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White Matter Correlates of Verbal Memory in Left Temporal Lobe Epilepsy: A Study of Structural Connectivity

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WHITE MATTER CORRELATES OF VERBAL MEMORY IN LEFT TEMPORAL LOBE
EPILEPSY: A STUDY OF STRUCTURAL CONNECTIVITY

By

RYAN BREWSTER

Under the Direction of Tricia Z. King, PhD

ABSTRACT

Verbal memory deficits are among the most prominent cognitive sequelae in individuals with left temporal lobe epilepsy (LTLE). However, relationships between verbal memory function and white matter integrity (WMI) in the left temporal lobe remain unclear. Current study aims included determining fractional anisotropy (FA) and mean diffusivity (MD) differences as an index of WMI between participants with left temporal lobe epilepsy (LTLE), participants with right TLE (RTLE), and controls, establishing group differences based on verbal memory function between TLE groups, and describing relationships between WMI and verbal memory function within TLE groups. Probabilistic tractography defined the left fornix (FRX), left uncinate fasciculus (UF), left parahippocampal cingulum (PHC), and a control region, the left corticospinal tract (CST), in 26 LTLE, 29 RTLE, and 20 control participants. The LTLE group demonstrated significantly lower fractional anisotropy (FA) along the PHC compared

with controls. LTLE and RTLE groups did not differ significantly on measures of verbal memory until analyses were restricted to participants with left-lateralized language functioning. PHC FA was negatively correlated with semantic memory function in LTLE, but positively associated with episodic memory functioning in RTLE. Overall, findings highlight the PHC as vulnerable in LTLE, and differentially related to verbal memory functioning based on TLE group. Both findings are likely secondary to left-lateralized white matter disruption in LTLE. The current study also highlighted the importance of identifying homogenous groups to more clearly identify brain-behavior relationships. Current findings further define left-lateralized white matter alternations and related verbal memory deficits in TLE. Implications for these findings are presented in context with previous TLE literature, and future directions for further study are discussed.

INDEX WORDS: White matter integrity, Temporal lobe epilepsy

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RYAN BREWSTER

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Georgia State University

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DEDICATION

I dedicate my work to my family, friends, and Nicole Ralph-Forton. Thank you all for your support and patience while I completed my training.

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1 INTRODUCTION

1.1 Epilepsy: Prevalence, Incidence, Subtypes, and Impact

Epilepsy is one of the most common neurological diagnoses worldwide. This neurological condition has been estimated to affect more than two million Americans (CDC, 2012). Estimates have suggested that up to 200,000 new cases of epilepsy are diagnosed in the United States each year (Hauser & Hesdorffer, 1990). The most visible and defining feature across epilepsy syndromes are recurrent and unprovoked seizures (Chang & Lowenstein, 2003). It is hypothesized that seizures in the majority of epilepsy syndromes occur as a result of increased electrochemical signal spread secondary to differences in connectivity, enhanced excitatory transmission, deficits in inhibitory mechanisms, and differences in neuronal properties at a cellular level (Duncan, Sander, Sisodiya, & Walker, 2006).

Seizure syndromes can be broadly divided into two categories: generalized or focal/partial. Generalized seizures are characterized by electrochemical disruptions that begin from multiple, widespread regions of the brain and often have an etiology involving a genetic component (Chang & Lowenstein, 2003). Affected brain regions may vary by event and involve a range of structures and networks. In contrast, focal epileptic syndromes are defined by seizures originating consistently from specific brain regions (i.e., localization-related epilepsy). As noted by early efforts to establish standardized classifications for epilepsy syndromes (Gastaut, Gastaut, Goncalves e Silva, & Fernandez Sanchez, 1975), focal epilepsy is considerably more prevalent than generalized epilepsy in adults.

Although seizures in the majority of patients diagnosed with epilepsy respond to pharmacologic therapy with antiepileptic drugs (AEDs), it has been estimated that between 22%-30% of patients present with medication-resistant epilepsy (Kwan & Brodie, 2000; Picot, Baldy-Moulinier, Daures, Dujols, & Crespel, 2008). Epilepsy treatment presents a significant financial cost for patients. One study estimated lifetime costs ranging from \$4,272 for patients with medically-controlled epilepsy to \$138,602 for patients with recurrent, intractable seizures (Begley, Annegers, Lairson, Reynolds, & Hauser, 1994). A follow-up study estimated an average lifetime cost of \$61,255 for adults with epilepsy (Begley et al., 2000), and an estimated cost of \$12.5 billion for the 2.3 million cases of epilepsy diagnosed in 1995. In some cases, epileptic seizures can pose a direct risk of mortality. Although the specific mechanism is unclear, seizures are a direct factor in sudden and unexpected death for an estimated 1.16 cases per 1000 patients with epilepsy (Thurman, Hesdorffer, & French, 2014).

Patients with epilepsy diagnoses can experience difficulties with cognitive, physical, and emotional functioning that negatively impact their quality of life. Taylor, et al. (2011) reviewed a large body of literature describing quality of life for patients with epilepsy and reported that a wide array of symptoms (e.g., difficulty with memory, emotional concerns, and seizure frequency) related to this diagnosis pose significant disruption to health-related quality of life for patients with epilepsy. In an effort to minimize the financial, cognitive, physical, and emotional impact of these symptoms, considerable efforts have been made to better understand seizure etiology, cognitive sequelae, and differences in brain structures of patients with epilepsy.

The current study is focused on temporal lobe epilepsy (TLE), a subtype of epilepsy that has been demonstrated to affect regions of the brain associated with memory function. Although a rich literature on TLE and verbal memory exists, additional research is necessary to determine relationships between specific neuroanatomical differences related to TLE and verbal memory. The current chapter reviews key literature describing relationships between white matter differences in TLE and verbal memory.

1.2 Early Studies of Memory Function and Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most common subtype of medication-resistant focal epilepsy (Spencer & Huh, 2008), and among the most studied forms of neurological disorder. Difficulties with sensory and motor functions, language skills, executive functioning, and memory have been related to both focal and propagated seizure activity in medication-resistant TLE (Hermann, Seidenberg, & Bell, 2002). Factors including structural abnormalities, seizure frequency, earlier age of seizure onset, and disruption of education due to epilepsy have been related to multiple impairments in cognitive function for TLE patients (Hendriks et al., 2004; Hoppe, Elger, & Helmstaedter, 2007). However, chief among the cognitive concerns experienced by patients with TLE are difficulties learning and recalling information (Strauss et al., 1995).

Research participation of patients with epileptogenic foci in the temporal lobes has helped to establish some of the most influential and longstanding concepts in neuropsychology (Hermann, Lin, Jones, & Seidenberg, 2009). Early research with this population presented a unique opportunity for the study and description of specific pre and post-surgical brain structure and memory function relationships. Although both

effectiveness of AEDs have increased significantly, neurosurgery is a prevalent treatment in medically resistant epilepsy (Wiebe, Blume, Girvin, & Eliasziw, 2001; Tellez-Zenteno, Dhar, & Wiebe, 2005) that has been argued to be underutilized (Engel, 2013).

Scoville and Milner published seminal work detailing double amnesia in the presence of reduced seizure frequency demonstrated by patients with intractable TLE following bilateral medial temporal lobectomy (Scoville, 1954; Scoville & Milner, 1957). H.M. was among these early patients. H.M.'s memory impairment was characterized by both retrograde amnesia (e.g., difficulty recalling events occurring within the three years before his surgery) and perhaps more remarkably, severe anterograde amnesia for declarative information despite generally intact learning for nondeclarative memory. It is important to note that although Milner's 1957 paper is often cited as evidence for hippocampal lesions leading to memory impairments, the author did not consider this to be the case as the lesion was described by the original surgeons to include the amygdala, adjacent parahippocampal gyrus, perirhinal cortex, and white matter connections including lateral (Yakovlev, 1972) and medial (Papez, 1937) limbic circuits (Squire, 2009).

