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Neurocognitive and Psychosocial Functions in Children with Frontal and Temporal Lobe Epilepsy

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Neurocognitive and Psychosocial Functions in Children with Frontal and Temporal Lobe Epilepsy

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Dedication

I would like to dedicate this manuscript to my mother and father, Melanie and Gerry Stefanatos, my sister, Alexandra Stefanatos, and my grandmother, Gloria Barnett. I will never be able to express how much their love and encouragement has meant to me over the past six years. I feel so blessed every day for their continued support. Thank you for always being my “rock”.

I also would like to dedicate this manuscript to the memory of Mr. George Reim and Dr. Maureen Dennis. Mr. Reim emboldened me to use my voice when I was simply content to remain quiet. Dr. Dennis’ passion for clinical research provided the inspiration for me to pursue a course of study directed towards understanding more about the detrimental impact of childhood disorders. I will forever be indebted to her for her support and guidance.

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Neurocognitive and Psychosocial Functions in Children with Frontal and Temporal Lobe Epilepsy

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A key construct at the foundation of cognitive and clinical developmental neuropsychology is the notion that cognitive functions are localized to specific cortical regions in the brain. Consistent with this, relatively stable cognitive and behavioral profiles have been described for adults diagnosed with the two most common focal-onset seizure disorders. Temporal lobe epilepsy (TLE) is primarily associated with impairments in memory functioning (Bell & Giovagnoli, 2007) and frontal lobe epilepsy (FLE) with impairments in executive and motor functioning (Patrikelis et al., 2009). However, the immature brain may be particularly vulnerable to the adverse effects of recurrent seizure activity, showing more widespread effects on cognitive processes and brain organization compared to adults (Korman et al., 2013). Despite these observations, few studies have directly compared performance between children with different epilepsy syndromes utilizing broad assessments spanning multiple domains (Williams, Griebel & Dykman, 1998). Consequently, the aim of this study was to evaluate the degree and selectivity of patterns of cognitive and psychosocial dysfunction in children with TLE and FLE.

Participants included 51 children between the ages of 6 and 16 years with

intractable epilepsy who were consecutively seen for a neuropsychological evaluation through the Dell Children's Medical Center Comprehensive Epilepsy Program. During this assessment, participants were administered a battery including measures of memory, executive, motor and intellectual functioning. In addition, parents completed questionnaires regarding their child's behavioral and psychosocial functioning. Contrary to the selective patterns of deficits typically described in adults, both the TLE and FLE groups demonstrated significant impairments relative to normative values on each of the domains assessed. Moreover, no significant differences were found between the two patient groups on any of the measures, with the exception of a task of visual memory.

These findings suggest that individuals with childhood-onset epilepsy exhibit fairly broad patterns of cognitive compromise that do not differ significantly with frontal lobe versus temporal lobe seizure localization. Furthermore, the range of deficits observed would not normally be expected with analogous seizure disorders acquired in adulthood. These results provide important insights into the organization of cognitive and behavioral functions following early neurological insults associated with epilepsy.

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1 BACKGROUND AND SIGNIFICANCE

1.1 FUNCTIONAL SPECIALIZATION IN THE BRAIN

Models of human brain function have traditionally conceptualized the cerebral cortex as being composed of various discrete regions, each dedicated to specialized, domain-specific functions (Anderson, 2010; Fodor, 1983; Fodor, 2000; Johnson, 2001). This hypothetical framework of modular organization evolved from neuropsychological studies involving adults with acquired circumscribed brain lesions and is based on the supposition that it is possible to dissociate different cognitive and behavioral processes in the brain by correlating the effects of damage to specific neural substrates with selective patterns of cognitive and behavioral impairment (Caramazza & Coltheart, 2006; Temple, 1997). More specifically, the lesion model attributes the processing of particular types of information to distinct areas of cortex, such that damage to those regions by injury or disease results in the selective disruption of associated cognitive and neural processes and conversely, the observed loss of skills is indicative of injury to that corresponding brain region (D'Souza & Karmiloff-Smith, 2011; Fama & Sullivan, 2014; Moses & Stiles, 2002). This line of research has allowed powerful inferences to be made about the organization of functional neural networks in adults.

Attempts have been made to apply this adult neuropsychological model to characterizing the pattern of impairment and preserved skills of various acquired and neurodevelopmental conditions in childhood (Karmiloff-Smith, 2013; Temple, 1997; Thomas & Karmiloff-Smith, 2002). However, profiles derived from adult participants with acquired neurological insults reflect neural and cognitive processes damaged within a mature state after an extended period of normal development (D'Souza & Karmiloff-

Smith, 2011; Karmiloff-Smith, 2013). Consequently, it has been argued that they provide limited information regarding the degree of specialization that exists in earlier stages of development or about the gradual process of relative modularization that may occur across childhood and adolescence (Dennis & Barnes, 1994; D'Souza & Karmiloff-Smith, 2011).

Early studies appeared to suggest that the brain was innately specialized from birth (e.g., Witelson & Paille, 1973). However, emerging studies have suggested that, despite some evidence of lateralization, cognitive and behavioral processes may not be functionally localized to specific cortical regions early in development (see Bell & Giovagnoli, 2007; Patrikelis, Angelakis, & Gatzonis, 2009). Instead, it has been proposed that a process of 'interactive specialization' may occur by which distinct neural networks become more specialized or segregated across ontogeny (Johnson, 2001; Johnson, 2011; Johnson, Grossman, & Kadosh, 2009). According to this view, the immature brain is anatomically less differentiated and more interconnected outside of regions typically regarded as canonical network structures in the adult brain (Fair et al., 2009; Wylie et al., 2014). Changes in the activation patterns of cortical regions occur across development as circuits of neurons become more restricted to subserve a narrower set of specific functions (Johnson et al., 2009; Tau & Peterson, 2010). Typical development, therefore, appears to be characterized by a process of increasing connectivity between brain regions subserving the same functional networks and corresponding decreases in activation between brain regions associated with other networks (Dosenbach et al., 2010; Fair et al., 2007; Fair et al., 2009), with the resulting endpoint being the formation of mature, functionally specialized neural networks (Ibrahim et al., 2014).

However, damage or disease sustained early in childhood has been suggested to fundamentally alter or compromise the typical trajectory of neural and behavioral specialization and development (Dennis et al., 2014). Specifically, it has been suggested that early brain injury may interfere with the process by which the transient projections that support cognitive processing during early development are typically eliminated (Nelson, 2000), resulting in atypical and more widely distributed brain networks (Maguire, Vargha-Khadem, & Mishkin, 2001; Sutula & Pitkänen, 2002). Consequently, attempts to generalize adult principles of functional specialization are limited given emerging indications of alternative patterns of neural organization which can develop in the brain following early injury (see Moses & Stiles, 2002). The findings from clinical studies specifically examining outcomes following early focal brain injury reveal considerable variability in the resulting profiles of deficits and apparent degree of functional recovery, which vary as a function of cognitive domain, site of lesion, timing of lesion onset and specific etiology (Dennis et al., 2014; Moses & Stiles, 2002).

1.2 EPILEPSY: *A Window on Brain Function and Development*

The study of epilepsy has been central to the conceptualization and understanding of human brain-behavior relationships. Seminal 19th century observations attributed specific disturbances of motor (Todd, 1849) and language (Hughlings-Jackson, 1866) function to neural exhaustion or inhibition caused by the repeated, sustained electrical discharges characteristic of seizures. Later, electrical cortical stimulation of conscious patients undergoing neurosurgical resections of epileptogenic regions of the brain resulted in important insights regarding the topographic nature of motor-sensory cortex and the circumscribed distribution of language areas (Almeida, Martinez, & Feindel,

2005; Ojemann, 1979; Penfield & Roberts, 1959). Classic observations by Scoville and Milner (1957) of anterograde amnesia following bilateral temporal lobe and hippocampal resection for treatment of intractable epilepsy demonstrated the critical role of the hippocampal formation and temporal lobe structures in mediating consolidation of newly learned material in long-term memory. In addition, the use of resective surgery in children with intractable epilepsy provided compelling demonstrations of developmental plasticity for higher cognitive functions following removal of entire hemispheres (Basser, 1962; Dennis & Kohn, 1975; Goodman & Whitaker, 1985).

More recently, epilepsy has been proposed as an ideal disorder for understanding brain-behavior relationships across different points in development (Matthews, 1992; Novelly, 1992). The study of epilepsy has been instrumental in understanding the mechanisms underlying cognitive decline in correlation with identified pathophysiological processes (see David, Bastin, Chabardes, Minotti, & Kahane, 2010; van Diessen et al., 2013a; van Diessen, Otte, Braun, Stam, & Jansen, 2013b). Recent technological advances have demonstrated significant alterations in the architecture of functional neural networks and connectivity patterns in individuals with epilepsy which appear to emerge from pathological brain dynamics that develop following recurrent seizure activity (Chavez, Valencia, Navarro, Latora, & Martinerie, 2010). A related body of literature within the field of clinical neuropsychology has focused on attempting to correlate the consequences of these pathogenic processes by examining the particular cognitive and behavioral profiles associated with specific epilepsy syndromes (see Helmstaedter & Kockelmann, 2006; Patrikelis, Angelakis, & Gatzonis, 2009). Given concerns that the current function-structure mapping framework derived from adult

research may not be appropriate to characterize the effects of damage to the immature brain (Moses & Stiles, 2002), establishing how recurrent seizures impact functioning in children with epilepsy can provide important insights into the emergence of cognitive and behavioral processes across development (Insel, 2009; Rapoport et al., 1999). Consequently, in this study, the profiles of children with two common focal epilepsy syndromes were compared in order to examine the impact of recurrent seizure activity on the emergence of cognitive and behavioral functions in the developing brain.

1.2.1 PREVALENCE

Epilepsy is a chronic neurological condition characterized by recurrent paroxysmal seizure activity (David et al., 2010; Fisher et al., 2014), which affects approximately 2-3 million people in the United States (Hirtz et al., 2007). By most definitions, seizures represent abnormal electrical events that are triggered by repetitive excessive or hypersynchronous activity of neurons in the brain, sufficient enough to result in alterations in behavior (Fisher et al., 2014; Fisher et al., 2005). While approximately 5-10% of the population may experience at least one seizure during the course of their lifetime (Wilden & Cohen-Gadol, 2012), only a proportion of these individuals subsequently develop epilepsy, which requires that the seizure activity be recurrent (Fisher et al., 2014). While epilepsy is the fourth most commonly diagnosed neurologic disorder among adults, it is the one of the most commonly diagnosed neurologic disorder in children and adolescents (see MacLeod & Appleton, 2007; WHO, 2012). Age-specific incidence rates have estimated that approximately 150,000 children under the age of 16 experience a first-time, unprovoked seizure each year, and of those, approximately 25% will subsequently receive a diagnosis of epilepsy (McAbee & Wark,

2000).

1.2.2 NEUROPHYSIOLOGY

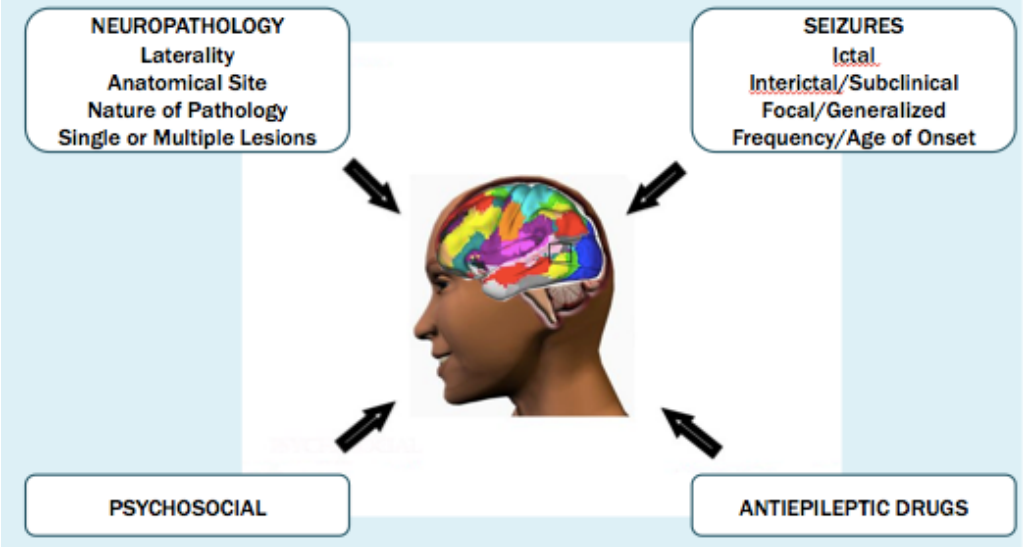
The electrical basis of epilepsy became evident in the latter part of the 19th century based on observations of pioneers in the field, such as Robert Bentley Todd (1849), John Hughlings-Jackson (1866) and Sir William Richard Gowers (1885). Since that time, clinical studies and animal models of epilepsy have been instrumental in elucidating the cellular and molecular mechanisms underlying seizure activity in the brain (see Wong, 2005). Ontogenetic changes in specific neurotransmitter systems including glutamate and GABA occur across development and can result in cortical imbalances in the excitatory and inhibitory influences in the brain (see David et al., 2010; Holmes & Ben-Ari, 2001; Sanchez & Jensen, 2001; Takesian & Hensch, 2013; Wong, 2005). Although these maturational changes in the molecular and cellular systems are critical for synapse formation and the organization of immature circuits into functional neural networks (Sur & Rubenstein, 2005; Wong, 2005), age-specific differences in physiology and metabolism appear to increase the susceptibility of the developing brain to the onset of abnormal electrical activity (Ben-Ari & Holmes, 2006; Holmes & Ben-Ari, 2001). In addition, this process of synaptic plasticity has been hypothesized to lower the seizure threshold and promote the reoccurrence of hyperexcitable neural circuits (Holmes & Ben-Ari, 2001; Wong, 2005), which is consistent with findings of increased incidence rates for seizure activity in early childhood (Newton, 2012; Olafsson et al., 2005; Wyllie, 2010).

1.2.3 NEUROPSYCHOLOGY

Around the time that the electrical basis of seizures was identified, it was also

recognized that prolonged or recurrent seizures could have profound, yet often specific, impacts on cognitive function. In 1984, Herman and Whitman introduced a model for understanding the effects of seizure activity on behavior which can be adapted to explain its effects on cognitive function as well. Behaviors evident in individuals with epilepsy appear to be influenced both by the brain-related factors that give rise to epilepsy and the effects of seizures. Specifically, the resulting neuropsychological and behavioral profiles of individuals with chronic seizure activity can be diverse, emerging from a complex matrix of factors including the initial epileptogenic processes, the resulting brain damage that can occur as a result of the recurrent seizures, and even as a result of the course of treatment (Helmstaedter & Kockelmann, 2006). In addition, the role of non-brain related factors, including social and emotional variables must also be acknowledged. The influence of these multiple factors is summarized in the illustration in Figure 1.

Figure 1 ***Factors Influencing Cognition in Epilepsy***



In the mature adult brain, recurrent electrical charges typically but not invariably results in specific abnormalities in cognitive function in the absence of significant structural damage to the brain (Hermann, Seidenberg & Bell, 2002a; Hermann et al.,

2002b). However, emerging evidence from histological investigations has clearly demonstrated that recurrent seizure activity is a dynamic process which can manifest in distinct patterns of morphological and functional changes in the developing brain (see Ben-Ari & Holmes, 2006; Curia et al., 2014; Holmes, 2013). MRI studies have demonstrated significant volumetric reductions in white matter and in brain connectivity in brain regions distant from the region of primary epileptogenesis in individuals with early-onset epilepsy (seizure onset before age 14) relative to those with late-onset seizure activity (Hermann et al., 2002a; Hermann et al., 2002b). Moreover, this pattern of diaschisis appears to correlate with more generalized patterns of neuropsychological dysfunction.

Accordingly, seizure onset early in life appears to disrupt the emergence of distinct regional functional and structural networks underlying cognition in the brain (Ibrahim et al., 2014; Kellerman, Bonilha, Lin, & Hermann, 2015; Widjaja, Zamyadi, Raybaud, Snead, & Smith, 2013a; Widjaja, Zamyadi, Raybaud, Snead, & Smith, 2013b; Widjaja et al., 2015). Specifically, children demonstrate greater internetwork connectivity and weaker intranetwork integration relative to typically developing controls (Widjaja et al., 2015), which has been correlated with various clinical features including epilepsy duration and cognitive outcomes (Ibrahim et al., 2014; Kellerman et al., 2015; Mankinen et al., 2012; Widjaja et al., 2013b). These patterns of functional and structural connectivity abnormalities have been noted to be most notable in individuals with an early age of seizure onset (Doucet et al., 2015). Moreover, there is substantial evidence to suggest that children with epilepsy display patterns of abnormalities which emerge immediately following, or even in some cases, predate the onset of the seizure activity

(Oostrom, Smeets-Schouten, Kruitwagen, Peters, & Jennekens-Schinkel, 2003), which likely reflect the negative effect of seizure activity in addition to the presence of antecedent neurobiological factors associated with the underlying epileptogenesis that may differentially influence cognition and behavior in children (Hermann & Seidenberg, 2007).

In summary, the presence of recurrent seizure activity during periods of increased neural maturation across development is associated with critical alterations in brain development and structure which appears to increase the vulnerability of children to cognitive decline relative to adults (Bjornes, Stabell, Henriksen, & Loyning, 2001; Glosser, Cole, French, Saykin, & Sperling, 1997; Hermann et al., 2002a; Hermann et al., 2002b; Kaaden & Helmstaedter, 2009). It has been suggested that the functional consequences of this disruption to neural networks may depend on the developmental stage and processes that are occurring at the time of seizure onset (Ben-Ari & Holmes, 2006; Hermann et al., 2002b; Spencer-Smith & Anderson, 2009). Significant progress has been made in the adult literature in understanding the cognitive and behavior difficulties that are shared across epilepsy syndromes, as well as those patterns which are unique to each (Bell & Giovagnoli, 2007; Elger, Helmstaedter & Kurthen, 2004; Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007; Lassonde, Sauerwein, Jambaqué, Smith, & Helmstaedter, 2000; Patrikelis et al., 2009). The literature has focused largely on the specific dynamics of functioning in adults with temporal lobe (TLE) and frontal lobe (FLE) epilepsies due to their high prevalence (Manford, Hart, Sander, & Shorvon, 1992; Wiebe, 2000). Additionally, unlike some neurological diseases in which generalized cognitive and behavioral impairments are observed, individuals with

location-specific epilepsies such as TLE and FLE have been found to have patterns of deficits involving cognitive functions specifically mediated by the cerebral area where the epileptogenic focus is located (see Bell & Giovagnoli, 2007; Patrikelis et al., 2009; Risse, 2006; Riva, Saletti, Nichelli, & Bulgheroni, 2002). Specifying the effects of these focal epilepsy syndromes on cognition and behavior in children can provide important insights into the organization of functions in the brain and is critical in order to assist in a better understanding of outcomes following early neurological insults in the developing brain.

1.3 LOCALIZATION-RELATED EPILEPSIES

1.3.1 TEMPORAL LOBE EPILEPSY

Temporal lobe epilepsy (TLE) is a focal-onset syndrome characterized clinically by the development of spontaneous seizure activity originating from structures within the temporal lobes (Chang & Lowenstein, 2003; Engel, 1989; Zhang et al., 2002). TLE is the most commonly diagnosed type of epilepsy, accounting for approximately 80% of all focal cases, with typical age of onset at 6-10 years (Wiebe, 2000). Patients with TLE also often present well-circumscribed underlying pathology and phenotypic expression (Helmstaedter, 2001). In particular, the mesial temporal lobe structures, including the hippocampus and the amygdala, have been demonstrated to be extremely susceptible to epileptogenic processes (see Aroniadou-Anderjaska, Fristch, Qashu, & Braga, 2008).

The genesis and progression of recurrent seizure activity in the temporal lobe appears to be related to the unique anatomical circuitry of the limbic structures and to changes in the electrophysiological functioning of neurons that occur in areas of the temporal lobe across development as a part of a natural process of neurogenesis (see

Kuruba, Hattiangady, & Shetty, 2009; Sharma et al., 2007). Specifically, particular histopathological features have been identified in individuals with TLE including abnormal loss of cells, structural changes including sprouting and cell dispersion and gliosis (see Curia et al., 2014). Preliminary research involving animal and human models suggests that the effect of seizures on neurogenesis in the hippocampal area may be more evident in the immature brain than in the mature adult brain (Rao, Hattiangady, & Shetty, 2008). For example, relative to individuals with adult-onset epilepsy and typically-developing controls, individuals with childhood-onset epilepsy have demonstrated significant reductions in volume of hippocampal tissue (Hermann et al., 2002a; Hermann et al., 2002b). Moreover, volumetric reduction abnormalities were noted outside of the temporal lobe, observed in all total lobar and cerebrum measurements.

1.3.1 FRONTAL LOBE EPILEPSY

In contrast, frontal lobe epilepsy (FLE) is a localization-based disorder that is characterized by recurring seizure activity arising from structures within the frontal lobe. FLE has been identified as the second most common type of focal epilepsy, accounting for approximately 20–30% of cases (Manford et al., 1992). The average age of onset of FLE is between 4-7 years old (Sinclair, Wheatley, & Snyder, 2004). Some studies have suggested that in children, the incidence and prevalence of extratemporal epilepsies (such as FLE) may actually be greater than rates of temporal epilepsies (e.g., Fogarasi, Janszky, Faveret, Pieper, & Tuxhorn, 2001). Clinical presentation of FLE has been noted to be more heterogeneous in terms of location and nature of underlying pathology (Helmstaedter, 2001; Jobst et al., 2000). Research appears to suggest significant differences in seizure semiology between adult and pediatric patients (Fogarasi et al.,

2001).

