NEUROPSYCHOLOGICAL PROFILES IN TEMPORAL LOBE EPILEPSY WITH AND WITHOUT A HISTORY OF TRAUMATIC BRAIN INJURY

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DEDICATION

I would like to thank the members of my Committee for their support and guidance throughout this process. A very special thank you to my family for the love and encouragement they have given me throughout my education. To my sister who is a constant source of pragmatism, humor, and courage. My mother for her gentle reassurance, warmth, hope, and unwavering belief in me. And finally, my father, who taught me to believe in myself, the value of hard work, and that goals worth having take perseverance. Each of them has shaped who I am today and given me the strength to reach my goals. For that, I am deeply grateful.

NEUROPSYCHOLOGICAL PROFILES IN TEMPORAL LOBE EPILEPSY WITH AND WITHOUT A HISTORY OF TRAUMATIC BRAIN INJURY

by

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NEUROPSYCHOLOGICAL PROFILES IN TEMPORAL LOBE EPILEPSY WITH AND WITHOUT A HISTORY OF TRAUMATIC BRAIN INJURY

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Abstract

Neuropsychological deficits have long been observed in those with temporal lobe epilepsy (TLE). Language and verbal memory are often impaired in individuals with left TLE and visuospatial and visual memory can be impaired in patients with right TLE. Traumatic brain injury (TBI) is the most common known cause of epilepsy. Given the heterogeneous nature of TBI, neurocognitive deficits can vary after injury; however, difficulty in memory, attention, processing speed, and executive functioning are consistently observed. Even though these two neurological conditions are

intertwined, very little is known about the combined effects on neurocognitive functioning. This study aimed to examine neuropsychological functioning in TLE patients with and without a history of TBI. It was predicted that those with a history of TBI would have greater deficits in attention, processing speed, and executive functioning than those without TBI. Binary logistic regression models were used to determine the value of an array of neuropsychological measures in differentiating those with and without TBI. Results suggested greater cognitive difficulties, particularly in executive functioning, in those with a history of TBI. Understanding that TLE patients with a TBI history could have greater cognitive impairments may assist with clinician interpretation of neuropsychological findings. Future research should expand on the current results to further describe differences in epilepsy populations with and without a history of TBI in a larger, more diverse sample, and with a greater number of individuals who completed semantic fluency and AVLT.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AVLT	Rey Auditory Verbal Learning Test
BNT	Boston Naming Test
CT	Computed Tomography
CVLT	California Verbal Learning Test
EEG	Electroencephalogram
MAE VN	Multilingual Aphasia Examination Visual Naming
MRI	Magnetic Resonance Imaging
MTS	Mesial Temporal Sclerosis
PTE	Posttraumatic Epilepsy
Rey-O	Rey Osterrieth Complex Figure
SPECT	Single-Photon Emission Computed Tomography
TBI	Traumatic Brain Injury
TLE	Temporal Lobe Epilepsy
WAIS	Wechsler Adult Intelligence Scale
WMS-LM	Wechsler Memory Scale-Logical Memory
WMS-VR	Wechsler Memory Scale-Visual Reproduction

CHAPTER ONE

Introduction

Epilepsy, defined as the presence of recurrent, unprovoked seizures, is a common neurological condition, affecting approximately 4.1 million Americans (Kobau, Luo, Zack, Helmers, & Thurman, 2012) and 50 million people worldwide (WHO, 2018). While the definition of seizures has evolved over years of research, the International League Against Epilepsy, in partnership with the International Bureau for Epilepsy defines seizures as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (Fisher et al., 2005). This definition is purposefully broad, as epilepsy is comprised of a diverse set of syndromes that cluster together to construct a complex and heterogeneous disorder (Fisher et al., 2017). Each of these syndromes or seizure types have a unique presentation (semiology) and associated symptoms, as seizures can originate in any area of the brain and from many different etiologies. Further, adding to the complexity of this disorder, approximately 40% of patients with epilepsy have more than one seizure type (Keranen, Sillanpaa, & Riekkinen, 1988), and seizure semiology varies widely. The repeated abnormal neuronal activity that characterizes epilepsy is associated with varying levels of neurological damage, as 54% of those with chronic epilepsy have accompanying cortical volume loss (Liu et al., 2003), while others experience cognitive and/or behavioral changes (Helmstaedter, Kurthen, Lux, Reuber, & Elger, 2003). Given the complex and diverse nature of epilepsy as a syndrome, it is not surprising that the diagnosis and treatment is also multifaceted.

When an epilepsy patient presents for evaluation, a variety of factors must be considered, including etiology, seizure classification, treatment options, and prognosis. Each of these factors are interwoven to create a complex clinical picture for each individual and play an important role in conceptualization and treatment of epilepsy; as such, all are briefly reviewed below. These factors are evaluated using multiple neurodiagnostic procedures, typically including observation of neurophysiology, neuroimaging, and neuropsychology. This review will provide a basis for understanding the syndrome and assist in demonstrating the importance of neuropsychological evaluation in individuals with epilepsy. As more than half of individuals with epilepsy have some degree of structural neurological damage from their disease (Liu et al., 2003) and many acquire injuries from falling during seizure activity (Kirby & Sadler, 1995; Wilson & Selassie, 2014), understanding the presence and nature of accompanying cognitive deficits is an important aspect of an epilepsy evaluation. As previously mentioned, etiology is a primary clinical consideration during an epilepsy evaluation with the most common known etiology as traumatic brain injury [TBI (IBIA, 2018)]. Up to 20% of all epilepsy cases are thought to be a result of TBI (Agrawal, Timothy, Pandit, & Manju, 2006; Annegers & Coan, 2000; Jennett, 1973; Semah et al., 1998), and individuals with epilepsy have an increased risk of TBI during seizure activity due to falls (Kirby & Sadler, 1995). Additionally, those with TBI, regardless of seizure history, can sustain structural and functional neurological changes that can result in cognitive decline (Belanger, Tate, & Vanderploeg, 2018; Roebuck-Spencer & Sherer, 2018). Neuropsychological assessment can help characterize the pattern of cognitive strengths and weaknesses in patients with a wide array of neurological disorders, including

epilepsy and TBI. Therefore, the use of neuropsychological techniques in epilepsy and TBI are discussed. As the cognitive presentation of individuals with epilepsy can vary due to the heterogeneous nature of the disease, there is a long history of neuropsychological research and cognitive phenotyping in epilepsy, which are reviewed. Finally, as epilepsy is characterized by repeated abnormal neuroelectrical activity that sometimes results in neurophysiological damage (Liu et al., 2003), theoretically, additional neurological risk factors or insults might exacerbate cognitive impairment and/or decline. For this reason, common cognitive deficits seen in TBI as well as the relationship between TBI and epilepsy are reviewed.

CHAPTER TWO

Review of the Literature

Etiology

A variety of different etiologies are associated with the development of epilepsy and can be broken down into six categories: structural, genetic, infectious, metabolic, immune, and unknown (Scheffer et al., 2017). Some examples of potential etiologies include developmental brain malformations, congenital conditions, brain tumors, stroke, neurodegenerative diseases, encephalopathy, and TBI (Eriksson, Rugg-Gunn, Symms, Barker, & Duncan, 2001; Falconer, Serafetinides, & Corsellis, 1964; Sander, 2003; Singh & Trevick, 2016; Sisodiya, 2000; Sisodiya, 2004). Additionally, the prevalence of etiologies vary with age and geographic location (Bell & Sander, 2001; Sander, 2003; Sander & Shorvon, 1996). For instance, developmental brain malformations, genetic factors, and congenital conditions are most commonly seen in children and adolescents, whereas brain tumors and neurodegenerative disease are more often seen in those who develop epilepsy later in life (Sander, 2003). Overall, the most common known etiology of seizures is TBI, resulting in what is known as posttraumatic epilepsy (PTE). The rates of PTE vary based on severity of TBI, time elapsed since injury, and age (Frey, 2003), with the highest rate of occurrence in young adults and those in military service (Agrawal et al., 2006; Annegers & Coan, 2000; Salazar et al., 1985). General reports suggest that between 4 and 56% of individuals with a TBI develop PTE (Frey, 2003), and approximately 20% of all epilepsy cases are thought to be associated with a previous TBI (Agrawal et al., 2006; Annegers & Coan, 2000; Jennett, 1973; Semah et al., 1998).

Determining the etiology of epilepsy can be critical in treatment planning (e.g. surgically removing a brain tumor, aggressively treating infection) and can provide information about prognosis (Beghi, Giussani, & Sander, 2015; Scheffer et al., 2017); however, epilepsy etiology is often unclear due to absence of structural abnormality or known precipitating event. It has been reported that in approximately 30% of all patients with epilepsy, the etiology is unknown (Hauser & Hesdorffer, 1990) and in fact may be multifactorial. Therefore, examining etiology is only one of multiple neurodiagnostic strategies used in epilepsy evaluations.

Seizure Classification

Epilepsy experts have developed a variety of ways to classify seizures in order to diagnose and describe disease characteristics to other professionals, patients, and caretakers. Each of these strategies was developed to meet the needs of the context in which they were developed. For example, the most recent seizure classification system was developed in a research setting by Blumenfeld (2014) to reflect the theory that epilepsy is a disease of the neural network, rather than or in addition to the dysfunction of discrete neurological regions. Furthermore, Centeno and Carmichael (2014) demonstrated that seizures could potentially arise from one of four networks: neocortical, thalamocortical, limbic, or brainstem. While the current research on the neural network is still in the early stages and not yet widely applicable in clinical settings (Fisher et al., 2017), it is important to consider that focal seizures can have more widespread cognitive effects than previously thought. This helps explain why patients with epilepsy sometimes manifest cognitive deficits that extend beyond their discrete seizure focus. For example, it has been consistently shown that those with temporal lobe epilepsy (TLE) sometimes

have language, processing speed, and executive functioning deficits in addition to more "focal" abnormalities or memory dysfunction, which is traditionally considered in TLE populations (Tracy & Tinker, 2018). Additionally, some cognitive functions are more localized than others; for instance, material- specific memory has long been associated with the temporal lobes, whereas processing speed is considered a frontal subcortical or white matter function. These less localized skills could be at greater risk for damage due to downstream affects or from a more global insult, such as a generalized seizure or TBI.

In order to provide a comprehensive epilepsy classification method, The International League Against Epilepsy established a task force lead by Fisher et al. (2017) to developed a multistep model. This model was designed to be broad and inclusive in order to provide an operational definition of epilepsy for patients at any age. The initial operational classification consists of three steps and is meant to provide therapeutic and prognostic information for all patients, even those who cannot be provided with a clear diagnosis. First, seizure onset is classified as either focal, generalized, or unknown. Thus, the first step specifies if the seizure originates from a discrete brain region (focal), the entire brain simultaneously (generalized), or if it is unclear (unknown). Next, the state of consciousness is determined. In cases of generalized onset, awareness of one's surroundings is always impaired; however, in a focal seizure, awareness can potentially be maintained. Therefore, a focal seizure can be classified as either *focal aware* (previously known as *simple partial*) or *focal impaired awareness* (previously known as *complex partial*). Motor involvement is then classified in all seizures with the presence of motor disturbance described as either *tonic-clonic* or *other motor involvement*. Finally, if a seizure has a focal onset and progresses to involve the entire brain, it is classified as

focal to bilateral tonic-clonic, previously known as *partial onset with secondary generalization* (Fisher et al., 2017). Understanding the current state of seizure classification is an important concept to contextualizing the different types of epilepsy syndromes in order to assist with treatment planning and accurately predicting prognoses.

For treatment planning, seizure types are commonly further classified by determining the anatomical region of seizure onset. This strategy is particularly useful in clinical settings when the treatment team is considering surgical resection of the epileptogenic tissue (see treatment options for more detail). It is well documented that the most common focal seizure type originates in the temporal lobe, known as temporal lobe epilepsy (TLE). Estimates suggest up to 66% of all epilepsy patients worldwide have TLE (Engel & Shewmon, 1993; Hauser & Kurland, 1975; Téllez-Zenteno & Hernández-Ronquillo, 2012; Wiebe, 2000).

Once the semiology is observed, epileptologists form hypotheses about potential seizure location(s) and use a variety of methods to gather evidence to either support or challenge the hypotheses. Some of the gold standard methods for seizure localization include surface, or scalp, EEG, neuroimaging, and neuropsychology. Surface EEG is used to examine patterns in neuroelectrical activity to help localize seizure onset and regions affected by the seizure activity (Cascino, 1996; Marsan & Zivin, 1970; Noachtar & Rémi, 2009; Salinsky, Kanter, & Dasheiff, 1987). In large academic medical centers, EEGs are often recorded continuously during an extended inpatient stay in an effort to capture several seizure events, particularly if the patient has multiple seizure types. The EEG is paired with video monitoring in order to match seizure semiology(ies) with EEG pattern(s) (Kilpatrick, Cook, Kaye, Murphy, & Matkovic, 1997; Sperling et al., 1992).

The overall pattern of activity observed through EEG is important in the classification of seizures, as there are distinct patterns that are well documented to correspond with specific epilepsy syndromes and etiologies (Noachtar & Rémi, 2009). However, locating epileptic regions on EEG is only one step in the diagnostic process, and with this information, medical professionals are able to continue to refine hypotheses about seizure localization.

While there is clear utility to surface EEG, this diagnostic tool has limitations. Whereas EEG is very useful in the detection and characterization of seizures, surface EEG can be distorted or have difficulty detecting abnormal neuroelectrical activity beneath the cortex. This is often due to interference from the skull and the normal neuroelectrical activity of the cortex that is more readily detectable. Additionally, the location of seizure onset can be difficult to determine if the seizure spreads quickly to other regions. In a study by Foldvary et al. (2001), surface EEG adequately localized TLE cases more often than extratemporal epilepsies. The authors accurately localized two thirds of all cases, though false localization occurred in 28% of occipital and 16% of parietal seizures. Another study by Williamson et al. (1993) showed that 42% of individuals with well lateralized TLE showed bilateral EEG activity that was preponderant over activity on the side of seizures. Thus, as with many other neurodiagnostic techniques, EEG is often not an effective lateralizing tool when used in isolation, suggesting the utility of multiple methods.

Another gold standard method used to identify focal brain abnormalities is neuroimaging, and in combination with EEG, has been shown to help lateralize seizures when visible anatomical abnormalities are present (Cascino et al., 1996; Cendes, 2013).