In fact, a recent study (Annese et al., 2014) described detailed findings from postmortem digital reconstruction and histological sectioning of H.M.'s brain. Specifically, the authors describe evidence of bilateral lesions including predominantly medial (vs. anterior) temporal lobe structures (e.g., the majority of the entorhinal cortex, significant portions of the amygdala, hippocampus, and portions of white matter underlying ablated medial temporal cortex). This suggests that even in this early study,

specific memory deficits were not conclusively attributed to a particular grey matter region (e.g., the hippocampus) in TLE, but instead to damage to a larger temporal network.

Penfield and Milner (1958) reported similarly drastic decreases in memory function independent from deficits in other areas of cognitive performance following unilateral left temporal lobectomy in two left TLE (LTLE) patients who were later determined to also have preexisting right temporal lobe lesions (Penfield & Mathieson, 1974). These unexpected post-surgical outcomes countered results from earlier studies that were unable to localize memory function to specific lesions and suggested that memory may rely upon whole-brain function (Lashley, 1950).

The initial studies completed by this group sparked a “new era” of memory research that extended to both human and animal models (Eichenbaum, 2013). Mishkin (1978), influenced by this work, demonstrated the first nonhuman primate model of amnesia. Although, neither amygdalotomy nor hippocampectomy produced any measurable memory deficit alone, a combined resection of both grey matter structures resulted in amnesia in rhesus macaques. Mishkin concluded that the combination of damage to the amygdala and hippocampectomy resulted in damage to both medial and lateral limbic circuits, leading to the memory deficits.

Zola-Morgan et al. conducted a series of lesion studies during the late 1980's that expanded upon Mishkin's findings. Of particular note, this group described that a lesion of the perirhinal and parahippocampal cortex could result in a more severe memory impairment (i.e., beyond that demonstrated by monkeys with hippocampal lesions), despite relative sparing of the hippocampus and the amygdala (Zola-Morgan,

Squire, Amaral, & Suzuki, 1989). These results suggested that damage to the perirhinal and parahippocampal cortex and the connections between this region and both the amygdala and hippocampus could result in amnesia. As illustrated by Figure 1, this region provides input to both the lateral and medial circuits involved in earlier studies of amnesic syndrome (Bauer, 2003). These studies demonstrate that memory impairments can result from damage to limbic structures beyond the hippocampus and amygdala, especially when there is a disruption in connectivity for both lateral and medial structures.

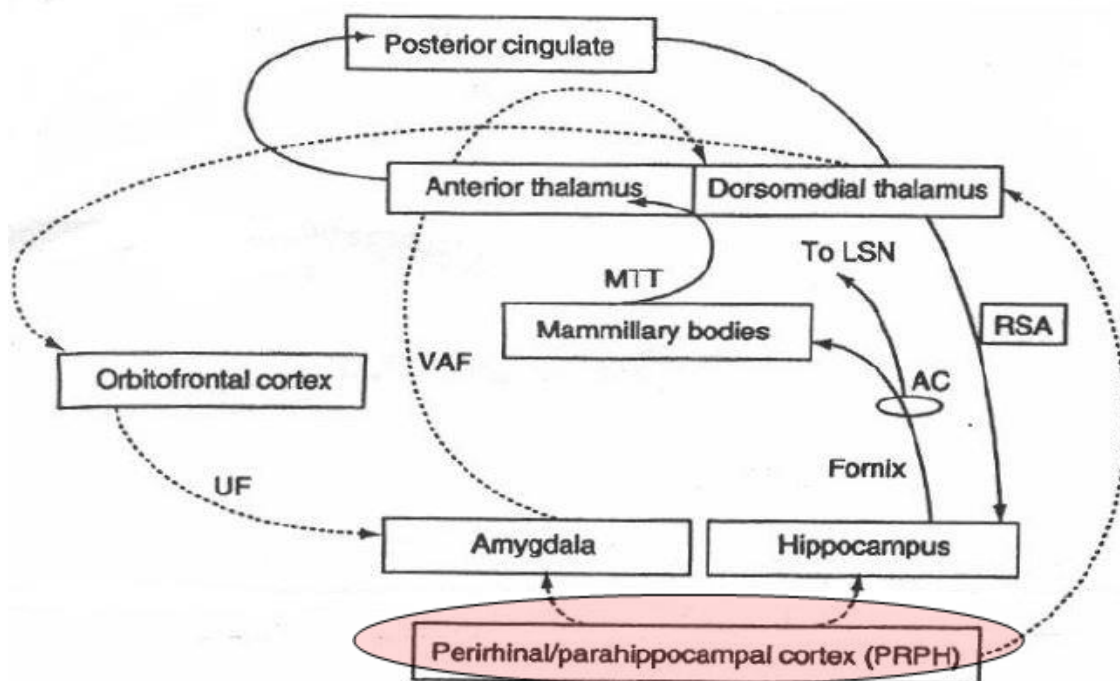


Figure 1.1 Amnesia lesion scenario.

Note: Described by Zola-Morgan et al. (1989) and illustrated by Bauer (2003). Solid lines mark medial limbic circuit and dotted lines mark lateral limbic circuit. Shaded oval represents lesion.

1.3 Material-Specific Model for Lateralized TLE Memory

Milner continued work towards identifying relationships between memory function and TLE-related factors, theorizing a material-specific model for lateralized temporal lobe function. Her findings suggested that structures contained in the language dominant (most commonly left) temporal lobe are mainly responsible for processing declarative verbal material and structures in the right temporal lobe are mostly devoted to nonverbal information (Milner, 1970, 1974). These findings have been supported by studies that demonstrate frequent verbal memory dysfunction following left hemisphere anesthetization (i.e., via the intracarotid sodium amobarbital or Wada test) and/or left temporal lobectomy in child (Jambaque et al., 2007) and adult TLE patients (Loring et al., 1991; Glosser, Saykin, Deutsch, O'Connor, & Sperling, 1995; Loring, Meador, Lee, & Smith, 2004; Lah, Lee, Grayson, & Miller, 2008).

Specific factors have been determined to affect memory outcomes suggested by the material-specific model. For example, one study described partial recovery in verbal memory function for patients who underwent more selective left amygdalohippocampectomy as opposed to left anterior temporal lobectomy (Paglioli et al., 2006). It should be noted however, that a recent meta-analysis comparing outcomes for both procedures suggested that neither procedure can be regarded as more likely to spare cognitive function.

Language dominance also has been shown to play a role, such that patients with LTLE but without left hemisphere language dominance have been demonstrated to experience relative sparing of verbal memory function, possibly reflecting a neuroanatomical reorganization of verbal memory systems (Kim, Yi, Son, & Kim, 2003).

The material specific model for memory function in epilepsy also has been criticized for being too restrictive. Saling's (2009) review of several studies of memory function and neuroanatomical factors in TLE suggested that verbal and nonverbal memory may not be mutually exclusive or opposite in terms of lateralization given findings that left and right seizure foci have been related to both poorer verbal and nonverbal memory function. Saling also theorized that there is a "tighter verbal-left nexus" of memory findings within TLE samples, but that current measures are not as effective in determining an equal representation of non-verbal memory in the right hemisphere.