Less is known about the mechanisms underlying epileptogenesis in individuals with FLE (Kanemura, Sano, Tando, Sugita, & Aihara, 2012). However, the frontal lobes undergo a protracted and well-specified course of neuroanatomical, neurophysiological and neurochemical changes throughout adolescence and into early adulthood (Sowell, Delis, Stiles, & Jernigan, 2001). These changes include synaptogenesis, synaptic pruning, increases in prefrontal myelination and reorganization of synaptic connections (Huttenlocher, 1979; Kinney, Brody, Kloman, & Gilles, 1988). During this period, the human cerebral metabolic rate is also higher than that in adulthood, which appears to increase its susceptibility among the cortical regions to repeated seizure activity (Chugani, Phelps, & Mazziotta, 1987). This process is believed to play a critical role in the development of functional neural networks, and the resulting pathogenesis of repeated seizure activity in the immature brain appears to be retardation of prefrontal lobe growth (Kanemura et al., 2012). Additionally, time-related factors such as epilepsy duration and age at epilepsy onset have been demonstrated to be associated with greater progression of structural abnormalities (Janszky et al., 2005).

1.4 DOMAINS OF FUNCTIONING

As mentioned previously, researchers have described a number of neuropsychological trends within adult populations with TLE and FLE. Consequently, the expected patterns of functioning of individuals with epilepsy will be discussed in the following order of domains: Memory, Executive, Motor, Intellectual and Psychosocial Functioning.

1.4.1 MEMORY FUNCTIONING

1.4.1.1 *Memory Functioning in TLE*

Converging evidence has widely demonstrated the involvement of the temporo-mesial and neocortical structures such as the hippocampus and parahippocampal cortex in memory networks in the brain (e.g., Burianova & Grady, 2007; Burianova, McIntosh, & Grady, 2010; Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). The earliest demonstrations of memory deficits following focal damage to the temporal lobe were derived from studies of the underlying pathology and surgical management of TLE (Milner, 1970; Penfield & Milner, 1958; Scoville & Milner, 1957). Subsequent work using functional and volumetric imaging in typically-developing individuals have widely demonstrated activation in the temporal lobes during completion of measures of memory functioning (e.g., Burianova & Grady, 2007; Burianova et al., 2010). However, individuals with TLE appear to display decreased activation in the temporal lobe during similar tasks (Bonelli et al., 2010). Smaller volume of the hippocampus has also been found to be associated with greater impairments in learning and recall in individuals with TLE (Baxendale, Thompson, & Paesschen, 1998; Corkin et al., 1997; Hermann et al., 2002a; Hermann et al., 2002b; Narayanan et al., 2012; Wilkinson et al., 2012). Moreover, these deficits can be observed in individuals without structural lesions of the temporal lobe (Bengner et al., 2006).

Specifically, individuals with TLE appear to have significant difficulty with the consolidation of information, which involves a process of stabilization of newly encoded memory traces within long-term storage (Helmstaedter, Grunwald, Lehnertz, Gleissner, & Elger, 1997; Hotting, Katz-Biletzky, Malina, & Lindenau, & Bengner, 2010). The

efficacy of this consolidation process has typically been demonstrated on standardized neuropsychological tasks of delayed recall, which assess the retention of recently learned information following a delay of approximately 20-30 minutes (Bell, Fine, Dow, Seidenberg, & Hermann, 2005; Elliott, Isaac, & Muhlert, 2014; Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006). On this type of measure, adults with TLE typically demonstrate significant impairments in declarative or episodic memory (e.g., Bell, 2006; Bell et al., 2005; Bengner et al., 2006; Exner et al., 2002; Jones-Gotman et al., 1997).

Emerging evidence has suggested that individual with temporal lobe dysfunction can also demonstrate poor learning and retention of previously learned information on measures of short-delay or "intermediate" recall, under conditions in which the material to be learned exceeds working memory capacity (supraspan) or takes several minutes to complete, when the information is not amenable to rehearsal or when a distracter task is presented between the study phase and the recall phase (see Baddeley, Jarrold, & Vargha-Khadem, 2011; Brady, Konkle, & Alvarez, 2011; Elliot et al., 2014; Hotting et al., 2010; Jeneson & Squire, 2011). In fact, recall tasks involving delays greater than 10 seconds have been demonstrated to be sensitive to damage to the temporal lobe in both animal (Alvarez, Zola-Morgan & Squire, 1994) and human studies (Hannula, Tranel & Cohen, 2006; Hartley et al., 2007; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Olsen et al., 2009; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema et al., 2007; Rains & Milner, 1994). Accordingly, a number of studies have also demonstrated deficits in verbal and non-verbal memory in TLE during immediate recall conditions (Bell, 2006; Bell et al., 2005; Bengner et al., 2006; Exner et al., 2002; Mameniskiene et al., 2006;). Individuals with TLE also appear to demonstrate unusually rapid memory loss or

accelerated forgetting of information relative to healthy controls, as demonstrated by a significant loss of details following a delay (Lah, Mohamed, Thayer, Miller, & Diamond, 2014; Mameniskiene et al., 2006; Narayanan et al., 2012; Wilkinson et al., 2012), which appears to reflect a failure of memory consolidation (Elliot et al., 2014).

Additionally, a number of neuropsychological and neuroimaging studies have demonstrated hemispheric specialization of memory processing in individuals with late-onset TLE (e.g., Gleissner, Helmstaedter, & Elger, 1998; Golby et al., 2002; Hermann, Seidenberg, Schoenfield, & Davies, 1997; Helmstaedter, Kurthern, Lux, Reuber, & Elger, 2003; Jokeit, Okujava, & Woermann, 2001; Jones-Gotman et al., 2010; Jones-Gotman et al., 1997; Pillon et al., 1999; Powell et al., 2005). Because verbal memory processes are typically subserved by the language-dominant hemisphere, individuals with left-sided TLE often demonstrate deficits in verbal memory, including word list recall and story recall (Helmstaedter & Elger, 1996; Helmstaedter et al., 1997; Jambaqué et al., 2007; Jones-Gotman et al., 2010; Lee, Yip, & Jones-Gotman, 2002). Evidence for a link between right-sided seizure activity and nonverbal memory in adults has been more inconsistent (Alessio et al., 2004; Baxendale et al., 1998; Lee et al., 2002; Smith, Bigel, & Miller, 2011), suggesting that visual-spatial memory such as visual reproduction and facial recognition may be a more bilateral process (Baxendale & Thompson, 2010; Saling, 2009; van Asselen et al., 2006).

Functional neuroimaging studies have confirmed age-related changes in recruitment of regions of the temporal lobe including the hippocampus and posterior parahippocampal gyrus for memory encoding across adolescence (Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Menon,

Boyett-Anderson, & Reiss, 2005). It has been demonstrated that an earlier age of seizure is associated with findings of significant volumetric reduction in total cerebrum and hippocampal tissue (Hermann et al., 2002a; Hermann et al., 2002b) and differential patterns of activation in the temporal lobe (Sidhu et al., 2015). Accordingly, decreased verbal and nonverbal memory efficiency has been observed in children with TLE relative to individuals with late-onset TLE (seizure onset after age 14) (Kaaden & Helmstaedter, 2009). Additionally, standardized memory tests have largely replicated findings of impairments on measures of immediate and delayed recall of narrative information (Gascoigne et al., 2014; Guimaräes et al., 2007; Jambaqué et al., 1993; Jambaqué et al., 2009; Nolan et al., 2004; Rzezak, Guimaräes, Fuentes, Guerreiro, & Valente, 2011; Rzezak, Guimaräes, Fuentes, Guerreiro, & Valente, 2012) and verbal learning, immediate and delayed list recall (Hernandez et al., 2003; Jambaqué et al., 1993; Nolan et al., 2004; Rzezak et al., 2012) relative to typically-developing controls. Particularly, this appears to be notable on tasks with high memory loads which exceed the 'primary memory buffers' of the neocortical working memory system due to delay length or capacity limitations (Gabrieli, Keane, & Stebbins, 1993). Studies have suggested that early seizure onset is associated with a significant neurodevelopmental hindrance in learning efficiency across various recall trials (Hernandez et al., 2003), which becomes most evident across adolescence (Helmstaedter & Elger, 2009). Additionally, it appears that children with TLE also demonstrate increased forgetting of verbal information (Gascoigne et al., 2014) and significant impairments in various aspects of memory for visual designs (Guimaräes et al., 2007; Nolan et al., 2004).

However, contrary to the adult literature, the majority of available research

suggests that hemispheric lateralization is largely irrelevant in predicting the domain of memory impairment in children. While some early studies appeared to demonstrate patterns of lateralized memory impairment in children (e.g., Cohen, 1992; Fedio & Mirsky, 1969; Jambaqué et al., 1993), these studies were limited by differences in seizure severity, age at time of testing and sample sizes between groups. More recently, a number of studies have demonstrated that impairments in verbal memory were comparable between children with left- and right TLE (e.g., Bigel & Smith, 2001a; Camfield et al., 1984; Gleissner, Helmstaedter, Schramm, & Eiger, 2002; Gonzalez, Anderson, Wood, Mitchell & Harvey, 2007; Helmstaedter & Elger, 2009; Nolan et al., 2004).

A cross-sectional study by Helmstaedter and Elger (2009) demonstrated that laterality effects in verbal memory are generally absent early in childhood. Specifically, they found that significant right-left differences were evident for verbal learning only in mid-adulthood (31-50 years old), while differences for verbal recall appeared to emerge in late adolescence. This finding is consistent with a series of longitudinal studies which have demonstrated that impairments in the recall of verbal information are not present early in development in individuals with TLE (Gonzalez et al., 2007), but become apparent across adolescence and young adulthood (Gonzalez, Mahdavi, Anderson, & Harvey, 2012). It has also been suggested that children with TLE are vulnerable to impairments in visual memory functioning regardless of lateralization of seizure activity (Gonzalez et al., 2012; Helmstaedter, Pohl, & Elger, 1995), although there have been some exceptions with facial memory (Bigel & Smith, 2001a; Gonzalez et al., 2007). The discrepancies between studies involving pediatric and adult samples suggest that the memory difficulties of children with TLE may be localized but not lateralized (Gonzalez

et al., 2007).

1.4.1.2 *Memory Functioning in FLE*

Classical studies did not describe memory impairment as a core feature of frontal lobe damage (see Centeno, Thompson, Koepp, Helmstaedter, & Duncan, 2010). Specifically, early studies of adults with frontal lobe lesions found no deficits on measures of memory and recognition compared with typically-developing controls (e.g., Janowsky, Shinamura, & Squire, 1989; Kesner, Hopkins, & Fineman, 1994). Additionally, early studies specifically examining memory functioning in adults with FLE suggested that recall and recognition skills were intact, suggesting that memory dysfunction is not a widespread deficit observed in this population (e.g., Delaney, Rosen, Mattson, & Novelly, 1980; Riva et al., 2002). However, emerging evidence from neuroimaging studies has suggested that frontal lobes may be involved in processes of encoding and retrieving (see Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Centeno et al., 2012; Fletcher, Shallice, & Dolan, 1998; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998). Accordingly, Baldo, Delis, Kramer and Shimamura (2002) found that adults with frontal lobe lesions recalled fewer items from a list following an initial list-learning phase and after short and long delays. Exner and colleagues (2002) also found that adults with FLE demonstrated decreased performance on measures of immediate and delayed verbal and nonverbal tasks relative to control participants. Centeno and colleagues (2012) suggested that approximately 20% of adults with FLE demonstrate impairments in memory functioning.

Furthermore, functional neuroimaging studies have demonstrated that declarative memory formation is associated with age-related increases in activation in specific

regions of the prefrontal cortex (Menon et al., 2005; Ofen et al., 2007). In particular, the emergence of more advanced memory skills including cognitive control mechanisms and strategy use are proposed to be mediated by development of the frontal lobes (Chiu et al., 2006), suggesting that early onset of seizure activity in the frontal regions may result in impairments in these skills. Accordingly, a number of studies have demonstrated impairments in aspects of encoding, free recall and retrieval on tasks of immediate and delayed narrative memory (Nolan et al., 2004; Picard et al., 2009), verbal list learning (Hernandez et al., 2003; Lopes, Monteiro, Fonseca, Robalo, & Simões, 2014), and abstract-visual memory (Nolan et al., 2004) in children with FLE. Notably, most studies have not described material-specific effects related to the lateralization of the epileptic focus (e.g., Centeno et al., 2012; Exner et al., 2002; Nolan et al., 2004).

1.4.1.3 *Comparison of Memory Functioning in FLE & TLE*

When performance is directly compared between the two groups, the findings have also been mixed. A few studies have found that individuals with TLE perform significantly worse than individuals with FLE on measures of verbal (Breier et al., 1996; Culhane-Shelbourne, Chapieski, Hiscock, & Glaze, 2002; Delaney et al., 1980) and visual memory (Breier et al., 1996). However, a growing number of studies have found no significant differences between individuals with FLE and TLE, suggesting that memory impairments may not be unique to a particular epilepsy syndrome (Cahn-Weiner, Wittenberg, & McDonald, 2009; Culhane-Shelbourne et al., 2002; Exner et al., 2002; Hernandez et al., 2003; Jambaqué et al., 1993; Lendt et al., 2002; Nolan et al., 2004; Rai et al., 2015; Sinclair et al., 2004).

1.4.1 EXECUTIVE FUNCTIONING

1.4.1.1 *Executive Functioning in FLE*

The role of the prefrontal cortex in subserving the complex behavioral and cognitive processes associated with executive functioning is well supported by evidence from lesion and neuroimaging studies (see Banich, 2009). Evidence linking executive function with the frontal lobes was first demonstrated in a series of case studies described by Milner (1962) and Luria (1966). Specifically, early case reports revealed significant impairments in aspects of executive functioning including anticipation, planning, execution and self-monitoring following injury to the frontal lobe due to trauma, degenerative disorders or tumors. Subsequent work involving neuroimaging in healthy controls have consistently revealed patterns of activation in the prefrontal cortex during the performance of tasks involving executive function (Berman et al., 1995; Marsh et al., 2006; Phelps, Hyder, Blamire, & Shulman, 1997). Findings of individual differences across tasks involving neurologically intact individuals suggest that executive functioning may involve several distinct subcomponents, including the ability to inhibit impulsive behaviors, the ability to shift the task set guiding behavior, and the ability to update the contents of working memory (Anderson, 2002; Banich, 2009).

Individuals with FLE appear to demonstrate insufficient activation in areas of the frontal lobes during tasks of executive functioning (Swartz et al., 1996). Consistent with this finding, a number of studies involving adult patients with FLE have described impairment in processes related to various aspects of executive functioning, including working memory (Exner et al., 2002; Helmstaedter et al., 1996) and aspects of metacognition (Helmstaedter, Kemper, & Elger, 1996; Upton & Thompson, 1997a;

Upton & Thompson, 1997b). For example, working memory is the process by which information is maintained and manipulated in mind when information is presented for learning (Baddeley, 1992; Jeneson & Squire, 2011), through an active process involving executive regulation and attention (Winston et al., 2013). Functional magnetic resonance imaging (fMRI) studies have demonstrated activation patterns in the bilateral frontal lobe during working memory tasks in typically developing individuals (Owen, McMillan, Laird, & Bullmore, 2005). These activation patterns have been found to be reduced in individuals with focal epilepsy (Vlooswijk et al., 2011), suggesting that working memory is dependent on frontal lobe integrity. Helmstaedter and colleagues (1996) examined specific patterns of neuropsychological impairment in a group of patients with FLE and found that approximately two-thirds of the patients with FLE demonstrated impairment on measures of executive functioning. Additionally, executive functioning deficits have been observed in patients following resection of the frontal region (Dulay, Busch, Chapin, Jehi, & Najm, 2013).

Boone and colleagues (1988) presented one of the earliest case studies on childhood FLE, describing impaired performance on tasks of attention, psychomotor speed, cognitive flexibility and planning ability. Similarly, Jambaqué and Dulac (1989) described difficulties with processing speed in a child with frontal-onset seizure activity. More recently, a number of studies have found that children displayed impairments on various aspects of executive skills (Luton, Burns, & DeFilippis, 2010; Riva et al., 2002; Riva et al., 2005; Sinclair et al., 2004). For example, children with FLE appear to demonstrate significant difficulties with aspects of processing speed and working memory when compared to available norms (Auclair, Jambaqué, Olivier, David, & Eric,

2005; Braakman et al., 2012; Bulteau et al., 2000; Hernandez et al., 2003). Difficulties in executive functioning appear to be more significant in children with early-onset FLE relative to late-onset FLE (Luton et al., 2010). Children with FLE have been described as demonstrating significantly greater difficulties in aspects of metacognition and behavioral regulation than neurotypical youth on a parent report measure of executive functioning (Campiglia et al., 2014; Luton et al., 2010; MacAllister et al., 2012). Additionally, individuals with early-onset FLE also appear to be more susceptible to deficits in self-monitoring, as indicated by an increased number of intrusions on a list-learning task (Hernandez et al., 2003; Riva et al., 2002). In general, these patterns of deficits appear to be unrelated to hemispheric effects of seizure localization, with regards to bilateral and unilateral foci (Culhane-Shelbourne et al., 2002; Hernandez et al., 2002). These findings of significant difficulties in executive functioning have even been found in pediatric cases in the absence of tumoral, gliotic or structural localised lesions (Prévost et al., 2006; Riva et al., 2002; Riva et al., 2005).

1.4.1.2 *Executive Functioning in TLE*

Executive dysfunction (ED) has also been observed in a number of studies of adults with TLE (see Stretton & Thompson, 2012; Zamarian et al., 2011). Hermann and Seidenberg (2007) conducted a cluster analysis involving individuals with TLE and found that approximately 29% displayed significant difficulties in memory, executive functioning and processing speed across a series of EF measures. In contrast, it has been generally argued that the acquisition and initial encoding of information is relatively intact in individuals with TLE (Cave & Squire, 1992; Stretton et al., 2013), enabling them to perform normally on measures assessing working memory. For example, individuals

with damage to the temporal lobe have been found to display intact working memory performance for strings of digits, words and nonsense visual patterns and shapes (Baddeley & Warrington, 1970; Cave & Squire, 1992; Drachman & Arbit, 1966; Milner, 1972; Wickelgren, 1968). However, emerging evidence seems to suggest that individuals with TLE may actually display significant deficits in working memory as well (Winston et al., 2013). While recent functional imaging studies have demonstrated activation in the medial temporal lobe during measures of working memory in typically-developing individuals (Axmacher et al., 2007; Cashdollar et al., 2009; Mainy et al., 2007; Schon, Quiroz, Hasselmo & Stern, 2009), individuals with TLE appear to have progressive deactivations in the hippocampus as working memory task demands increase (Stretton et al., 2012; Winston et al., 2013). Accordingly, a number of studies have found that individuals with left and right TLE demonstrate poorer performance across measures of working memory relative to control participants (Abrahams et al., 1999; Axmacher et al., 2007; Black et al., 2010; Owen et al., 2005; Stretton et al., 2013; Wagner, Sziklas, Garver, & Jones-Gotman, 2009).

Some studies have replicated this finding of ED in children with TLE (e.g., Guimaräes et al., 2007; Rzezak et al., 2009; Rzezak et al. 2007; Rzezak et al., 2012). It has been estimated that executive dysfunction can be observed in up to 50-84% of children and adolescents with TLE (Igarashi et al., 2002; Rzezak et al., 2009; Rzezak et al., 2007; W. Wang et al., 2011). In fact, earlier age of onset has been associated with more difficulty on tasks of executive functioning in individuals with late-onset TLE individuals with TLE (Strauss, Hunter, & Wada, 1993). For example, children with TLE have been found to be impaired on tasks of processing speed (Hernandez et al., 2003;

Schmidt et al., 2015) and on a parent-report measure of executive dysfunction (Campiglia et al., 2014), while Longo, Kerr and Smith described significant difficulties in working memory.

1.4.1.3 *Comparison of Executive Functioning in FLE & TLE*

Only a few studies have directly compared FLE and TLE groups on measures of executive function. The majority of these studies have involved only adult participants with later-onset epilepsy (e.g., Cahn-Weiner et al., 2009; Delaney et al., 1980; Exner et al., 2002; Helmstaedter et al., 1996; Rai et al., 2015). Some studies have suggested that adults with FLE displayed more significant weaknesses in working memory, psychomotor speed and attention/memory span than those with TLE (Helmstaedter et al., 1996). However, the majority of studies have found no significant differences between adults with FLE and TLE (Cahn-Weiner et al., 2009; Exner et al., 2002; Rai et al., 2015). With regards to early-onset epilepsy, a few studies have demonstrated that children with FLE display more difficulty with processing speed relative to matched peers with TLE (Hernandez et al., 2003; Sinclair et al., 2004). Additionally, individuals with FLE were found to demonstrate an increased number of intrusions relative to individuals with TLE (Hernandez et al., 2003). However, other studies have failed to discriminate between children with FLE and TLE on measures of executive functioning (Campiglia et al., 2014; Longo et al., 2013).

1.4.1 MOTOR FUNCTIONING

1.4.1.1 *Motor Functioning in FLE*

The frontal lobes have widely been demonstrated to be involved in the mediation of motor planning and coordination (Meier, Afalo, Kastner, & Graziano, 2008).

Recurrent seizure activity in the frontal lobe appears to result in significant changes in motor networks in the brain, as demonstrated through neuroimaging (Woodward et al., 2014a; Woodward et al., 2014b), direct cortical stimulation (Branco et al., 2003) and transcranial magnetic stimulation (Labyt, Houdayer, Cassim, Bourriez, Derambure, & Devanne, 2007). Additionally, motor symptoms are commonly observed during the ictal period of a seizure in individuals with FLE (Woodward et al., 2014b). Accordingly, a number of studies have examined motor coordination and sequencing skills in adults with late-onset FLE and found significant impairments (Helmstaedter et al., 1996; Upton & Thompson, 1996). When specifically examining these functions in children with FLE, Hernandez and colleagues (2002) described significant difficulties on a task motor coordination and speed. Specifically, approximately 88% of children with FLE obtained scores that fell 1 SD or below the available norm values, while 44% performed 2 SD below. Lendt and colleagues (2002) found that approximately 67% of children with FLE demonstrate impairments in motor coordination. This is consistent with the results of other studies which have also demonstrated significant difficulties with motor coordination and speed compared to typically-developing controls (Helmstaedter et al., 1996; Riva et al., 2002; Riva et al., 2005; Sinclair et al., 2004).