Prior to the advent of MRI in the late 1970s, CTs were the only available imaging method to observe gross neuroanatomy and potential structural abnormalities. An early study by Guberman (1983) showed that 51 out of 196 epilepsy patients (26%) had abnormal CT scans, which included neoplasms, arteriovenous malformations, atrophy, infarcts, calcified lesions, and low- density or enhancing lesions. Currently, MRI is more often used in patients with epilepsy, as resolution is superior, tissues are more distinguishable, and smaller lesions are more evident (Stefan et al., 1987). MRI is particularly sensitive to detecting mesial temporal sclerosis (MTS), which includes atrophy of the hippocampus (International League Against Epilepsy, 2004). While not specific to epilepsy, MTS is commonly observed in TLE (Blümcke et al., 2013). As many as 39% of patients with TLE have some degree of hippocampal sclerosis (Blümcke & Spreafico, 2012), which increases to 70% in patients with pharmacoresistant epilepsy seeking surgical treatment (Bernasconi, 2006; Cendes, Caramanos, Andermann, Dubeau, & Arnold, 1997). The presence and severity of MTS are likely influenced by age of epilepsy onset, seizure frequency and severity, genetic predisposition and early life events such as TBI, febrile seizures, hypoxia, and/or central nervous system infection (Blümcke et al., 2013). While atrophy is most often more severe in one hemisphere (i.e. left or right), damage is generally bilateral and progressive (International League Against Epilepsy, 2004). In those with MTS (39% of all TLE cases), the presence of atrophy accurately lateralizes TLE in as many as 71% of cases (Cascino et al., 1991).

While MRI can detect MTS with relative accuracy, it is not uncommon for epilepsy patients to have normal MRIs, or an absence of focal or asymmetrical findings, as some studies have noted normal MRIs in 20% to 25% of individuals with epilepsy

(Murro et al., 1993; Stefan et al., 1987). Also, it should be noted that healthy individuals can have abnormal MRIs; an early study by Kuzniecky et al. (1987) found that MRI abnormalities were seen in 71% of patients with temporal lobe epilepsy, though 6% of healthy volunteers and neurological patients without epilepsy also had MRI abnormalities. In addition, it has been shown that seizures can induce reversible brain lesions that are visible on MRI. Cianfoni et al. (2013) found that of patients who had an identifiable lesion on MRI within the first week after a seizure, 58% had no evidence of lesions when scanned again within the next 150 days. These studies demonstrate variability in the diagnostic utility of structural neuroimaging techniques, which suggests the need for additional methods to help lateralize and localize seizures. Other commonly used techniques include invasive EEG [implantation of depth electrodes with in the predicted epileptic regions (Casdagli et al., 1996; Casdegli et al., 1997; Zumsteg & Wieser, 2000)], single photon emission computed tomography [SPECT (Cragar, Berry, Fakhoury, Cibula, & Schmitt, 2002; Ho et al., 1994; Stefan et al., 1987)], and positron emission tomography [PET (Debets et al., 1990; Mauguière & Ryvlin, 2004; Spencer, 1994). However, similar to EEG, CT, and MRI, each of these techniques have limitations, necessitating the use of multiple measures to lateralize and localize seizure onset. To supplement these various neurophysiologic and neuroimaging techniques, it is considered the standard of care to compare results to neuropsychological functioning (Loring, 2010).

Treatment and Prognosis

The first line of treatment for epilepsy is often a schedule of antiepileptic drugs, as medications have been shown to suppress seizures in many patients (Hauser & Lee,

2002; O'Donoghue & Sander, 1996; Sander, 2003; Sander, 1993). Despite the success of antiepileptic drugs in treating epilepsy, between 20% and 40% of all epilepsy patients become pharmacoresistant or medically intractable (Beghi et al., 2015; Cockerell et al., 1997; Engel et al., 2003; Sander, 2003; Sander, 1993). Among the various types of epilepsy, patients with TLE have been noted to be the most likely to become pharmacoresistant (Engel, 1998). Additionally, TLE patients with MTS are at the highest risk of becoming intractable (Sisodiya, Lin, Harding, Squier, & Thom, 2002).

In the case of pharmacoresistant epilepsy, surgical resection is a potential treatment option. Resection is most common in TLE as those who undergo surgical intervention tend to have a higher rate of seizure freedom and experience less cognitive decline post-surgery than patients who undergo resections of the frontal or parietal lobes (Engel, 1996; Meier & French, 1966). In the case of TLE, surgical candidates most often undergo anterior temporal lobectomy of either the left or right side, whichever is suspected to be the location of seizure onset (Engel et al., 2003). This is done in hopes of removing epileptogenic tissue and therefore, eliminating or reducing seizure frequency. It has been suggested that between 64% and 66% of TLE patients who underwent anterior temporal lobectomy became free of disabling seizures (Engel et al., 2003; Téllez-Zenteno, Dhar, & Wiebe, 2005). Furthermore, when seizures are reduced with surgical intervention, remaining seizure activity is often responsive to pharmacological treatment (Ivnik, Sharbrough, & Laws, 1987; Téllez-Zenteno, Dhar, Hernandez-Ronquillo, & Wiebe, 2007).

When it comes to epilepsy, prognosis usually refers to the probability of attaining seizure reduction or freedom with treatment (Beghi et al., 2015; Sander, 2003). A variety

of factors are thought to contribute to epilepsy prognosis, including the number of seizures experienced before treatment initiation, seizure type (e.g., nocturnal seizures, focal seizures), family history of epilepsy, etiology, specific patterns of EEG abnormalities, and poor early response to medication (Beghi et al., 2015; Berg & Shinnar, 1991; Hauser & Hesdorffer, 1990; Hopkins, Garman, & Clarke, 1988). However, there is a small body of research done in countries without readily available antiepileptic drugs demonstrating that as many as 46% of patients achieve long-term remission (at least two years without a seizure) in the absence pharmacological treatment (Placencia et al., 1992), suggesting that seizure remission may occur in a significant number of patients regardless of treatment (Sander, 1993; Shinnar & Berg, 1994).

Several factors can help predict post-surgical prognosis in intractable TLE. First, accurate classification through lateralization and localization of seizure focus is important to achieving the best prognosis post-surgery (Beghi et al., 2015). Additionally, the occurrence of strictly unilateral temporal interictal epileptiform discharges has significant predictive value for a successful temporal lobe resection. In these instances, 85% of individuals with unilateral interictal discharges have been found to be seizure- free, in comparison to 52% of patients with bilateral interictal discharges (Schulz et al., 2000). Conversely, patients with mesial TLE as a result of MTS and who show frequent interictal epileptiform discharges have a poorer prognosis for resective epilepsy surgery than patients with rare interictal epileptiform discharges (Krendl, Lurger, & Baumgartner, 2008).

Neuropsychological Findings in TLE

As epilepsy is a condition that results in and/or from neuroanatomical damage, it is not uncommon for individuals to exhibit behavioral, emotional, and cognitive abnormalities. Understanding each of these aspects of epilepsy provides information on current functioning, can assist in treatment planning, and provides post-intervention prognostic indicators (Beghi et al., 2015; Jones-Gotman et al., 2010). In the evaluation of patients with epilepsy, the addition of neuropsychological assessment can be used in a variety of ways. Such assessment provides information relevant to lateralization/ localization of epileptic region(s) to assist in seizure classification, as well as differentiate between neurological, psychological, and social contributions to patient presentation. This information can be additive to treatment planning by helping assess suitability for surgery, predicting cognitive functioning after treatment, monitoring cognition over time, and providing information about psychological status. Furthermore a neuropsychological evaluation can assess health literacy, providing information on the understanding and appreciation of procedures, and offer psychoeducation to the patient and families about cognitive and psychiatric symptoms as well as possible outcomes (Wilson et al., 2015). The role of neuropsychology is to enhance epilepsy evaluations by quantifying and characterizing cognitive and emotional functioning through establishing a cognitive profile of the individual's strengths and weaknesses in multiple cognitive domains and assess their current psychological status (Jones-Gotman et al., 2010; Lassonde, Sauerwein, Gallagher, Thériault, & Lepore, 2006). Additionally, as impairments on neuropsychological testing may correlate with anatomical areas of dysfunction (Hermann, Wyler, Somes, Berry, & Dohan, 1992; Lencz et al., 1992; Saling et al., 1993;

Sass et al., 1990), results are used in combination with other diagnostic techniques to lateralize and localize the epileptogenic focus. Furthermore, neuropsychological evaluations can be additive to treatment planning and assist in predicting prognosis. In TLE specifically, neurocognitive testing is used to evaluate the integrity of the temporal lobes, to help lateralize impairment, localize seizure focus, and predict functioning post-temporal lobe resection surgery (Jones-Gotman et al., 2010). The valuable contribution of neuropsychology to epilepsy evaluations has been consistently acknowledged by the National Institute of Health, describing neuropsychology as essential for all preoperative epilepsy evaluations (Loring, 2010).

In presurgical epilepsy evaluations, neuropsychological results are in agreement with other neurodiagnostic techniques in 66% to 73% of patients (Ogden-Epker & Cullum, 2001; Williamson et al., 1993), and if cognitive testing is consistent with other neurodiagnostic techniques in lateralizing seizures, it has been shown to be a favorable predictor of postoperative outcomes. If neuropsychological results are inconsistent or discordant with presumed localization based upon other techniques, this provides impetus for further investigation about seizure characteristics such as the potential for multiple foci (Jones-Gotman et al., 2010; Lassonde et al., 2006), atypical neuro-organization, or extratemporal network involvement (Tracy & Tinker, 2018). In an early study by Hermann, Seidenberg, Schoenfeld, and Davies (1997), the authors assessed the performance of 107 patients with TLE on measures of intelligence, academic achievement, language, visuospatial skills, learning and memory, attention, and problem-solving skills. The authors noted more impairment than was previously expected in TLE, with decline in crystalized intelligence (WAIS-R Verbal Comprehension Index and

Perceptual Organization Index), academic achievement, language, visuospatial skills, and memory. In contrast, attention/concentration and executive functioning were spared in the TLE sample.

A follow-up study by Hermann, Seidenberg, Lee, Chan, and Rutecki (2007) suggested the existence of three cognitive phenotypes in temporal lobe epilepsy relating to level and pattern of deficits: 1. minimally impaired (47%), 2. memory impaired (24%), and 3. memory, executive functioning, and processing speed impaired (29%). The third and most impaired cognitive phenotype was characterized by patients who were older, had a longer duration of epilepsy, were prescribed more medications, and demonstrated abnormal white matter tracts and cerebral spinal fluid volume. A follow-up neuroimaging study by Dabbs, Jones, Seidenberg, and Hermann (2009) found that those in the worst cognitive function group had bilateral thinning in the cortex, thalamus, caudate, and cerebellum as well as in the corpus callosum and the left hippocampus. These studies provide further evidence for downstream or network level impairment in severe epilepsy rather than a discrete lesional pattern.

While extratemporal network involvement likely accounts for a portion of disagreement between lateralization techniques, it has also been found that patients with discordant or nonlateralizing neuropsychological findings often have right temporal seizure origin (Williamson et al., 1993). Accurately lateralizing right TLE based solely on neurocognitive testing can be more challenging than lateralizing left TLE (Barr et al., 1997; Hermann et al., 1997). This is likely due, in part, to humans' high level of language-dependence and use of verbal labels when describing or encoding non-verbal information. Neurocognitive lateralization challenges may also be related to the

underlying connections and networks involved in cognitive processing. For example, a recent fMRI investigation found a positive correlation between delayed nonverbal memory scores and the connection between the left mesial temporal lobe and the medial portal cortex in patients with right TLE. In contrast, verbal memory scores were negatively correlated with the connection between the left mesial temporal lobe and the posterior cingulate cortex (Doucet, Osipowicz, Sharan, Sperling, & Tracy, 2013). The authors argued that these relationships suggest that those with right TLE have adaptive connectivity changes in the contralateral hemisphere to help compensate for nonverbal memory deficits, while those with left TLE have maladaptive changes in the pathological hemisphere. This could potentially explain some of the difficulties that are often faced by neuropsychologists when attempting to lateralize right TLE. Regardless of these lateralization challenges, neuropsychological evaluations remain an important diagnostic tool, assist with treatment planning, and provide important data about cognitive and psychological outcomes.

In examining TLE pre-surgical evaluation findings, neuropsychologists often compare test performances associated with dominant hemisphere function to those more associated with nondominant hemisphere- related abilities in order to assist in lateralizing the epileptogenic focus. This strategy is meant to provide a "control" by comparing presumably preserved functioning to impaired functioning. In reality, this strategy is not always successful, as individuals with epilepsy can present with relatively intact neurocognitive performances, have bilateral and multiple anatomical regions that are affected, or have damage to extratemporal regions that are connected via the neural network (Helmstaedter, 2008; Hermann, Loring, & Wilson, 2017; Tracy & Tinker, 2018;

Wisniewski, Wendling, Manning, & Steinhoff, 2012). Cognitive research on epilepsy has demonstrated that approximately 29% of individuals with temporal lobe epilepsy also have impairment in executive functioning and processing speed (Hermann et al., 2007). However, even with these lateralizing challenges, this initial strategy of profile interpretation is often helpful as it is the beginning of a multistep process approach to profile conceptualization employed by the neuropsychologist (Jones-Gotman et al., 2010). Using this strategy, neuropsychologists often compare verbal memory (dominant) to nonverbal memory performance (non-dominant) to try to help lateralize and localize functional impairment. Although there are variety of available neuropsychological measures, some are better at lateralizing and localizing regions of dysfunction than others (Jones-Gotman et al., 2010; Lezak, Howieson, Bigler, & Tranel, 2012).

While the most robust body of literature on the neuropsychological evaluation of epilepsy has focused on memory functioning in TLE, other studies have demonstrated that assessment of global cognitive functioning is often useful. When considering test selection, a neuropsychological assessment that examines a variety of domains in addition to memory can provide additional lateralization evidence as well as help mediate previously discussed challenges faced in neuropsychological assessment (i.e., multiple seizure sites, bilateral impairment, damage in extratemporal regions). In 2011, an NINDS task force (Loring et al., 2011) suggested that at a minimum, all epilepsy evaluations should include measures of IQ, overall mental status, memory, naming, executive functioning, and attention. Therefore, a broader set of cognitive measures is advantageous in epilepsy evaluations.