These findings are consistent with a meta-analytic review of studies examining memory function following right temporal lobectomy. Vaz (2004) demonstrated that patients with RTLE do not present with consistent deficits on nonverbal visuospatial memory. Another study suggested that inconsistent findings for nonverbal memory tasks could be due to a higher level of difficulty and variety of paradigms involved in non-verbal memory tasks compared to verbal memory tasks (Pillon et al., 1999). It also is difficult to disentangle what strategies participants may be using to complete nonverbal tasks (e.g., patients may be using names to remember items).

The previous literature suggests that current measures of verbal memory function are more effective in assessing relationships between left-lateralized insult and memory dysfunction compared with the efficacy of commonly available nonverbal memory measures in determining a link between right-lateralized damage and memory function. Likely as a result of this, the relationships between verbal memory measures and left temporal hemisphere function also have been observed more consistently.

Taking these prior findings into account along with the aims of the present study, the remainder of this section will focus on relationships between verbal memory function and structural differences related to LTLE.

1.4 Verbal Semantic and Episodic Memory Function in LTLE

When describing verbal memory, a distinction should be made between semantic and episodic memory function. Although both are subtypes of declarative memory, Endel Tulving theorized a separation between semantic and episodic memory systems (Tulving, 1985b, 1985a). Tulving defined semantic memory as the recall of previously learned symbolically representable factual knowledge. Episodic memory was defined as the recall of information from personally experienced events. He theorized that episodic memory evolved from semantic memory, and could be a uniquely developed factor in human cognition (Tulving, 2002).

There has been considerable research into the relationship between semantic and episodic memory. Both the extent to which the semantic and episodic memory systems are related, and if the formation of either system is dependent upon the development of the other have been questioned. Based upon theories about the evolutionary basis of episodic memory, Tulving suggested that general knowledge could be stored in the semantic memory system without episodic memory involvement (Tulving & Markowitsch, 1998), but that information storage in episodic memory (mediated through medial temporal lobe structures including the hippocampus) requires structure provided by the semantic memory system.

Tulving's theory has been supported by work that has demonstrated that semantic and episodic memory abilities manifest at different points during development.

The semantic memory system has been demonstrated to begin development in infancy (Quinn & Eimas, 1997) whereas episodic memory has been demonstrated to develop later, most rapidly during early childhood, as structures in the temporal lobe mature (de Haan, Mishkin, Baldeweg, & Vargha-Khadem, 2006; Willoughby, Desrocher, Levine, & Rovet, 2012). Taken together with Tulving's theory, these findings suggest that if the semantic memory system is established first developmentally, semantic memory may provide structure necessary to accurately recall an episode. This is supported by a child study demonstrating better episodic memory recall within a category for participants with greater memory for semantic information about the category (Schneider, Körkel, & Weinert, 1989). Adult performance on episodic memory tasks also has been demonstrated to be aided by semantic similarity between list items (Howard & Kahana, 2002).

Similar to earlier studies of memory function in patients with TLE that sparked a new era of memory research, concurrent study of semantic and episodic memory within patients with TLE has suggested that further research into these memory systems is necessary. Hermann et al. (1992) suggested that including aspects of verbal semantic memory (e.g., retrieval from lexical storage) as a covariate when studying verbal episodic memory function (e.g., list learning) in LTLE patients could yield a "clearer picture" of verbal memory function. Later work by this group (Hermann et al, 1995) demonstrated that independent measurement of semantic memory composed of picture naming and vocabulary performance as well as episodic memory function composed of list learning and story recall could be accomplished within a TLE sample.

It also should be noted that vocabulary is a major component of general intelligence. In fact, the relationship between vocabulary and general intelligence is considered to be strongly predictive of both verbal and performance IQ in children (Bornstein & Haynes, 1998) and also has long been considered to be reflective of stable “premorbid” intelligence (Lezak, 1983; Wolfram et al., 1986). More recent work by Dennis et al. (2009) has recommended that measures of IQ should not be considered as covariates in neurodevelopmental disorders as differences in IQ are often integral features of these disorders, usually do not satisfy the statistical or methodological requirements of a covariate, and may result in overcorrected and/or anomalous findings.

Giovagnoli (1999) demonstrated a separation between semantic and episodic memory factors with a sample of Italian-speaking adolescents and adults with TLE diagnoses. A factor analysis revealed that word list and story recall loaded onto an episodic memory factor. Measures created by Snodgrass & Vanderwart (1980) including a naming task with black and white line drawings (i.e., Picture Naming) and questions about functional and contextual features of verbally presented items (i.e., The Semantic Questionnaire) loaded onto a semantic memory factor. The authors concluded that findings of impaired performance on these verbal semantic memory tasks, in the context of average language (operationalized by Token Test and Spontaneous speech performance) and abstract reasoning performance in the LTLE group, suggested that left temporal structures play a specific role in semantic recall.

These findings highlighted the presence of semantically-related verbal deficits along with previously described verbal episodic memory deficits for patients with LTLE. Similar results, including a separation of semantic and episodic memory factors also

have been reflected in a sample of children with TLE (Smith & Lah, 2011). Of note, story recall loaded onto both semantic and episodic memory factors in this younger sample. The author's highlighted this finding as consistent with other TLE literature theorizing that more complex verbal material (including stories) are dependent upon the involvement of both systems (Saling, 2009). However, the strongest component loading for story memory was on episodic memory.

A follow-up study (Giovagnoli, Erbetta, Villani, & Avanzini, 2005), found that a semantic memory factor composed of Picture Pointing to word prompt, Picture Naming, Drawing From Memory, Object Decision Hard, and the Pyramid and Palm Trees test was related to the side of seizure focus, such that lower scores were noted for LTLE patients. Further, Picture Naming, a semantic measure from the measure created by Snodgrass & Vanderwart (1980), was more difficult for participants with lesions within the lateral portion of the left temporal lobe (vs. participants with a left mesial TLE diagnosis). These findings are consistent with studies describing difficulties with semantic memory in patients with neuropathology (e.g., semantic dementia) predominantly affecting lateral temporal structures (e.g., the temporal neocortex) with little hippocampal involvement (Hodges & Patterson, 1996; Scahill, Hodges, & Graham, 2005). Generally, episodic memory deficits have been demonstrated to be most closely related to diagnoses (e.g., focal traumatic brain injury and early Alzheimer's disease) that include damage to more medial areas of the limbic system including the hippocampus, thalamus, mammillary bodies, and posterior cingulate (Tulving, 2002; Kramer et al., 2003; Nestor, Fryer, Smielewski, & Hodges, 2003; Nestor, Fryer, & Hodges, 2006).

Considering the findings presented above, it is possible that disruptions along structural connections between medial and lateral limbic system components may explain the combined semantic and episodic memory dysfunction previously described in TLE samples. Poor structural connectivity between components of both major circuits in the limbic system may have a negative impact upon communication necessary for retrieval of both verbal semantic and episodic information. Although early studies of the limbic system were unable to examine differences in structural connectivity between these components, recent advancements in imaging technology allow for this type of microstructural analysis and were the focus of the current study.

1.5 Diffusion Tensor Imaging as a Tool for Uncovering Brain-Behavior

Relationships

Diffusion imaging is an emerging technique utilizing in-vivo structural MRI data. Whereas functional magnetic resonance imaging (fMRI) allows for the identification of which brain regions are active during an experimental task relative to a control task, diffusion imaging allows investigators an opportunity to identify and compare the morphometry and quality of white matter pathways between selected brain regions. This method enables researchers to examine structural connectivity through visualization of water diffusion speed and path through brain tissue. This visualization presents an exciting opportunity for researchers to study the quality of white matter connections between key regions of the brain and has been successfully employed to study multiple diseases and disorders (Mori & van Zijl, 2002).