1.4.1.2 *Motor Functioning in TLE*

Helmstaedter and colleagues (1996) compared the performance of individuals with TLE to normative standards and found no significant impairments in motor sequencing. However, one study specifically examining motor functioning in children with TLE found that approximately 38% of participants performed 1 SD below average and 25% performed 2 SD below average when compared to available norms (Hernandez

et al., 2002). This is consistent with another study that additionally found that approximately 25% of participants with TLE demonstrated impairments with motor coordination and speed (Lendt et al., 2002).

1.4.1.3 *Comparison of Motor Functioning in FLE & TLE*

Helmstaedter and colleagues (1996) described more significant deficits in motor coordination and speed in adults with FLE than with TLE. A number of other studies have additionally found that the performance of children with FLE was significantly inferior to that of children with TLE (Hernandez et al., 2002; Lendt et al., 2002; Sinclair et al., 2004).

1.4.2 INTELLECTUAL FUNCTIONING

1.4.2.1 *Intellectual Functioning in FLE*

Most studies investigating the neural basis of intelligence have suggested that intelligence differences emerge from a functional network primarily involving the frontal lobe structures (See Jung & Haier, 2007). Specifically, brain imaging data obtained with positron emission tomography (PET), functional magnetic resonance imaging (fMRI) commonly demonstrate activation in frontal brain areas including the lateral prefrontal cortex during completion of intellectually-demanding measures which appear to correlate highly with performance (Duncan et al., 2000; Gray, Chabris, & Braver, 2003; Langer et al., 2012; Pamplona, Neto, Rosset, Rogers, & Salmon, 2015; Song et al., 2008). It has generally been suggested that intellectual functioning can be unaffected in adults with late-onset FLE (Farrant et al., 2005; Helmstaedter et al., 1996; Milner, 1975; Upton & Thompson, 1996). This is consistent with findings of adults with frontal lobe lesions who also demonstrate intact performances on measures of IQ (Hebb & Pennfield, 1940;

Milner, 1964; Stuss, Gallup, & Alexander, 2001).

However, it has been posited that intelligence reflects a cumulative process which undergoes rapid growth across development (Spreen, Risser, & Edgell, 1995). Specifically, it has been demonstrated that level of intellectual functioning differs as a function of changes in patterns of cortical growth that manifest across childhood and adolescence (Shaw et al., 2006). This appears to be related to the structural and metabolic reorganization of neural circuitry that occurs in the prefrontal cortex during this time (Shaw et al., 2006). Accordingly, research has frequently demonstrated that children with early-onset FLE demonstrate poorer performance on measures of intellectual functioning relative to normal controls (Braakman et al., 2012; Nolan et al., 2003; Prévost, Lortie, Nguyen, Lassonde, & Carmant, 2006; Sinclair et al., 2004). For example, Lopes and colleagues (2013) compared performance of children with FLE to a sample of typically developing children on a task of intellectual functioning and found that children with FLE performed significantly poorer on the Full Scale IQ (FSIQ), Verbal Comprehension (VCI), and Processing Speed (PSI) Indices. Specifically, they demonstrated that approximately 28% of participants with FLE performed in the below average range and 19% performed in the borderline range. Additionally, individuals with early age of onset of FLE have been demonstrated to have significantly greater impairment in intellectual functioning relative to individuals with late onset FLE (Dikmen & Matthews, 1977; Dikmen, Matthews & Harley, 1975; O'Leary et al., 1983). Consequently, it has been suggested that FLE with onset in early development results in depressed intellectual functioning (Braakman et al., 2012). It has been suggested this pattern might be related to decreased connectivity within the frontal lobe (Braakman et al., 2013). Most notably,

individuals with FLE appear to have difficulty with aspects of 'fluid intelligence', including processing speed and working memory skills (Gottlieb, Zelko, Kim, & Nordli, 2012; Lopes et al., 2013; Roca et al., 2010).

1.4.2.2 *Intellectual Functioning in TLE*

It has been reported that the proportion of individuals with TLE who demonstrate impairments in intellectual functioning is relatively small, suggesting that IQ may not be affected by the pathogenic effects of recurrent seizure activity in the temporal lobe (W. Wang et al., 2011). Previous studies have largely suggested that intellectual functioning can be relatively unaffected in late-onset TLE when compared to typically-developing control participants (Aikia, Salmenpera, Partanen, & Kalviainen, 2001; Hermann et al., 2002a; Hermann et al., 2002b; Kaaden & Helmstaedter, 2009; Seidenberg, Hermann, Haltiner, & Wyler, 1993; Upton & Thompson, 1996). Additionally, intellectual level appears to be stable even after resection of the temporal lobes (Williams et al., 1998).

However, a number of studies have suggested that participants with early-onset TLE may display significantly lower performance on a measure of cognitive functioning when compared with healthy controls (Hermann et al., 2002a; Hermann et al., 2002b; Mataro, Junque, Vinas, & Escartin, 1998; Szabó et al., 1998) or when compared with individuals with late-onset TLE (Cormack et al., 2007; Kaaden & Helmstaedter, 2009). For example, Cormack and colleagues (2007) found that intellectual dysfunction was highly prevalent in children with early-onset TLE, with approximately 57% presenting with an IQ below 79. Guimaräes and colleagues (2007) also found that children with TLE demonstrated significant lower intellectual functioning than control participants, although they notably limited participation of individuals with IQ scores less than 70, resulting in

an overall IQ estimate that was still in the average range for their study sample. This finding of decreased intellectual functioning is unexpected given the focal epileptogenic processes typically associated with TLE (Hermann et al., 2002a; Hermann et al., 2002b; Kaaden & Helmstaedter, 2009), and suggests a particular vulnerability of the developing brain to early seizure activity (Cormack et al., 2007).

1.4.2.3 *Comparison of Intellectual Functioning in FLE & TLE*

A limited number of studies have attempted to directly compare the pattern of intellectual functioning between focal epilepsy syndromes. Consistent with expectations placed forward by the functional specialization theory, a number of studies have demonstrated a trend for children with FLE to have lower estimates of intellectual functioning compared to children with TLE (Hernandez et al., 2002; Lopes et al., 2013; Nolan et al., 2003). Other studies have been more variable. For example, Exner and colleagues (2002) found no significant differences in the IQ estimates between individuals with FLE and TLE, with approximately 60% of FLE and 50% of TLE participants in their sample demonstrating below average performance on a measure of intellectual functioning. It is notable that the age of seizure onset in the group of TLE patients was significantly lower than the FLE group, which may have contributed to the decreased estimates of intellectual functioning demonstrated by the TLE participants. However, other emerging studies have also suggested that when children with FLE and TLE are directly compared, there are no significant differences in their level of cognitive functioning (Hernandez et al., 2003; Nolan et al., 2004).

1.4.3 PSYCHOSOCIAL FUNCTIONING

1.4.3.1 *Psychosocial Functioning in TLE*

Converging evidence from both neuroimaging and case studies have demonstrated the role of the temporal lobes in conveying susceptibility to various internalizing behavior problems. Congenital and acquired brain damage of the temporal lobe have been found to result in patterns of affective dysregulation, including anxiety, and depression (e.g., Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). This is thought to reflect dysfunction of the limbic structures, which have been implicated in the modulation of emotional responses (Helmstaedter & Kurthen, 2001; Swinkels, Van Emde Boas, Kuyk, Van Dyck, & Spinhoven, 2006). Neuroimaging studies in typically-developing adults have additionally demonstrated that temporal lobes structures such as the hippocampus and amygdala are significantly reduced in size in the context of depression (Sheline, 2003). Consequently, it has been suggested that recurrent seizure activity originating in the temporal lobes may disrupt the functioning of these structures and increase the vulnerability for depression in individuals with TLE (Hecimovic et al., 2014; Salpekar et al., 2013), given their shared pathogenic mechanisms (Pereira & Valente, 2013). Accordingly, a number of studies have reported an increased rate of internalizing behavior problems in individuals with late-onset TLE compared with a normative sample (Quiske, Helmstaedter, Lux, & Elger, 2000; Perini et al., 1996; Pizzi, Chapin, Tesar, & Busch, 2009). For example, Sanchez-Gistau and colleagues (2010) demonstrated frequent comorbidities of anxiety and depression. It has been suggested that the rates of internalizing behaviors in individuals with late-onset TLE may be approximately 43-55% (Hecimovic et al., 2014; Helmstaedter & Witt, 2012; Kanner,

2003; Perini et al., 1996).

Research examining the behavioral profiles of children with TLE has been more limited (Cankurtaran, Ulug, Saygi, Tiryaki, & Akalan, 2005; McLellan et al., 2005; Pereira & Valente, 2013; Salpekar et al., 2013). However, emerging evidence appears to suggest that internalizing behavior problems may be even more prevalent than is typically seen in individuals with late-onset TLE. A number of studies have reported rates as high as 80% of participants had difficulty with depressive symptoms (McLellan et al., 2005; Pereira & Valente, 2013). It has also been suggested that children with TLE demonstrate high frequency of other comorbid internalizing behaviors, including anxiety disorders (Salpekar et al., 2013). Participants with temporal lobe foci also demonstrated difficulties with social, somatic and attention problems on a parent-report measure of emotional/behavioral functioning (Salpekar et al., 2013).

1.4.3.2 *Psychosocial Functioning in FLE*

Early reports suggest that frontal anomalies may also result in characteristic patterns of emotional and behavioral functioning (Helmstaedter, 2001; Prévost et al., 2006). For instance, in a number of case studies of children with FLE (e.g., Boone et al., 1988; Jambaqué & Dulac, 1989; Perez, Davidoff, Despland, & Deonna, 1993), the onset of the epilepsy was marked by sudden impairments in inattention, hyperactivity, impulsiveness, aggressiveness and disinhibition. Emerging research has suggested that children with FLE may be especially vulnerable to the emergence of behavioral adjustment and self-regulation (Colonelli et al., 2012; Parisi et al., 2010). It has been suggested that the overall prevalence of psychiatric comorbidity in children with FLE is approximately 52% (Colonelli et al., 2012), with the prevalence of externalizing behavior

problems estimated at approximately 10-30%. Additionally, parent-report measures of psychosocial functioning have indicated greater than typical difficulties with attention (Hernandez et al., 2003; Lassonde et al., 2000; Prévost et al., 2006; Sinclair et al., 2004), social (Lassonde et al., 2000; Sinclair et al., 2004) and thought problems (Lassonde et al., 2000; Sinclair et al., 2004). However, Sinclair and colleagues (2004) also found that children with FLE were rated as having elevated internalizing behavior problems.

1.4.3.3 *Comparison of Psychosocial Functioning in FLE & TLE*

With regards to patterns of psychological/behavioral functioning across various epileptic syndromes, some studies have suggested that found that the most commonly described area of difficulty reported for patients with extratemporal foci was with attention problems (Hernandez et al., 2003; Salpekar et al., 2013), while somatic problems and depression were increased in patients with temporal lobe seizure foci (Salpekar et al., 2013). However, other studies have found no significant differences between children with FLE versus TLE. For example, Sinclair and colleagues (2004) reported that both groups demonstrate significant difficulties with internalizing behavior function relative to normative standards. Almane, Jones, Jackson, Seidenberg and Hermann (2014) compared rates of behavior and psychological problems among groups of children with FLE, TLE and a normative sample. They found that the children with epilepsy were described as significantly more impaired across several scales (including Total Problems, Total Competence, Total Internalizing, Total Externalizing, School Competence, Thought Problems, and Attention Problems) when compared with healthy controls. However, when Almane and colleagues examined specificity of parent-reported behavioral issues between epilepsy syndromes, they found no specific syndrome effects.

These findings suggest that the behavioral differences may be largely independent of epilepsy syndrome in children with recurrent seizure activity.

1.5 SUMMARY OF EXISTING LITERATURE

Over the past few decades, significant progress has been made in attempting to identify syndrome-specific neurobehavioral phenotypes associated with localization-related epilepsies such as TLE and FLE (see Elger et al., 2004; Nolan et al., 2003). Based on the available literature, distinct profiles have emerged, with individuals with TLE demonstrating increased impairments in short- and long-term memory functioning compared to typically-developing control participants, while individuals with FLE demonstrate more significant difficulties with motor, executive and intellectual functioning. While there has been less research attempting to identify the behavioral correlates of FLE and TLE, it has been posited that individuals with FLE demonstrate more significant difficulties with aspects of externalizing behavior problems while individuals with TLE demonstrate increased impairments in internalizing behavior problems.

However, reported studies of chronic epilepsy have been significantly biased towards describing the cognitive and behavioral profiles of individuals with late-onset TLE and FLE, despite the high incidence and prevalence rates of early childhood-onset epilepsies. This is particularly problematic, given that many cases of late-onset seizure disorders result from an identifiable injury or insult (symptomatic) such as tumors, venous malformations and mesial temporal sclerosis (Salanova et al., 1998), while children typically present with recurrent seizures for which there is no clear identifiable cause (idiopathic). Consequently, the observed pattern of cognitive and behavioral

deficits in adulthood may be related to the underlying condition rather than the effects of the seizure disorder itself (Culhane-Shelbourne et al., 2002).

Accordingly, risk factors for the development and severity of cognitive deficits in children with FLE and TLE have not been clearly specified. Studies of epilepsy-related factors, such as age at seizure onset and seizure type or frequency, have been largely inconsistent with regards to their impact on the emergence of cognitive and behavioral impairments. The most prevalent finding has been for age at onset of seizure activity as a significant risk factor for poorer cognitive outcome (Berg et al., 2008; Bulteau et al., 2000; Cormack et al., 2007; Derry et al., 2008; Exner et al., 2002; Hernandez et al., 2002; Lopes et al., 2014; Nolan et al., 2003; Prévost et al., 2006; Riva et al., 2002; Riva et al., 2005). Other variables have also been described as possible moderators of cognitive decline including seizure frequency (Derry et al., 2008; Nolan et al., 2003; Riva et al., 2002; Upton & Thompson, 1996), lateralization of the epileptic focus (Hernandez et al., 2002; Riva et al., 2002), use of more than two anti-epileptic drugs (AEDs) (Bulteau et al., 2000; Derry et al., 2008; Nolan et al., 2003), seizure severity (MacAllister et al., 2012; Rzezak et al., 2009) and duration of epilepsy (Bigel & Smith, 2001a; Exner et al., 2002; Nolan et al., 2004; Lopes et al., 2014; Riva et al., 2005; Upton & Thompson, 1996).

For example, it has also been found that the relationship between epilepsy syndrome and intellectual ability is moderated by number of AEDS and seizure frequency (Berg et al., 2008; Nolan et al., 2003). The effect of age of onset appears to be the most significant predictor of reduced intellectual functioning and is present even when factors such as seizure control, number of AEDs, duration of epilepsy and extent of pathology are controlled (Cormack et al., 2007; Kaaden & Helmstaedter, 2009; Korman,

Krsek, Duchowny, Maton, Pacheco-Jacome, & Rey, 2013; Vasconcellos et al., 2001), implying that developmental processes have an independent effect on cognitive outcome. However, other studies have been more inconsistent regarding the association among these factors, demonstrating no correlation between the results on various cognitive tests and epilepsy risk factors (Braakman et al., 2012; Hernandez et al., 2002; Lopes et al., 2014; MacAllister et al., 2012; Prévost et al., 2006; Riva et al., 2005). One of the biggest methodological weaknesses of previous studies has been the failure to systematically examine the impact of these aforementioned features on neurocognitive and behavioral functioning (Hernandez et al., 2002).

Another notable limitation of the existing literature has been that most studies have only compared performance in one domain of functioning and/or with a sample from only one population (e.g., only TLE or only FLE), rather than demonstrating possible disassociations by comparing performance on various domains of functioning between TLE and FLE samples (Culhane-Shelbourne et al., 2002). Furthermore, it has been suggested that many studies have involved the use of different selection criteria and neuropsychological test batteries and measures that were neither age-specific nor sufficiently sensitive to detect subtle findings or deficits in children (Centeno et al., 2010; Cormack, Vargha-Khadem, Wood, Cross, & Baldeweg, 2012). It has also been argued that the existing literature may be limited and more inconsistent in findings due to relatively low sample sizes in studies of childhood-onset epilepsy (Longo et al., 2013), particularly in studies attempting to directly compare between focal epilepsies (see Table 1). A larger sample may allow more robust statistical analysis patterns of functioning with specific epilepsy variables such as effects of laterality and seizure localization.

Additionally, the existing literature has largely failed to explicitly examine the cognitive and behavioral profiles of children with medication-resistant epilepsy, despite indications that refractory seizures are associated with a greater degree of impairment in children (e.g., Bjornes et al., 2001; Nolan et al., 2003).

Table 1 ***Studies Comparing Children with FLE and TLE***

Reference	TLE	FLE	Memory	EF	Motor	Intell	Psy
Campiglia et al. (2014)	25	28	-	X	-	-	-
Culhane-Shelbourne et al. (2002)	12	15	X	X	-	-	-
Hernandez et al. (2002)	8	16	-	X	X	-	-
Hernandez et al. (2003)	16	16	X	X	-	-	X
Jambaqué et al. (1993)	29	12	X	-	-	-	-
Lendt et al. (2002)	12	12	X	X	X	X	
Longo et al. (2013)	47	19	-	X	-	-	-
Nolan et al. (2003)	40	34	-	-	-	X	-
Nolan et al. (2004)	32	25	X	-	-	-	-
Riccio et al. (2015)	18	10	X	X		X	

Another limitation of the existing literature regards the treatment and evaluation of intellectual functioning. Many studies have incorporated exclusionary criteria limiting the inclusion of participants with Full-Scale IQ scores <70 (e.g., Bailet & Turk, 2000; Bell, 2006; Gleissner et al., 2002; Hermann et al., 2007; Hernandez et al., 2003; Lopes et al., 2014; Luton et al., 2010). While this has typically been conducted in order to increase the homogeneity of the sample, this practice is problematic in that this represents a significant proportion of the typical population of children with epilepsy (Longo et al., 2013) and renders the clinical groups less representative of the population with epilepsy (Campiglia et al., 2014). Additionally, individuals with intellectual impairment are commonly seen in clinical practice, and other publications have been able to assess cognitive functioning meaningfully in these individuals (Gonzalez et al., 2007; Nolan et al., 2004; Sinclair et al. 2004). In other studies, an IQ score within the average range has

been specifically used as an inclusion criterion for participation (e.g., Culhane-Shelburne et al., 2002; Gascoigne et al., 2014; Gleissner et al., 2002; Guimaräes et al., 2007; Hernandez et al., 2003; Lassonde et al., 2000), which raises the concern of a selection bias in the literature. Finally, IQ has sometimes been used a covariate in studies of epilepsy (e.g., Gascoigne et al., 2014; Nolan et al., 2004; Upton & Thompson, 1996), despite indications that this treatment of the IQ variable is inappropriate in individuals with neurodevelopmental or acquired conditions (Dennis et al., 2009; Hebb, 1947; Hebb, 1949; Williams & Mateer, 1992). It has been argued that this practice is problematic given that intelligence is an outcome measure of recurrent seizure activity (Hershey et al., 1998).

Additionally, while most of the existing studies have described full-scale IQ estimates derived from measures in the Wechsler series, most have used previous editions of the test or combined data across several prior test editions (e.g., Alessio et al., 2004; Bailet & Turk, 2000; Bell, 2006; Berg et al., 2008; Blackburn et al., 2007; Cormack et al., 2007; Cormack et al., 2012; Culhane-Shelbourne et al., 2002; Gonzalez et al., 2007; Guimaräes et al., 2007; Hermann et al., 2007; Hernandez et al., 2002; Hernandez et al., 2003; Lopes et al., 2014; Luton et al., 2010; Nolan et al., 2004; Riccio, Pliego, Cohen, & Park, 2015; Riva et al., 2002; van Mil, Reijis, van Hall, & Aldenkamp, 2008). However, it has been indicated that content and structure of the WISC-III and WISC-R is significantly different from the WISC-IV (Sattler & Dumont, 2004; Strauss, Sherman, & Spreen, 2006), which limits the generalizability of the findings (Sherman, Brooks, Fay-McClymont, & MacAllister, 2012). Studies exploring differences between TLE and FLE typically have utilized the FSIQ as an outcome measure. The FSIQ includes measures of

working memory and processing speed, with the rationale being that research that suggests both working memory and processing speed are important factors that contribute to overall intellectual functioning (e.g., Heinz-Martin, Oberauer, Wittmann, Wilhelm, & Schulze, 2002). However, there is a significant body of evidence suggesting that individuals with FLE have more difficulty with working memory and processing speed, which may deflate their score on the FSIQ (Hernandez et al., 2003; Longo et al., 2013). Consequently, it is critical that studies employ a measure of intellectual functioning that is less dependent on working memory and processing speed in order to derive a purer estimation of general intellectual functioning in children with TLE and FLE.

With regards to the executive functioning literature, one significant limitation has been that few studies have incorporated both objective and subjective measures of executive functioning. It has been argued that many laboratory tests of executive functioning lack ecological validity and may not be appropriate for assessing frontal lobe functions in children (Luton et al., 2010), which may explain some of the discrepancies in the literature (Upton & Thompson, 1996). Consequently, a number of editorials and emerging studies have highlighted the importance of incorporating both report and laboratory measures of neuropsychological functioning (Dennis et al., 2014; Luton et al., 2010; MacAllister et al., 2012).

Finally, a limitation and contributing factor to the discrepant findings within the literature has been the significant variability in the measures employed to characterize memory functioning (Williams & Haut, 1995; Yeates, Enrile, Loss, Blumenstien, & Delis, 1995). Many of the measures described were designed for adults and may not be developmentally appropriate for use with children and adolescents (Williams et al.,

2001). Consequently, it is important to explore memory functioning on a standardized measure that is sensitive to memory functioning in children. Additionally, it has been suggested that one limitation with previous research has been its focus on strictly quantitative aspects of learning and memory (i.e., "what" information is remembered), to the exclusion of more qualitative process elements (i.e., "how" information is remembered) (Centeno et al., 2010).