In addition to careful test selection, neuropsychologists should be thoughtful about premorbid intellectual functioning, age of seizure onset, seizure frequency, and MTS when assessing patients with TLE. Some research has indicated that children with epilepsy have lower IQs than their typically developing peers (Berg et al., 2008). Berg et al., (2005) found that 23% of pediatric epilepsy cases were receiving special education prior to seizure onset, potentially suggesting a greater susceptibility to seizures in those who may have longstanding deficits. More recently, a review by Hermann, Jones, Jackson, and Seidenberg, (2012) noted consistent literature siting abnormal cognition, brain structure, and behavior at the time of seizure onset in children, as well as reported neurobehavioral difficulties prior to onset. Also, cognitive dysfunction is more commonly observed in patients with an earlier age of onset and greater seizure frequency (Langfitt, 2010) and is associated with more diffuse cognitive deficits (Helmstaedter, 2005; Hermann et al., 1997; Hermann et al., 2007). According to the International League Against Epilepsy commission report (2004), individuals with TLE and MTS most commonly have impaired episodic memory, with verbal memory being more systematically affected than visual memory. Including these factors as context for conceptualization and careful test selection is important in maximizing the contribution of neuropsychological measures in estimating the lateralization and localization of seizure onset. Because language, visuospatial, verbal and visual memory tend to be among the more lateralized cognitive abilities in TLE (Jones-Gotman et al., 2010; Lezak et al., 2012), these functions are reviewed in detail below (see summary in Table 1) in terms of which measures are the most useful in lateralizing and localizing TLE.

----------Insert Table 1 here----------

Language lateralization. Language in most healthy individuals usually develops in the left hemisphere, with 76-96% of the population showing left hemisphere language dominance (Knecht et al., 2000; Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999). A variety of factors correlate with language dominance and performance in patients with focal epilepsy, such as seizure location and frequency, epilepsy duration and age of onset, presence of MTS, and handedness (Hamberger & Cole, 2011). Additionally, some of these factors are also associated with cognitive impairment including MTS (International League Against Epilepsy, 2004) and handedness [if language reorganization and crowding have occurred (Brázdil et al., 2005; Elger, Helmstaedter, & Kurthen, 2004)]. Furthermore, the relationship between TLE and language impairment has been well documented (Hermann et al., 1992). Some well researched and commonly used language tasks include fluency measures and confrontation naming tests. Verbal fluency tasks measure the ability to produce words quickly that are either semantically or phonemically related. Confrontation naming measures involve having subjects come up with the name of an object presented in a picture. The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) and the Multilingual Aphasia Examination Visual Naming subtest (MAE VN; Benton, Hamsher, & Sivan, 1994) are popular confrontation naming measure used in epilepsy evaluations.

In the literature relating to verbal fluency, N'Kaoua, Lespinet, Barsse, Rougier, and Claverie (2001) evaluated 45 TLE patients (22 left, 23 right) and 22 healthy controls with semantic fluency (Animals) and phonemic fluency [FAS; (Gladsjo et al., 1999)]. Those with left TLE had deficits in both semantic and phonemic fluency whereas those with right TLE had deficits in semantic fluency. Other research by Raspall, Donate,

Boget, et al. (2005) compared 29 TLE patients with clearly defined seizure onset determined by ictal EEG and neuroimaging findings (12 left TLE, 17 right TLE). Language measures included the BNT and semantic fluency (Animals). The authors found those with left TLE performed significantly worse on the BNT than those with right TLE [left M_{Raw} = 44.5(7.8), right M_{Raw} = 50.9(4.1); Mann-Whitney U = 44; p = 0.010]. Furthermore, when all of the cognitive variables (including semantic fluency) were entered into a regression model, BNT was the only significant predictor of seizure lateralization, correctly classifying 69% of cases. The same year, Busch, Frazier, Haggerty, and Kubu (2005) examined the utility of the BNT in predicting side of seizure resection in 217 adult right-handed patients with medically intractable TLE (108 left, 109 right). In the analyses, the BNT was a significant predictor of side of surgery (R^2 = 0.093; B = -0.066; $p < 0.001$) and significantly added to a prediction model that included intellectual functioning and visual and verbal memory scores (R^2 = 0.310; ΔR^2 = 0.123; BNT B = -0.147; $p < 0.001$).

In another study, Loring et al. (2008) compared BNT performances in a group of 135 TLE subjects (69 left; 66 right), to performances on MAE VN of a separate group of 173 TLE patients (79 left; 94 right). Results demonstrated that both the BNT and MAE VN showed significant differences between the left and right groups; however, the BNT had a larger magnitude of difference and was more predictive of group membership than the MAE VN [BNT: left M_{Raw} = 43.1(8.9), right M_{Raw} = 48.1(8.9); $p < .001$ (cohen's d = .56); MAE VN: left M_{Raw} = 42.3(8.8), right M_{Raw} = 45.6(9.3), p = .02 (cohen's d = .36)]. Most recently, Umfleet et al. (2015) retrospectively studied 143 TLE patients (65 left; 78 right) who were administered the BNT and compared performance in those with left

versus right TLE. The authors found that performance was significantly lower in those with left TLE than those with right TLE, though both groups scored within the average range (left M_{Raw} = 48.25 (9.31), right M_{Raw} = 51.78 (6.20); p = .008). A summary of language results in TLE is presented in Table 1.

Visuospatial lateralization. Non-verbal abilities such as visuospatial, visual perception, spatial ability, and constructional skills are generally thought to be mediated by the non-dominant hemisphere (Jones-Gotman et al., 2010). However, evaluating these types of skills in TLE populations has presented some challenges due to an overlap of skills that can prevent visuospatial tasks from clearly measuring what is intended (i.e., poor construct validity). One commonly discussed example is the use of compensatory strategies to improve performance when tasks are difficult. One such strategy is verbalization or talking through the task. By recruiting the cognitive resources of the dominant hemisphere (i.e. verbalizing), the ability to detect nondominant impairment is then washed out. This results in the absence of significant visuospatial findings in those with right temporal seizure origin, even if subtle deficits exist (Williamson et al., 1993). These challenges have been supported by the literature on visuospatial functioning in individuals with right TLE. For example, Hermann et al., (1997) examined a wide range of neuropsychological measures in 107 TLE patients (62 left, 45 right) including the Hooper Visual Orientation Test (Hooper, 1983), a test that requires the mental assembly of picture pieces to identify an image, and Judgement of Line Orientation (Benton, Hannay, & Varney, 1975) in which patients are required to match the orientation of a line to an array of choices. While both measures were significantly lower than the normative data, neither adequately differentiated between left and right TLE (Hooper Visual

Orientation Test: left M_{Raw} =24, right M_{Raw} =25; Judgment of Line Orientation: left M_{Raw} = 22.8, right M_{Raw} =22.7). In a study introducing design fluency, a measure that requires the production of novel shapes, Jones-Gotman & Milner (1977) noted that those with right TLE made more 'namable' drawings than those with left TLE and healthy controls, even after they were prompted to only draw novel shapes (χ^2 =20.87, p<0.001). Other research by Gleissner, Helmstaedter, and Elger (1998) examined performance on the German version of WAIS Block Design (Tewes, 1991), a task that requires individuals to manipulate a set of blocks to match a presented design, in 25 right TLE patients with (n=15) and without (n=10) MTS. It was noted that when compared to healthy controls, those with MTS were significantly impaired on Block Design while those without were within normal limits. However, the study did not compare the sample to those with left TLE. In contrast, there is limited research demonstrating qualitative differences between left and right TLE populations on another common visuospatial test, the Rey Osterrieth Complex Figure (Rey-O; Osterrieth, 1944), a task that involves accurately copying a complex figure from a stimulus. In two separate studies by Frank and Landeira-Fernandez (2008) and Giovagnoli, Erbetta, Villani, and Avanzini (2005), patients with right TLE committed more qualitative spatial errors on the Rey-O than those with left TLE. A summary of visuospatial results in TLE is presented in Table 1.

These studies demonstrate variable support for impaired visuospatial skills in right TLE. These findings are consistent with previous reports that visuospatial deficits are less common in right TLE than language dysfunction in left TLE (Barr et al., 1997; Hermann et al., 1997), and continues to support the notion that those with right TLE are more difficult to lateralize. However, as visuospatial difficulties *can* be observed in right

TLE, these measures remain an important part of the epilepsy battery; though intact visuospatial performance does not preclude the presence of a right lateralized seizure focus.

Learning and memory lateralization. Learning and memory consolidation is a major function of the temporal lobes, particularly the hippocampus and surrounding mesial temporal lobe structures (Blumenfeld, 2010). As the TLE population is heterogeneous and has varying degrees of MTS, memory and language can also be spared to varying degrees (Bell & Davies, 1998). Within the context of neuropsychological evaluations of patients with TLE, learning and memory measures are some of the tests used to evaluate the integrity of the temporal lobes, help lateralize impairment, localize seizure focus, and predict functioning post- temporal lobe resection surgery in TLE (Jones-Gotman et al., 2010).

Verbal memory is usually associated with the dominant hemisphere and nonverbal/visual memory tends to be more associated with nondominant hemisphere. While a robust and consistent body of literature supports the association between verbal learning and memory deficits and damage in the dominant temporal lobe in a variety of cognitive disorders (Cohen, 1992; Delaney, Rosen, Mattson, & Novelly, 1980; Helmstaedter, Grunwald, Lehnertz, Gleißner, & Elger, 1997; Hermann, Wyler, Richey, & Rea, 1987; Mayeux, Brandt, Rosen, & Benson, 1980; Seidenberg et al., 1997), research findings on visual memory deficits due to nondominant temporal lesions is not well supported (Barr et al., 1997; Delaney et al., 1980; Raspall et al., 2005; Saling, 2009; Wisniewski, Wendling, Manning, & Steinhoff, 2012). Other research suggests that while verbal memory impairment is most prominent in left TLE, verbal memory deficits can

also be observed in patients with right TLE (Bell & Davies, 1998; Chelune, Naugle, Lüders, Sedlak, & et al, 1993). Additionally, it is not uncommon for patients with right TLE to perform within normal limits on visual memory measures, as patients may employ verbalization strategies to compensate for nonverbal deficits and/or may have widespread non-verbal network organization, reducing the involvement of the temporal lobe (Wisniewski et al., 2012). Furthermore, nonverbal memory measures tend to overlap with other skills such as attention and visuospatial skills as well as overlap with dominant temporal lobe functions (Bell & Davies, 1998; Jones-Gotman et al., 2010). Therefore, it is important to understand which neuropsychological tests are most sensitive to differentiating dominant from nondominant temporal lobe dysfunction.

Verbal memory. There are multiple measures available to assess verbal learning and memory. Some of the more common measures include the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987, 2000)), Rey Auditory Verbal Learning Test (AVLT; Rey, 1964; Schmidt, 1996), and Wechsler Memory Scale Logical Memory subtest (WMS LM; PsychCorp., 2009; Wechsler, 1945; Wechsler, 1997; Wechsler, 1987). Loring et al. (2008) compared two word list learning measures, the CVLT and the AVLT, on their ability to accurately lateralize left vs right TLE cases. The AVLT is a 15-item word list, learned over five trials, followed by a distractor list, a free recall of the original 15 words, and an additional free recall after a delay. The CVLT was modeled after the AVLT and is a 16 item word list, learned over five trials, with a distractor list that requires an immediate recall. It additionally requires free and cued immediate recall followed by delayed free, cued, and recognition trials. Loring et al. (2008), administered the AVLT to 189 participants (91 left, 98 right) and the CVLT to

212 different individuals (113 left, 99 right), all from the Bozeman Neuropsychology Epilepsy Database (Loring et al., 2008). The results demonstrated that both measures detected significant group differences between left vs. right TLE, as individuals with left lateralized seizures performed consistently worse on both word lists. However, the difference on the AVLT was significantly larger than the CVLT [AVLT raw total learning (right M – left M) = 4.8, $p < .002$ (cohen's d = .47); CVLT raw total learning (right M – left M) = 3.1, $p < .03$ (cohen's d = .29)]. In follow-up logistic regression analyses that included both verbal memory measures and age of seizure onset, the AVLT total learning score was the only significant predictor of seizure laterality, demonstrating the AVLT as the more sensitive measure in this population. In another study, Raspall et al. (2005) compared 29 participants (12 left, 17 right) on the AVLT total learning and delayed memory scores. Differences on the AVLT total score between left and right TLE approached significance [left $M_{Raw} = 43.5$; right $M_{Raw} = 46.8$; difference (right M – left M) = 3.3; $p = 0.072$]. Soble et al. (2014) used logistic regression models including multiple verbal memory measures and demonstrated that AVLT delayed recall was able to predict seizure lateralization with 70.2% accuracy.

The Wechsler Memory Scale (WMS) and its more recent versions (WMS-R, WMS-III, WMS-IV) is another widely used measure in epilepsy centers. Each version has contained verbal memory components including Logical Memory I & II (LM I & II). LM I consists of an immediate recall trial of two short stories, while LM II is free recall of story details after a delay, followed by a recognition trial in the most recent versions. Despite widespread use and the ability of verbal list learning tests to distinguish left vs right hemisphere dysfunction, a number of studies have suggested that WMS story recall

is actually poor at lateralizing seizures in TLE when used alone. In 2005, Raspall et al. (2005) compared 29 TLE participants (12 left, 17 right) on LM I & II of the WMS-III. They did not find a significant difference on LM I [left $M_{T\text{-}score}$ = 36.9(12.0), right $M_{T\text{-}score}$ = 36.8(10.1), difference (right – left) = 0.1] or LM II [left $M_{T\text{-}score}$ = 20.6(8.7), right $M_{T\text{-}score}$ = 22.0(7.6), difference (right – left) = 1.4] between left and right TLE. More recently, Soble et al. (2014) examined the clinical utility of the WMS-IV in 57 TLE patients (28 left, 29 right). A MANOVA in this relatively small sample revealed that left and right TLE participants did not differ on the Auditory Memory Index ($F(1,55) = 1.02$, $p = 0.32$). Additionally, a logistic regression analysis that included Logical Memory II and Verbal Paired Associates II was not predictive of seizure lateralization ($p = .14$). Furthermore, Umfleet et al. (2015) compared 143 patients with TLE (65 left, 78 right) on the standard scores of LM I & II (versions WMS-Revised, WMS-III, or WMS-IV). A logistic regression found that neither LM 1 [left M_{SS} = 91.86(14.1), right M_{SS} = 95.18(16.08), difference (right – left) = 3.32] or LM II (left M_{SS} = 88.51(13.98), right M_{SS} = 93.38(15.74), difference (right – left) = 4.87) were significant predictors of side of seizure. In contrast to these findings, Moore and Baker (1996) examined 138 patients (77 left, 61 right) and found that those with left TLE had significantly lower WMS-R Verbal Memory Index [left M_{SS} = 78.04(16.81), right M_{SS} = 84.28(15.20), difference (right – left) = 6.24], LM I [left M_{Raw} = 16.72(8.02), right M_{Raw} = 19.95(7.09), difference (right – left) = 3.23], and LM II [left M_{Raw} = 11.33(8.27), right M_{Raw} = 14.54(7.39), difference (right – left) = 3.21]. A summary of verbal memory results in TLE is available in Table 1.