Diffusion Tensor Imaging (DTI) is an analysis technique that yields several measures useful in determining differences in white matter integrity. White matter

integrity (WMI) is generally described as a measure of the structural properties of white matter fiber tract connections in the brain that contribute to electrochemical communication between regions. Through an examination of how water molecules flow along white matter paths, an approximation of WMI (i.e., how well the fibers conduct information between areas of the brain) can be constructed. Low white matter integrity has been theorized to contribute to reduced communication between important areas of the brain, and has been related to varying levels of dysfunction across a wide variety of diagnoses (FitzGerald & Crosson, 2011; Jang, 2011; Potgieser et al., 2014).

Two of the most common analysis techniques are Tract-Based Spatial Statistics (TBSS) and probabilistic tractography. TBSS is an automated approach that is usually applied to explore whole-brain white matter differences between groups (Smith et al., 2006). Probabilistic tractography is used to determine the most probable dominant white matter pathway between selected regions within individual participant data (Behrens et al., 2003). Whole-brain TBSS is often considered to be a more exploratory approach when compared to probabilistic tractography as it can be used to characterize widespread white matter differences without a priori hypothesis about specific white matter pathways.

Fractional Anisotropy (FA) and Mean Diffusivity (MD) are two of the most common measures of WMI. Fractional Anisotropy (FA) is a directional measure of the organization (size, myelination and density) of white matter fibers (Basser & Pierpaoli, 1996). Higher FA values have been described as an indication of increased WMI as it is theorized that a higher FA value is consistent with a stronger directional coherence for a given area of white matter. Mean Diffusivity (MD) yields an overall measure of

diffusion in the brain tissue. Increases in MD have been related to neurological insult and brain disease as a gross measure of tissue structure integrity (Miles et al., 2008; Thivard et al., 2007; Wozniak et al., 2006). This measure is a more general indicator of diffusion across tissue and lacks the directional information included in FA. Higher MD is theorized to be an indication of water diffusion through a region that is not bound (i.e., guided by the structure expected to be provided by white matter axons).

1.6 Relationships between WMI and Memory Function in TLE

As noted above, white matter connections adjacent to the hippocampus and other structures involved in the limbic system can have an important effect on memory function. Several studies have used multiple forms of diffusion imaging analyses to describe WMI differences related to TLE diagnoses (see Table 1.1). It is important to note that the studies described were limited to samples that have not undergone surgical intervention as the current study focused on clarifying relationships between white matter and memory differences in presurgical TLE patients.

Table 1.1 Presurgical TLE DTI Study Summary

STUDY	GROUPS	KEY FINDINGS
(Rodrigo et al., 2008) Manual Tractography of AF and IFOF (1.5T)	8 LTLE (AR: 14-44) 12 RTLE (AR: 16-46)	LTLE: Trend towards left AF FA higher than right AF FA. RTLE: Left AF FA higher than right AF FA
(Focke et al., 2008) Whole-Brain DTI w/ TBSS (3T)	21 LTLE (AR:17-62) 12 RTLE (AR: 22-54)	LTLE vs. NT: Areas of lower FA across the left temporal lobe (including the cingulum, superior temporal gyrus, mesial temporal pole, parahippocampal gyrus, FRX), thalamus, and AF. Widespread areas of higher MD across the left temporal lobe

	37 NT (AR: 18-70)	(including the cingulum and hippocampus), and thalamus RTLE vs. NT: Widespread areas of lower FA along left and right superior temporal gyrus, left and right FRX, left and right corpus callosum, right parahippocampal gyrus and cingulum
(Lin, Riley, Juranek, & Cramer, 2008) Manual Tractography of the UF and AF (3T)	9LTLE+3RTL E (MA: 38±3) 10 NT (MA: 42±3)	TLE vs. NT: FA lower and MD higher along UF and AF ipsilateral to seizure onset compared to controls. Lower UF FA correlated with earlier age of seizure onset.
(Yu et al., 2008) Whole-Brain Voxel-Based Approach (1.5T)	12 LTLE + 11 RTLE (11-43) 13 NT (14-42)	LTLE+RTLE vs. NT: Reduced white matter volume across bilateral, frontal, parietal, and occipital lobes. Reduced white matter volume in the corpus callosum. RTLE group demonstrated some areas of higher FA compared to controls LTLE did not and demonstrated more regions of reduced WMI overall.
(Ahmadi et al., 2009) Manual Tractography of UF, PHC, FRX, AF, IFOF (1.5T)	10 LTLE+ 11 RTLE MA:37.3 (10.0) 21 NT MA:33(10.2)	LTLE: reduced FA compared to controls in left IFOF, SLS, FRX, and anterior thalamic radiations. Reduced FA compared to controls in right PHC, anterior thalamic radiation, and IFOF. RTLE: FA reduced compared to controls in right ILF FA in bilateral UF and bilateral parahippocampal gyrus correctly classified 90% of patients into right and left TLE.
(Hagler et al., 2009) Manual vs. Automated Tractography of CC,	16 LTLE + 5 RTLE (AR: 21-54)	TLE: Overall trend for widespread decreased FA compared with NT across the majority of fiber tracts analyzed with both methods (e.g.,

<p>Forceps Major, Forceps minor, PHC, FRX, IFOF, ILF, Pyramidal tract, SLF, anterior thalamic tract, UF</p> <p>(1.5T)</p>	<p>21 NT (AR:21-52)</p>	<p>Left PHC, left FRX, left and right IFOF, left SLF, left UF CC, left and right forceps major and minor,) especially low FA for LTLE.</p>
<p>(Concha, Livy, Beaulieu, Wheatley, & Gross, 2010)</p> <p>Manual Tractography and Histological analysis of Fornix</p> <p>(1.5T)</p>	<p>9 LTLE+ 2 RTLE (AR:33-60)</p>	<p>Presurgical DTI measures along fimbria-fornix predicted postsurgical histological features (e.g., Smaller axon membrane circumference).</p>
<p>(Bonilha et al., 2012)</p> <p>Automated ROIs Used for Graph Theory-Based Connectivity</p> <p>(3T)</p>	<p>5 LTLE + 7 RTLE (MA:37.5±9.8)</p> <p>26 NT (MA:34.3±8.8)</p>	<p>TLE: Demonstrated lower fiber density in limbic networks compared with NT. Unexpectedly, TLE group also demonstrated increased limbic network clustering and notable efficiency suggesting a reorganization of limbic system.</p>
<p>(Concha, Kim, Bernasconi, Bernhardt, & Bernasconi, 2012)</p> <p>Manual Tractography of the UF, ILF, and AF</p> <p>(28 participants on 1.5T and 23 participants on 3T)</p>	<p>18 LTLE + 12 RTLE (MA:30±9)</p> <p>21 NT (MA:30 ± 7)</p>	<p>TLE: Demonstrated higher MD restricted to temporal lobe ipsilateral to seizure focus. Correlation observed between shorter time since last seizure and higher MD. Higher MD for ipsilateral UF, AF, and ILF compared with NT.</p>
<p>(An et al., 2014)</p> <p>Whole-brain TBSS</p>	<p>17 LTLE (AR:18-42)</p>	<p>LTLE vs NT: Reduced FA in the left PHC, anterior thalamic radiation, and ILF</p>