1.6 STUDY RATIONALE

In summary, children appear to be particularly vulnerable to the adverse effects of epilepsy on neurodevelopmental processes. Emerging research provides strong evidence of a significant neurodevelopmental hindrance in individuals with an earlier onset of seizure activity. Studying pediatric populations provide a better understanding of the impact of the lesion and epileptogenic activity in the absence of long-lasting epilepsy or medication exposure (Helmstaedter & Elger, 2009). Specifically, targeted studies involving pediatric populations could help to disentangle the impact of chronic seizure activity on cognitive, behavioral and emotional problems at different stages of brain development (Chapieski et al., 1994). Understanding the specific cognitive and behavioral profiles of children with focal epilepsy has particular clinical importance for identifying appropriate recommendations and accommodations for care within the medical, family, and school settings.

In particular, investigation of the effect of recurrent seizure activity on cognitive and psychosocial development of children with intractable epilepsy is critical. Specifically, the use of information from the neuropsychological assessment can also play an important role in the pre-surgical work-up when determining eligibility for

resective surgery. Correct identification and removal of the epileptogenic foci in the brain has implications for obtaining successful outcomes with regards to seizure control for patients with medically intractable epilepsy. The results of the neuropsychological assessment are often compared with pre-surgical neurodiagnostic findings (EEG, MRI, MEG, and PET) to improve lateralization and localization of the epileptogenic zone (Loddenkemper & Kotagal, 2005). It has even been argued that the pre- and post-operative assessment of memory and executive functioning can be used as standards for the quality and outcome control of surgical treatment (Helmstaedter & Elger, 2009). However, the value of this approach is predicated on the idea that specific and localized cognitive profiles can be observed based on a particular pattern of brain function (or dysfunction). This highlights the importance of determining consistent patterns of functioning across the different epilepsy syndromes and at various points of development.

Consequently, the purpose of the current study was to make a significant contribution to the epilepsy literature by directly comparing cognitive and behavioral deficits in children and adolescents with TLE and FLE using developmentally appropriate assessment tools.

2 SPECIFIC AIMS AND HYPOTHESES

The first objective of this study was to determine whether children with TLE and FLE demonstrate impairments in aspects of intellectual, motor, memory and executive functioning. Specifically, performance on a number of neuropsychological measures of cognitive, behavioral and emotional functioning routinely used for presurgical evaluation was compared against standardized norms and between groups. Based on traditional assumptions, it was hypothesized that participants with seizures originating in the temporal lobe would demonstrate significant weaknesses in immediate and delayed verbal narrative memory, immediate and delayed verbal list learning, immediate abstract visual memory and an increased rate of forgetting of information relative to normative expectations and to participants with FLE. However, it was expected that their performance on measures of intellectual, motor and executive functioning would be intact relative to normative expectations.

In contrast, it was hypothesized that participants with FLE would display significant impairments in aspects of executive functioning including metacognition and behavioral regulation on a parent-report measure relative to reference values and to participants with TLE. Participants with FLE would also demonstrate significant deficits on laboratory measures of processing speed and working memory and demonstrate significantly slower performance on a task of motor coordination when compared with normative values and participants with TLE. Finally, it was hypothesized that participants with FLE would display lower estimates of overall intellectual functioning compared to normative expectations and to participants with TLE. By contrast, it was expected that their performance on measures of memory functioning would be within normal limits.

The second objective of the study was to examine whether children with TLE and FLE demonstrate characteristic patterns of psychosocial functioning. Based on past studies, it was hypothesized that participants with TLE would display significantly higher scores on a scale of internalizing behavior problems, while participants with FLE would demonstrate significantly higher scores on a scale of externalizing behavior problems. Additionally, given the clinical importance of identifying individuals with scores that fall in the "clinically significant" range of pathology, scores on specific subscales within the internalizing and externalizing domains were examined. Specifically, it was hypothesized that a higher proportion of participants with TLE would present with scores that fall in the "clinical"/at-risk" range on the "Internalizing" factor scale and related subscales, while a higher proportion of participants with FLE would present with scores that fall in the "clinical"/at-risk" range on the "Externalizing" factor scales and related subscales. In addition, in order to understand more about the role of age, age of seizure onset, lateralization of seizure onset, and nature of pharmacologic treatment (monotherapy vs polytherapy), the impact of these factors on performance was analyzed.

3 METHODOLOGY

3.1 PARTICIPANTS

The participants in the present study included children between the ages of 6 and 16 years with focal epilepsy who had been consecutively referred by Dell Children Medical Center to Austin Neuropsychology, PLLC or to the Neuropsychology Department at Pediatric Specialty Services, for a comprehensive neuropsychological assessment while undergoing evaluation for epilepsy surgery. Deidentified data from a database of more than 150 children was reviewed to determine whether or not they met inclusion/exclusion criteria for this study. All children had unilateral seizure foci in the frontal or temporal lobes documented by a board-certified neurologist with expertise in pediatric epilepsy. Classification was based on a standard protocol that potentially included a comprehensive neurological examination, video EEG monitoring, cortical imaging (MRI scans), single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetoencephalography (MEG) and a review of clinical semiology and case history (Wagner et al., 2009). In each case, diagnostic procedures initially began with the least invasive method (i.e., scalp EEG) and proceeded to more invasive methods until strong evidence of seizure activity originating within the frontal or temporal lobes was obtained in the absence of any discordant information. This approach of diagnosis has been used in several other studies (e.g., Hershey et al., 1998; Nolan et al., 2004; Riccio et al., 2015; Smith & Lah, 2011). Potential participants for this study were excluded if there were indications of multiple contributory areas of seizure focus (e.g., generalized or multilobar distributed discharges documented on previous EEG studies). To prevent confounding of results from acquired neurological conditions known

to result in alterations in neuropsychological function, additional exclusion criteria included a documented concurrent, progressive neurological or serious medical condition other than epilepsy.

The summary demographic information for the children who met criteria for inclusion in this study is presented in Table 2. Participants included 27 youth identified with seizure onset from the temporal lobe (18 males, 9 females; mean age 12.48 years) and 24 youth with seizure onset emanating from the frontal lobe (18 males, 6 females; mean age 11.29 years). 81.5 percent of the TLE sample (n = 22) was determined to be right-handed, while 18.5% (n =5) was left-hand dominant. 83.3% percent of the FLE sample (n = 20) was determined to be right-handed, while 16.7% (n = 4) was left-hand dominant. Additionally, on a report measure of family stress, the majority of parents (50%) of children in the TLE group endorsed having a "typical" level of stress at the time of testing, while 37.5% (n = 6) endorsed a "higher than typical" level of stress, 6.3% (n = 1) endorsed a very high level of stress and 6.3% (n = 1) endorsed very little stress. In the FLE group, 20.8% (n = 5) of parents endorsed having a "typical" level of stress at the time of testing, 20.8% (n = 5) endorsed a "higher than typical" level of stress, 12.5% (n = 3) endorsed a very high level of stress, 8.3% (n = 2) endorsed less than typical stress and 4.2% (n = 1) endorsed very little stress. Data from 19 families were not included in this analysis due to failure to complete the measure. Fisher's exact tests and independent samples t-tests were completed which revealed no significant group differences with respect to sex, handedness, family stress or age. The summary medical and clinical information were all explored in follow-up analyses.

Table 2 ***Demographic Information of Participants***

VARIABLE	TLE (n = 27)	FLE (n = 24)	SIGNIFICANCE
Gender, N ***(%)***			
Male	18 *(66.7%)*	18 *(75%)*	p = .55†
Female	9 *(33.3%)*	6 *(25%)*	
Age, Mean ***(SD)***	12.48 *(3.20)*	11.29 *(3.44)*	t(49) = 1.28, p = .21‡
Handedness, N ***(%)***			
Right	22 *(81.5%)*	20 *(83.3%)*	p = 1.0†
Left	5 *(18.5%)*	4 *(16.7%)*	
Family Stress, N ***(%)***			
Very Little Stress	1 *(6.3%)*	1 *(4.2%)*	
Less than Typical Stress	0 *(0%)*	2 *(8.3%)*	p = †.56
Typical Stress	8 *(50%)*	5 *(20.8%)*	
Higher than Typical Stress	6 *(37.5%)*	5 *(20.8%)*	
Very High Stress	1 *(6.3%)*	3 *(12.5%)*	

† Fisher's exact test, ‡ Independent samples t-test

3.2 PROCEDURE

All assessment measures were administered at Austin Neuropsychology Clinic or Pediatric Specialty Services/Dell Children's Medical Center by an experienced psychometrist using a comprehensive battery of standardized neuropsychological measures with established reliability and validity. Prior to neuropsychological assessment, informed consent was obtained for use of the clinical data for research purposes with approval from the center's institutional review board (IRB). The neuropsychological evaluation included measures of intelligence, memory, executive function and motor speed. The tests were administered and scored using standard administration and scoring criteria. At the initial time of assessment, parents completed questionnaires regarding their child's psychosocial/behavioral functioning. Additionally, parents completed a background information form in order to obtain relevant demographic information.

3.3 INSTRUMENTS

3.3.1 ASSESSMENT OF MEMORY

3.3.1.1 *Verbal Memory (List Learning)*

Verbal episodic declarative memory was assessed using the California Verbal Learning Test – Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994). The CVLT-C is a list-learning measure designed specifically for use with pediatric populations that permits the obtainment of both quantitative (e.g., number of words learned and recalled after delays) and qualitative (e.g., strategies, processes, and errors) estimates of learning and memory (Williams et al., 2001). During this measure, a 16-word list was presented repeatedly over five trials, each word belonging to 1 of 4 semantic categories. Immediately after each trial, the participant was asked to recall as many of the words as they could in any order. Following the fifth trial, a second list involving novel words was presented and participants were asked to recall items from this distractor list. Then the participant was asked to recall the original list in uncued and cued conditions. After a 20-min delay, the participant was again prompted to recall the original list in free recall and cued recall conditions. Finally, the participant was asked to complete a yes/no recognition test to identify items from the original list.

A measure of short-delay recall was derived based on the total number of words the participant was able to remember from the original list immediately after they finished recall of the distractor list (short-delay free recall condition), and a measure of long-delayed recall was based on the number of words the participant was able to remember from the original list following a 20 minute time delay (delayed free recall condition). These measures have been proposed to assess temporomedial processes of

long-term consolidation and retrieval (Helmstaedter et al., 1997; Helmstaedter & Elger, 2009). The total number of words across the five repetitions of the original list was included as a measure of the more neocortical aspects of learning and short-term memory (Elger et al., 1997; Helmstaedter & Elger, 2009; Helmstaedter et al., 1997). The CVLT-C has been administered in studies of individuals with epilepsy (e.g., Culhane-Shelburne et al., 2002; Gascoigne et al., 2014; Hernandez et al., 2003; Riva et al., 2002; Riva et al., 2005; Williams et al., 2001), and these variables in particular have been shown to be sensitive to left temporal dysfunction (Aikia et al., 2001; Culhane-Shelbourne et al., 2002; Hernandez et al., 2003; Jambaqué et al., 1993).

Additionally, loss of information between the initial apprehension trial and delayed recall conditions was derived by comparing scaled scores from the initial recall of the original list (trial 1) and the long delay free recall condition using a formula developed by Wilkinson and colleagues (2012): initial apprehension span (Imm) to delayed recall (Del) forgetting = (Imm - Del)/(Imm). Consequently, a higher score was indicative of more accelerated forgetting over the immediate recall to delayed recall interval. This comparison provided a more robust measure of memory decay by correcting for potentially differing performance levels in initial apprehension span and has been suggested to reflect temporal lobe dysfunction (Wilkinson et al., 2012). This score was presented as a proportion of information lost (no normative data was available for this measure).

Table 3 ***California Verbal Learning Test - C***

DEPENDENT VARIABLE	HYPOTHESIS
Short Delay Free Recall Scaled Score	TLE < FLE
Long Delay Free Recall Scaled Score	TLE < FLE
Trial 5 Total Recall Scaled Score	TLE < FLE
Forgetting Proportion Score	TLE > FLE

3.3.1.2 *Verbal Memory (Narrative)*

TOMAL-2: Memory for Stories (Reynolds & Bigler, 1994) is a verbal memory subtest that measures semantic and sequential recall. In contrast to the CVLT-C, in which the test material was presented several times, the stories in this task were presented only once, which has been suggested to yield a more direct measure of hippocampus-dependent episodic memory (Jambaqué et al., 2007). During this task, the participant was required to listen to two short verbal narratives read out loud by the examiner. The specific narratives selected for each participant was dependent on age. Immediately after the recitation of each story, the participant was prompted to repeat as many details from the story as they could, in any order. The participant was then asked to provide details from the story again following a 30-minute delay.

Scaled scores were derived from the Immediate and Delayed Recall conditions based on the total number of story details recalled. Additionally, loss of information between the immediate and delayed recall conditions was expressed as a proportion (see formula above). Similar measures have been used to explore memory functioning in prior studies of individuals with FLE and TLE (e.g., Exner et al., 2002; McDonald, Bauer, Grande, Gilmore, & Roper, 2001), with story recall suggested to be particularly sensitive to temporal lobe dysfunction due to its increased demands for verbal comprehension (Culhane-Shelburne et al., 2002).

Table 4 ***TOMAL-2 Memory for Stories***

DEPENDENT VARIABLE	HYPOTHESIS
Immediate Recall Scaled Score	TLE < FLE
Delayed Recall Scaled Score	TLE < FLE
Forgetting Proportion Score	TLE > FLE

3.3.1.3 *Abstract Visual Memory*

TOMAL: Abstract Visual Memory (Reynolds & Bigler, 1994) is a nonverbal memory subtest that involves the immediate recognition and discrimination of geometric images. The participant was shown a figure from a stimulus book and prompted to study the design. After approximately 5 seconds, the examiner turned to a second page where several abstract figures, one of which was the original target, were displayed. The participant was then asked to indicate which figure was previously presented.

A scaled score was derived from the total number of target designs correctly identified. Importantly, the target items in this task are abstract and hard-to-be-verbalized (Schmitt & Decker, 2008), which has been proposed to provide a purer assessment of nonverbal memory (Narayanan et al., 2012) and to more directly reflect right temporo-limbic functions (Helmstaedter et al., 1995). Performance on similar delayed match-to-sample measures have been found to be impaired in individuals with temporal lobe epilepsy (e.g., Jeyaraj et al., 2013).

Table 5 ***TOMAL-2 Abstract Visual Memory***

DEPENDENT VARIABLE	HYPOTHESIS
Immediate Recall Scaled Score	TLE < FLE

3.3.2 ASSESSMENT OF EXECUTIVE FUNCTIONING

3.3.2.1 *Working Memory*

WISC-IV Digit Span is a measure of working memory and attention and concentration. On the Digits Backwards task, the participant was required to recall the numbers in reverse sequence.

The number of digits recalled correctly on Digits Backward was summed together to derive a scaled score for this measure. Similar digit recall tasks have been found to be sensitive to the effects of increasing working memory load and appear to be subserved by the frontal lobes (Owen, 2000). Additionally, performance on span tasks is impaired in individuals with FLE and has been proposed to be sensitive to differences between individuals with frontal and temporal lobe seizure onset (e.g., Helmstaedter et al., 1996; Upton & Thompson, 1996).

Table 6 ***WISC-IV Digit Span Backwards***

DEPENDENT VARIABLE	HYPOTHESIS
Digit Span Backwards Scaled Score	TLE > FLE

3.3.2.2 *Behavioral Regulation & Metacognition*

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is a specialized questionnaire completed by parents that assesses executive function behaviors in the school and home environment. The BRIEF is composed of 86 items measuring 8 theoretically and statistically derived domains of executive function: Working Memory, Inhibit, Initiate, Plan/Organize, Organization of Materials, Monitor, Emotional Control, and Shift. Scores were derived on two composite scales labeled the Behavioral Regulation Index (BRI) (comprised of the Inhibit, Shift, and Emotional Control scales) and the Metacognition Index (MCI) (comprised of the Initiate,

Working Memory, Plan/Organize, Organization of Materials, and Monitor scales).

This measure has been demonstrated to have good basic psychometric properties and validity (.80 to .98; Gioia et al., 2000). It has also been used within other studies of individuals with epilepsy (e.g., MacAllister et al., 2012; Parrish et al., 2007; Pulsipher et al., 2009; Sherman, Slick, & Eyrl, 2006; Slick, Lautzenhiser, Sherman & Eyrl, 2006) and was demonstrated to be sensitive to frontal lobe dysfunction (e.g., Campiglia et al., 2014; Luton et al., 2010). Performance on this measure was reverse-scored so that lower scores indicated increased difficulty.

Table 7 ***BRIEF***

DEPENDENT VARIABLE	HYPOTHESIS
Metacognition Composite Score	TLE > FLE
Behavioral Regulation Composite Score	TLE > FLE

3.3.2.3 *Processing Speed*

WISC-IV Coding assesses aspects of executive functioning including psychomotor speed and coordination, attention, short-term memory, and cognitive flexibility. The participant was required to copy geometric symbols paired with shapes or numbers as quickly as possible. WISC-IV Symbol Search is a timed subtest which required the participant to visually scan geometric symbols to determine if they matched the stimulus symbol.

Scaled scores were derived from the WISC-IV Coding and Symbol Search tasks that reflect the number of target stimuli correctly identified and the number of stimulus symbols correctly matched, respectively. These measures have been demonstrated to be more sensitive to dysfunction in children with FLE than TLE (Hernandez et al., 2003).

Table 8 ***WISC-IV Processing Speed Index***

DEPENDENT VARIABLE	HYPOTHESIS
Symbol Search Scaled Score	TLE > FLE
Coding Scaled Score	TLE > FLE

3.3.2.4 *Self-Monitoring*

A measure of self-monitoring and impulsivity was derived using the California Verbal Learning Test – Children (CVLT-C; Delis et al., 1994).

A scaled score was derived by summing together the total number of intrusion errors made on all recall trials. CVLT-C process scores, including the measure of intrusion errors, have been typically described as measuring executive functioning (Denckla, 1996; Levin et al., 1991) and have been suggested to improve across the course of development (Delis et al., 1994). In past research, children with FLE have been found to make more intrusion errors than children with TLE (Hernandez et al., 2003), suggesting that this measure is sensitive to frontal lobe dysfunction (Baldo et al., 2002; Turner, Cipolotti, Yousry, & Shallice, 2007). Performance on this measure was reverse-scored so that lower scores indicated increased number of intrusions.

Table 9 ***CVLT-C***

DEPENDENT VARIABLE	HYPOTHESIS
Intrusions Scaled Score	TLE > FLE

3.3.3 ASSESSMENT OF MOTOR FUNCTIONING

3.3.3.1 *Motor Coordination/Speed*

The Grooved Pegboard (Trites, 1989) is a task of psychomotor speed and fine motor coordination in which the participant was required to place grooved pegs into slots on a pegboard. The participant was first required to complete the entire board with their

dominant hand. The board was then reset and the participant completed the entire board with their non-dominant hand.

Standardized scores for dominant hand and non-dominant hand performance were based on time to completion. Similar measures of motor coordination have been found to be impaired in individuals with FLE (e.g., Hermann et al., 2007; Hernandez et al., 2002; Riva et al., 2005).

Table 10 ***Grooved Pegboard***

DEPENDENT VARIABLE	HYPOTHESIS
Dominant Hand Scaled Score	TLE > FLE
Non-Dominant Hand Scaled Score	TLE > FLE

3.3.4 ASSESSMENT OF INTELLECTUAL FUNCTIONING

3.3.4.1 *Intelligence/General Abilities*

The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) is a nationally standardized measure of intelligence for children between the ages of 6 and 16. Various subtests were administered within four composite areas, including Verbal Comprehension (Similarities, Vocabulary and Comprehension), Perceptual Reasoning (Block Design, Matrix Reasoning and Picture Concepts), Processing Speed (Cancellation and Symbol Search) and Working Memory (Digit Span, Letter-Number Sequencing).

The WISC measure has been recommended for the clinical assessment of children by the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements for Epilepsy (Sherman et al., 2012). Various editions of the WISC have been utilized in studies of individuals with epilepsy (e.g., Berg et al., 2008; Blackburn et al., 2007; Cormack et al., 2007; Guimaräes et al.,

2007; van Mil et al., 2008). Scaled scores on each of the subtests were summed in order to derive a Full Scale IQ (FSIQ) score which can be used as a measure of general intellectual functioning. Children with FLE have been demonstrated to have depressed FSIQ scores relative to typically-developing populations (Braakman et al., 2012; Nolan et al., 2003; Prévost, Lortie, Nguyen, Lassonde, & Carmant, 2006; Sinclair et al., 2004). In order to appreciate the full impact of FLE and TLE on cognitive functioning, all ranges of Full-Scale IQ were included in the study.

The GAI is a composite score that is based on the three Verbal Comprehension (Similarities, Vocabulary and Comprehension) and three Perceptual Reasoning subtests (Block Design, Matrix Reasoning and Picture Concepts). The elimination of the Processing Speed and Working Memory subtests from this estimate of intellectual functioning reduces concerns about the influence of working memory and processing speed when summarizing verbal comprehension and perceptual reasoning abilities, respectively.

Table 11 ***WISC-IV***

DEPENDENT VARIABLE	HYPOTHESIS
General Ability Index	TLE > FLE
Full Scale IQ	TLE > FLE

3.3.5 ASSESSMENT OF PSYCHOSOCIAL FUNCTIONING

3.3.5.1 *Internalizing/Externalizing Behavior Problems*

The Child Behavior Checklist (Achenbach & Rescorla, 2001) is a behavior-rating questionnaire designed for 6- to 18-year old children. The checklist consists of a number of descriptions of behavioral and emotional problems as observed by parents and other caregivers. The respondent was asked to respond to 118 items by rating the child's

behavior over the previous 6 months on a 3-point Likert scale (e.g., 0 = "not true"; 1 = "somewhat or sometimes true"; 2 = "very or often true").

