11	61.00 (12.42)	[53.49, 68.51]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 12

Parent-Reported Anxiety by Lateralization

	Left			Right		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	31	51.03 (10.74)	[45.75, 55.31]	37	55.71 (13.48)	[51.04, 60.38]
2° Gen	8	56.50 (18.82)	[48.27, 64.73]	10	62.63 (13.31)	[53.43, 71.83]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 13

Parent-Reported Anxiety by Side-Effect Profile

	Behavioral			Nonbehavioral		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	39	52.72 (11.08)	[48.64, 56.80]	29	54.28 (13.54)	[49.55, 59.00]
Generalized	5	55.00 (14.65)	[43.61, 66.39]	16	48.50 (11.65)	[42.13, 54.87]
2° Gen	16	56.62 (12.68)	[50.26, 62.99]	8	68.88 (19.08)	[59.87, 77.88]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 14

Parent-Reported Anxiety by Therapy Regimen

	Monotherapy			Polytherapy		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	27	52.30 (12.32)	[47.28, 57.31]	41	54.10 (12.09)	[50.03, 58.17]
Generalized	18	49.44 (11.35)	[43.31, 55.58]	3	53.67 (20.21)	[38.63, 68.71]
2° Gen	10	62.90 (17.71)	[54.66, 71.14]	14	59.14 (15.82)	[52.18, 66.11]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 15

Correlations among Continuous Variables

	Age	Age at Onset	#AEDs	Median Income[a]	FSIQ[b]
Anxiety	.30**	25**	.21*	-.072	.135

[a] Log10 Transformed for normality
[b] Intelligence Estimate
*p<.05. **p<.01.

Table 16

Parent-Reported Anxiety by Ethnicity

Ethnicity	Seizure Type	M	SD	95% CI
Caucasian	Partial	53.27	11.68	48.25 to 58.29
	Generalized	52.00	13.02	43.46 to 60.54
	2° Gen	66.55	18.05	58.82 to 74.27
AA	Partial	50.63	15.72	44.22 to 57.03
	Generalized	46.14	8.93	36.46 to 55.82
	2° Gen	53.25	11.00	40.44 to 66.06
Latino	Partial	54.10	10.54	49.35 to 58.86
	Generalized	50.29	13.61	40.61 to 59.97
	2° Gen	56.89	13.26	48.35 to 65.43
Asian[a]	Partial	44.00	NA	NA
	Generalized	NA	NA	NA
	2° Gen	NA	NA	NA

Note. 2° Gen = Partial Seizures with Secondary Generalization; AA = African-American. Means presented are estimated marginal means.
[a]Not included in statistical analysis. Means presented are estimated marginal means.

Table 17

Parent-Reported Anxiety by Handedness

Handedness	Seizure Type	M	SD	95% CI
Right	Non 2° Gen	53.15	11.99	50.38 to 55.93
	2° Gen	57.50	14.85	52.02 to 62.98
Left	Non 2° Gen	47.46	10.68	40.67 to 54.25
	2° Gen	76.75	10.50	64.50 to 89.00

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 18

Parent-Reported Anxiety by Etiology

Etiology	Seizure Type	M	SD	95% CI
Idiopathic	Partial	52.88	10.68	43.86 to 61.90
	Generalized	49.12	10.49	42.93 to 55.31
	2° Gen	64.57	12.99	54.93 to 74.21
Symptomatic/ Cryptogenic	Partial	52.52	12.11	49.31 to 59.74
	Generalized	51.33	16.15	40.92 to 61.75
	2° Gen	59.12	16.95	52.93 to 65.31

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 19

Parent-Reported Anxiety by MRI Findings

	Normal			Abnormal		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	18	53.67 (11.21)	[47.79, 59.54]	53	52.19 (12.19)	[48.77, 55.61]
Generalized	16	46.81 (10.59)	[40.58, 53.04]	2	54.50 (6.36)	[36.88, 72.12]
2° Gen	12	65.00 (15.91)	[57.81, 72.19]	12	56.42 (15.17)	[49.22, 63.61]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Means presented are estimated marginal means.

Table 20

Parent-Reported Anxiety by EEG Findings

	Normal			Abnormal		
Seizure	*n*	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI
Partial	7	1.74 (.11)	[1.66, 1.81]	64	1.71 (.11)	[1.68, 1.73]
Generalized	6	1.66 (.07)	[1.58, 1.74]	17	1.69 (.11)	[1.64, 1.74]
2° Gen	4	1.75 (.04)	[1.65, 1.85]	20	1.77 (.12)	[1.73, 1.82]

Note. 2° Gen = Partial Seizures with Secondary Generalization. Anxiety was transformed using a Log10 command. Means presented are estimated marginal means.

Table 21

Psychiatric Diagnoses Frequencies of the Sample

Diagnosis	All	Partial	Generalized	2° Gen
ADHD	14	7	5	2
Anxiety Disorder	5	3	0	2
Asperger's Disorder	1	1	0	0
Autism	1	0	1	0
Depression	6	3	0	3
Oppositional Defiant Disorder	1	0	1	0
No Disorder	92	59	16	17

Note. 2° Gen = Partial Seizures with Secondary Generalization; Anxiety Disorders includes Generalized Anxiety Disorder and Anxiety Disorder NOS; Depression includes Major Depressive Disorder

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