Visual memory. In terms of visual memory, few studies have demonstrated the ability of such measures to differentiate right from left TLE. In an early study by

Hermann, Connell, Barr, and Wyler (1995), 77 patients with unilateral TLE (48 left, 29 right) were compared pre- and postoperatively on the Warrington Recognition Memory Test for Faces (Warrington, 1984), a face recognition memory task. ANOVA results on the preoperative Faces score was not significant [left M_{scaled} = 7.4(3.1), right M_{scaled} = 7.2(3.1)], though postoperatively, significant differences between groups were seen [left M_{scaled} = 7.9(3.8), right M_{scaled} = 5.6(2.7)]. Another common visual memory measure is WMS Visual Reproduction I & II (VR I & II). VR I is made up of 5 geometric shapes that become increasingly more complex. The items are administered with a 10 second exposure period followed by the removal of the stimulus and immediate recall of the item. VR II requires recall of as many different items as possible after a 25 minute delay. In terms of performance on VR I & II, Umfleet et al. (2015) examined performance of 143 patients (65 left, 78 right) using a logistic regression, that included multiple memory measures; VR I or II did not significantly differentiate left from right TLE (VR I: left M_{SS} = 100.44(16.91), right M_{SS} = 99.80(19.10), difference (left – right) = 0.64; VR II: left M_{SS} = 98.89(16.49), right M_{SS} = 96.84(15.76), difference (left – right) = 2.05). Soble et al. (2014) examined the WMS-IV Visual Memory Index, VR I & II, and Faces I & II in 57 TLE patients (28 left, 29 right). The authors found no difference between groups on the Visual Memory Index ($F(1,55) = 0.99$, $p = 0.32$), and a logistic regression analysis that included VR and Faces was not predictive of seizure lateralization ($p = .14$). Consistent with these individual studies, a meta-analysis of nonverbal memory functioning following right anterior temporal lobectomy by Vaz (2004) examined postsurgical changes of 22 different visual/nonverbal memory measures. Results showed that the Warrington Recognition Memory Test for Faces score was the only variable that

consistently declined postoperatively. Vaz concluded that there does not seem to be a significant difference between left and right TLE patients in terms of current visual/nonverbal memory measures, which has remained the consistent consensus since the meta-analysis was published. A summary of visual memory results in TLE is available in Table 1.

Research on the neurocognitive functioning of those with TLE has demonstrated consistent evidence of deficits in verbal list learning/memory and confrontation naming, with some evidence of impaired phonemic fluency in those with left TLE (Busch et al., 2005; Loring et al., 2008; N'Kaoua et al., 2001; Raspall et al., 2005; Soble et al., 2014; Umfleet et al., 2015). Support for story memory impairment in left TLE (Moore & Baker, 1996; Raspall et al., 2005; Soble et al., 2014; Umfleet et al., 2015) and visuospatial and visual memory impairment in right TLE is less consistent, though some studies have demonstrated these deficits (Barr et al., 1997; Frank & Landeira-Fernandez, 2008; Giovagnoli et al., 2005; Gleissner et al., 1998; Hermann et al., 1995, 1997; Jones-Gotman & Milner, 1977; Soble et al., 2014; Umfleet et al., 2015; Vaz, 2004). Furthermore, approximately 29% of TLE cases have decline in processing speed and executive functioning (Hermann et al., 2007). Multiple factors could contribute to the specific pattern of cognitive results within TLE, such as seizure lateralization and localization, MTS, emotional status, antiepileptic medications, and etiology (Lezak et al., 2012; Wilson et al., 2015). While many studies have examined the role of neuropsychology in lateralization and localization, as well as the cognitive effects of MTS, emotional status, and antiepileptic drugs, little is known about the neuropsychological consequences of epilepsy etiology. TBI is the most common known etiology of epilepsy (IBIA, 2018), and

TBI and epilepsy are inherently intertwined as up to 20% of all epilepsy cases are thought to be a result of TBI (Agrawal et al., 2006; Annegers & Coan, 2000; Jennett, 1973; Semah et al., 1998), and between 2-3% of those with pre-existing epilepsy who are treated in an emergency department have acquired a head injury during a seizure (Wilson & Selassie, 2014). However, there is currently a paucity of research examining the cognitive relationship between TBI and epilepsy. It is conceivable that individuals with TLE and a history of TBI could have increased dysfunction as TBI alone can result in cognitive deficits (Belanger et al., 2018; Roebuck-Spencer & Sherer, 2018). Understanding the potentially synergistic interaction of these neurological conditions is important to understanding neuropsychological functioning in epilepsy as a whole. In order to adequately describe how TBI may add to the complicated cognitive presentation of TLE, the neuropsychological evaluation of TBI must first be reviewed.

Neuropsychological Evaluation of TBI

TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon, Schwab, Wright, & Maas, 2010). This definition is broad as the nature of TBI is quite heterogeneous, including variability in mechanism and severity of injury (mild to severe), individual patient differences, and recovery environment (e.g. rehabilitation, rest vs. return to activity). The injury alone is highly complex, effecting the location of the initial impact and inflicting more global damage due to impacts against the skull and absorbing energy from a blow (Gennarelli & Graham, 2005; Graham, Gennarelli, & MacIntosh, 2002). As the brain is jostled during the injury, it can sustain cortical damage from additional impact against the skull and/or twisting which causes axons to shear or fray and bridging veins to tear. Other effects of

injury could include subdural hematoma and diffuse vascular injury (Gennarelli & Graham, 2005). Finally, the pathophysiological process of trauma, known as the neurometabolic cascade, includes abrupt neuronal depolarization, release of excitatory neurotransmitters, ionic shifts, changes in glucose metabolism, altered cerebral blood flow, and impaired axonal function. This process can cause swelling and changes in neurochemistry and function for weeks after injury, leading to increased vulnerability during this period and potentially cause further damage (Giza & Hovda, 2001).

Over time, it has become apparent that certain individuals are at greater risk for sustaining a TBI than others. For example, adolescent males (Cassidy et al., 2004), those of minority race/ethnicity, individuals with lower socioeconomic status (Arango-Lasprilla et al., 2011; Arango-Lasprilla & Kreutzer, 2010) and a lower level of education (Kesler, Adams, Blasey, & Bigler, 2003) have higher rates of TBI. Additionally, those with a history of head injury are at increased risk for subsequent TBIs (Saunders et al., 2009). These risk factors should be taken into consideration when examining cognition in TBI as many have been shown to correlate with neuropsychological performance.

There is an extensive body of literature demonstrating a variety of cognitive impairments after TBI. It is well known that there is a positive correlation between neuropsychological deficits and severity of injury, with persistent dysfunction regularly seen in moderate to severe injuries (Draper & Ponsford, 2008; Schretlen & Shapiro, 2003). Cognitive deficits tend to be global and pervasive in those with moderate to severe TBI in addition to significant behavioral effects which can include difficulty returning to school/work and psychosocial difficulty. In these cases, the majority of neuropsychological measures tend to be below expectation and could distinguish those

with TBI from healthy controls (Levin, Shum, & Chan, 2014). In those with uncomplicated mild TBI, resolution of cognitive impairments typically occurs within three months in the majority of cases (Belanger et al., 2005). However, there have been many documented cases of persistent cognitive, social, and behavioral symptoms in mild TBI as well (Levin et al., 2014). It is not surprising that TBI typically has widespread and variable cognitive affects, as forces involve the whole brain, rather than a discrete region of impact, although greater damage in certain regions relating to the trauma is common. For example, regardless of location of impact, the frontal and temporal lobes are more vulnerable as they are often damaged by boney protrusions during the injury. Similarly, white matter is also regularly damaged due to shearing injuries. Post-injury deficits in memory as well as difficulty with attention, processing speed, and executive functioning are most commonly reported (Draper & Ponsford, 2008; Fork et al., 2005; Herrmann et al., 2001; Kinnunen et al., 2011; Scheid, Walther, Guthke, Preul, & Von Cramon, 2006), each of which will be briefly reviewed. However, deficits in visuospatial skills, attention, memory, executive functioning, language, social cognition, as well as emotional factors are regularly studied and observed by clinicians (Levin et al., 2014).

In terms of memory function, individuals with TBI often have difficulty in encoding, acquisition, consolidation, and retrieval of information during the acute phase of injury. However, there is some debate about if persisting or long-term deficits remain attributable to multiple memory processes or if deficits are primarily defined by difficulty in consolidation. For instance Wright and Schmitter-Edgecombe (2011) compared 23 TBI participants to 25 healthy, age and education matched controls on the AVLT to examine verbal encoding, consolidation, and retrieval during the acute and chronic

phases (one year later). Those with moderate to severe TBI performed significantly worse on AVLT total learning, short-delay recall, and long-delay recall in both phases. However, recovery was noted to have improved recall during the chronic phase. More specifically, encoding and consolidation deficits accounted for a large portion of the variance in verbal memory impairment in both the acute and chronic phases. However, memory recovery over time appeared to be due to improvements in consolidation, as encoding performance remained consistent across time points. Vanderploeg et al. (2014) compared 105 individuals with moderate to severe TBI to healthy controls to examine encoding, acquisition, consolidation, and retrieval of verbal memory (CVLT) at acute and follow-up visits six-months and one year later. Those with moderate to severe TBI had impaired retrieval at all three time points but the pattern suggested some recovery over time. Encoding, acquisition, and consolidation were all impaired during the acute phase, however, only consolidation was impaired at the six-month and one-year follow-ups.

In addition to memory, executive functioning, attention, and processing speed are frequently impaired in those with TBI. Kashluba, Hanks, Casey, and Millis (2008) found that performances on WAIS Block Design, Wisconsin Card Sorting Test (perseverative errors), phonemic fluency, and Symbol Digit Modalities Test were all impaired and differentiated between complicated mild TBI and moderate TBI. Kinnunen et al. (2011) showed that those with chronic deficits after TBI had impairments on WAIS Similarities and Matrix Reasoning, Trail Making Test A & B, the Stroop Test, and phonemic fluency. Additionally, Finnanger et al. (2013) noted that a group with moderate TBI performed worse on measures of executive functioning [Category Test, D-KEFS (Verbal Fluency, Trail Making Test, Color Word Interference Test, and Tower Test subtests)] when

compared to healthy controls. Furthermore, those with severe TBI performed worse on motor function (grooved pegboard), processing speed [D-KEFS (Trail Making Test, Color-Word Interference Test), Symbol Digit Modality Test], verbal memory (California Verbal Learning Test- Second Edition), and executive functioning [Category Test, D-KEFS (Verbal Fluency, Trail Making Test, Color Word Interference Test, and Tower Test subtests)] than the healthy controls. Furthermore, Draper and Ponsford (2008) noted individuals with a TBI history performed worse on Symbol Digit Modalities Test, WAIS Coding, and the AVLT when compared to age, education, and sex matched controls.

When considering those with mild TBI, Belanger et al. (2005) conducted a meta-analysis examining the effect sizes of 39 studies to determine overall cognitive functioning as well as for each of the different cognitive domains in individuals with mild TBI. When compared to controls, a significant and moderate to large effect size was demonstrated for the mild TBI group in eight of the nine cognitive domains: global cognitive ability, attention, executive functions, fluency, memory acquisition, delayed memory, language, and visuospatial skills (effect sizes ranging from 0.21-0.77). In the post-acute phase of mild TBI (>90 days), moderate to large overall effect sizes were observed but no individual cognitive domain had a significant effect size. This suggests that neuropsychological deficits in a variety of domains can persist, even in those with mild injuries (a summary of cognitive effects of TBI can be found in Table 2). When considering the potentially additive cognitive effects of TBI in epilepsy, the possibility of persistent deficits in mild TBI should be considered and provides support for examining the spectrum of TBI rather than just those with moderate to severe injuries.

These studies are only a few in a vast body of research that demonstrates the presence of persistent cognitive impairment across the spectrum of TBI. As TBI and epilepsy have been inextricably linked and each condition has potentially significant cognitive impairment, it is important to understand how the combination of conditions effects neuropsychological functioning. If those with a history of TBI were more cognitively impaired than those without, this could influence conceptualization of those cases, treatment planning, and prognosis. Therefore, TBI should be a consideration in the neuropsychological evaluation of epilepsy and the potentially greater cognitive effects in patients with epilepsy should be thoroughly explored. While the literature examining the combined neuropsychological effect of TBI and epilepsy is quite limited, the available research is reviewed below.

Posttraumatic epilepsy. It is estimated that 80% of patients with PTE experience their first seizure within 12 months post injury, and more than 90% experience the first seizure by the end of the second year (da Silva et al., 1990). Additionally, as many as 86% of patients who experience an initial seizure post TBI have a second seizure within the next two years and receive a diagnosis of epilepsy (Frey, 2003). The epilepsy classification breakdown for those with PTE is similar to the general epilepsy populations, with the largest number of patients presenting with temporal lobe epilepsy (TLE; 57%), followed by frontal lobe epilepsy (35%) and an equal number with occipital and parietal lobe epilepsies (3%; Gupta et al., 2014).