The resulting profile consists of eight narrowband syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Aggressive Behavior, Rule-Breaking Behavior, and Attention Problems, Thought Problems, and Social Problems), which are obtained by summing all of the ratings of the items that constitute a scale. The CBCL also yields two broadband dimensions labeled Internalizing Problems (subordinate scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints) and Externalizing Problems (subordinate scales: Aggressive Behavior, Rule-Breaking Behavior). Finally, an overall symptom index (Total Problems) was obtained by summing all of the items. Scores for the CBCL consist of raw scores and converted to standardized score based on the standardization sample provided by the CBCL scoring program. The CBCL has been used in a growing body of literature in order to characterize the presentation of behavioral problems in individuals with epilepsy (e.g., Almane et al., 2014; Salpekar et al., 2013; Sinclair et al., 2004). Performance on this measure was reverse-scored so that lower scores were indicative of increasing behavioral problems, with scores above 60 in the borderline range and above 70 in the clinically elevated range. On this measure, children with TLE have typically been associated with greater ratings of difficulties with internalizing behaviors (Salpekar et al., 2013), while children with FLE have typically been rated as having more significant problems with externalizing behaviors (Hernandez et al., 2003; Lassonde et al., 2000; Prévost et al., 2006; Sinclair et al., 2004).

Table 12 ***Child Behavior Checklist***

DEPENDENT VARIABLE	HYPOTHESIS
Internalizing Behaviors Composite Score	TLE > FLE
Anxious/Depressed T-Score	TLE > FLE
Withdrawn/Depressed T-Score	TLE > FLE
Somatic Complaints T-Score	TLE > FLE
Externalizing Behaviors Composite Score	TLE < FLE
Aggressive Behavior T-Score	TLE < FLE
Rule-Breaking Behavior T-Score	TLE < FLE
Attention T-Score	TLE < FLE

4 RESULTS

4.1 POWER ANALYSIS

A power analysis, conducted using G*Power 3.1.5 (Faul, Erdfelder, Buchner, & Lang, 2009), was conducted in order to determine the necessary sample size for this study. Using an effect size (Pillai's V = 0.288) based on composite scores derived from available pilot data, the recommended sample size to obtain 81% power is approximately 50. Thus, the study was adequately powered to test the main hypotheses. A comparison with other studies with similar goals revealed that this is one of the largest sample sizes comparing TLE and FLE described in the literature, suggesting that previous studies may have been significantly underpowered.

4.2 DATA PREPARATION

Raw test scores on each of the neuropsychological measures were converted to age-appropriate standardized scores using available test standardization norms. Table 13 depicts the cognitive domains and specific abilities assessed and the test measures in this study. Individual test scores (z-scores, standard scores) were subsequently converted to T-scores with a mean score of 50 and a standard deviation of 10 to provide a single metric for comparison across tests. The exception was the rate of forgetting data, which is presented as a proportion of information lost (no normative data was available for this subtest). Missing data ranged from approximately 1 to 5% on each of the neuropsychological data points due to failure of the child to complete a particular measure. Most researchers have agreed that the statistical analyses are unlikely to be biased when the percentage of missing data is below 5% (Bennett, 2001; Peng et al., 2006; Schafer, 1999). While other studies have simply used pairwise or listwise deletion

methods for missing data points, a large body of literature has suggested that these procedures are suboptimal (see Allison, 2010; Närhi et al., 2001; Schlomer, Bauman & Card, 2010). Expectation maximization method has been recommended as the best practice for managing missing data points (see Närhi, Laaksonen, Hietala, Ahonen, & Lyyti, 2001; Schlomer, Bauman, & Card, 2010). Consequently, missing values for continuous variables were imputed using the expectation maximization method (Tabachnick & Fidell, 2001).

All data was tabulated in Microsoft Excel® format and was subsequently analyzed through the SPSS 22.0 computer software. Descriptive statistics were computed in order to examine any violations of the normality of the distribution and homoscedasticity and to ensure that statistical assumptions were met. Specifically, measures of central tendency, distribution, and frequency were computed for each variable across each of the diagnostic groups (TLE and FLE) in order to identify any possible univariate outliers. Levene's test was used to evaluate homogeneity of variance across the two groups, and histograms and Shapiro-Wilk's test were examined to examine departures from normality. Outliers in the cognitive test results were retained but were winsorized by being rescored to correspond to the upper and bottom fifth and 95th percentile scores (Tabachnick & Fidell, 2007; Wilcox, 2005). This computation corrected for excessive distribution skewing but provided protection for clinically important deviations from the mean.

Possible group differences on demographic and medical information were screened using parametric (independent sample t-tests) tests for continuous variables (age, age of onset of seizure activity, duration of seizure activity) and nonparametric tests

(Fisher's exact test analysis) for categorical variables (gender, number of AEDS). In order to determine impairment on the individual cognitive and behavioral domains within each diagnostic group (objective 1), scores on test measures were analyzed by comparing group means to normative standards, using one-sample t-tests (e.g., Cahn-Weiner et al., 2009; Riva et al., 2005; Sinclair et al. 2004; Williams et al., 2001). Subscales that assessed memory, executive functioning, internalizing and externalizing behaviors were additionally grouped into overall composite domains. Independent samples t-tests were conducted to determine whether children with FLE and TLE differed on these composite domains of functioning. A significance level of $p < .05$ was utilized in order to interpret these data results. Between-group differences in the various subdomains were also explored by means of independent samples t-tests.

In an attempt to conduct a conservative assessment of these data, a 5% false discovery rate statistical threshold was adopted to control for multiple comparisons. While many studies have performed the Bonferroni or another study-wide error adjustment in order to adjust for an increased number of analyses, it has been suggested that those approaches are limited in that they do not distinguish between data- versus hypothesis-driven testing and they require the researcher to make certain inferences which can lead to inconsistencies in the findings (Glickman, Rao, & Schultz, 2014). Consequently, the false discovery rate has been proposed as an approach which is more conservative than simply comparing all p-values to an alpha level of .05, but provides more power than the Bonferroni adjustment.

Table 13 ***Neuropsychological Test Battery***

DOMAIN	SUBDOMAINS	TEST
Memory Functioning	Verbal (List Learning) Verbal (Narrative) Abstract Visual Memory Working Memory	CVLT-C TOMAL-2 MFS TOMAL-2 AVM WISC-IV Digit Span Bwds
Executive Functioning	Metacognition, Behavioral Reg Processing Speed Self-Monitoring	BRIEF WISC-IV Coding, Symbol Search CVLT-C
Motor Functioning	Speeded Fine Motor	Grooved Pegboard
Intellectual Functioning	FSIQ, General Ability Index	WISC-IV
Psychosocial Functioning	Internalizing Behaviors Externalizing Behaviors	Child Behavior Checklist Child Behavior Checklist

Additionally, because group analyses do not permit the exploration of individual differences in performance, scores on the overall memory and executive functioning domains were classified as impaired or intact based on the approach described by Aikia (2001) and Gonzalez et al. (2007). Specifically, scores of 1 standard deviation or greater below the mean ($T \geq 40$) were classified as impaired. Performance on these domains was compared using Fisher's exact tests to determine the proportion of participants in each group who demonstrated impaired performance. Additionally, a series of exploratory Fisher's exact tests was used to examine the proportion of participants who fell within the clinical range within each of the individual subdomains of the internalizing and externalizing composite domains. Within each of these analyses, a 5% false discovery rate statistical threshold was adopted to control for multiple comparisons.

4.3 GROUP ANALYSES

4.3.1 DEMOGRAPHICS

The summary medical and clinical information for the current sample are presented in Table 14. The average age of seizure onset for the TLE group was 5.78 years

(*SD* = 4.88 years), while the average age for the FLE group was 7.65 years (*SD* = 3.94 years). The average duration of seizure activity was 6.70 years (SD = 4.79 years) for the TLE group and 3.65 years (SD = 2.87 years) for the FLE group. Within the TLE group, 48.1% (n = 13) of participants' seizures originated within the right hemisphere of the brain and 51.9% (n = 14) in the left hemisphere of the brain. Within the FLE group, 50% (n = 12) of participants' seizures originated within the right hemisphere of the brain and 50% (n = 12) in the left hemisphere of the brain. Of the TLE group, six patients demonstrated structural lesions on neuroimaging, whereas the remaining 18 TLE patients exhibited no identifiable structural lesion. Lesions included tuberous sclerosis (n = 2), tumor (n=1) cavernous malformation (n = 1) and cystic lesion (n = 2). Of the FLE group, three patients had observable structural lesions on neuroimaging, while the remaining 25 FLE patients exhibited no identifiable structural lesion. Lesions included cortical dysplasia (n = 2) and venous anomaly (n = 1).

Following procedures used by Bailet and Turk (2000), Bulteau and colleagues (2000), Smith, Elliot, and Lach (2002), seizure frequency was classified on an ordinal scale (see Table 14). Within the TLE group, 33.3% (n = 9) experienced seizures weekly while approximately 29.6% (n = 8) experienced seizures daily, 14.8% (n = 4) experienced seizures monthly, 7.4% (n = 2) experienced seizures quarterly and 7.4% (n = 2) experienced seizures yearly. Within the FLE group, 33.3% (n = 8) experienced seizures occurring monthly, 33.3% (n = 8) experienced seizures daily, 12.5% (n = 3) experienced seizures weekly, 12.5% (n = 3) experienced seizures quarterly and 4.2% (n = 1) experienced seizures yearly. 7.4% of participants with TLE (n = 2) and 4.2% of participants with FLE (n = 1) were not experiencing seizures at the time of testing. 25.9%

of participants (n = 7) with TLE were prescribed one anticonvulsant at the time of testing and 74.1% (n = 20) were prescribed polytherapy. Of the FLE group, 20.8% (n = 5) were prescribed one anticonvulsant, 75% (n = 18) were prescribed polytherapy, and 4.2% (n = 1) was not prescribed any anticonvulsants at the time of testing. Medications for both epilepsy groups included carbamazepine, clobazam, diazepam, divalproex sodium, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, valproic acid and zonisamide.

A series of independent samples t-tests were conducted comparing the TLE and FLE groups on the clinical variables including age at seizure onset and duration of epilepsy. In addition, a Fisher's exact test was performed comparing the laterality of focus, seizure frequency and the number of individuals on monotherapy with those on polytherapy between the groups. Overall, the two groups were statistically equivalent on every variable measured that related to age of onset, frequency of seizure activity, lateralization of seizure activity and number of medications, although participants with TLE demonstrated an increased duration of seizure activity relative to the FLE group.

Table 14 Clinical Information of Participants

VARIABLE	TLE (n = 27)	FLE (n = 24)	SIGNIFICANCE
Age at Onset *Mean (SD)*	5.78 (*4.88)*	7.65 *(3.94)*	t(49) = -1.49, p = .14‡
Duration *Mean (SD)*	6.70 (*4.79)*	3.65 *(2.87)*	t(49) = 2.72, p = .01‡
Laterality of Focus *N (%)*			
Right	13 *(48.1%)*	12 *(50.0%)*	p = 1.0†
Left	14 *(51.9%)*	12 *(50.0%)*	
Seizure Frequency *N (%)*			
None	2 *(7.4%)*	1 *(4.2%)*	
Yearly	2 *(7.4%)*	1 *(4.2%)*	
Quarterly	2 *(7.4%)*	3 *(12.5%)*	p = .41†
Monthly	4 *(14.8%)*	8 *(33.3%)*	
Weekly	9 *(33.3%)*	3 *(12.5%)*	
Daily	8 *(29.6%)*	8 *(33.3%)*	

Number of AEDs *N (%)*			
No Current Therapy	0 *(0.0%)*	1 *(4.2%)*	
Monotherapy	7 *(25.9%)*	5 *(20.8%)*	p = .74†
Polytherapy	20 *(74.1%)*	18 *(75.0%)*	

† Fisher's exact test, ‡ Independent samples t-test

Additionally, a series of exploratory independent sample t-tests initially were conducted to compare participants with a left-hemisphere seizure focus with participants with a right-lateralized seizure focus within the TLE and FLE groups to determine the impact of laterality of seizure focus on performance on the memory tasks. As the cognitive performances of children with right and left focus were not significantly different (see Table 15), all right- and left-lateralized participants were grouped together within the FLE and TLE groups.

Table 15 Comparison Between Right- and Left-Hemisphere

	TLE	**FLE**
	Right-Hem. vs. Left-Hem.	**Right-Side vs. Left-Side**
CVLT-C List A Total Recall	t(12) = -.86, p = .41	t(12) = -.46, p = .65
CVLT-C Immediate Free Recall	t(12) = -.99, p = .34	t(12) = .19, p = .85
CVLT-C Delayed Free Recall	t(12) = -1.11, p = .29	t(12) = -.36, p = .73
TOMAL-2 MFS Immediate Recall	t(12) = -.98, p = .35	t(12) = -.10, p = .92
TOMAL-2 MFS Delayed Recall	t(12) = -.89, p = .39	t(12) = .35, p = .73
TOMAL-2 AVM Immediate Recall	t(12) = -1.34, p = .21	t(12) = -.65, p = .53

4.3.2 CORRELATIONS

A correlation matrix was generated to examine whether any of the effects of demographics and epilepsy-related variables (including age at testing, age at onset of seizure activity, duration of seizures, frequency of seizures and number of AEDs) were related to neuropsychological performance within each patient group. Pearson correlations were used for normally distributed variables, and Spearman correlations were used for non-normally distributed variables. The correlation matrix did not reveal any significant relationships between age at seizure onset, number of anticonvulsant

medications, or illness duration and performance on the cognitive and behavioral outcome measures. However, number of prescribed AEDS was positively correlated with increased ratings of family stress within the FLE group.

Table 16 Correlation Matrix

	Age at Testing		Age at Onset		Duration	
	TLE	**FLE**	**TLE**	**FLE**	**TLE**	**FLE**
CVLT-C Total Recall List A	-.18	.05	-.00	.15	-.12	-.15
CVLT-C Immediate Free Recall	-.29	.21	.07	.10	-.27	.12
CVLT-C Delayed Free Recall	-.27	.20	-.24	.20	.06	-.03
TOMAL-2 MFS Immediate Recall	-.35	.26	-.02	.18	-.22	.06
TOMAL-2 MFS Delayed Recall	-.19	.16	.06	.05	-.18	.13
TOMAL-2 AVM Immediate Recall	-.08	.25	.03	.30	-.08	-.11
BRIEF Metacognition	.18	.06	.12	.09	.01	-.05
BRIEF Behavioral Regulation	.18	.13	.12	.09	-.13	-.04
WISC-IV Digit Span Backwards	.31	.28	.05	.25	.16	-.02
CVLT-C Intrusions	-.13	-.14	-.22	-.18	.14	.08
WISC-IV Symbol Search	.00	.22	-.02	.02	.03	.24
WISC-IV Coding	-.36	.21	-.19	.22	-.05	-.05
WISC-IV GAI	-.08	.01	.06	.06	-.11	-.07
WISC-IV FSIQ	-.23	-.12	.04	-.21	-.24	.14
CBCL Internalizing	.37	.07	.01	.14	.11	-.12
CBCL Externalizing	.18	.23	.20	.10	.04	.15
Family Stress	-.02†	-.27†	-.20†	-.18†	.18	.12

	Seizure Frequency		Number of AEDS	
	TLE	**FLE**	**TLE**	**FLE**
CVLT-C Total Recall List A	-.33†	.05†	.12	-.18
CVLT-C Immediate Free Recall	-.08†	.21†	-.23	-.23
CVLT-C Delayed Free Recall	-.25†	.20†	-.14	-.14
TOMAL-2 MFS Immediate Recall	-.17†	.26†	-.23	.01
TOMAL-2 MFS Delayed Recall	-.22†	.16†	-.22	.16
TOMAL-2 AVM Immediate Recall	-.19†	.25†	-.13	.08
BRIEF Metacognition	.12†	.37†	.11	.11
BRIEF Behavioral Regulation	-.07†	.13†	-.03	-.03
WISC-IV Digit Span Backwards	-.01†	.04†	-.11	-.28
CVLT-C Intrusions	-.10†	-.14†	-.05	-.05
WISC-IV Symbol Search	-.16†	.18†	-.10	-.10
WISC-IV Coding	-.25†	-.02†	-.34	-.34
WISC-IV GAI	-.30†	.03†	-.16	-.16
WISC-IV FSIQ	-.21†	-.02†	-.24	-.24
CBCL Internalizing	-.24†	-.17†	-.10	-.08

CBCL Externalizing	-.00†	-.07†	.02	-.21
Family Stress	-.11†	-.12†	-.07†	.62†*

† Spearman correlation coefficient
* Correlation significant at the .05 level (2-tailed)

4.3.3 MEMORY FUNCTIONING

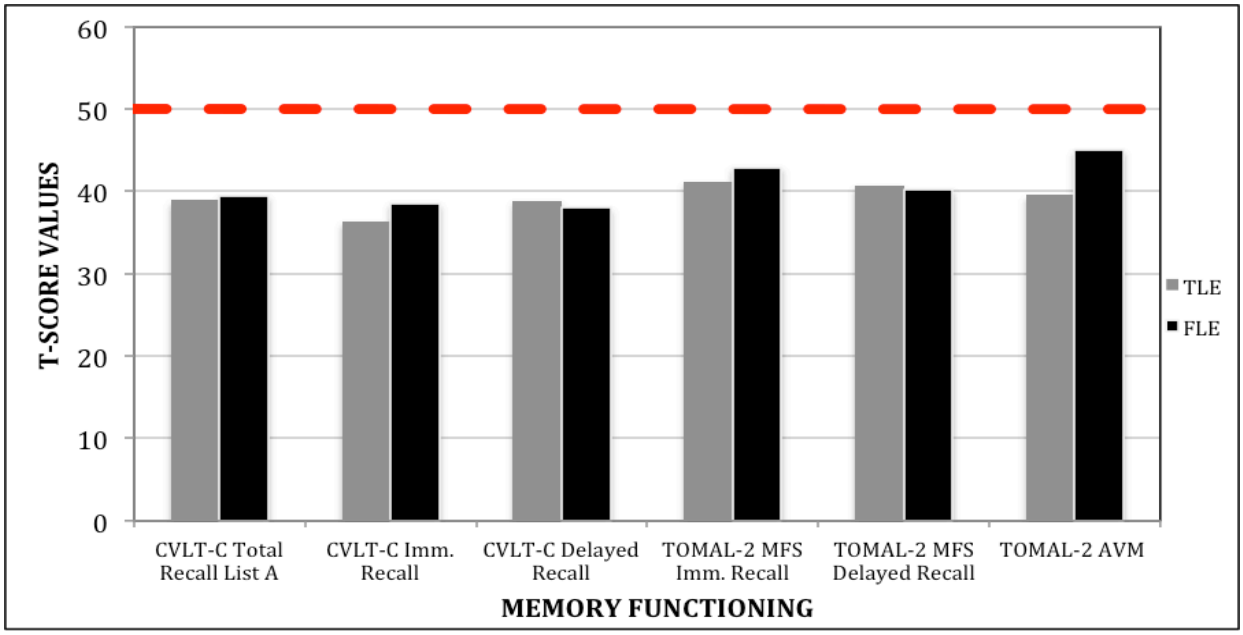
The first goal was to examine whether children with TLE and FLE demonstrate significant impairments in memory functioning. Based on the literature, children with TLE were expected to exhibit impairment in immediate and delayed verbal narrative memory, immediate and delayed verbal list learning, immediate abstract visual memory and an increased rate of forgetting of information relative to normative values and to children with FLE. By contrast, it was expected that children with FLE would perform within normal limits on measures of memory functioning.

Table 17 MEMORY FUNCTIONING: Comparison to Population Norms

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
CVLT-C Total Recall List A	**38.91** ***(8.11)*** **t(26) = -7.10, p = .000*** **	**39.46** ***(12.71)*** **t(23) = -4.06, p = .000*** **
CVLT-C Immediate Free Recall	**36.37** ***(13.69)*** **t(26) = -5.17, p = .000*** **	**38.58** ***(14.23)*** **t(23) = -3.93, p = .000*** **
CVLT-C Delayed Free Recall	**38.89** ***(14.50)*** **t(26) = -3.98, p = .000*** **	**38.03** ***(13.56)*** **t(23) = -4.32, p = .000*** **
TOMAL-2 MFS Immediate Recall	**36.37** ***(13.69)*** **t(26) = -5.17, p = .000*** **	**38.58** ***(14.23)*** **t(23) = -3.93, p = .000*** **
TOMAL-2 MFS Delayed Recall	**40.70** ***(10.66)*** **t(26) = -4.53, p = .000*** **	**40.22** ***(7.45)*** **t(23) = -6.43, p = .000*** **
TOMAL-2 AVM Immediate Recall	**39.54** ***(10.16)*** **t(26) = -5.35, p = .000*** **	**44.98** ***(10.11)*** **t(23) = -2.43, p = .020**

* Significant, p<.05, ** Significant, p<.01, *** Significant, p<.001

Figure 2 ***MEMORY FUNCTIONING: Means***



As Table 17 indicates, one-sample t-tests demonstrated that children with TLE fell significantly below the normative mean on all six of the verbal memory measures. Additionally, overall means for the children that children with FLE fell significantly below normative values, although after adjusting for multiple comparisons, the finding for the FLE group on TOMAL-2 AVM was no longer significant.

Table 18 MEMORY FUNCTIONING: Comparison Between Groups

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
Memory Composite	38.82 *(10.23)*	39.98 *(8.68)*

MEASURE	TLE vs. FLE	Effect Size
Memory Composite	t(49) = -.43, p = .67	*d* = .12
CVLT-C Immediate Free Recall	t(49) = -.57, p = .57	*d* = .16
CVLT-C Delayed Free Recall	t(49) = .21, p = .84	*d* = .06
CVLT-C Total Recall List A	t(49) = -.19, p = .85	*d* = .05
TOMAL-2 MFS Immediate Recall	t(49) = -.66, p = .51	*d* = .06
TOMAL-2 MFS Delayed Recall	t(49) = .19 p = .85	*d* = .05
TOMAL-2 AVM Immediate Recall	t(49) = -1.91, p = .06	*d* = .54

Additionally, the various neuropsychological measures were grouped into overall

memory composite (see Table 18). An individual samples t-test comparing performance between children with FLE and TLE on the overall memory composite was non-significant. Follow-up analyses comparing performance between the groups on the individual subtests were also non-significant, although a trend was noted for children with TLE to demonstrate worse performance on the TOMAL-2 Abstract Visual Memory task relative to children with FLE.