(1.5T)	<p>15 RTLE (AR:18-43)</p> <p>34 NT (AR:18-44)</p>	<p>RTLE vs. NT: Reduced FA in right FRX, right anterior thalamic radiation, CC, right IFOF, and right UF</p> <p>LTLE vs. RTLE: Lower FA for LTLE along the left UF. Reduced FA for RTLE along right IFOF, ILF, and UF. More frontal regions implicated for RTLE while majority of changes in left temporal region for LTLE</p>
<p>(Barron, Tandon, Lancaster, & Fox, 2014)</p> <p>Probabilistic Tractography and Volumetrics with ROIs Including Thalamus, Amygdala, and Entorhinal Cortex, Hippocampus, and Parahippocampus</p> <p>(3T)</p>	<p>7 LTLE (AR:19-44)</p> <p>+</p> <p>12 RTLE (AR:25-65)</p> <p>19 NT (age-matched)</p>	<p>TLE vs. NT: decreased tract volume observed for thalamo-hippocampal pathways compared to NT. Regional hippocampal and thalamic volume decreased ipsilateral to seizure focus compared to NT.</p>
<p>(Besson et al., 2014)</p> <p>Automated Whole-Brain Tractography used for Graph Theory-Based Connectivity</p> <p>(3T)</p>	<p>19 LTLE (MA:39.8±10.8)</p> <p>20 RTLE (MA:39.3±9.4)</p> <p>18 NT (AR:18-44)</p>	<p>LTLE: Reduced connectivity strongly lateralized to the left temporal lobe compared to NT.</p> <p>RTLE: focal connectivity loss compared to NT present but much less pronounced.</p>
<p>(Li et al., 2014)</p> <p>Whole Brain TBSS Adapted to Analysis</p>	<p>15 LTLE (MA:43.5±18.9)</p>	<p>LTLE: More distinguishable from NT compared with RTLE. The left temporal lobe, frontal lobe, and UF play largest roles in separating LTLE from NT group.</p>

with Fractional Anisotropy Asymmetry Method (FAA) (3T)	15 RTLE (MA: 38.9±13.4) 14 NT (40.2±6.8)	
(Imamura et al., 2016) Whole Brain TBSS and probabilistic tractography applied to identify seizure propagation tracts (3T)	10 LTLE (MA: 33.5; AR: 23-45) 8 RTLE (MA: 29.8; AR: 18-45) 18 NT (MA: 31.3; AR: 18-47)	TLE: Reduced FA compared with controls was determined along seizure propagation tracts (UF, FRX, and AF), more pronounced than lower FA along control tracts (CST and ILF) Overall MD higher in patients vs. controls but not tract specific.
(Chiang et al., 2016) Automated Tractography with random forests (RF; machine learning) applied to determine best hippocampal connectivity model	17 LTLE (MA: 37.3 +/- 11.6) 11 RTLE (MA: 44.6 +/- 12.8) 28 NT (MA: 37.8 +/- 8.9)	TLE vs. NT: increased MD bilaterally in hippocampus, PHC, FRX, and right external capsule LTLE: increased MD in ipsilateral UF and external capsule. Decreased FA left PHC RF analyses demonstrated MD in right hippocampus and FA of left external capsule were best predictors of laterality
<p><i>Note:</i> LTLE- participants with left TLE diagnoses RTLE- participants with right TLE diagnoses NT- Neurotypical Control Participants +- Analyzed together AR- age range in years MA-mean age (SD) FA- fractional anisotropy (increases typically considered better quality white matter)</p>		

MD- mean diffusivity (increases typically considered lower quality white matter)
UF-uncinate fasciculus
PHC-parahippocampal cingulum
FRX-fornix
CC-corpus callosum
AF-arcuate fasciculus
IFOF-inferior frontal occipital fasciculus
ILF-inferior longitudinal fasciculus
STS-superior temporal sulcus

A pattern of decreased connectivity between structures and white matter tracts ipsilateral to seizure foci is a common finding for studies that used DTI to determine white matter differences between LTLE, RTLE, and control groups (Otte et al., 2012). However, the majority of studies report that white matter differences are more restricted to the limbic system for LTLE groups compared with more diffuse areas of lower WMI involving both temporal and extratemporal regions in the RTLE groups. This finding is highlighted by whole-brain DTI studies (Focke et al., 2008; An et al., 2014; Besson et al., 2014).

A recent study demonstrated that the use of an emerging method (i.e., Fractional Anisotropy Asymmetry) to describe whole-brain white matter skeleton asymmetry among an LTLE group, RTLE and a control group (Li et al., 2014). The authors reported that although the RTLE group was distinguishable from the control group, the highest degree of asymmetry was detected between the LTLE group and controls. Further, the difference between patients with a left temporal seizure focus and controls were driven mostly by WMI differences within the left temporal lobe and along the uncinate fasciculus (UF).

Studies focused on describing WMI along specific pathways demonstrated a similar pattern of a lower WMI along tracts ipsilateral to seizure foci. However, when WMI along the left and right tracts were compared between groups, stronger relationships are more commonly described for tracts between left-lateralized limbic structures and groups with left temporal seizure foci (Lin et al., 2008; Ahmadi et al., 2009; Hagler et al., 2009). One study focusing on particular white matter tracts (Ahmadi et al., 2009) reported that WMI differences along the UF and within the parahippocampal gyrus correctly classified 90% of their sample into either LTLE or RTLE groups, a finding consistent with more recent findings using a whole-brain white matter asymmetry calculation reported above (Li et al., 2014). Three particular white matter tracts emerge as demonstrating particularly reduced WMI within TLE groups: the uncinate fasciculus (UF), fornix (FRX), and white matter adjacent to the parahippocampal gyrus (i.e., parahippocampal cingulum; PHC). This is particularly relevant as the UF, FRX and cingulum have previously been identified as preferential pathways allowing for seizure propagation and secondary neuronal damage in TLE (Mayanagi, Watanabe, & Kaneko, 1996; Imamura et al., 2016) and have been recently identified as tracts with commonly lower WMI on patients with ipsilateral seizure foci (Stylianou, Hoffmann, Blat, & Harnof, 2016).

Table 1.1.2 Presurgical TLE DTI + Memory Study Summary

STUDY	GROUPS	FINDINGS
(Lui et al., 2005) Whole-Brain and Regional (hippocampus and parahippocampal gyrus) MD Analysis	9 LTLE + 11 RLTE (AR: 18-48); 20 NT (AR:19-47)	<u>DTI</u> TLE: Whole-brain, bilateral hippocampus, and bilateral parahippocampal gyrus MD higher than NT group. Hippocampus and parahippocampal regions ipsilateral to seizure focus demonstrated higher MD vs. contralateral hippocampus and parahippocampal regions.