Patients with PTE have some unique disease characteristics and specific risk factors when compared to others with epilepsy. In regard to EEG findings, interictal epileptiform discharges and subclinical seizure activity (i.e. abnormal epileptiform

activity on EEG without clinical features) tend to be higher in PTE patients, with the highest incidence in those with penetrating TBIs (Olson, 2004). Apart from sustaining a penetrating TBI, there are a set of risk factors that increase the likelihood of developing epilepsy following head injury, which include loss of consciousness, prolonged post-traumatic amnesia (three days or more), depressed skull fracture, intracerebral hemorrhage, diffuse cerebral contusions, early post-traumatic seizure (<1 week post injury), and acute subdural hematoma with surgical evacuation (Agrawal et al., 2006; Englander et al., 2003; Iudice & Murri, 2000; The Brain Trauma Foundation, 2000; Yablon, 1993). Of these, contusions and subdural hematomas are the most robust risk factors for delayed onset PTE, which can begin even decades after injury (Annegers & Coan, 2000). Furthermore, there are a variety of neurobiological changes that may occur following a TBI in patients who develop PTE, such as extra-axial hematomas, parenchymal contusions, traumatic subarachnoid hemorrhage, diffuse axonal injury, and diffuse intracranial hypertension (Diaz-Arrastia, Agostini, Madden, & Van Ness, 2009). These studies seem to suggest that PTE occurs more often in individuals with moderate to severe injuries, and while the risk of developing PTE clearly increases with severity of injury, those with mild TBI also have an increased risk for unprovoked seizures (Mahler et al., 2015).

Even though PTE is a well-documented occurrence, the cognitive consequences of the combination of damage from epilepsy and TBI are not well understood. Currently, the literature on cognition in PTE has compared TBI groups with and without PTE. An early investigation by Dikmen and Reitan (1978) was designed to study the cognitive profile of PTE. The authors compared three groups (normal control, PTE without

complications, and PTE with persistent focal neurological signs) on the Wechsler-Bellevue Intelligence Scale- Form I (Wechsler, 1946), Halstead Neuropsychological Test Battery (Reitan & Wolfson, 1985), and the Trail Making Test (Armitage, 1946). Dikmen and Reitan found that head injured patients with residual focal neurological signs (e.g., those with hemiplegia, hemiparesis, aphasia, hemianesthesia, visual field defects, etc.) and PTE showed severe generalized neuropsychological deficits. Furthermore, those with PTE and persistent focal neurological signs performed significantly worse than those in the other two groups on Verbal IQ (Controls: $M_{T\text{-score}} = 57.55$; PTE: $M_{T\text{-score}} = 49.22$; PTE with neurological signs: $Mean_{T\text{-score}} = 44.00$) which included Comprehension (Controls: $Mean_{T\text{-score}} = 56.75$; PTE: $Mean_{T\text{-score}} = 50.07$; PTE with neurological signs: $Mean_{T\text{-score}} = 44.00$), and Similarities (Controls: $Mean_{T\text{-score}} = 56.30$; PTE: $Mean_{T\text{-score}} = 49.85$; PTE with neurological signs: $Mean_{T\text{-score}} = 44.50$).

Twenty years later, Haltiner, Temkin, and Dikmen (1997) examined the relationship between posttraumatic seizures and TBI severity in performance on neuropsychological and psychological measures. These researchers followed 210 adults for 1 year after moderate to severe TBI. Of the sample, 18% developed seizures within the initial year after injury, and these individuals had the most severe TBIs. At a one-year post injury follow-up, participants were assessed with a battery of neuropsychological measures (Finger Tapping, Seashore Rhythm Test, Trail Making Test, Stroop Test, WMS LM & VR, Verbal IQ, Performance IQ, Category Test). Those with the greatest neuropsychological impairments were those with PTE, who performed significantly worse on all neuropsychological measures examined. In addition, these individuals were more dependent on others for activities of daily living, demonstrating greater functional

impairment. However, when injury severity was statistically controlled, these differences were no longer significant, potentially suggesting that worse outcomes in those with PTE were largely due to the effects of severe brain injury rather than the co-existence of seizures. While this research was an important initial step toward understanding the relationship between TBI and epilepsy, it has limitations that have not been addressed in the current literature. The authors compared those with PTE to others with TBI; however, to date there has not been a study that has examined the neuropsychological differences between groups of patients with PTE and epilepsy in the absence of a history of TBI. Furthermore, the tests used were limited as it excluded measures of confrontation naming and word lists as well as measures previously shown to differentiate PTE and TBI (i.e., Similarities and Comprehension).

Most recently, Mazzini et al. (2003) followed 143 Italian patients with severe TBI (coma $\geq$ 6 hours), comparing those who developed epilepsy to those who did not, on a variety of neuropsychological measures. All patients who awoke from coma in a non-neurovegetative state underwent a neuropsychological evaluation that included the Stroop Test, Reaction Time Test (a go/no-go visual reaction time task), Digit Cancellation Test, Raven's Colored Matrices, Verbal Learning, Corsi Block Tapping Test, Token Test, object naming, phonetically cued word-fluency, semantic fluency, Judgement of Line Orientation, and Tactile Form Perception. For the purposes of analysis, the neuropsychological variables were classified as normal, mildly impaired, or severely impaired. In addition, participants were also evaluated on a variety of psychological variables. There were no significant differences on any cognitive measures, though individuals with PTE had higher rates of personality disorders, disinhibited behavior,

irritability, and aggressive or agitated behavior. However, the study has several limitations when applied to other epilepsy and TBI populations. First, the study was conducted in Italy and used some Italian neuropsychological measures, making it difficult to generalize these results to dissimilar populations. Next, rather than examining the spectrum of neuropsychological scores, the authors chose to categorize individuals in one of three groups: normal, mildly impaired, and severely impaired. Additionally, the authors examined the differences in the percentage of "severely impaired" patients in each group, which could have limited the ability to detect subtle differences. In addition, this study lacks well supported language and memory measures (e.g. confrontation naming and word lists). Finally, the authors only examined the effects of severe TBI on cognition after the development of PTE, excluding milder injuries. Furthermore, much like the limitations of the Haltiner et al. (1997) study, the authors only compare the PTE group to another group with TBI, not a group with epilepsy. A summary of cognitive function in PTE is listed in Table 2.

----------Insert Table 2 here----------

While these studies are useful in beginning to understand the cognitive consequence of TBI in epilepsy, this research has focused on the comparison between PTE patients and others with TBI, leaving a paucity in research comparing PTE to non-traumatic epilepsy. Without a direct comparison of PTE to others with epilepsy, it is difficult to parse out what deficits are due to epilepsy and what deficits are due to the combination of TBI and epilepsy. As PTE is the most common known etiology of epilepsy (20% of all cases), it is important to understand how these individuals may differ from others with epilepsy. For example, attention/concentration, processing speed, and

executive functioning are noted to be spared in approximately 71% of TLE cases (Hermann et al., 1997; Hermann et al., 2007); however, these cognitive abilities are consistently noted to be impaired in individuals with TBI (Draper & Ponsford, 2008; Fork et al., 2005; Herrmann et al., 2001; Kinnunen et al., 2011; Scheid et al., 2006). Therefore, it is possible that those with TLE and a history of TBI could consistently demonstrate deficits in attention/concentration, processing speed, and executive functioning that are less common in those with TLE without a history of TBI. Furthermore, previous research has examined individuals with moderate to severe TBIs but is lacking in the exploration of cognition in the full range of TBI among individuals with epilepsy. Finally, given that a primary treatment of pharmacoresistant TLE is temporal lobectomy and neuropsychological assessment is an essential component of the pre-surgical evaluation (Loring, 2010), it could be helpful to understand the effects of TBI on patients with TLE to assist with treatment planning.

This study aims to examine neuropsychological profile differences in TLE patients with and without a history of TBI. It was hypothesized that those with a history of TBI should have greater deficits in attention, processing speed, and executive functioning. This study utilized a sizable sample of TLE patients treated at a large academic medical center for pre-surgical evaluation. Factors such as age at testing, age of seizure onset, education, race/ethnicity, sex, premorbid IQ, and MTS were included, as each is associated with higher rates of TBI or greater impairment in TLE.

CHAPTER THREE

Hypotheses

Overall Aim: To investigate cognitive differences between patients with temporal lobe epilepsy with and without a history of traumatic brain injury.

Hypothesis 1: In a group of patients with TLE, demographic characteristics (age, race/ethnicity, education, sex, and premorbid IQ) and features associated with epilepsy (MTS, age of seizure onset, seizure lateralization, and depression) will be predictive of those with and without TBI history. Of these variables age, education, sex, MTS, and age of seizure onset are expected to be significant predictors.

Hypothesis 2: In a group of individuals with TLE, a set of neuropsychological predictor variables will differentiate epilepsy patients with and without a history of TBI. Of the neuropsychological measures, BNT, semantic fluency, WMS-III Logical Memory II, WAIS-III Block Design, WMS-III Faces II, Trails A and B, WMS-III Working Memory Index, and WCST perseverative errors are expected to be significant predictors of TBI history.

Hypothesis 3: In those with TLE, a combination of neuropsychological predictors, demographic characteristics, and epilepsy features will differentiate epilepsy patients with and without a history of TBI. The variables included will be those that were found to have a $p \leq 0.25$ in previous analyses. Of the variables, education, sex, MTS, age of seizure onset, BNT, semantic fluency, WMS-III Logical Memory II, WAIS-III Block Design, WMS-III Faces II, Trails A and B, WMS-III Working Memory Index, and WCST perseverative errors are expected to be significant predictors of those with and without a history of TBI.

CHAPTER FOUR

Methodology

Participants

Data for this retrospective study were obtained from an IRB-approved neuropsychology registry for patients who were evaluated for epilepsy surgery as part of their routine care at The Cleveland Clinic. The full database dates back to 1986 and contains over 1,900 participants. For the purposes of this study, participants were selected for inclusion from the larger database if they met the following criteria: 1) age 18 to 60 at time of neuropsychological testing, 2) diagnosed with focal temporal lobe epilepsy, 3) had completed the at least 90% of the neuropsychological measures of interest, 4) had information regarding presence/absence of past head injury available in electronic health records, and 5) had adequate performance validity on cognitive test results[1]. Participants with a history of prior neurosurgery or MRI and/or pathological evidence for brain tumor or focal cortical dysplasia were excluded. Lateralization of epilepsy was based on the consensus of a multidisciplinary team as either left, right, left greater than right, right greater than left, and bilateral. Only those with well-defined lateralized TLE (i.e. clear left or right), had their TBI prior to seizure onset, were clearly right or left handed, and had a clear presence or absence of MTS were included. All selected subjects completed neuropsychological testing between 8/2000 and 9/2016 as there was little change in the neuropsychological protocol during that time.

A review of electronic health records was completed by a trained research coordinator to obtain head injury variables relevant to this study that were not available in the existing neuropsychology registry database. These variables included age of first head

injury, presence/absence of multiple head injuries, mechanism of injury, if injury resulted from a seizure-related fall, presence/absence of loss of consciousness (including duration), coma history, if head injury resulted in a doctor visit or hospitalization, and if a diagnosis of concussion or traumatic brain injury was given. Only cases that could clearly be identified as having a presence or absence of TBI, of any severity, and at any time in relation to seizure onset, were included.

The initial data set consisted of 293 participants. Participants were separated into two groups, those with a history of TBI (TBI+) and those without a history of TBI (TBI-). Eight individuals within the TBI+ sample had their first TBI after the onset of epilepsy and were excluded from analysis. Another 12 individuals who were judged to have non-lateralized, bilateral involvement were removed. An additional 10 participants were excluded as they were not clearly right or left handed, and three more had questionable MTS on MRI findings, thus they were removed from the analyses. The final analyses included 260 participants, 77 with a history of TBI (TBI+) and 183 without (TBI-). Multiple attempts were made to maintain the same number of observations in each analysis, but additional participants were removed due to missing or incomplete data depending on the variables included in the model. The number individuals included in each analysis are listed.

Finally, as TBI severity accounted for neuropsychological differences in previous studies of PTE (Haltiner et al., 1997), a TBI severity index was created in an attempt to examine the role of severity in cognitive performances within the TBI+ group. To accomplish this, subjects in the TBI+ group were separated into mild injury and >mild injury based upon available information about each TBI. This was determined by

examining the combination of potential severity indicators: loss of consciousness (LOC; yes, no, unknown), duration of LOC (estimated in minutes), concussion diagnosis (yes, no, unknown), if the patient was seen by a doctor as a result of injury (yes, no, unknown), hospitalization due to injury (yes, no, unknown), how many days they were hospitalized, coma (yes, no, unknown), duration of coma (estimated in days), and a review of chart notes regarding injury details, as available. If the patient had any of the following indicators, they were determined to be in the >mild injury group: loss of consciousness for thirty minutes or longer, hospitalization for more than 1 day, or coma of any length of time. As the data were limited for many participants, chart notes were heavily relied upon. If something within the description of injury was concerning for a more severe injury (e.g., involved in a motor vehicle accident and suffered a skull fracture) and the indicators were inconclusive, the patient was coded as >mild injury. Similarly, if the TBI notes suggested a mild injury (e.g., struck in the head with a baseball bat with brief loss of consciousness) and the rest of the indicators were benign, the patient was coded as mild injury. If the indicators were inconclusive and there were no notes, the individual was coded as mild injury.

Measures

Neuropsychological measures were selected to sample from a wide range of cognitive domains known to be affected in epilepsy and/or TBI including intellectual functioning, attention, processing speed, language, visuospatial skills, visual and verbal memory, and executive functioning. Within each domain, individual measures were selected to include the largest potential sample size with complete data and minimize missing scores. The specific cognitive measures selected for analysis are listed in Table 3

along with a brief summary of available research supporting use in patients with epilepsy and/or TBI. The Beck Depression Inventory (BDI), a measure that indicates presence and severity of depressive symptoms, was included to assess mood at the time of testing.