Table 19 MEMORY FUNCTIONING: Proportions

MEASURE	TLE vs. FLE
CVLT-C Forgetting Proportion	t(44) = -.24, p = .69
TOMAL-2 MFS Forgetting Proportion	t(44) = .00, p = .06

Independent samples t-tests were also used to explore differences in the proportion of information lost at delay (see Table 19). The results of this analysis indicated that there were no significant differences between groups with respect to loss of information, although a trend was noted for children with TLE to demonstrate greater forgetting on the TOMAL-2 Memory For Stories task relative to children with TLE.

4.3.4 EXECUTIVE FUNCTIONING

The second goal of this project was to examine whether there were significant differences in executive functioning performance between participants with TLE and FLE. It was hypothesized that children with FLE would display significant impairments on laboratory measures of processing speed and working memory and in aspects of executive functioning including metacognition and behavioral regulation on a parent-report measure relative to normative standards and to participants with TLE. In contrast, children with TLE were expected to demonstrate intact levels of executive functioning.

Table 20 EXECUTIVE FUNCTIONING: Comparison to Population Norms

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
BRIEF Metacognition	**38.06 *(10.80)*** **t(26) = -5.75, p = .000*** **	**36.24 *(9.64)*** **t(23) = -6.99, p = .000*** **
BRIEF Behavioral Regulation	**40.63 *(13.44)*** **t(26) = -3.56, p = .002** **	**42.67 *(11.82)*** **t(23) = -3.04, p = .006** **
WISC-IV Digit Span Backwards	**33.89 *(6.66)*** **t(26) = -12.57, p = .000*** **	**32.53 *(9.13)*** **t(23) = -9.37, p = .000*** **
CVLT-C Intrusions	**45.56 *(16.89)*** **t(26) = -1.37, p = .183**	**49.66 *(11.66)*** **t(23) = -.14, p = .88**
WISC-IV Symbol Search	**36.19 *(11.73)*** **t(26) = -6.12 p = .000*** **	**35.68 *(10.74)*** **t(23) = -6.53, p = .000*** **
WISC-IV Coding	**32.03 *(8.72)*** **t(26) = -10.71, p = .000*** **	**30.73 *(8.65)*** **t(23) = -10.92, p = .000*** **

* Significant, p<.05, ** Significant, p<.01, *** Significant, p<.001

Figure 3 *EXECUTIVE FUNCTIONING: Means*

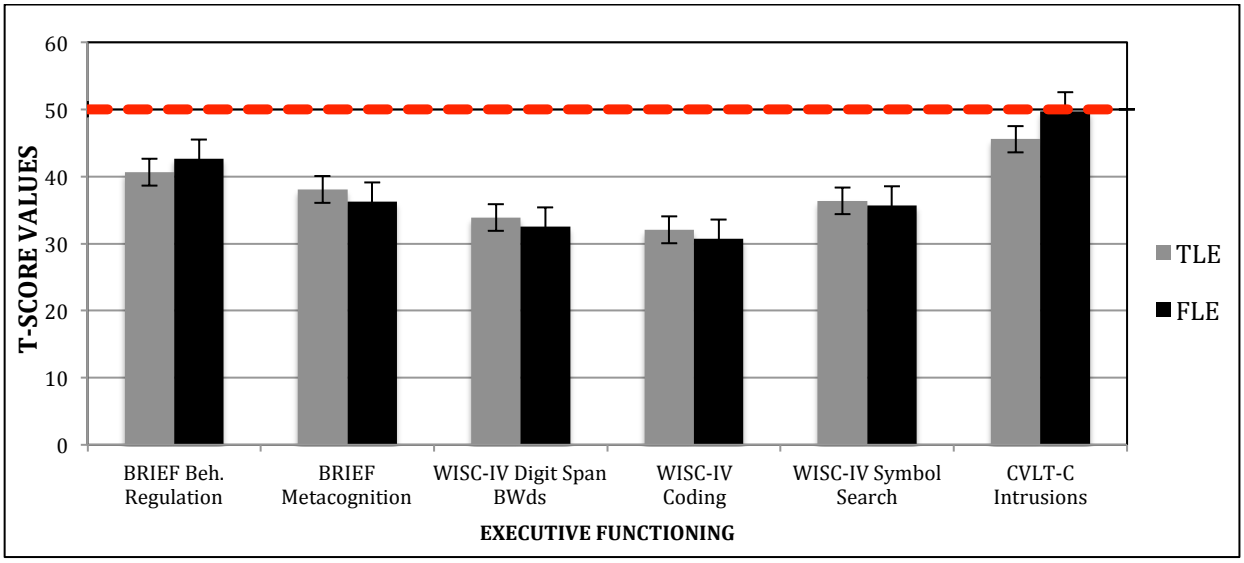


Table 20 displays the group means for the six measures of executive functioning from the subscales of the BRIEF, CVLT-C and WISC-IV. Overall means for both children with TLE and FLE fell significantly below the normative mean on all of the individual measures, with the exception of the CVLT-C Intrusions subscale.

Table 21 EXECUTIVE FUNCTIONING: Comparison Between Groups

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
Executive Composite	38.82 *(10.23)*	39.98 *(8.68)*

MEASURE	TLE vs. FLE	Effect Size
EF Composite	t(50) = .22, p = .83	*d* = .12
BRIEF Metacognition	t(50) = .74, p = .46	*d* = .18
BRIEF Behavioral Regulation	t(50) = -.62, p = .54	*d* = .16
WISC-IV Digit Span Backwards	t(50) = .24, p = .45	*d* = .17
CVLT-C Intrusions	t(50) = -.98, p = .34	*d* = .28
WISC-IV Symbol Search	t(50) = .09, p = 84	*d* = .05
WISC-IV Coding	t(50) = .78, p = .44	*d* = .15

Additionally, the various neuropsychological measures were grouped into overall executive functioning composite (see Table 21). No significant differences were found between the two epilepsy groups on the overall composite measure or on any of the individual subscales.

4.3.5 MOTOR FUNCTIONING

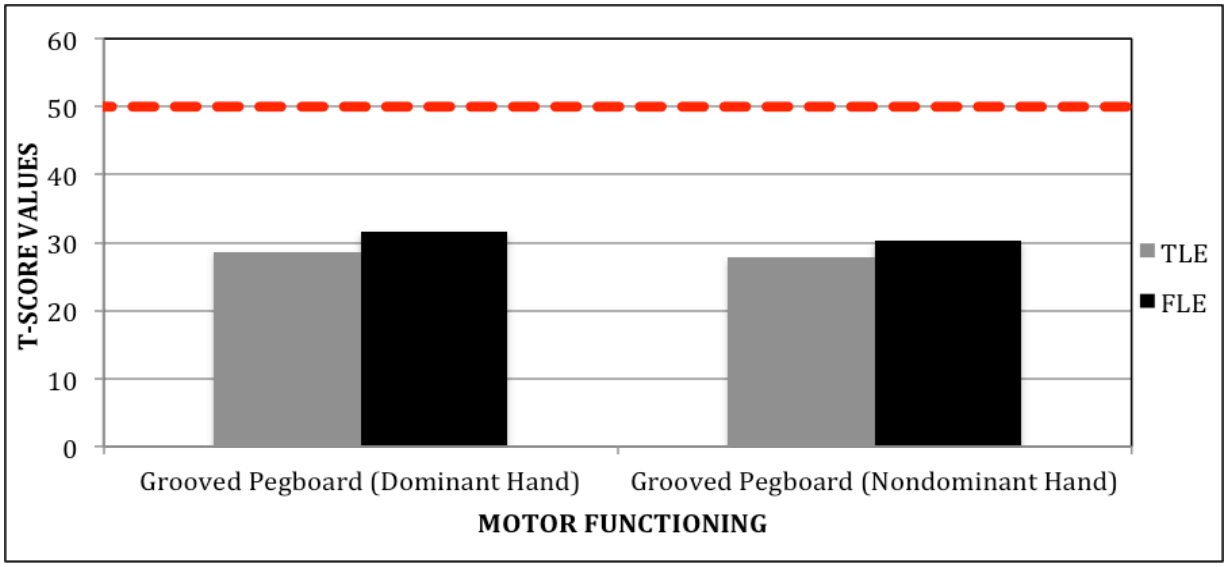
The third goal was to examine whether there were significant differences in motor functioning between participants with temporal and frontal lobe epilepsy. Children with FLE were expected to exhibit more significant impairment in motor coordination and speed relative to normative values and to children with FLE. It was expected that children with TLE would perform within the normal limits.

Table 22 MOTOR FUNCTIONING: Comparison to Population Norms

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
Grooved Pegboard Dom.	**28.67 *(15.14)* t(26) = -7.32, p = .000*** **	**31.61 *(15.95)* t(23) = -5.65, p = .000*** **
Grooved Pegboard Non-Dom.	**27.76 *(15.42)* t(26) = -7.49, p = .000*** **	**30.25 *(13.98)* t(23) = -6.92, p = .000*** **

* Significant, p<.05, ** Significant, p<.01, *** Significant, p<.001

FIGURE 4 ***MOTOR FUNCTIONING: Means***



One sample t-tests revealed that both children with FLE and TLE scored below expected levels of functioning on tests of fine-motor coordination bilaterally when compared to available normative data (see Table 22).

Table 23 MOTOR FUNCTIONING: Comparison Between Groups

MEASURE	TLE vs. FLE	Effect Size
Grooved Pegboard Dom.	t(49) = -.68, p = .50	*d* = .19
Grooved Pegboard Non-Dom.	t(49) = -.60, p = .55	*d* = .17

Independent samples t-tests directly comparing the FLE and TLE groups were non-significant (see Table 23).

4.3.6 INTELLECTUAL FUNCTIONING

The fourth goal was to examine whether there were significant differences in intellectual functioning between participants with TLE and FLE. Children with FLE were expected to exhibit more significant impairment in intellectual functioning relative to normative standards and to children with FLE, while children with TLE were expected to have estimates of intellectual functioning in the normal range.

Table 24 INTELLECTUAL FUNCTIONING: Comparison to Population Norms

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
WISC-IV FSIQ	**32.14** ***(10.73)*** **t(26) = -8.64, p = .000*** **	**33.95** ***(7.35)*** **t(23) = -10.68, p = .000*** **
WISC-IV GAI	**34.86** ***(12.24)*** **t(26) = -6.42, p = .000*** **	**38.86** ***(9.25)*** **t(23) = -5.90, p = .000*** **

* Significant, p<.05, ** Significant, p<.01, *** Significant, p<.001

Figure 5 ***INTELLECTUAL FUNCTIONING: Means***

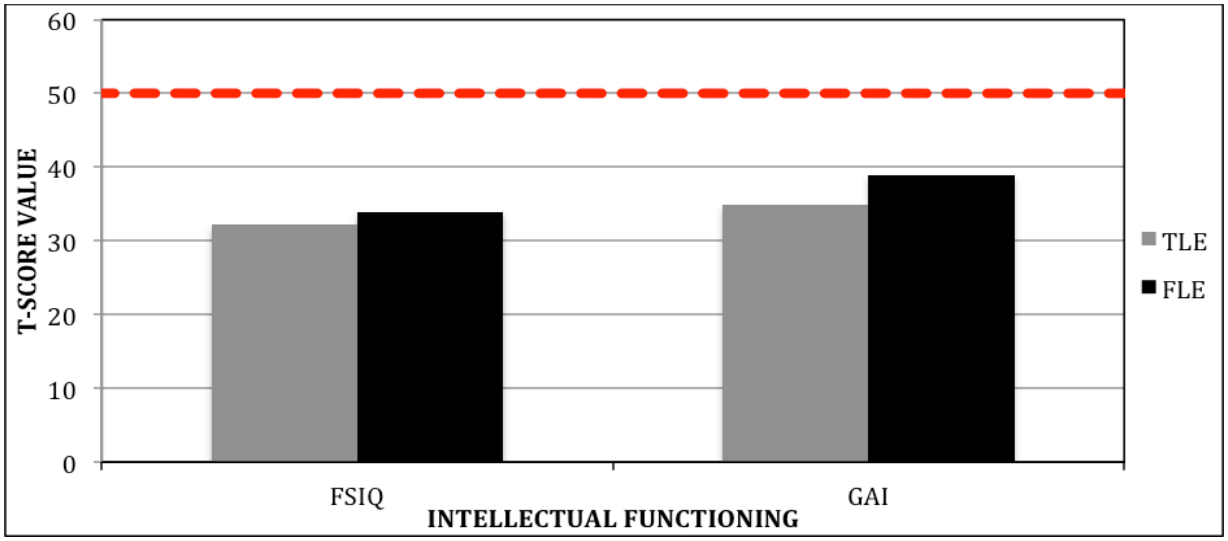


Table 24 displays the group means for the two composite scores of intellectual functioning from the WISC-IV. One sample t-tests revealed that overall means for both groups of children fell significantly below the normative mean for both the FSIQ and GAI estimates.

Table 25 INTELLECTUAL FUNCTIONING: Comparison Between Groups

MEASURE	TLE vs. FLE	Effect Size
WISC-IV FSIQ	t(49) = -.69, p = .49	*d* = .20
WISC-IV GAI	t(49) = -1.30, p = .20	*d* = .37

When directly compared with one another, a series of independent samples t-tests did not yield a significant difference between the groups for either FSIQ or GAI (see Table 25).

4.3.7 PSYCHOSOCIAL FUNCTIONING

The second objective of the study was to examine the behavioral profiles of children with FLE and TLE. It was hypothesized that participants with TLE would display significantly higher scores on a scale of internalizing behavior problems, while participants with FLE would demonstrate significantly higher scores on a scale of externalizing behavior problems.

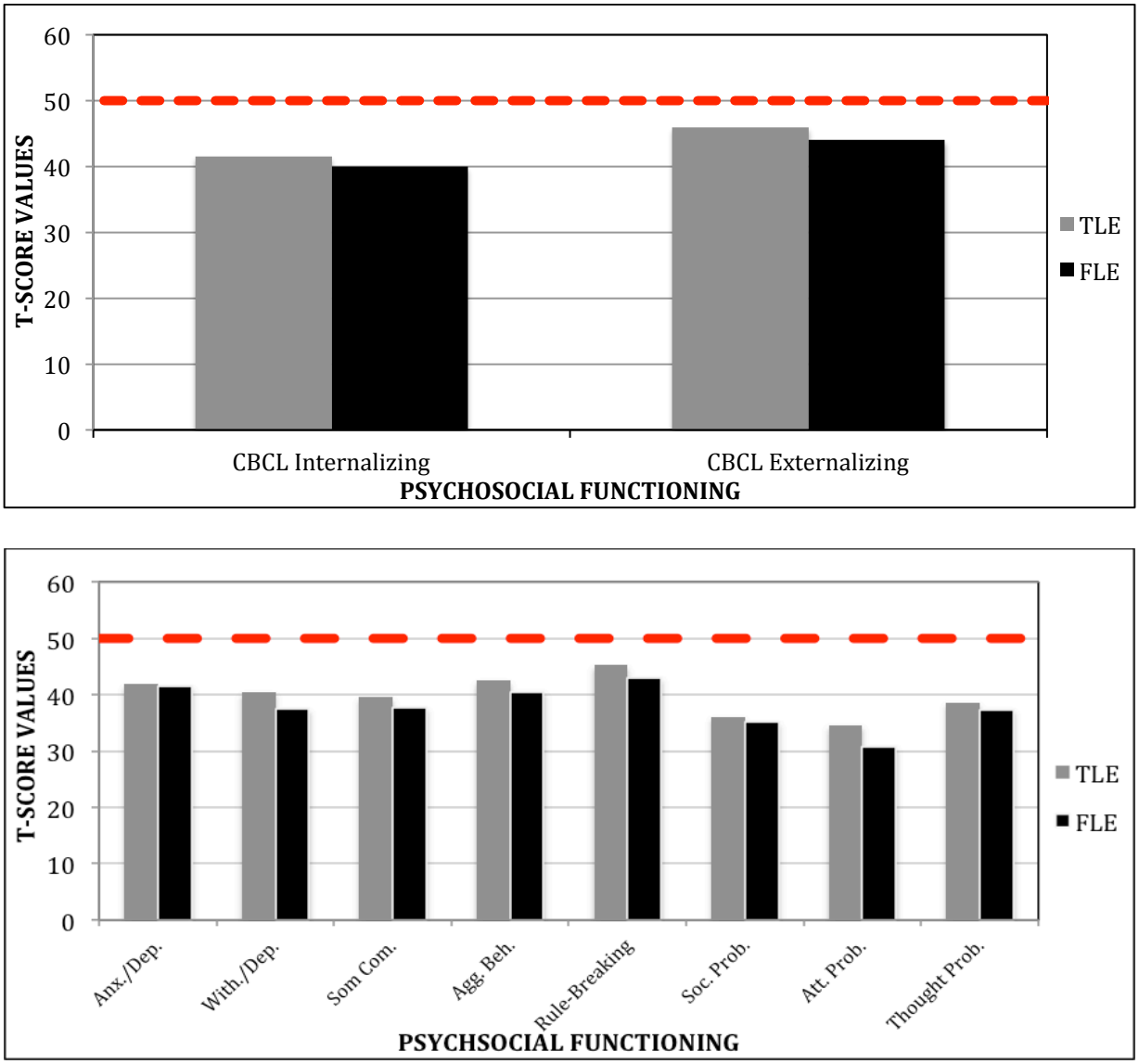
Table 26 PSYCHOSOCIAL FUNCTIONING: Comparison to Population Norms

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
CBCL Internalizing Behaviors	**41.50** ***(10.14)*** **t(26) = -4.35, p = .000*** **	**40.00** ***(9.33)*** **t(23) = -5.25, p = .000*** **
CBCL Externalizing Behaviors	**45.93** ***(9.82)*** **t(26) = -2.16, p = .041**	**44.04** ***(11.83)*** **t(23) = -2.47, p = .022**

MEASURE	TLE MEAN *(SD)*	FLE MEAN *(SD)*
Anxious/Depressed	**41.84** ***(8.32)*** **t(24) = -5.05, p = .000*** **	**41.50** ***(8.84)*** **t(23) = -4.71, p = .000*** **
Withdrawn/Depressed	**40.44** ***(8.03)*** **t(24) = -5.95, p = .000*** **	**37.42** ***(7.68)*** **t(23) = -8.02, p = .000*** **
Somatic Complaints	**39.52** ***(9.11)*** **t(24) = -7.05, p = .000*** **	**37.67** ***(8.57)*** **t(23) = -7.05, p = .000*** **
Social Complaints	**36.04** ***(9.10)*** **t(24) = -7.67, p = .000*** **	**35.08** ***(10.45)*** **t(23) = -7.00, p = .000*** **
Thought Problems	**38.60** ***(9.02)*** **t(24) = -6.32, p = .000*** **	**37.33** ***(7.96)*** **t(23) = -3.87, p = .000*** **
Aggressive Behavior	**42.52** ***(7.81)*** **t(24) = -4.79, p = . 000*** **	**40.54** ***(11.96)*** **t(23) = -4.49, p = .000*** **
Rule-Breaking Behavior	**45.24** ***(6.43)*** **t(24) = -3.70, p = . 001*** **	**43** ***(7.64)*** **t(23) = -8.98, p = .000**** **
Attention Problems	**34.64** ***(12.54)*** **t(24) = -6.12, p = . 000*** **	**30.75** ***(10.51)*** **t(23) = -2.16, p = .001*** **

* Significant, p<.05, ** Significant, p<.01, *** Significant, p<.001

FIGURE 6 ***PSYCHOSOCIAL FUNCTIONING: Means***



Within-group differences in behavioral functioning were explored using one-sample t-test analyses (see Table 26). Both groups demonstrated significant impairment relative to normative data in internalizing behavior problems and in the individual subdomains. Both the FLE and TLE participants also were rated below the normative mean in externalizing behavior problems, although after controlling for multiple comparisons, this finding was no longer significant.

Table 27 PSYCHOSOCIAL FUNCTIONING: Comparison Between Groups

MEASURE	TLE vs. FLE	Effect Size
CBCL Internalizing Behaviors	t(49) = .55, p = .59	*d* = .15
CBCL Externalizing Behaviors	t(49) = .62, p = .54	*d* = .17

Independent samples t-tests also did not yield an overall difference between the groups for either internalizing or externalizing behavior problems (see Table 27).

4.4 INDIVIDUAL ANALYSES

To examine individual patterns of performance across the various cognitive and behavioral domains, performance on each of the domains was classified at intact or impaired and compared. Performance on these composite domains was compared using Fisher's exact tests to determine the proportion of participants in each group who had impaired performance in each domain. Additionally, given that the past research involving psychosocial/behavioral outcomes of children with FLE and TLE has been equivocal, a series of exploratory Fisher's exact tests were used to examine the proportion of participants who fell within the clinical range on each of the individual subscales of the internalizing and externalizing composite domains (see Table 28). It was hypothesized that a higher proportion of participants with TLE would present with scores that fall in the impaired range on domains assessing hypothesized "temporal-lobe" functions (memory functioning, internalizing behaviors), while a higher proportion of participants with FLE would present with scores in the impaired range on domains assessing hypothesized "frontal-lobe" functions (executive functioning, externalizing behavior).