(1.5T)		<p align="center"><u>Episodic Memory (Raw Scores)</u></p> <p>TLE: Negative correlations between left hippocampus MD and delayed list learning</p>
<p>(Diehl et al., 2008)</p> <p>Manual Tractography of UF (1.5T)</p>	<p>18 LTLE (AR: 24-47); 10 RTLE (AR: 29-55); 10 NT (age and gender matched)</p>	<p align="center"><u>DTI</u></p> <p>NT: FA higher in left vs. right UF LTLE vs. NT: FA lower and MD higher in left UF; MD higher in right UF RTLE vs. NT: FA lower in left UF; MD higher in right and left UF</p> <p align="center"><u>Episodic Memory (Standard Scores)</u></p> <p>LTLE: Left UF MD negatively correlated with immediate and delayed episodic memory.</p>
<p>(McDonald et al., 2008)</p> <p>Automated, Atlas-based Fiber Selection of UF, PHC, FRX, AF, IFOF (1.5T)</p>	<p>9 LTLE + 8 RTLE (MA:34.1) 17 NT (MA:38.7)</p>	<p align="center"><u>DTI</u></p> <p>LTLE: FA lower and MD higher than RTLE and NT in left UF. FA lower and MD higher than RTLE and NT in left and right AF; FA lower and MD higher than RTLE and NT in left PHC; FA lower and MD higher than RTLE and NT in left IFOF.</p> <p>RTLE: FA lower than NT in right PHC; MD lower than NT in left PHC; MD lower than NT in left and right AF;</p> <p align="center"><u>Episodic Memory (Raw Scores)</u></p> <p>Immediate Story Recall: negatively correlated with left and right UF MD; negatively correlated with left PHC MD; negatively correlated with left IFOF MD</p> <p>Delayed Story Recall: negatively correlated with left UF MD; positively correlated with right AF FA; negatively correlated with left and right AF MD; negatively correlated with left PHC MD; negatively correlated with left IFOF MD;</p> <p align="center"><u>Semantic Memory (Raw Scores)</u></p> <p>Picture Naming: positively correlated with: left and right UF FA and negatively correlated with left UF MD; positively correlated with left and right AF FA and negatively correlated with left and right AF MD; positively correlated with left IFOF FA.</p>

<p>(Yogarajah et al., 2008) Manual Tractography of parahippocampal gyrus (1.5 T)</p>	<p>8 LTLE (22-47); 10 RTLE (AR: 22-47); 10 NT (AR: 23-50)</p>	<p><u>DTI</u> LTLE vs. NT: FA lower in left parahippocampal gyrus</p> <p><u>Episodic Memory (% Correct)</u> List Learning: correlated with left parahippocampal gyrus FA</p>
<p>(Voets et al., 2009) Manual Tractography of UF and FRX and fMRI (3T)</p>	<p>9 LTLE (AR:18-47) 10 NT (AR:24-38)</p>	<p><u>DTI and Functional Connectivity</u> FA along the FRX correlated positively with functional connectivity measures and was reduced compared to NT.</p> <p><u>Episodic Memory (z-scores)</u> No relationship determined between diffusion measures and immediate or delayed story recall.</p>
<p>(Riley et al., 2010) Whole Brain DTI w/ TBSS + Tractography of Resulting Significantly Different Clusters (3T)</p>	<p>10 LTLE + 2 RTLE (AR:20-52) analyzed together 10 NT (AR:33-55)</p>	<p><u>DTI</u> TLE group composed predominantly of LTLE participants demonstrated lower FA than NT in clusters within the ipsilateral anterior temporal lobe, mesial temporal lobe, and cerebellum. Contralateral frontal and parietal lobe also included clusters of lower FA compared with NT.</p> <p><u>Episodic Memory (Standard Scores)</u> TLE and NT group: FA in the anterior temporal lobe (including the UF) correlated positively with delayed list recall. FA in the left mesial temporal lobe (including FRX) was linked to immediate episodic memory recall.</p> <p><u>Semantic Memory (Standard Score)</u> No relationships between Picture Naming and WMI were determined.</p>
<p>(Widjaja et al., 2013) Whole-Brain White Matter Analysis with Automated Segmentation (3T)</p>	<p>6 LTLE+ 3 RTLE (subset of 40 children with other types of localization-related epilepsy analyzed together)</p>	<p><u>DTI</u> TLE: FA in left and right temporal, left and right frontal, right parietal, and right occipital regions lower than NT.</p> <p><u>Episodic Memory (z scores)</u> No relationships determined between WMI and list learning</p> <p><u>Semantic Memory (z scores)</u> Right temporal FA correlated positively with</p>

	25 NT (AR:8-18)	picture naming.
(McDonald et al., 2014)	13 LTLE MA: 36.6 (13.3)	<p style="text-align: center;"><u>Episodic Memory (Scaled Scores)</u></p> <p>Higher MD of left UF, PHC, and bilateral ILF and IFOF, associated with lower story recall for combined TLE group. No relationships determined between WMI and story memory for NT groups. After covarying out age and left hippocampal volume, MD of the left ILF only approached significance for immediate story recall.</p>
Comparison of Predictive value of DTI and sMRI	13 RTLE (MA: 37.1 (12.5)	
(1.5T)	35 NT MA:38.2 (12.2)	
<p><i>Note:</i> LTLE- participants with left TLE diagnoses RTLE- participants with right TLE diagnoses NT- neurotypical control Participants +- Analyzed together AR- age range in years MA-mean age (SD) FA- fractional anisotropy (increases typically considered better quality white matter) MD- mean diffusivity (increases typically considered lower quality white matter) UF-uncinate fasciculus PHC-parahippocampal cingulum FRX-fornix CC-corpora callosa AF-arcuate fasciculus IFOF-inferior frontal occipital fasciculus ILF-inferior longitudinal fasciculus STS-superior temporal sulcus</p>		

These tracts and adjacent grey matter structures also are highlighted in studies describing relationships between WMI and memory functioning within TLE (See Table 2). WMI along the left UF has been found to correlate with verbal episodic memory recall within multiple TLE samples (Diehl et al., 2008; McDonald et al., 2008; Riley et al., 2010) and in other populations with different diagnoses including amyotrophic lateral sclerosis, mild traumatic brain injury, brain tumors, and controls (Niogi et al., 2008; Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Christidi et al., 2013; Riggs et al.,

2014). Together, these findings suggest that the UF is a key component of the white matter system mediating episodic memory retrieval. However, the damage along the UF also has been related to poor performance on semantic memory measures (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Papagno et al., 2011), even within the same TLE sample (McDonald et al., 2008). This finding is not unexpected given that the UF has been identified as a component of the lateral limbic circuit (Bauer, 2003) and the principal fiber tract connecting the structures within the anterior temporal and inferior frontal lobes (Schmahmann et al., 2007) which contain structures (e.g., the amygdala and orbitofrontal cortex) that are important for a wide variety of language, memory, and emotional functions. This pathway has been hypothesized to allow for the association of stimuli with name, emotional salience, and language; all processes that are aided by accurate retrieval of verbal semantic information (Von Der Heide, Skipper, Klobusicky, & Olson, 2013).

Table 1.1.3 Memory Studies Reporting Relationships Between the UF and Memory

	Episodic	Semantic
Previous Theory Suggests	(<u>Von Der Heide, Skipper, Klobusicky, & Olson, 2013</u>)	(<u>Bauer, 2003</u>) (<u>Von Der Heide et al., 2013</u>)
Previous Findings	<u>List Learning</u> (Diehl et al., 2008) (Riley et al, 2010) (Niogi et al., 2008) (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009) (Christidi et al., 2013) (Riggs et al., 2014)	<u>Picture Naming</u> (McDonald et al., 2008) (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009)
	<u>Story Recall</u> (McDonald et al., 2008 and 2014) (Christidi et al., 2013) (Riggs et al., 2014)	

Predictions For Current Study	Positive Correlation with UF WMI	Positive Correlation with UF WMI
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WMI of the mesial temporal lobe including the left FRX has been correlated with episodic memory recall within a TLE sample (Riley et al., 2010). Two other TLE studies included hypotheses about a relationship between the FRX and verbal memory recall, but were unable to reveal this relationship. McDonald et al. (2008) suggested that this may have been due to the lack of FRX WMI difference between their TLE and control samples. A study by Voets et al. (2009) also was unable to determine the difference between FRX FA in a TLE group and controls, but was limited by a small sample size. However, the FRX has been strongly related to episodic memory recall in other populations including hypoxia, older adults, mild cognitive impairment (MCI), and TBI (Kesler, Hopkins, Blatter, Edge-Booth, & Bigler, 2001; Aggleton & Brown, 2006; Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011; Zhuang et al., 2012; Miller, Munyon, Fastenau, Bailey, & Sweet, 2014). There have been studies describing impairments in semantic memory recall following damage to the FRX, although the strongest effects are usually demonstrated in the presence of concurrent damage to other structures (Spiers, Maguire, & Burgess, 2001; Poreh et al., 2006). Of note, poor WMI along the FRX has been reported to affect semantic organization on verbal memory tasks (Takei et al., 2008). This major component of the medial limbic circuit provides connectivity between the hippocampus, thalamus, and mammillary bodies (Bauer, 2003).