----------Insert Table 3 here----------

Data Analysis

Descriptive statistics included frequencies and percentages for categorical variables (sex, race/ethnicity, handedness) and means and standard deviations for normally distributed continuous variables [age, education, WAIS-III Vocabulary (estimate of premorbid IQ), and BDI]. All neuropsychological variables were converted to standardized, demographically adjusted T scores. The BNT, semantic fluency, phonemic fluency, Trails A, Trails B, WCST perseverative errors were age-, education-, and sex- adjusted using the widely used Heaton neuropsychological test norms (Heaton, Grant, & Matthews, 1991); WMS-III Logical Memory I, WMS-III Logical Memory II, WMS-III Faces I, WMS-III Faces II, and WMS-III Working Memory Index were age adjusted using the WMS-III norms (Wechsler, 1997); AVLT total learning, delayed recall, and recognition were age adjusted using the AVLT norms (Schmidt, 1996); WAIS-III Similarities, WAIS-III Block Design, and WAIS-III Matrix Reasoning were age adjusted using the WAIS-III norms (David Wechsler, 1997); WCST categories completed were age adjusted using a table produced from a meta-analysis by Rhodes (2004). After a review of the literature, Rhodes (2004) was determined to be the best resource for this purpose.

Demographic characteristics of the two groups were compared using t-tests or Mann-Whitney U tests for continuous variables and chi-square or Fishers Exact Test for

categorical variables. For logistic regression models, a goodness of fit measure, the Hosmer-Lemeshow statistic was examined for hypotheses 1-3; $p>0.4$ was considered a good fit of the model to the data (Hosmer, Lemeshow, & Klar, 1988). The statistical assumptions for all analyses were examined to ensure the appropriateness of each analysis. The level of significance was set at $p\leq0.05$ for all primary variables and $p\leq0.15$ for demographic/epilepsy characteristics in the final models. These *p* values were selected to be conservative for inclusion of these measures in the model. In order to ensure the reliability of the logistic regression models, the sample size in the smaller of the two groups needed to meet or exceed 5 observations per predictor variable (Tabachnick & Fidell, 2013). The sample size of 77 individuals in the smaller of the two groups (TBI+) was adequate to examine approximately 14 predictor variables. Statistical analyses were conducted using IBM™ SPSS version 25.0 (SPSS, Inc., Chicago, IL).

Hypothesis 1: In a group of patients with TLE, some demographic characteristics (age, race/ethnicity, education, sex, and premorbid IQ) and features associated with epilepsy (MTS, age of seizure onset, seizure lateralization, and depression) will be predictive of those with and without TBI history. Of these variables age, education, sex, MTS, and age of seizure onset are expected to be significant predictors.

A stepwise logistic regression model was used to determine the demographic/epilepsy characteristics for predicting group membership. Variables included in the initial model were age, education, race/ethnicity, sex, handedness, MTS, premorbid IQ, age of seizure onset, and seizure lateralization. A final model was fit to the data and ROC analysis was run to determine the area under the curve for the model.

Hypothesis 2: In a group of individuals with TLE, a set of neuropsychological predictor variables will differentiate epilepsy patients with and without a history of TBI. Of the neuropsychological measures, BNT, semantic fluency, WMS-III Logical Memory II, WAIS-III Block Design, WMS-III Faces II, Trails A and B, WMS-III Working Memory Index, and WCST perseverative errors are expected to be significant predictors of TBI history.

A stepwise logistic regression model was used to determine which neuropsychological measures accurately predicted history of TBI in epilepsy. The measures included the BNT, WAIS-III Similarities, Phonemic Fluency, WAIS-III Block Design, WAIS-III Matrix Reasoning, WMS-III Logical Memory I, WMS-III Logical Memory II, WMS-III Faces I, WMS-III Faces II, Trails A, Trails B, WMS-III Working Memory Index, WCST perseverative errors, WCST categories completed. Each variable was carefully selected based on previous literature in epilepsy and TBI (as summarized in Table 3). A final model was fit to the data and ROC analysis was run to determine the area under the curve for the model.

Hypothesis 3: In those with TLE, a combination of neuropsychological predictors, demographic characteristics, and epilepsy features will differentiate epilepsy patients with and without a history of TBI. The variables included will be those that were found to have a $p \leq 0.25$ in previous analyses. Of the variables, education, sex, MTS, age of seizure onset, BNT, semantic fluency, WMS-III Logical Memory II, WAIS-III Block Design, WMS-III Faces II, Trails A and B, WMS-III Working Memory Index, and WCST perseverative errors are predicted to be significant predictors of those with and without a history of TBI.

A stepwise logistic regression model was planned to determine which set of neuropsychological variables and demographic/epilepsy characteristics were the best predictors of group membership (TBI+, TBI-). The number of predictor variables was limited in the equation in order to satisfy the requirement of 5 observations per predictor in the smaller of the two groups. Therefore, the demographic/epilepsy characteristics and neuropsychological variables determined to be at the $p \leq 0.25$ level (Hosmer & Lemeshow, 1989) in the previous analyses were included in the combination logistic regression in order to identify the best combination of variables to predict group membership. A final model was fit to the data and ROC analysis was run to determine the area under the curve for the model.

CHAPTER FIVE

Results

Demographically, the TBI+ group had significantly more males, were older at the age of seizure onset, and had a lower rate of MTS than the TBI- group. The demographic information for both groups is listed in Table 4.

----------Insert Table 4 here----------

Three separate logistic regression models were developed to find the best set of predictors for individuals in the TBI+ group: 1. demographic/epilepsy characteristics only, 2. neuropsychological variables only, and 3. the combination of demographic/epilepsy characteristics and neuropsychological variables. Model building began with a stepwise logistic regression followed by a final enter model based on the wald *p* values listed below. All statistical assumptions were met for logistic regression models. ROC curves were run for each final model.

1. Demographic/epilepsy characteristics model: variables included age, race/ethnicity, education, sex, premorbid IQ (estimated with WAIS-III Vocabulary), MTS, age of seizure onset, depression, and side of seizure. As the sample was predominantly Caucasian (~95%), all other race/ethnicity groups were combined to create a non-Caucasian group for the purpose of the analyses. The final model included variables at $p \leq 0.15$, which was selected to conservatively include demographic/epilepsy characteristics in the model (Hosmer & Lemeshow, 1989).

2. The neuropsychological model included BNT, WAIS-III Similarities, WAIS-III Block Design, WAIS-III Matrix Reasoning, phonemic fluency (FAS), WMS-III Logical Memory I, WMS-III Logical Memory II, WMS-III Faces I, WMS-III Faces II, WMS-III

Working Memory Index, Trails A, Trails B, WCST perseverative errors, WCST categories completed. The final neuropsychological model included variables at $p \leq 0.05$. Follow-up analyses in a subset of participants were run to include semantic fluency (Animals) and AVLT total, delay, and recognition scores as only a select number of individuals completed these measures. The follow-up analyses are listed in Appendix A.

3. The combination of demographic/epilepsy characteristics and neuropsychological variables included sex, age of seizure onset, side of seizures, MTS, WAIS-III Vocabulary, WCST categories completed, WAIS-III Similarities, WAIS-III Matrix Reasoning, WMS-III Working Memory Index, and Trails B, all of which were determined to be at the $p \leq 0.25$ level in previous analyses (Hosmer & Lemeshow, 1989). The final combination model included demographic/epilepsy characteristic variables at $p \leq 0.15$ and neuropsychological variables at $p \leq 0.05$. Follow-up analyses in a subset of the participants were run to include semantic fluency (Animals) and AVLT scores as only a select number of individuals completed these measures. The follow-up analyses are presented in Appendix B.

The demographic/epilepsy characteristics model that best fit the data [Hosmer and Lemeshow Test (H-L) $p = 0.855$] excluded four participants due to incomplete data (n = 256). Significant predictors of TBI+ included sex [male, odds ratio = 1.839, 95% confidence interval (95% CI): 1.038 - 3.257, $p = 0.031$], older age of seizure onset (odds ratio = 1.040, 95% CI: 1.018 - 1.062, $p < 0.001$), left side of seizure (odds ratio = 1.595, 95% CI: 0.884 - 2.878, $p = 0.130$), and a lower score on WAIS-III Vocabulary (odds ratio = 0.972, 95% CI: 0.943 - 1.002, $p = 0.134$) which was used as an estimate of premorbid

IQ (Table 5). The ROC curve was significant [area under the curve = 0.689, 95% CI: 0.617 - 0.760, $p<0.001$ (Table 6)].

----------Insert Table 5 here----------

----------Insert Table 6 here----------

The neuropsychological model indicated that lower scores on the WAIS-III Similarities and WCST categories completed were significantly predictive of TBI+ group membership when run in separate models. However, when combined into one model, these variables together did not adequately differentiate between the TBI+ and TBI- group. WAIS-III Similarities (H-L $p = .686$) excluded 4 participants due to incomplete data [n=256, odds ratio = 0.970, 95% CI: .941 – 0.999, $p = 0.045$ (Table 7)]. The ROC curve was significant [area under the curve = 0.586, 95% CI: 0.510 - 0.663, $p = 0.039$ (Table 6)]. WCST categories completed (H-L $p = 0.121$) excluded 2 participants due to incomplete data [n=258, odds ratio = 0.985, 95% CI: 0.971 – 1.000, $p = 0.048$ (Table 7)]. The ROC curve was not significant [area under the curve = 0.571, 95% CI: 0.493 - 0.648, $p = 0.073$ (Table 6)].

----------Insert Table 7 here----------

The combination model that best fit the data (H-L $p = 0.806$) excluded 4 participants due to incomplete data (n=256). Significant predictors of TBI+ included sex (male, odds ratio = 1.984, 95% CI: 1.108 – 3.552, $p = 0.021$), an older age of seizure onset (odds ratio = 1.039, 95% CI: 1.018 – 1.060, $p <0.001$), left side of seizure (odds ratio = 1.594, 95% CI: 0.882 – 2.879, $p = 0.122$), and a lower score on WAIS-III Similarities [odds ratio = 0.957, 95% CI: 0.926 – 0.989, $p = 0.008$ (Table 8)]. The ROC

curve was significant [area under the curve = 0.707, 95% CI: 0.637 - 0.777, p<.001 (Table 6)].

----------Insert Table 8 here----------

Follow-up t-tests were run to compare the two groups' neuropsychological performances. These comparisons demonstrated that those in the TBI+ group had generally lower scores across cognitive measures, but significantly lower scores only on WAIS-III Similarities and WCST categories completed (Table 9).

----------Insert Table 9 here----------

Finally, a series of t-tests were run comparing the two TBI severity groups [mild injury (n = 52), >mild injury (n = 25)] on the different demographic and cognitive measures. The analyses revealed similar scores across groups, although those in the >mild injury group had significantly lower scores on WMS-III Logical Memory I ($F(1,735) = 8.84$; $p = .004$), WMS-III Logical Memory II ($F(1,414) = 4.21$; $p = .044$), and letter fluency [(FAS); $F(1,469) = 4.33$; $p = .041$].

CHAPTER SIX

Discussion

Cognitive deficits can often be observed in TLE (Jones-Gotman et al., 2010; Lezak et al., 2012) and TBI (Levin et al., 2014; Lezak et al., 2012). Common deficits in TLE include impaired memory in approximately 53% of cases, accompanied by executive dysfunction and slowed processing speed in 29% of individuals (Hermann et al., 2007). Additionally, language impairments are often observed in those with left TLE, most notably confrontation naming and verbal fluency (Busch et al., 2005; Loring et al., 2008), while visuospatial/visuoconstructional skills can be impaired in those with right TLE (Frank & Landeira-Fernandez, 2008; Gleissner et al., 1998). In those with TBI, cognitive deficits are heterogeneous, although difficulties in memory, attention, processing speed, and executive functioning are common (Levin et al., 2014).

Epilepsy and TBI are often linked, with 20% of epilepsy cases resulting from a TBI (Agrawal et al., 2006). Additionally, an estimated 2-3% of epilepsy cases that present to the emergency department have sustained a TBI secondary to seizures (Wilson & Selassie, 2014). Given that each of these neurological conditions are documented to have cognitive consequences, it is important to understand the combined effects for individuals with both, particularly given the role of neuropsychological assessment in the evaluation of presurgical TLE patients. Although a wide body of literature is available on cognitive deficits in TLE, very few studies have examined or controlled for a history of TBI in this population. Additionally, the limited research that does explore cognition in PTE has exclusively compared PTE with TBI. This leaves a paucity of literature that examines the differences between PTE and non-TBI-related epilepsy. Furthermore, these

studies only examine the effects of moderate to severe injury, excluding those with mild TBI. Finally, the results of these studies are mixed, leaving a limited understanding of cognition in those with epilepsy and a history of TBI.

While previous investigations have begun to characterize cognition in PTE, each of these studies faced inherent limitations when comparing PTE to TBI. First, the heterogeneous nature of TBI can create problems in comparing one TBI group to another as participants in each group often differ in a number of ways (e.g. severity, mechanism of injury, individual differences, recovery process, etc.). Each of the available studies attempted to control for differences in a variety of ways, such as including only those who awoke from a coma in a non-neurovegitative state (Mazzini et al., 2003) or statistically controlling for severity of injury [e.g. as determined by Glasgow Coma Scale and neurological symptoms (Haltiner et al., 1997)]. However, these rather crude approaches to control for variability has likely contributed to the mixed results of this small body of research. Another limitation includes treatment of those with a TBI history and epilepsy. These individuals almost always receive ongoing treatment by epilepsy specialists, with seizure classification, treatment planning, recommendations, and prognosis provided using the same model for all epilepsy patients. As very little is known about the differences between epilepsy patients with and without a TBI history, providers could be lacking important information to appropriately describe and treat those with a TBI history. For these reasons, we chose to compare individuals with TLE who did or did not have a history of TBI to address many of these limitations in the current literature. This study included all severities of TBI to address the narrow range included in previous studies. Additionally, we examined differences in performance on a variety of

neurocognitive tests including measures of language, visuospatial skills, verbal memory, visual memory, attention, processing speed, and executive functioning, to provide updated and a more comprehensive neuropsychological approach than previous studies.