Table 28 Secondary Analyses

	Children with TLE		Children with FLE		P
Task	Intact *(%)*	Impaired *(%)*	Intact *(%)*	Impaired *(%)*	-
Memory	12 *(44.4%)*	15 *(55.6%)*	11 *(45.8%)*	13 *(54.2%)*	.57
EF	11 *(40.7%)*	16 *(59.3%)*	11 *(45.8%)*	13 *(54.2%)*	.47
Internalizing	17 *(63%)*	10 *(37%)*	12 *(50%)*	12 *(50%)*	.26
Externalizing	17 *(68%)*	8 *(32%)*	14 *(58.3%)*	10 *(41.7%)*	.34

	TLE		FLE		P
Task	Intact *(%)*	Impaired *(%)*	Intact *(%)*	Impaired *(%)*	-
Anxious/Depressed	14 *(56%)*	11 *(44%)*	15 *(62.5%)*	9 *(49 %)*	.77
Withdrawn/Depressed	12 *(48%)*	13 *(52%)*	8 *(33.3%)*	16 *(66.7%)*	.23
Somatic Complaints	13 *(52%)*	12 *(48%)*	7 *(29.2%)*	17 *(70.8%)*	.09
Aggressive Behavior	16 *(64%)*	9 *(36%)*	15 *(62.5%)*	9 *(37.5%)*	.57
Rule-Breaking	20 *(80%)*	5 *(20%)*	16 *(66.7%)*	8 *(33.3%)*	.23
Attention Problems	8 *(32%)*	17 *(68%)*	6 *(25%)*	18 *(75%)*	.41
Thought Problems	11 *(44%)*	14 *(56%)*	8 *(33.3%)*	16 *(66.7%)*	.32
Social Problems	8 *(32%)*	17 *(68%)*	7 *(29.2%)*	17 *(70.8%)*	.54

These analyses revealed that the frequency of significantly impaired performance in the two patient groups was comparable, with the Fisher's exact tests demonstrating no group differences on any of the subscales.

4.5 ADDITIONAL ANALYSES

Due to the fact that duration of seizure activity was significantly different between groups, the analyses were subsequently rerun using duration as a covariate. However, this did not affect the pattern of the results. Similarly, due to concerns that performance on the cognitive measures could be affected by level of intelligence, the analyses were also rerun utilizing intelligence as a covariate, although this also did not significantly change the results of the analyses.

5 DISCUSSION

5.1 SUMMARY

A major limitation of the extant literature on childhood-onset epilepsy is the paucity of studies that have directly compared performance between individuals with localization-related syndromes. Additionally, there are few reports utilizing broad, comprehensive assessments of functioning spanning multiple cognitive domains (Williams et al., 1998). Moreover, only a very limited number of studies have specifically evaluated children with medically-refractory epilepsy, despite indications that approximately 30% of patients with epilepsy have inadequate seizure control with drug therapy (Kwan & Brodie, 2000). Consequently, this study examined the cognitive and behavioral profiles of children with frontal or temporal lobe seizure disorders, with onset occurring during formative periods of neurodevelopment when regions of the brain are being sculpted by synaptic proliferation and axonal myelination, as well as subtractive processes intended to eliminate ineffective circuitry and refine both structure and function.

5.2 MEMORY FUNCTIONING

5.2.1 TEMPORAL LOBE EPILEPSY

The results indicated that, as expected, participants with TLE demonstrated significant impairment relative to normative values in various aspects of memory functioning. Story recall has been proposed to be a sensitive indicator of temporal lobe dysfunction in adults with TLE (Frisk & Milner, 1990). Children with TLE in the current study were found to perform in the low average range on measures of immediate and

delayed recall of narrative information. This is consistent with other studies which have compared children with TLE to typically-developing controls (Gascoigne et al., 2014; Guimaräes et al., 2007; Jambaqué et al., 1993; Jambaqué et al., 2009; Nolan et al., 2004; Rzezak et al., 2011; Rzezak et al., 2012). It has been proposed that this characteristic pattern of impairment on measures of narrative memory may emerge due to a failure in the consolidation of the memory trace from short-term memory to long-term storage (Loiseau et al., 1982, as cited in Jambaqué et al., 1993).

A similar profile was observed in the short and long delay recall conditions of the CVLT-C. This is also consistent with previous studies utilizing verbal list-learning paradigms in children with TLE (Hernandez et al., 2003; Jambaqué et al., 1993; Rzezak et al., 2012). In addition, children with TLE in the present study demonstrated poor memory efficiency during an initial learning phase on the CVLT-C, which has also been noted in other studies (Hernandez et al., 2003; Nolan et al., 2004). It has been suggested that this impaired initial encoding of information may result in the decreased performance on delayed recall (Jambaqué et al., 1993).

Helmstaedter, Wietzke and Lutz (2009) demonstrated that CVLT scores differentially load on to factors reflecting "learning efficiency" and "long-term memory," suggesting that this particular memory measure may be uniquely sensitive to different aspects of epilepsy-related impairment. This finding highlights the importance of incorporating list-learning measures into standard batteries of memory functioning. It has been proposed that these factors may map on to anatomically-differentiable memory subsystems. Based on surgical outcome data with adults, Helmstaedter and colleagues (1997) suggested that processes of learning and short-delay memory may be subserved by

temporolateral structures, while the temporomesial structures may be functionally specialized for processes related to long-term consolidation. The findings in the current study suggest that both aspects can be disrupted in children with TLE. This pattern could imply that the sample was comprised of mixed subgroups of children with temporolateral or temporomesial pathology; however, it is often difficult to differentiate this in children (see Strengths and Limitations). Alternatively, this pattern may indicate that memory subsystems are not highly differentiated in children due to anomalies of network development related to the presence of seizure activity in the developing brain.

It is also notable that the children with TLE did not display a lateralized pattern of memory impairment on the verbal memory tasks. The literature is inconsistent with regard to whether laterality effects are present in children with TLE. The present results are consistent with most previous studies that have examined list-learning and story in recall in children with TLE (e.g., Bigel & Smith, 2001a; Helmstaedter & Elger, 2009; Nolan et al., 2004). Specifically, it has been suggested that the presence of seizures in childhood may disrupt the development of expected patterns of hemispheric-specialization in children.

The results of the current study also suggest that children with TLE demonstrate significant impairment in immediate recall on a measure of abstract-visual memory, with performance in the low average range. Previous studies have also shown significant impairments in various aspects of memory for abstract designs (Guimaräes et al., 2007; Jambaqué et al., 1993; Nolan et al., 2004). However, on the whole, impairments in nonverbal memory have been less consistently described relative to verbal memory (e.g., Gascoigne et al., 2014; Rzezak et al., 2012).

A notable criticism of previous studies has been the use of visual memory paradigms utilizing target items that are easy to verbalize (i.e., simple geometric shapes or pictures of items), which permits dual encoding using compensatory verbal memory strategies (Helmstaedter et al., 1995). It has been proposed that selective nonverbal deficits in individuals with right-hemisphere TLE may only emerge when the verbal load for a particular target surpasses the capacity of compensatory verbal memory due to its complexity. For example, facial memory has been found to be particularly sensitive to damage to the right hemisphere (Bigel & Smith, 2001a). Consequently, the robust impairment in abstract-visual memory demonstrated in the TLE group in the present study may be related to the fact that the target items on the TOMAL-2 are abstract and hard-to-verbalize (Schmitt & Decker, 2008), which permitted a more direct and sensitive assessment of right temporal functioning (Helmstaedter et al., 1995), or because the ability to verbally encode visual information is less developed in children (Jambaqué et al., 1993). The current findings suggest that children with TLE demonstrate impairments in visual memory functioning regardless of lateralization of seizure activity (Helmstaedter et al., 1995). This may relate to the better sensitivity of the TOMAL-2 AVM test relative to other tests such as the WRAML-2, which in some studies show a pattern of performance in TLE that is no different from controls (Gascoigne et al., 2014).

5.2.2 FRONTAL LOBE EPILEPSY

The results of the current study also disclosed significant impairments in verbal memory performance in children with FLE. This was evident on tasks of verbal learning and immediate and delayed story recall relative to normative groups. When performance between the two groups was directly compared, children with FLE could not be reliably

differentiated from children with TLE based on the verbal memory measures (Hernandez et al., 2003; Jambaqué et al., 1993; Nolan et al., 2004; Sinclair et al., 2004). In contrast, Culhane-Shelbourne and colleagues (2003) found that children with TLE demonstrated significantly poorer performance on immediate and delayed story recall than children with FLE. However, it is notable that participants in that study were not medically-refractory, suggesting that increased severity of seizure activity may be associated with more generalized patterns of impairment. However, the findings in the current study are consistent with emerging literature suggesting that difficulties in verbal memory are not restricted to children with TLE (Hernandez et al., 2003; Nolan et al., 2004; Picard et al., 2009).

Performance on the abstract visual memory task was also decreased in the current study relative to the normative value, although when the significance values were adjusted to account for the multiple analyses, this finding was no longer statistically significant. Findings have been more inconsistent in the literature regarding the patterns of visual memory deficits in individuals with FLE. Specifically, some studies have suggested that children with FLE do not display significant impairments on tasks of picture or design memory, which may be due to the more basic visual stimuli utilized on the WRAML-2 (Culhane-Shelbourne et al., 2002). In contrast, children with FLE have been found to be impaired on tasks of visuospatial ordering (Nolan et al., 2004) and on the Rey-Osterrieth Complex Figure test, although it can be argued that this finding may have been confounded by the greater graphomotor demands of the task (Hernandez et al., 2003). Interestingly, there was a trend towards significantly poorer performance in the TLE group relative to the FLE group on the measure of abstract visual memory.

Specifically, the TLE group performance was in the low average range, while the FLE demonstrated performance in the average range, suggesting that the TOMAL-2 Abstract Visual Memory subtest may be more sensitive to differences in memory recall between FLE and TLE. Additionally, no significant differences were demonstrated in the current study between children with right- and left-sided FLE, which is consistent with a previous study (Nolan et al., 2004).

5.2.3 SUMMARY: FLE VS. TLE

Results of the current study found similar patterns of memory functioning in children with TLE and FLE. It has been proposed that these similar patterns of memory impairment in children with TLE and FLE may represent a common outcome associated with different underlying mechanisms that depend on the area of the brain impacted by the seizure activity (McDonald, Delis, Norman, Tecoma, & Iragui-Madozi, 2005). Specifically, it has been suggested that memory problems may arise in patients with TLE due to a disruption in encoding or the consolidation of new information into long-term storage, whereas memory impairments in individuals with FLE may be related to difficulties with attention, self-monitoring and effective strategization, which in turn can impede encoding and retrieval of information (Centeno et al., 2010; Hernandez et al., 2003; Turner et al., 2007). This is consistent with findings that children with FLE have been noted to have more marked difficulties with attention and strategization during memory recall (Hernandez et al., 2003).

5.3 EXECUTIVE FUNCTIONING

5.3.1 FRONTAL LOBE EPILEPSY

As expected, participants with FLE demonstrated significant impairment across

most of the measures of executive functioning used in this study. As a group, the children with FLE performed in the borderline range on a laboratory measure of processing speed. This is consistent with observations initially put forth in a case study by Jambaqué and Dulac (1989) and subsequently replicated in a series of studies completed by Auclair and colleagues (2005), Braakman and colleagues (2012), Bulteau and colleagues (2000), Hernandez and colleagues (2003) and Longo and colleagues (2013).

Participants in the FLE group also performed significantly below reference values (borderline range) on a measure of working memory. A similar degree of impairment on digit span tasks has been described both in adults (Rai et al., 2015; Zamarian et al., 2011) and children with FLE (Braakman et al., 2012; Longo et al., 2013). The current findings suggest that these subtests of the WISC-IV are sensitive to frontal lobe dysfunction, although they are not necessarily measures that are specific to frontal lobe impairment. Specifically, it has been suggested that other patient populations without focal dysfunction of the frontal lobes have been found to display difficulties with the backwards span and information processing tasks, including multiple sclerosis (Feuillet et al., 2007) and specific language impairment (Baddeley, Gathercole, & Papagno, 1998). Consequently, it has been suggested that performance on these tasks can be affected by impairments in language and regulatory systems that allocate attentional resources during complex tasks or with disruption of white matter in other areas of the brain (Jung & Haier, 2007).

The children in the current study were also rated to be in the low average range in behavioral regulation and the borderline range in metacognitive abilities on a parent-report measure of executive functioning. These findings of impairment on subjective

measures of executive functioning are consistent with previous reports within the child literature (Campiglia et al., 2014; Luton et al., 2010; MacAllister et al., 2011). However, subjective rating scales are not consistently embedded into study protocols assessing executive functioning, which is problematic given concerns that many laboratory tests of executive functioning lack ecological validity and may not be appropriate for assessing frontal lobe functions in children (MacAllister et al., 2012; Upton & Thompson, 1996). For example, it has been suggested that children with later seizure onset (after age 7) may perform better when provided with a more structured testing environment with fewer distractions than when in their home or school settings (Luton et al., 2010). Consequently, the results of the current study highlight the importance of assessing executive functioning performance using both quantitative and qualitative methods.

Interestingly, children with FLE did not present with significant impairment on a measure of self-monitoring. Baldo and colleagues (2002) found that adults with frontal lobe lesions made more intrusions in their recall than typical controls. Additionally, two previous studies involving children with FLE observed an increased number of intrusions on a list-learning task relative to normative data (Hernandez et al., 2003; Riva et al., 2002). However, it is important to note that the study completed by Hernandez and colleagues was limited by relatively small and discrepant sample sizes (16 FLE patients compared with 8 TLE patients). The study by Riva and colleagues was also flawed; specifically, these investigators acknowledged that the high mean number of intrusive errors was mainly attributable to one participant that they failed to remove from analyses. In contrast, a subsequent study completed by Riva and colleagues in 2005 found no significant elevations in number of intrusions in their FLE sample. The CVLT-C

Intrusions process index has been theoretically linked to the construct of executive function. However, Beebe, Ris and Dietrich (2000) found that the CVLT-C learning process indices demonstrate low correlations with other commonly accepted measures of executive functioning. Consequently, they concluded that the CVLT-C Intrusions process score may not represent a valid measure of executive functioning. The failure to find patterns of impairment in the FLE group in the present study on this measure provides additional evidence that contraindicate the use of this scale to assess frontal lobe dysfunction.

5.3.2 TEMPORAL LOBE EPILEPSY

Participants with TLE also demonstrated significant impairment across the various measures of executive functioning. As a group, the children with TLE performed in the borderline range on the processing speed and working memory tasks. No significant differences were found when children with FLE and TLE were compared directly on these measures of executive functioning. This finding of poorer performance on the processing speed measure is consistent with a previous studies conducted by Hernandez and colleagues (2003) and Longo and colleagues (2013). Additionally, the digit span task has been shown to be sensitive to working memory difficulties in groups of adults with intractable epilepsy (Rai et al., 2015; W. Wang et al., 2011; Zamarian et al., 2011). However, the finding of poorer performance in the TLE group in the current study stands in contrast to three previous studies which found no significant differences between children with TLE and a control group on a measure of working memory (Guimaräes et al., 2007; Rzezak et al., 2012). It is notable that these previous studies did not include children with medically-refractory epilepsy, suggesting that intractability of

seizure activity may be associated with increased impairment in functioning. Specifically, the pathological activity associated with chronic seizures has been suggested to disrupt the normal dynamics of neuronal working memory networks, leading to more significant functional impairments (Verduzco-Flores, Ermentrout, & Bodner, 2009). Future explorations of working memory performance in children with TLE should attempt to compare performance between children with differing levels of epilepsy severity.

The current study also revealed significant impairments on the BRIEF parent-report for the TLE group, with scores in the low average range on the Behavior Regulation and Metacognition indices. These impairments could not be reliably distinguished from the pattern of impairment observed in the FLE group. A limited number of studies have been utilized the BRIEF to assess executive functioning in children in heterogeneous epilepsy populations (MacAllister et al., 2012; Parrish et al., 2007; Sherman et al., 2006). However, these studies have failed to distinguish more specifically between patients with frontal and extra-frontal localization-related epilepsies. Only one recent study has specifically utilized a parent-report measure to examine executive dysfunction in children with TLE, which found that participants displayed a similar pattern of impairment as their FLE counterparts (Campiglia et al., 2014). This study provides additional evidence suggesting that the BRIEF is sensitive to executive dysfunction in individuals with TLE, but that ratings may be globally similar regardless of the area of seizure focus or the particular EF domain being examined.

Finally, similar to the findings for the FLE group, children with TLE failed to demonstrate significant difficulties in self-monitoring on the CVLT-C Intrusions subscale. This is consistent with one previous study which examined performance on this

subscale in children with TLE (Hernandez et al., 2003).

5.3.1 SUMMARY: FLE VS. TLE

Results of the present study revealed similar patterns of executive dysfunction in children with TLE and FLE. While it has become standard practice to make attributions of impairments on executive measures to frontal lobe dysfunction (Stuss & Alexander, 2000), research is equivocal as to whether executive functions can be reliably and specifically localized to the frontal lobes (e.g., Miyake et al., 2000; Welsh, 2002). A review of the existing literature has revealed significant inconsistencies, with certain studies finding no significant deficits on tasks of executive functioning in individuals with frontal lobe damage, and others finding that impairments in executive function can be robust even in individuals with extrafrontal injury (see Alvarez & Emory, 2006). An alternative view which has emerged in the literature suggests that executive functions represent "higher-level" cognitive functions which serve to regulate distributed "lower-level" cognitive processes and behaviors (Alvarez & Emory, 2006; Zelazo, Carter, Reznick, & Frye, 1997). Within this conceptualization, executive functioning emerges from interactions between diffuse anatomical and functional brain areas such as the frontal, temporal and parietal lobes. As a result, executive function can often be impaired with damage to the diverse areas of the cortex, although in some instances, it may be maximal with frontal lobe damage. The results from the current study are consistent with this view, suggesting that focal epileptiform activity within either the frontal or temporal lobes can be associated with significant patterns of difficulties in various aspects of executive functioning.

5.4 INTELLECTUAL FUNCTIONING

5.4.1 FRONTAL LOBE EPILEPSY

The results from the current analyses indicated that children with FLE performed significantly below the average on a measure of full-scale intelligence. Specifically, the mean Full Scale IQ estimate for the FLE group fell in the borderline range of functioning. This finding of depressed intellectual functioning is broadly consistent with previous studies (Braakman et al., 2012; Nolan et al., 2003; Prévost et al., 2006; Sinclair et al., 2004). One major limitation of the pediatric literature has been that the vast majority of published studies have prohibited the inclusion of children with full scale IQs lower than 70 in their study samples (e.g., Bell et al., 2006; Gleissner et al., 2002; Lopes et al., 2014; Luton et al., 2010), and even more conservative clinical cut-offs (IQ > 80) have been used in others (Bailet & Turk, 2000; Culhane-Shelbourne et al., 2002). However, it is critical to be able to provide documentation of the full range of intellectual performance in children with intractable epilepsy (Cormack et al., 2007). Additionally, the estimates of intellectual functioning obtained in the previous studies have been based on administration of outdated editions of the WISC (e.g., Braakman et al., 2012; Nolan et al., 2003; Prévost et al., 2006; Sinclair et al., 2004). This practice is problematic, given that content and structure of the WISC-III and WISC-R is significantly different from the WISC-IV (Sattler & Dumont, 2004; Strauss et al., 2006), which limits the generalizability of the findings (Sherman et al., 2012). Consequently, the present study has provided one of the first unrestricted estimates of intellectual functioning, in a larger sample of children than has previously been described in the literature.

It is also one of the first studies to specifically assess intellectual performance

using an updated version of the WISC, in a group of children that are actively being considered for epilepsy surgery. Epilepsy has long been recognized to exert negative effects on cognitive and behavioral development in children. Children with "uncomplicated epilepsies" may show close to normal cognitive development over time (Hermann, Seidenberg, & Jones, 2008; Jones, Siddharth, Gurbani, Shields, & Kaplan, 2010). However, a substantial proportion of children (~30% +) demonstrate complicated forms of epilepsy with increased intractability to medication in which cognitive development is significantly impacted (Ellenberg, Hertz & Nelson, 1986; Nolan et al., 2003). Over a quarter of these individuals demonstrate IQ estimates below 80 after approximately 10 years post-seizure onset (Berg et al. 2008). Rathouz and colleagues (2014) followed children with new-onset epilepsy for a period of time to evaluate the effect of epilepsy on their cognitive development. In these relatively complicated cases, it was apparent that cognitive problems in some cases preceded onset of the epilepsy. Following onset, epilepsy seemed to exert relatively little to mild effects on cognitive development. By contrast, a recent longitudinal study by Van Iterson and colleagues (2014) characterized the influence of epilepsy on intelligence as a continuous downward-progressing function, where decline was likely to be maximal later in time.

The mean score for the General Ability Index (GAI) for the FLE group was also significantly below the normative values. Interestingly, a closer examination of the scores revealed that estimates of intellectual functioning derived from the GAI fell in the low average range, while estimates based on the FSIQ fell in the borderline range, although this difference was not statistically different.

It has been reported that working memory and processing speed demonstrate a

wide range of correlations with measures of intellectual functioning (see Fry & Hale, 2000). Given indications in the literature of increased difficulties with processing speed and working memory in children with FLE (Auclair et al., 2005; Braakman et al., 2012; Bulteau et al., 2000; Hernandez et al., 2003), it was hypothesized that inclusion of measures of processing speed and working memory in the full scale intellectual functioning composite could lead to a deflation in the derived estimates for individuals with FLE. However, the results of the current study suggest that removal of these indices does not result in meaningful change in the IQ estimate for individuals with frontal lobe dysfunction. It has been suggested that the frontal cortex may subserve intellectual abilities due to its role in cognitive control and flexibility (Duncan et al., 2000).

5.4.2 TEMPORAL LOBE EPILEPSY

Children with TLE also demonstrated estimates of full-scale intellectual functioning that corresponded to the borderline range. This pattern of significantly decreased performance relative to normative values is consistent with several prior studies (Guimaräes et al., 2007; Cormack et al., 2007; Hermann et al., 2002a; Hermann et al., 2002b; Mataro et al., 1998; Nolan et al., 2003). Additionally, when children with FLE and TLE were directly compared, no significant differences in their level of FSIQ were found (e.g., Hernandez et al., 2002; Nolan et al., 2003). Culhane-Shelbourne and colleagues (2002) found that their TLE sample obtained a lower FSIQ relative to their sample of FLE participants; however, it is notable that their exclusionary criteria limited the participation of individuals with IQ scores below 70, which likely skewed their estimate of intellectual functioning.