Table 1.1.4 Memory Studies Reporting Relationships Between the Fornix and Memory

Episodic

Semantic

Previous Theory Suggests	(Bauer, 2003) (Aggleton & Brown, 2006)	
Previous Findings	<u>List Learning</u> (Metzler-Baddeley et al., 2011) (Zhuang et al., 2012) (Miller et al., 2014) <u>Story Recall</u> (Kesler et al., 2001) (Zhuang et al., 2012)	
Predictions For Current Study	Positive Correlation with FRX WMI	No Correlation

The parahippocampal cingulum (PHC) is the inferior section of the cingulum that runs along the ventral aspect of the hippocampal formation and parahippocampal gyrus. This white matter pathway is a component of the medial limbic circuit and provides connectivity between the posterior cingulate gyrus, the perirhinal/parahippocampal cortex, and the hippocampus (Schmahmann et al., 2007; Wakana et al., 2007). WMI along the left PHC and within the left parahippocampal gyrus has been correlated to episodic memory recall in TLE samples (McDonald et al., 2008; Yogarajah et al., 2008) and other clinical groups including TBI and MCI (Wu et al., 2010; Delano-Wood et al., 2012). However, the regions connected by the PHC (i.e., posterior cingulate, hippocampal, and parahippocampal connectivity) also have been theorized to be an interface between lateral semantic retrieval and medial episodic memory systems (Levy, Bayley, & Squire, 2004; Binder, Desai, Graves, & Conant, 2009).

Table 1.1.5 Memory Studies Reporting Relationships Between the Parahippocampal Cingulum and Memory

	Episodic	Semantic
Previous Theory Suggests	(Levy et al., 2009) (Binder et. all., 2009)	(Levy et al., 2009) (Binder et. all., 2009)
Previous Findings	<u>List Learning</u> (McDonald et al., 2008) (Yogarajah et al., 2008)	<u>Picture Naming</u>

	(Wu et al., 2010) (Delano-Wood et al., 2012)	
	<u>Story Recall</u> (McDonald et al., 2008 and 2014) (Delano-Wood et al., 2012)	
Predictions For Current Study	Positive Correlation with PHC WMI	Positive Correlation with PHC WMI

It also should be noted that few studies have explored relationships between both episodic and semantic memory performance and WMI in TLE (See Table 4.). Of three studies that have included semantic and episodic memory measures and DTI analyses (McDonald et al., 2008; Riley et al., 2010; Widjaja et al., 2013), only McDonald et al. reported concurrent relationships between WMI and both semantic and episodic memory performance. This study applied an automated, atlas-based approach (Hagler et al., 2009) to determine relationships between WMI along several white matter tracts in the brain and performances on language and memory measures. This technique differs from manual approaches (e.g., probabilistic tractography) that allow for the delineation of white matter pathways determined on an individual level based on fiber tracking within each participant. Tracts selected from a predetermined atlas (Hagler et al., 2009) were applied to the study sample. Although automated methods are considerably faster than manual methods, automated approaches usually rely on atlas-based neurotypical samples and are less applicable to detecting individual differences that might be present, particularly within clinical samples that may present with unexpected white matter organization.

Additionally, as the focus of the study was not to determine differences between semantic and episodic memory function, McDonald et al. used story recall as their

single verbal memory measure. As noted earlier, story memory has been reported to load onto both semantic and episodic memory factors in younger TLE samples (Smith & Lah, 2011). As such, without determining if story memory loads more heavily on semantic or episodic memory within this sample, it would be difficult to determine if the relationships between the UF and PHC and story recall reported are evidence of episodic and/or semantic involvement of WMI along these tracts.

Table 1.1.6 Previous WMI vs. Verbal Memory Findings with TLE Samples

	UF	FRX	PHC
Episodic	<u>List Learning</u> (Diehl et al., 2008) (Yogarajah et al., 2008) (Riley et al, 2010)	<u>List Learning</u> (Riley et al, 2010)	<u>List Learning</u> (McDonald et al., 2008) (Yogarajah et al., 2008)
	<u>Story Recall</u> (McDonald et al., 2008)		<u>Story Recall</u> (McDonald et al., 2008)
Semantic	<u>Picture Naming</u> (McDonald et al., 2008)		

1.7 Potential Confounds and Covariates

Other factors have been found to be related to both verbal memory function and WMI in TLE. In some cases TLE patients with an earlier age of seizure onset have been found to demonstrate better verbal memory performance following temporal lobectomy compared to patients with a later seizure onset (Powell, Polkey, and McMillan, 1985; Wolf et al., 1993; Gleissner et al. 2002). It has been theorized that this is due to an earlier age of onset allowing for a higher degree of functional reorganization that results in improved function, although the specific mechanisms of this reorganization are unclear (Powell et al., 1985; Patariaia et al., 2004, 2005). However, other studies have

found an association between an earlier age at seizure onset and poorer verbal memory recall (Kent et al., 2006; Jokeit et. al., 2001; Hendriks et al., 2004). The authors of these studies suggest that a longer duration of time with seizures and a high seizure frequency could contribute to disrupted memory.

Widespread differences in WMI have been previously correlated with age (Davis et al., 2009). A relatively consistent pattern of increases in WMI throughout the brain until late adulthood followed by consistent decline beginning in late middle age (in typically-developing samples) has been identified (Pfefferbaum & Sullivan, 2003; Salat et al., 2005). Both type (e.g., phenytoin) and duration of anti-epileptic (AED) treatment have been found to be related to reduced WMI and verbal memory recall (Lee et al., 2003; Gunbey et al., 2011). Given the previous relationships demonstrated between these factors, WMI, and verbal memory, the current study will consider the potential role of these variables as covariates or confounds in subsequent analyses.

1.8 The Current Study

Despite substantial previous research on verbal memory in LTLE, the specific relationships between white matter integrity along key components of the limbic system and verbal semantic memory and episodic memory processes remain unclear. Although previous studies have reported a distinction between performance on semantic and episodic memory tasks in LTLE, no study has identified the potentially distinct white matter tracts involved in these verbal memory abilities. The current study addresses this gap in the literature by focusing on specific relationships between WMI along individually delineated white matter tracts passing through the left lateral (more commonly attributed to semantic recall) and medial (more commonly associated with

episodic recall) temporal lobe regions and composite episodic and semantic memory factors. Unlike previous DTI studies, a theory-based approach guided hypotheses about specific relationships in an effort to determine if tracts more vulnerable to disruptions related from left-sided seizure foci in LTLE differentially predicted semantic and episodic memory recall.

1.8.1 Aim 1: Group Differences in Limbic System Connectivity

Patients with LTLE are more vulnerable compared to patients with RTLE to disruptions along left-lateralized white matter tracts. However, patients with RTLE have been noted to demonstrate diffuse bilateral neuroanatomical differences compared with healthy controls (Focke et al., 2008; Ahmadi et al., 2009). The first aim of the present study was to determine if group differences within the current sample of patients with LTLE, RTLE, and healthy controls could be established based on the integrity of white matter connections between the amygdala and orbitofrontal cortex (via the left uncinate fasciculus; UF), between the hippocampus, thalamus, and mammillary bodies (via the left FRX), and among the hippocampus, parahippocampal cortex, and thalamus (via the parahippocampal cingulum; PHC). White matter integrity was determined through the calculation of FA and MD along ROIs defined by probabilistic tractography.