In the present investigation, the demographic/epilepsy characteristics logistic regressions indicated that individuals with a TBI prior to seizure onset were more likely to be male, have left TLE, an older age of seizure onset, and lower estimated premorbid IQ. The finding of more males in the sample is consistent with previous research demonstrating a higher rate of TBI in males (Cassidy et al., 2004), but these results additionally suggest that those in the TBI+ group had a lower estimated premorbid IQ. One potential explanation for lower WAIS-III Vocabulary scores in the present sample is that those with a TBI may have had poorer education quality or lower SES, as Vocabulary is highly correlated with education (Kaufman, McLean, & Reynolds, 1988). This would support previous research suggesting that those of lower SES and lower education tend to have higher rates TBI (Arango-Lasprilla et al., 2011; Arango-Lasprilla & Kreutzer, 2010; Kesler et al., 2003). Interestingly, years of education was not a significant predictor of TBI history in these analyses. An older age of onset was a consistent predictor of TBI+ group membership in all regressions that included this variable. This may support the current theory that those with PTE may have a reduced threshold for seizure activity (Statler, Swank, Abildskov, Bigler, & Steve, 2008), such as an increased inflammatory response, which ultimately spurs the development of unprovoked seizures (Webster et al., 2017). Without a TBI as a precipitating event, it is possible that these individuals would have never developed epilepsy, particularly as the

age of onset in our TBI+ group (25 years old) is not in an age range that is associated with a high risk of epilepsy onset (Shafer, 2014).

When considering neuropsychological measures, those with a history of TBI had worse performances on all cognitive tests examined, to varying degrees. In separate logistic regressions, lower scores on WAIS-III Similarities and WCST categories completed significantly differentiated those with and without at TBI history. Poorer performance on each of these measures supports the hypothesis that those with a TBI history would demonstrate more executive dysfunction, as WCST and WAIS-III Similarities are both frontally mediated tasks. Given that executive functioning is a broad construct, these tasks demonstrate different facets of this cognitive ability. For example, the WCST requires novel problem solving (Monchi, Petrides, Petre, Worsley, & Dagher, 2001), whereas WAIS-III Similarities assesses the ability to understand and describe abstract verbal relationships (Davies & Piovesana, 2015; Lezak et al., 2012). Lower performance on each of these measures demonstrates potential dysfunction across different components of executive functioning.

When demographic variables were added into the prediction model, individuals who were male, had left lateralized seizures, an older age of seizure onset, and a lower score on WAIS-III Similarities were most likely to have a TBI history. It should be noted that when the neuropsychological measures were combined with demographic variables, WAIS-III Similarities emerged as a predictor of TBI history and removed WAIS-III Vocabulary from the analysis. This is likely due to the high correlation between Vocabulary and Similarities (Wechsler, 1997), suggesting that Similarities is more strongly associated with TBI history. This again is consistent with the hypothesis that

those with a TBI history would demonstrate greater executive dysfunction, as Similarities requires higher order abstract verbal reasoning skills (Davies & Piovesana, 2015; Lezak et al., 2012). Although difficulties in executive functioning have been noted in many individuals with TLE, these deficits are also consistently reported in TBI. It was predicted that even when compared to those with TLE, subjects with a history of TBI would have significantly poorer performances due to the added neurological damage of the injury in vulnerable areas like the frontal lobes. Additionally, Dikmen and Reitan (1978) found that Similarities differentiated individuals with PTE from those with TBI alone, suggesting that performance on Similarities may be influenced by the combination of TBI and seizures above and beyond either of these conditions alone. These results are somewhat consistent with previous findings by Mazzini et al. (2003); although they did not find differences in cognitive test results between TBI and PTE, there was a significantly higher incidence of disinhibited behavior in those with PTE. Disinhibited behavior is associated with dysfunction of anterior brain systems and is often associated with executive dysfunction (Blumenfeld, 2010).

Follow-up analyses (Appendix A and B) suggest greater verbal memory and semantic fluency difficulty in those with TBI, as AVLT Recognition and Animals were significant predictors of TBI history in the analyses. Furthermore, recognition memory tasks have been shown to have prefrontal activation in fMRI studies (Donaldson, Petersen, Ollinger, & Buckner, 2001; Hoppstädter, Baeuchl, Diener, Flor, & Meyer, 2015; Rugg, Fletcher, Chua, & Dolan, 1999) demonstrating that recognition tasks require executive functioning. As AVLT Recognition was a significant predictor in a subset of the data, this may further support the role of executive dysfunction in those with a history

of TBI. However, the results of the subset analyses should be interpreted with caution due to the limited number of individuals who completed the measures in the current sample.

Limitations and Future Directions

Despite the large overall data set, given the limited number of participants with available category fluency (Animals) and AVLT data, these variables had to be excluded from the main analyses. Inclusion of these measures with a larger sample size would be important to replicate and extend the findings. In addition, preliminary results of a small subset of the dataset suggest that both Animals and AVLT may be helpful in differentiating individuals with and without a TBI history in TLE populations.

Another potential limitation is that although the dataset utilized had a wide range of ages and a good distribution between men and women, the sample was predominantly Caucasian (approximately 95%). With limited racial/ethnic minority representation, it is difficult to know if these results would generalize to non-Caucasian individuals. While research on differences in epilepsy among minority groups is limited, Burneo et al. (2006) did not find a race/ethnicity difference in seizure recurrence after surgery suggesting appropriate lateralization in minority populations. However, it would still be advantageous to repeat this research in a more diverse population.

An additional consideration is that participants in this sample included only individuals with pharmacoresistant TLE who were being evaluated for surgery. As many of those with well controlled TLE do not have cognitive deficits (Hermann et al., 2007), it is difficult to discern if these would be consistent in a population with well controlled epilepsy. However, those with epilepsy that is well managed with medication(s) have

lower risk treatment options and are on fewer antiepileptic drugs. Therefore, lateralizing epilepsy and characterizing cognition in this group is often unnecessary.

In terms of TBI, the lack of a well formulated severity indicator was a limitation of this study. In previous PTE research, severity of injury accounted for the majority of group differences (Haltiner et al., 1997), removing the presence of seizure as a significant predictor. However, the present study differed from Haltiner et al. (1997) as we compared an epilepsy population with and without the presence of TBI rather than a TBI population with and without the presence of epilepsy. In this way, severity of injury was less of a contributing factor as it only influenced one group (TBI+) rather than the entire sample. One consideration prior to completing regression analyses was the potential for non-significant results if individuals with mild TBI were included. The concern was those with mild injuries would have less severe cognitive deficits and may wash out the effects of TBI on cognition. Interestingly, those with >mild injury preformed significantly worse on WMS-III Logical Memory I & II as well as FAS, variables that were not significant predictors of TBI history. This could suggest that those with moderate to severe injuries have greater impairments on these measures. If this is true, it is possible that the inclusion of those with mild TBI increased the mean performance among the group and therefore removed Logical Memory and FAS as significant predictors in the regression models. It would be important to repeat the study in a sample with more clearly defined injury severity to bolster the understanding of cognition in TLE populations with a history of TBI. However, even with these potential limitations, our results still demonstrated group differences in executive functioning regardless of TBI severity.

Finally, our sample did not include an outcome indicator. Therefore, we do not know how patients with or without a TBI history faired post-surgery in terms of cognitive functioning. It is possible that post-surgical cognitive outcomes for those with and without a TBI history are similar regardless of pre-surgical differences. Further exploration of post-surgical outcomes is warranted not only to better understand the results of the present study but also to appreciate prognosis and cognitive risks in TLE populations with a history of TBI.

Conclusions

These results provide some support for greater executive dysfunction in patients with TLE and a history of TBI when compared to those without a history of TBI. Poorer performances on two executive functioning measures, WAIS-III Similarities and WCST, significantly differentiated between groups (TBI+, TBI-). Both measures were able to differentiate those with and without TBI regardless of the TBI severity. Follow up analyses in a subset of the sample noted greater impairment on Animals and AVLT Recognition in those with a history of TBI. Although these results are preliminary, it may suggest greater language and verbal memory impairment in addition to strengthening support for the presence of executive dysfunction. Understanding that TLE patients with a TBI history may have greater cognitive impairments may assist with clinician interpretation of neuropsychological findings.

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Table 1.
Cognition in Temporal Lobe Epilepsy

Measure	Description	Research
Language		
Boston Naming Test (60 item)	Confrontation naming	Reliably differentiated between left and right in several studies (Loring et al., 2008; Raspall et al., 2005; Umfleet et al., 2015). Also predicted side of surgery above measures of intellectual functioning and visual and verbal memory (Busch, Frazier, Haggerty, & Kubu, 2005).
Multilingual Aphasia Examination Visual Naming	Confrontation naming	Significantly predicted group membership (left vs. right) but at a smaller magnitude than BNT (Loring et al., 2008).
Phonemic Fluency (FAS)	Ability quickly generate words that begin with the same letter	Impaired in those with left TLE but intact in those with right TLE (N'Kaoua et al., 2001).
Semantic Fluency (Animals)	Ability to quickly generate semantically related words	Impaired in both left and right TLE (N'Kaoua et al., 2001) and did not significantly predict side of seizure (Raspall et al., 2005).
Visuospatial Skills		
Hooper Visual Orientation Test	Mental manipulation of picture pieces to identify an image	Impaired in both left and right TLE patients (Hermann et al., 1997).
Judgment of Line Orientation	Match the orientation of a line to an array of choices	Impaired in both left and right TLE patients (Hermann et al., 1997).
Design Fluency	Ability to produce novel designs	Significantly more individuals with right TLE produced 'namable' designs than those with left TLE and healthy controls (Jones-Gotman & Milner, 1977).
WAIS Block Design	Manipulate a set of blocks to match a presented design	In those with right TLE, performance was impaired for individuals with MTS but normal in those without MTS (Gleissner et al., 1998).
Rey-Osterrieth Complex Figure Copy	Ability to accurately copy a complex figure from a stimulus	Those with right TLE made more qualitative spatial errors than those with left (Frank & Landeira-Fernandez, 2008; Giovagnoli et al., 2005).
Verbal Memory		
AVLT	Learning and memory of a word list	Those with left TLE performed worse than those with right TLE on total learning and was the most sensitive verbal memory measure (Loring et al., 2008). Delayed recall was also predictive of left vs. right TLE (Soble et al., 2014).

CVLT	Learning and memory of a word list	Total learning was somewhat less sensitive than the AVLT but still differentiated between left and right TLE (Loring et al., 2008).
WMS Logical Memory	Immediate and delayed recall of story details	Mixed literature, though several studies showed poor lateralization ability (Moore & Baker, 1996; Raspall et al., 2005; Soble et al., 2014; Umfleet et al., 2015)
Visual Memory		
Warrington Faces	Recognition of faces	No differences were observed in preoperative evaluations but those with right TLE performed significantly worse postoperatively (Hermann et al., 1995) and performance declined over time in those with right TLE (Vaz, 2004).
WMS Visual Reproduction	Immediate and delayed memory for a series of geometric pictures	Showed poor lateralization ability in TLE (Soble et al., 2014; Umfleet et al., 2015).
WMS Faces	Immediate and delayed memory for faces	Research on WMS Faces specifically is limited, but existing literature showed poor lateralization ability in TLE (Soble et al., 2014).

Note: Wechsler Adult Intelligence Scale (WAIS); Rey Auditory Verbal Learning Test (AVLT); California Verbal Learning Test (CVLT); Wechsler Memory Scale (WMS)

Table 2.
Neuropsychological Impairment in Traumatic Brain Injury & Posttraumatic Epilepsy

Measure	Description	Research
Global	General functioning in all cognitive domains	All domains have been shown to be impaired in the acute phase of mild TBI (Belanger et al., 2005).
Language		
WAIS Comprehension	A judgment task that measures the ability to provide practical answers to word problems	Those with complicated posttraumatic epilepsy performed worse than controls and those with uncomplicated posttraumatic epilepsy (Dikmen & Reitan, 1978).
WAIS Similarities	Understanding of abstract verbal relationships	Those with complicated posttraumatic epilepsy performed worse than controls and those with uncomplicated posttraumatic epilepsy (Dikmen & Reitan, 1978).
Phonemic Fluency	Ability to think of words that begin with the same letter quickly	Those with chronic cognitive deficits after TBI demonstrated impaired performances on FAS (Kinnunen et al., 2011).
Memory		
AVLT	Learning and memory of a word list	Total, short delay, long-delay, encoding, and consolidation are all impaired, in moderate to severe TBI. Improvement from acute to chronic phase (Wright & Schmitter-Edgecombe, 2011).
CVLT	Learning and memory of a word list	Encoding, acquisition, and consolidation were impaired in the acute stage of moderate to severe TBI, while only consolidation was impaired in the chronic stage (Vanderploeg et al., 2014). Those with severe TBI perform worse than those with moderate TBI (Finnanger et al., 2013).
Attention/Processing Speed		
Symbol Digit Modality Test	Processing speed through matching numbers with symbols within 90 seconds	Has been impaired along the spectrum of TBI; mild to severe (Draper & Ponsford, 2008; Finnanger et al., 2013; Kashluba et al., 2008).
Stroop	Trials that include ability to quickly name colors, read color words, and inhibit overlearned responses	Those with chronic cognitive deficits after TBI demonstrated impaired performances on each trial (Kinnunen et al., 2011). Lower performance in those with moderate to severe TBI when compared to healthy controls (Finnanger et al., 2013).

Trails A	Visual scanning, attention, and processing speed	Those with chronic cognitive deficits after TBI were slower than what would be expected based on age, sex, and education matched norms (Kinnunen et al., 2011). Lower performance in those with moderate to severe TBI when compared to healthy controls (Finnanger et al., 2013).
Executive Functioning		
Trails B	Quick mental set shifting	Those with chronic cognitive deficits after TBI were slower than what would be expected based on age, sex, and education matched norms (Kinnunen et al., 2011). Lower performance in those with moderate to severe TBI when compared to healthy controls (Finnanger et al., 2013).
WCST Perseverative Errors	Ability to solve problems efficiently	Has been impaired along the spectrum of TBI; mild to severe (Kashluba et al., 2008).
Category Test	Pattern analysis and problem solving	Impaired in moderate to severe TBI when compared to healthy controls (Finnanger et al., 2013).
Tower Test	Planning and problem solving	Impaired in moderate to severe TBI when compared to healthy controls (Finnanger et al., 2013).