Results indicated that the IQ estimate from the GAI for the TLE group was also

significantly below the normative values. A comparison between the FSIQ and GAI estimates for the TLE group revealed no significant differences. Additionally, no significant differences were observed when performance on the GAI for the TLE and FLE participants were directly compared.

5.4.1 SUMMARY: FLE VS. TLE

The findings from the present study indicate that children with TLE and FLE perform similarly on measures of intellectual functioning. There have been considerable efforts made in the last 20 years to identify the neural underpinnings of general intelligence (Gläscher et al., 2010). While the most consistent findings have associated intellectual functioning with activations in the prefrontal cortex (Duncan et al., 2000), it has also been posited that intellectual functioning may instead involve communication across various distributed cortical regions (Jung & Haier, 2007). One theory that has emerged in the literature is the Parieto-Frontal Integration Theory (P-FIT), which suggests that the neural substrates involved in general intelligence include cortical regions in the frontal, parietal, occipital and temporal association cortices (Jung & Haier, 2007). Interestingly, a recent study conducted using voxel-based lesion symptom mapping revealed the role of a circumscribed region of the frontal pole, in addition to a distributed network involving various cortical regions and their white matter connections (Gläscher et al., 2010). Consequently, the findings in the current study provide additional evidence that dysfunction in either the frontal or temporal regions can result in significant impairments in intellectual functioning.

5.5 MOTOR FUNCTIONING

5.5.1 FRONTAL LOBE EPILEPSY

As expected, children with FLE displayed significant impairments in motor coordination and speed on the Grooved Pegboard Test (GPT). Specifically, the participants performed in the borderline range in both the dominant and non-dominant hand conditions. This is consistent with the results of a previous study examining motor functioning in children with FLE (Hernandez et al., 2002). However, a series of studies completed by Riva and colleagues (2002, 2005) failed to demonstrate significant differences between their FLE group and normative data during conditions in which the participants completed a peg placement task, the Purdue Pegboard task (PPBT), during unimanual conditions. Participants with FLE were only significantly impaired relative to reference values during an "assembly" condition in which they were required to place pegs while alternating hands.

Hernandez and colleagues (2002) also noted more significant difficulty on the bimanual coordination condition of the PPBT in their study of children with FLE. Based on these observations, the researchers suggested that frontal lobe dysfunction associated with FLE does not interfere with performance on measures of simple motor speed but may significantly impact performance on measures of speed when more complex aspects of motor activity and its coordination are involved (Hernandez et al., 2002; Riva et al., 2002; Riva et al., 2005).

The PPBT was originally constructed for use with adults and utilized in industrial and occupational assessments. Consequently, it has been suggested to be less appropriate for assessing motor coordination in children (Y. Wang et al., 2011). While the GPT does

not have a comparable bimanual condition, it is generally considered to be a more complex motor processing task due to its added requirement of sensory-motor integration and executive planning (Merker & Podell, 2011; Roy & Square-Storer, 1994). Taken together with trends observed in the previous studies, the results from the current study suggest that the GPT may be more sensitive to deficits in psychomotor speed in children with FLE than the Purdue Pegboard task. Mitrushina, Boone, Razani, and D'Eli (2005) also noted that the GPT was sensitive to problems in FLE that were not apparent on simple motor speed tasks such as finger tapping and grip strength.

5.5.2 TEMPORAL LOBE EPILEPSY

As a group, the children with TLE in the present study also scored below expected levels of functioning on the GPT. Relative performance deficits were apparent in both left and right hands when compared to available normative data. Very few studies are available in the literature which have specifically examined motor functioning in individuals with TLE. The present findings are, however, consistent with one study that was completed involving adult participants with FLE (Hermann et al., 2007). The results are also consistent with a previous study which assessed motor coordination and speed in participants with early-onset epilepsy using the bimanual condition of the PPBT (Hernandez et al., 2002). As in their study, comparisons between the FLE and TLE did not reveal significant differences.

5.5.1 SUMMARY: FLE VS. TLE

The results from the present study suggest that children with TLE and FLE demonstrate similar levels of impairment on a measure of motor coordination and speed. Various regions have been identified in the frontal lobes that are involved in the planning

and execution of motor activity (Rizzolatti & Luppino, 2001). Specifically, individuals with FLE demonstrate decreased patterns of activation in the frontal lobe of the epileptic hemisphere during measures of motor functioning (Woodward et al., 2014a; Woodward et al., 2014b). This correlated with poorer performance relative to typical controls. The mechanisms contributing to the observed pattern of impairment in the TLE group are less clear. However, there are anatomical pathways connecting the medial temporal area to the premotor areas of the frontal cortex (Schwartz, 1994). Consequently, it is conceivable that epileptiform activity may extend from the temporal lobe to frontal cortex through this distributed processing pathway and may contribute to neurodevelopmental differences that result in the difficulties seen in the TLE group during tasks of visuo-motor processing.

5.6 PSYCHOSOCIAL FUNCTIONING

In the current study, significantly increased internalizing behaviors were noted in both TLE and FLE groups in comparison to normative values. Additionally, both TLE and FLE groups were rated as having increased externalizing behaviors, although after controlling for multiple analyses, these findings were no longer significant. The TLE and FLE groups did not differ from each other, indicating that both groups show a similar pattern of deviation in psychosocial functioning. Additionally, a closer examination of performance on the individual subscales comprising these broader domains revealed a similarly elevated problem scores across all the subscales. As a group, the children with TLE and the children with FLE also demonstrated clinical elevations on the thought problems, somatic problems, attention problems and social adjustment problems subscales. Taken together, the results of the present study suggest that recurrent difficult

to control seizure activity early in childhood is associated with broad difficulties in psychosocial/emotional functioning.

These findings are generally consistent with the results of other investigations utilizing the CBCL in children with localization-related epilepsy (LRE). Almane and colleagues (2013) found similarly broad behavioral problems in children with newly diagnosed and recent-onset focal epilepsy. As in the present study, their cohort of children with focal epilepsies exhibited mean scores on these scales that were on average discrepant by a standard deviation or more in comparison to normative values. Interestingly, they found similar levels of difficulties in a cohort of children with idiopathic generalized epilepsy (IGE), although the children with IGE showed less impairment in social problems compared to their cohort with TLE and FLE.

5.7 IMPLICATIONS

Taken together, the findings of the current study argue against the existence of epilepsy syndrome-specific patterns of neuropsychological and behavioral dysfunction in individuals with childhood-onset epilepsy (Hermann et al., 2002b). To be more specific, both the TLE and FLE groups presented with significant impairment across a range of domains including memory, executive, intellectual, motor and psychosocial functioning. These results are unexpected given the focal epileptogenic effects typically described in the adult literature, although they are consistent with a growing body of research suggesting that recurrent seizure activity can have a critical impact on the course of programmed developmental processes (Anderson, Spencer-Smith, & Wood, 2011).

Perspectives from early animal and human studies suggested that brain insults sustained in childhood during a period of maximal brain plasticity could induce

significant cerebral reorganization, resulting in better functional recovery than insults sustained later in development (Kennard, 1936; Kennard, 1940; Woods, 1980). However, other researchers have regarded early brain injury as a 'vulnerability' factor, resulting in an abnormal trajectory of development, reduced neural resources and more severe functional deficits than would be expected following comparable injuries sustained in later childhood or adulthood (Anderson et al., 2011; Giza & Prins, 2006; Hebb, 1947; Hebb, 1949; Jacobs, Harvey, & Anderson, 2007). Consequently, the current study is consistent with theoretical perspectives suggesting that damage to the immature brain can result in a generalized pattern of cognitive and behavioral dysfunction and generally poorer functional recovery (Anderson et al., 2011).

The observation that children with seemingly diverse areas of seizure onset can produce similar cognitive and behavioral profiles provides additional evidence suggesting that the presence of recurrent seizure activity during early brain maturation disrupts the process of regional and hemispheric specialization that typically occurs across early childhood (Williams et al., 1998). Specifically, the findings of impairments in so-called "frontal lobe functions" in children with TLE and so-called "temporal lobe functions" in children with FLE suggests that localizationism may not represent a complete or sufficient account of functional organization in the brain (Stevens, 2009).

Neuroimaging studies have increasingly demonstrated that the human cerebral cortex is organized into complex networks of neurons connecting distinct areas of the brain that communicate with each other in a functionally specific manner (Schmidt, Petkov, Richardson, & Terry, 2014). Over the course of ontogeny, circuits of neurons develop greater domain-specificity through the strengthening or reorganizing of

frequently engaged neural connections ('Hebbian' connectivity) and the elimination of extraneous synapses or connections (Stevens, 2009; Tau & Peterson, 2010). Long-distance structural connectivity appears to emerge due to the synchronous activity of these networks of neurons (Varela, Lachaux, Rodriguez, & Martinerie, 2001). It has been suggested that most cognitive processes are not completely localized to a discrete brain region, but instead are mediated by the functional integration of the widely-distributed neuronal assemblies that comprise these neural networks (Burianova et al., 2010; Stevens, 2009).

The resulting neural networks form the structural substrate for distributed interactions among specialized brain systems for highly complex cognitive functions such as memory, EF and intelligence (Bola & Sabol, 2015; Hagmann et al., 2008; Stam, 2010). For example, participants commonly demonstrate increases in activity in the hippocampal region across various tasks of memory functioning (Burianova & Grady, 2007; Burianova et al., 2010). However, whole-brain analyses have additionally revealed concomitant changes in activation in various temporal areas including the middle, superior and inferior temporal gyri, as well as the caudate nucleus, inferior frontal gyrus, lingual gyrus, and inferior parietal lobule, suggesting the existence of an extended common functional network which mediates declarative memory retrieval. Similar extended networks have been observed for executive functions, including the frontal, temporal and parietal lobes (Alvarez & Emory, 2006; Riley, Moore, Cramer, & Lin, 2011; Zelazo et al., 1997), and intellectual functioning, including cortical regions in the frontal, parietal, occipital and temporal association cortices (Jung & Haier, 2007). These functional networks appear to undergo significant reorganization across development (Boersma et

al., 2011), which correlates with the emergence of various cognitive skills (Langer et al., 2012; van den Heuval & Sporns, 2009).

There is an abundance of research demonstrating that early seizure onset disrupts development at multiple levels with respect to anatomy and biochemistry (Holmes, 2005; Holmes & Ben-Ari, 2001). Consequently, it has been suggested that recurrent seizure activity may result in the development of atypical and more widely distributed neural networks compared to those seen in individuals with typically-developing brains (e.g., Maguire et al., 2001; Sutula & Pitkänen, 2002). Significant alterations in structural and functional network connectivity have been identified in individuals with TLE (Bartolomei, Bettus, Stam, & Guye, 2013; Berhardt, Hong, Bernasconi, & Bernasconi, 2013; Bonilha et al., 2007; Haneef, Lenartowicz, Yeh, Engel Jr., & Stern, 2014; Mankinen et al., 2012) and FLE (Vaessen et al., 2012). For example, in addition to the primary area of seizure focus, individuals with epilepsy often demonstrate abnormalities in cortical thickness, cortical complexity and atrophy which often extend beyond the initial area of epileptogenic focus to both ipsilateral and contralateral temporal and extratemporal lobe regions, including subcortical areas (e.g., Bonilha, Rorden, Castellano, & Cendes, 2005; Mueller et al., 2010) and neocortex (McDonald et al., 2008). Additionally, neuroimaging studies have demonstrated interictal hypometabolism and volume loss in various regions assumed to be part of this temporal-extratemporal network, regardless of the initial area of seizure onset (e.g., Hermann al., 2002a). More widely distributed neuroanatomic abnormalities have been associated with a greater increase in impairments in cognition (Dabbs, Jones, Seidenberg, & Hermann, 2009; Riley et al., 2011). Adults and children with epilepsy also appear to demonstrate abnormal

intrinsic brain connectivity (Haneef et al., 2014; Mankinen et al., 2012; Widjaja et al., 2013a; Widjaja et al., 2013b), as demonstrated by the degree of coactivation of different neural regions in the absence of processing demands (Kelly & Castellanos, 2014; Stevens, 2009). These patterns of resting-state connectivity are similarly correlated with significant impairments in neuropsychological functioning (Widjaja et al., 2013a; Widjaja et al., 2013b). The findings in the current study are consistent with a growing literature suggesting that childhood-onset seizure disorders are associated with greater susceptibility to cognitive and behavioral impairment, which likely reflects reorganization of functional and structural connectivity networks in the brain (Doucet et al., 2015; Korman et al., 2013).

Network analysis and related methodologies have also suggested that these pathologic network mechanisms in TLE and FLE may play a critical role in the genesis, propagation and expression of seizures (see Richardson, 2010; Spencer, 2002). Alterations in the neural networks connecting distinct areas of cortex appear to emerge from the same mechanisms that give rise to recurrent seizure activity; specifically, the ictal and interictal states of epilepsy are characterized by dysregulation within neural networks and (Sloviter, 1996) and the corresponding neurotransmitter (Engelborghs et al., 2000) systems. According to the 'kindling' model, the repeated pattern of excitatory and inhibitory influences induces the neural system to become increasingly susceptible to recurrent seizure activity (Morimoto, Fahnestock, & Racine, 2004). Studies involving the administration of direct electrical cortical stimulation to a neural system have demonstrated clinical manifestations and EEG discharges which often outlast the initial electrical stimulus or appear to evolve in presentation (see David et al., 2010; Kovac,

Kahane, & Diehl 2015). These observations have been used to suggest that the seizure activity has propagated along the neural connections along connected regions of a wider neural network (Bonilha et al., 2010; Kovac et al., 2015). Diffusion weighted imaging (DWI) has demonstrated that late-myelinating tracts are more vulnerable in epilepsy than early myelinating tracts, particularly in tracts ipsilateral to the side of seizure onset (Lee et al., 2013). Consequently, it has been proposed that vulnerability to seizure activity within any one part of the network can affect functioning broadly at all other parts in the network (Spencer, 2002), due to the propagation of the seizure activity to other areas within the neural network. Accordingly, the findings in the current study of generalized patterns of impairment across multiple functions could potentially be explained by damage to cortical and subcortical networks that are still immature and atypically interconnected at the time of onset of the seizures (Mabbott & Smith, 2003). Additionally, this emerging body of literature also provides a compelling rationale for why certain brain regions (e.g., temporal, frontal lobes) and cognitive functions (e.g., memory, executive) may be particularly vulnerable to the pathologic effects of recurrent seizure activity, as these are still undergoing substantial reorganization across development.

5.8 STRENGTHS AND LIMITATIONS

Despite only partial support for the original hypotheses, there are a number of strengths of this study. One is that the sample size is larger than what has typically been reported in pediatric epilepsy studies (see Table 1). Although other studies have compared children with FLE to those with matched controls and/or standardization samples or compared children of various etiologies on one domain of functioning, few

studies have attempted to systematically compare performance on measures spanning a range of domains (Williams et al., 1998). Performance was compared using widely used measures of neuropsychological functioning that were age-specific and could be implemented as part of a standard neuropsychological battery. Additionally, one of the biggest methodological weaknesses of previous studies of children with epilepsy has been the tendency to disregard the impact of various demographic and clinical variables. In response to this limitation, the current study included analyses of several of these epilepsy variables in order to rule out their potential confounding effects. The analyses demonstrated that the two epilepsy groups were closely matched on many of the variables that have been proposed to impact cognitive functioning, including age of onset of seizure activity, frequency of seizures and nature of pharmacological treatment. Finally, this study is one of the first to provide estimates of levels of memory, executive, motor, intellectual and psychosocial functioning specifically for children with intractable epilepsy.

However, several study limitations also need to be considered. The current measures were administered as part of a clinical evaluation for children in candidacy for epilepsy surgery. It was not possible to control for the possibility of brief or subclinical ictal activity occurring during the assessment (Nolan et al., 2004; Wilkinson et al., 2012) or differences in individual antiepileptic drug regimens (Nolan et al., 2004), which may have adversely affected performance on the neuropsychological measures. The cross-sectional design also prohibits understanding about whether the deficits observed in the current study are permanent or whether the emergence of those particular skills are merely delayed (Anderson et al., 2010). A longitudinal design would help to elucidate the

impact of early seizure onset on the presentation of cognitive and psychosocial functions relative to normal developmental trajectories. Additionally, in the current study, performance was compared to reference normative data. Future research should involve comparing each clinical group to a healthy comparison group (Anderson et al., 2010). However, it has been suggested that the use of normative data may actually be preferred over a comparison group, in order to avoid comparisons to small groups with potentially inflated IQ scores which may cause misinterpretations of the study findings (e.g., Ballantyne, Spilkin, Hesselink, & Trauner, 2008).

One additional limitation of the current study is regarding potential heterogeneity in the specific area of onset of seizure activity and/or the extent and type of pathology in the TLE and FLE groups. It is possible that this variability may have obscured possible associations between specific areas of cortex within the temporal and frontal lobes and particular patterns of impairment (Luton et al., 2010). For example, it has been suggested that the orbitofrontal, mesial, and dorsolateral regions within the frontal lobes are involved in different types of processing, with damage to these different areas each corresponding to a unique pattern of impairment in memory, social behavior, and executive functioning (Turner et al., 2007). Additionally, it has been suggested different temporal structures may represent distinct functional systems subserving different aspects of declarative memory performance (Helmstaedter & Elger, 2009), with the mesial structures mediating long-term consolidation and retrieval of new information (Helmstaedter et al., 1997) and the lateral structures involved in the processing of short-term or working memory and in the storage of long-term memories (Helmstaedter et al., 1997; Squire, 1992), or semantic memory (Patterson, Nestor, & Rogers, 2007).

Relatedly, while the majority of children with early-onset epilepsy are nonlesional, pathologies associated with epilepsy can include developmental malformations like cortical dysplasias and vascular malformations, neoplastic lesions, neuronal loss, and structural atrophy as in hippocampal sclerosis and infectious causes (Bigel & Smith, 2001a). In adults, lesional pathology (e.g., hippocampal sclerosis) has been shown to result in greater memory impairment as compared with other types of hippocampal pathology (e.g., tumors) (Helmstaedter & Elger, 2009; Helmstaedter et al., 1997; Lah et al., 2014) or with epilepsy of unknown cause (Alessio et al., 2004; Narayanan et al., 2012), suggesting that the extent and type of pathology may differentially influence outcomes. Consequently, an even larger sample of participants with more homogenous and well-specified pathology may allow for a better understanding of these potential relationships and increase the statistical power attributed to the findings.

However, few studies have been able to systematically explore or characterize patient groups at that level nor has the impact of different neuropathologies on cognitive functioning been well studied due to the challenges associated with obtaining a sizeable group of patients with well-characterized lesions restricted to a particular area of the brain (Riva et al., 2005). Furthermore, accurate delineation of focal onset of seizures, particular in FLE, is often limited given the large surface of buried cortical regions in the frontal lobes (Culhane-Shelbourne et al., 2002; Damasio, 1985). Additionally, the majority of studies which have attempted to more clearly specify the impact of specific patterns of pathology have not consistently revealed significant differences related to area of pathology (i.e., mesial or lateral) or lesion type, particularly in children (e.g., Aikia et

al., 2001; Bigel & Smith, 2001b; Gascoigne et al., 2014; Gonzalez et al., 2007; Mabbott & Smith, 2003; Nolan et al., 2003). Bigel and Smith (2001a) also found no significant impact of lesion size on degree of cognitive impairment. It has been suggested that the inclusion of children with various etiologies in the current study makes it more representative of the general epilepsy population (Campiglia et al., 2014).

5.9 CONCLUSION

Overall, the findings of patterns of generalized impairment in the current study suggest that the classification of a "focal-onset" of seizures may be conceptually limited, in that seizures affecting any part of a functional neural network can result in a similar pattern of impairment. Moreover, models of seizure activity have demonstrated that networks early in development are more likely to give rise to generalized seizure activity across the network because they are less stable and thus more likely to propagate ictal discharges (Terry, Benjamin, & Richardson, 2012). These findings challenge the concept of "localization-related" or "focal" epilepsies, and also assumptions about specific focal origins of associated cognitive deficits in epilepsy disorders (Richardson, 2010). Interestingly, emerging from this growing body of literature, a revised approach to categorizing seizures and types of epilepsy has recently been proposed by The International League Against Epilepsy (ILAE) Commission on Classification and Terminology (Berg et al., 2010). This proposition advocates transitioning away from current conceptualizations of epilepsy as either ‘‘focal" or ‘‘generalized" onset and instead embracing a mechanism-based classification system which conceptualizes seizures as occurring broadly within distributed brain networks (Berg & Scheffer, 2011; Terry et al., 2012). Accordingly, it has been proposed that the patients may be best

grouped according to affected networks, rather than affected regions (Carter, Shulman, & Corbetta, 2012).

These findings also have critical implications for how the assessment of neuropsychological functioning is incorporated within the evaluation process for determining eligibility for surgical resection, suggesting that neurological dysfunction in individuals with early-onset epilepsies may not be reliably differentiated on the basis of neuropsychological profiles, depending perhaps on the features of their seizure disorder (e.g., duration, severity). These factors can reportedly result in declining cognitive performance and more generalized areas of impairment (Rathouz et al., 2014). This pattern may be most prominent in children with medication-resistant epilepsy, which is consistent with previous indications that refractory seizures often are associated with a greater degree of impairment in children (e.g., Bjornes et al., 2001; Nolan et al., 2003). Consequently, this study emphasizes the importance of early neuropsychological assessment in children with intractable epilepsy in order to document level of impairment/function, establish a baseline to track functioning and assist in treatment recommendations.

In conclusion, while pediatric studies have provisionally adopted the function-structure mapping framework of the adult lesion studies, the results from the current study suggest that individuals with childhood-onset epilepsy exhibit generalized patterns of cognitive compromise, regardless of seizure type. These results provide support for contemporary models of the brain which propose a distributed, but integrated neural network subserving various cognitive and behavioral development. Further, damage or injury sustained to any brain region during development may render children vulnerable

to a range of deficits that would not normally be expected with analogous seizure disorders acquired in adulthood. Consequently, these findings highlight the need for more thoughtful and comprehensive evaluation and provision of recommendations for care for individuals with early-onset seizures.

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