Note: Wechsler Adult Intelligence Scale (WAIS); Rey Auditory Verbal Learning Test (AVLT); California Verbal Learning Test (CVLT); Wisconsin Card Sorting Test (WCST)

Table 3.
Neuropsychological Measures by Cognitive Domain

Measure	Description	Rationale for use and research to support
Premorbid IQ		
WAIS-III Vocabulary	Expressive vocabulary	Crystalized ability, is considered an adequate estimation of premorbid IQ (Yates, 1954 McFie 1975 & Krull 1995)
Language		
Boston Naming Test (60-item)	Confrontation naming	Well supported ability to predict left lateralized TLE. (Loring et al., 2008; Raspall et al., 2005; Umfleet et al., 2015)
WAIS-III Similarities	Understanding of abstract verbal relationships	Differs in those with uncomplicated posttraumatic epilepsy and complicated posttraumatic epilepsy (Dikmen & Reitan, 1978) and has been impaired in those with chronic deficits after TBI (Kinnunen et al., 2011).
Semantic Fluency (Animals)	Generation of semantically related words quickly	Impaired in both left and right TLE (N'Kaoua et al., 2001) and did not significantly predict side of seizure (Raspall et al., 2005).
Phonemic Fluency (FAS)	Generation of words that begin with the same letter quickly	Can be impaired in those with chronic deficits after TBI (Kinnunen et al., 2011), and was significantly impaired in those with left TLE (N'Kaoua et al., 2001).
Visuospatial		
WAIS-III Block Design	3D block construction	Has been impaired along the spectrum of TBI; mild to severe (Kashluba et al., 2008).
WAIS-III Matrix Reasoning	Visual pattern analysis	Those with chronic cognitive deficits after TBI demonstrated impairment (Kinnunen et al., 2011).
Verbal Memory		
WMS-III Logical Memory I	Immediate recall of story details	Mixed literature, though several studies show poor lateralization ability (Moore & Baker, 1996; Raspall et al., 2005; Soble et al., 2014; Umfleet et al., 2015)
WMS-III Logical Memory II	Delayed recall of story details	Mixed literature, though several studies show poor lateralization ability (Moore & Baker, 1996; Raspall et al., 2005; Soble et al., 2014; Umfleet et al., 2015)
AVLT	Learning and memory of a word list	Total learning and delayed recall are well supported ability to predict side of seizure (Loring et al., 2008; Soble et al., 2014).

Visual Memory		
WMS-III Faces I	Immediate memory for faces	Research on WMS Faces is limited, but one study shows poor lateralization ability in TLE (Soble et al., 2014).
WMS-III Faces II	Delayed memory for faces	Research on WMS Faces is limited, but one study shows poor lateralization ability in TLE (Soble et al., 2014).
Attention/Processing Speed		
Trails A	Visual scanning, attention, and processing speed	Those with chronic cognitive deficits after TBI were slower than expected based on age, sex, and education matched norms (Kinnunen et al., 2011).
WMS-III Working Memory Index	Mental manipulation of auditory information	No current support found but may be additive as an attention measure.
Executive Functioning		
Trails B	Visual scanning, processing speed, and mental set shifting	Those with chronic cognitive deficits after TBI were slower than expected based on age, sex, and education matched norms (Kinnunen et al., 2011).
WCST Perseverative Errors	Ability switch problem solving strategies without repeated errors	Has been impaired along the spectrum of TBI; mild to severe (Kashluba et al., 2008).
WCST Categories Completed	Problem solving and set shifting	No current support found but is regularly used in a variety of neurocognitive testing and may be an additive executive functioning measure.

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Rey Auditory Verbal Learning Test (AVLT); Wechsler Memory Scale Third Edition (WMS-III); Wisconsin Card Sorting Test (WCST)

Table 4.
Demographic/Seizure Characteristics by TBI Group

	TBI- (n = 183)	**TBI+ (n = 77)**	***p***
Age at neuropsychological testing, M (SD)	37.89 (11.28)	40.30 (10.31)	0.108
Years of education, M (SD)	13.30 (2.29)	13.30 (2.49)	0.999
Age of recurrent seizure onset, M (SD)	18.34 (13.30)	24.95 (14.58)	<0.001
Sex, male	40.4%	54.5%	0.037
Race, Caucasian	94.5%	94.8%	0.930
Handedness, Right	92.3%	89.6%	0.469
Mesial Temporal Sclerosis	59.3%	45.5%	0.040
Side of seizure, Left	54.1%	64.9%	0.107
WAIS-III Vocabulary, M (SD)	46.21 (10.30)	45.96 (9.78)	0.374

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Mean (M); Standard Deviation (SD)

Table 5.
Final Logistic Regression Model for Demographic/Seizure Characteristics Predicting TBI Status

	Odds ratio	95% confidence intervals for odds ratio		Wald *p*
Measures (n = 256)		**Lower**	**Upper**	
Sex (male)	1.839	1.038	3.257	0.031
Age of Recurrent Seizure Onset (years)	1.040	1.018	1.062	<0.001
Side of seizures (left)	1.595	0.884	2.878	0.130
WAIS-III Vocabulary	0.972	0.943	1.002	0.134

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III)

Table 6.
ROC Curves of Final Logistic Regression Models

	Area Under the Curve	95% confidence interval for ROC		*p*
Final Model		**Upper**	**Lower**	
Demographic/Epilepsy Characteristics	0.689	0.617	0.760	<0.001*
WAIS-III Similarities	0.586	0.510	0.663	0.039*
WCST Categories Completed	0.571	0.493	0.648	0.073
Combination	0.707	0.637	0.777	<0.001*

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Wisconsin Card Sorting Test (WCST)

Table 7.
Final Logistic Regressions Models for Neuropsychological Measures Predicting TBI Status

	Odds ratio	95% confidence interval for odds ratio		Wald *p*
Measures		**Lower**	**Upper**	
I. WAIS-III Similarities (n = 256)	0.970	0.941	0.999	0.045
II. WCST completed categories (n = 258)	0.988	0.974	1.001	0.076

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Wisconsin Card Sorting Test (WCST)

Table 8.
Final Logistic Regressions Model for Neuropsychological Measures and Demographic/Epilepsy Characteristics Combined Predicting TBI Status

	Odds ratio	95% confidence interval for odds ratio		Wald *p*
Measures (n = 256)		**Lower**	**Upper**	
Sex (male)	1.984	1.108	3.552	0.021
Age of Recurrent Seizure Onset (years)	1.039	1.018	1.060	<0.001
Side of seizures (left)	1.594	0.882	2.879	0.122
WAIS-III Similarities	0.957	0.926	0.989	0.008

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III)

Table 9.
Neuropsychological Adjusted T-scores by TBI Group

Measure	**TBI-**	**TBI+**	***p***
WAIS-III Similarities	46.30 (9.26)	43.69 (9.44)	0.043
WAIS-III Block Design	48.10 (10.35)	46.62 (8.70)	0.282
WAIS-III Matrix Reasoning	51.12 (11.07)	49.91 (10.63)	0.424
WMS-III Working Memory Index	46.15 (10.18)	45.97 (10.51)	0.900
WMS-III Logical Memory I	46.05 (10.28)	44.86 (9.65)	0.391
WMS-III Logical Memory II	45.05 (10.68)	43.68 (10.12)	0.344
WMS-III Faces I	45.41 (8.72)	44.78 (8.51)	0.595
WMS-III Faces II	46.08 (8.64)	45.75 (8.85)	0.776
Boston Naming Test (60-item)	36.82 (9.87)	35.46 (10.97)	0.329
Trails A	48.43 (11.59)	46.95 (11.01)	0.342
Trails B	46.85 (13.92)	43.75 (13.41)	0.101
WCST Categories Completed	43.41 (16.74)	38.63 (19.38)	0.046
WCST Perseverative Errors	44.90 (14.01)	41.43 (13.21)	0.070
Phonemic Fluency (FAS)	38.92 (10.85)	38.27 (10.78)	0.661
BDI-II	12.48 (9.91)	13.22 (8.61)	0.575

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Wechsler Memory Scale Third Edition (WMS-III); Wisconsin Card Sorting Test (WCST)

Footnote

[1] Good performance validity was determined through a combination of clinical impression of effort by the neuropsychologist and the Victoria Symptom Validity Test (VSVT). The VSVT is a forced choice computerized task that includes the number of correct responses, a time latency variable, and three trials of easy and difficult items. Although a likely valid cutoff score of 16 or above for difficult items is recommended by the VSVT authors (Slick, Hopp, Strauss, & Thompson, 2005; Slick, Hopp, Strauss, & Spellacy, 1996), a more conservative cutoff score of 18 for difficult items was set for this study. Grote et al. (2000) noted that 93.3% of a sample of epilepsy surgical candidates obtained a score of 21 or higher on difficult items, while 100% of the sample scored 18 or more on this measure.

Appendix A

Follow-up Logistic Regression Models for Neuropsychological Measures Predicting TBI Group Membership

A subset of the data (subset A; n = 154; 102 TBI-, 52 TBI+) included individuals who completed a semantic fluency measure (Animals). Demographically, those within the TBI+ group in subset A were significantly older at the age of seizure onset than the TBI- group. The demographic information for both groups is listed in Table A1. Due to a reduced number of observations, Animals and neuropsychological measures at the $p \leq 0.25$ level (Hosmer & Lemeshow, 1989) from the original neuropsychological measures logistic regression model were included (WCST categories completed, WAIS-III Similarities, WAIS-III Matrix Reasoning, WMS-III Working Memory Index, Trails B, and Animals). The logistic regression model indicated that lower scores on Animals would likely be important for predicting membership within TBI+ group (n = 154, odds ratio = 0.986, 95% CI: 0.972 - 0.941, $p = .077$); however, when included in the model, Animals was significant at the $p<0.1$ level.

A second subset of the data (subset B; n = 68; 42 TBI-, 26 TBI+) included individuals who completed the AVLT total, delay, and recognition. Demographically, those within the TBI+ group in subset B had a significantly older age of onset and a higher rate of left TLE. The demographic information for both groups is listed in Table A2. As done previously, due to a reduced number of observations, neuropsychological measures at the $p \leq 0.25$ level in subset A analyses were included (WAIS-III Similarities, WCST categories completed, Animals, AVLT total, delay, and recognition). The model (n = 68; H-L Test $p = 0.157$) that included lower scores on AVLT recognition (odds ratio

= 0.937, 95% CI: 0.887 - 0.990, p = .019) was the best fit for the data and significantly predicted TBI+ group membership. The ROC curve was significant (area under the curve = 0.665, 95% CI: 0.524 - 0.806, p = 0.023).

Table A1.
*Demographic/Epilepsy Characteristics by TBI Group for Subset A**

	TBI- (n = 183)	**TBI+ (n = 77)**	***p***
Age at neuropsychological testing, M (SD)	37.57 (11.63)	41.52 (10.27)	0.124
Years of education, M (SD)	13.18 (2.45)	13.46 (2.42)	0.494
Age of recurrent seizure onset, M (SD)	20.46 (14.55)	26.69 (14.73)	0.013
Sex, male	42.2%	56.2%	0.731
Race, Caucasian	96.1%	92.3%	0.444
Handedness, Right	93.1%	86.5%	0.236
Mesial Temporal Sclerosis	55.4%	38.5%	0.060
Side of seizure, Left	50.9%	59.6%	0.393
WAIS-III Vocabulary, M (SD)	45.77 (9.55)	45.28 (10.56)	0.772

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Mean (M); Standard Deviation (SD)
*Subset A contains individuals that completed Animals

Table A2.
*Demographic/Epilepsy Characteristics by TBI Group for Subset B**

	TBI- (n = 101)	**TBI+ (n = 52)**	***p***
Age at neuropsychological testing, M (SD)	39.33 (12.03)	41.50 (11.28)	0.463
Years of education, M (SD)	13.79 (2.52)	13.46 (2.32)	0.597
Age of recurrent seizure onset, M (SD)	20.24 (14.74)	28.62 (15.35)	0.028
Sex, male	33.3%	46.2%	0.316
Race, Caucasian	95.2%	96.2%	0.999
Handedness, Right	92.9%	84.6%	0.415
Mesial Temporal Sclerosis	56.1%	42.3%	0.322
Side of seizure, Left	45.2%	73.1%	0.043
WAIS-III Vocabulary, M (SD)	47.14 (10.53)	44.69 (11.02)	0.363

Note: Wechsler Adult Intelligence Scale Third Edition (WAIS-III); Mean (M); Standard Deviation (SD)
*Subset B contains individuals that completed AVLT

Appendix B

Follow-up Logistic Regression Models for Neuropsychological Measures and Demographic/Epilepsy Characteristics Combined

The combination model of subset A[1] that best fit the data (n = 154; H-L $p = 0.703$). Significant predictors included older age of seizure onset (odds ratio = 1.034, 95% CI: 1.010 – 1.060, $p = 0.006$) and a lower score on Animals [odds ratio = 0.963, 95% CI: 0.931 - 0.996, $p = 0.029$ (Table B1)]. The ROC curve was significant (area under the curve = 0.678, 95% CI: 0.588 - 0.767, $p<0.001$). The combination model of subset B[2] that best fit the data (n = 68; H-T $p = 0.251$) included older age of seizure onset (odds ratio = 1.047, 95% CI: 1.009 - 1.087, $p = 0.016$), left side of seizure (odds ratio = 2.801, 95% CI: 0.888 – 8.835, $p = 0.079$) and a lower score on AVLT recognition [odds ratio = 0.932, 95% CI: 0.878 - 0.932, $p = 0.021$ (Table B2)]. The ROC curve was significant (area under the curve = 0.763, 95% CI: 0.645 - 0.881, $p<0.001$).

[1] Subset A contains individuals that completed Animals (TBI- = 183; TBI+ = 77).
[2] Subset B contains individuals that completed AVLT (TBI- = 101; TBI+ = 52).

Table B1.
Final Logistic Regressions Model for Neuropsychological Measures and Demographic/Epilepsy Characteristics Combined Predicting TBI Status for Subset A

	Odds ratio	95% confidence interval for odds ratio		Wald *p*
Measures (n = 256)		**Lower**	**Upper**	
Age of Recurrent Seizure Onset (years)	1.034	1.010	1.060	0.006
Animals	0.963	0.931	0.996	0.029

Note: Subset A contains individuals that completed Animals

Table B2. Final Logistic Regressions Model for Neuropsychological Measures and Demographic/Epilepsy Characteristics Combined Predicting TBI Status for Subset B

	Odds ratio	95% confidence interval for odds ratio		Wald *p*
Measures (n = 256)		**Lower**	**Upper**	
Age of Recurrent Seizure Onset	1.047	1.009	1.087	0.016
Side of seizures (left)	2.801	0.888	8.835	0.079
AVLT recognition	0.932	0.878	0.932	0.021

Note: Rey Auditory Verbal Learning Test (AVLT)
Subset B contains individuals that completed AVLT