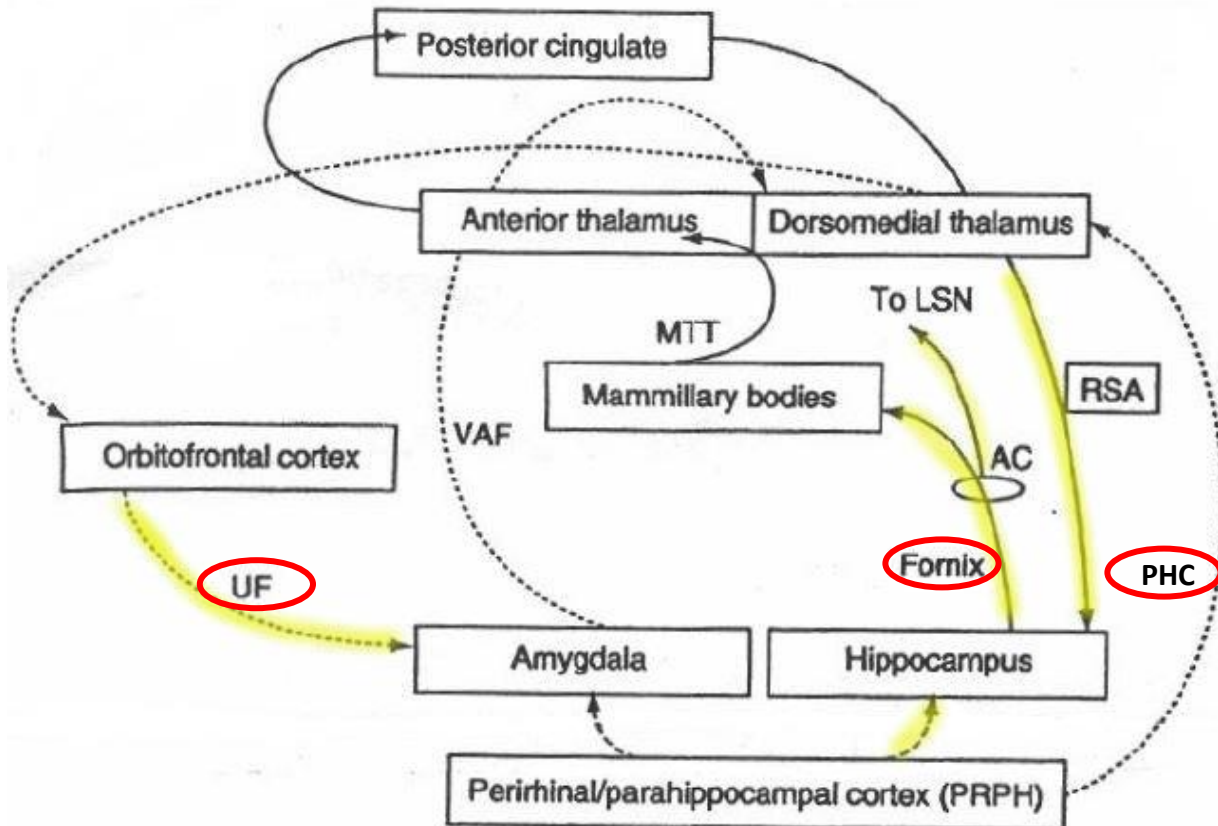


Figure 1.2 Lateral and medial limbic circuits

Note: As described and illustrated by Bauer (2003). Solid lines mark medial limbic circuit and dotted lines mark lateral limbic circuit. Ovals mark white matter tracts of interest to the current study.

1.8.1.1 Aim I Hypothesis A

It was hypothesized that the LTLE group would demonstrate lower white matter integrity (WMI; lower mean fractional anisotropy [FA] and higher mean diffusivity [MD]) than both the RTLE group and healthy controls along three tracts previously implicated in both semantic and episodic memory recall: the left parahippocampal cingulum (PHC), left fornix (FRX), and left uncinate fasciculus (UF). To determine the specificity of these findings, a tract that is not hypothesized to be involved in memory function (i.e., the left corticospinal tract; CST) was compared between groups.

Memory-Related Tract Hypothesis: LTLE WMI < RTLE WMI < Control WMI

Control Tract Hypothesis: LTLE WMI = RTLE WMI < Control WMI

1.8.2 Aim 2: Group Differences on Tasks Requiring Semantic And Episodic Memory Retrieval

The second aim of the study was to determine if group differences (LTLE vs. RTLE) could be established on measures of verbal memory. It has been suggested that the semantic memory system develops separately from the episodic memory system (Quinn & Eimas, 1997; Murphy, 2002), but contributes to more accurate episodic recall (Schneider, Korkel, & Weinert, 1989), and is more likely to be impaired following left temporal lobectomy and preserved following right temporal lobectomy (Wilkins & Moscovitch, 1978). However, verbal episodic memory impairment is commonly considered a hallmark neuropsychological finding in LTLE and also is impaired following left temporal lobe resection. Although the current study is focused on presurgical memory performance, these post-surgical findings suggested that the current presurgical LTLE group would demonstrate poorer verbal memory function than the RTLE group.

1.8.2.1 Aim 2 Hypothesis A

We predicted that group differences would be established on semantic and episodic memory performance such that the LTLE group would perform more poorly than the RTLE group on both episodic and semantic measures.

Episodic and Semantic Recall: LTLE < RTLE

1.8.2.2 Aim 2 Hypothesis B

Although both semantic and episodic measures reflect verbal declarative memory performance, the distinction between episodic and semantic memory tasks was important in determining the differential contributions of WMI along the presently selected white matter tracts to both semantic and episodic recall systems (i.e., Aim 3). Previous factor analyses have identified distinct semantic and episodic memory factors within other samples with TLE (Smith, 2011; Giovagnoli 1999; Giovagnoli 2005). These factors provided a method to account for the most amount of variance for our chosen constructs. We predicted that a principal components analysis (PCA) would confirm two factors. Performance on word list delayed recall (Rey AVLT Delayed Recall) and story memory delayed recall (WMS-4 Logical Memory II) were expected to load most heavily on an Episodic Recall factor. Word-definition recall (WAIS-4/WASI Vocabulary) and object naming (Boston Naming Test) were expected to load most heavily on a Semantic Recall factor.

1.8.3 Aim 3: Exploration of WMI and Related Semantic and Episodic Memory Function

The third aim of this study was to establish relationships between WMI along selected tracts within the limbic system and memory function. Determining relationships between WMI and memory performance findings resulting from the previous two aims was intended help describe the unique contributions of each of the three fiber tracts in predicting performance on both semantic and episodic memory function in TLE.

1.8.3.1 Aim 3: Hypotheses

Lower WMI along the FRX (a component of the medial limbic system) was hypothesized to be associated with lower performance on the episodic memory factor in the LTLE group. Lower WMI along the UF (a component of the lateral limbic system) and PHC (a component theorized to bridge both the lateral and medial limbic systems) were both expected to be associated with lower semantic and episodic memory factor in the LTLE group. WMI along the control tract (CST) was not expected to be related with either type of memory factor across groups. UF, FRX, and PHC WMI were expected to be independent of performance on a control task (Grooved Pegboard). In addition WMI along these tracts was not expected to be related to either type of memory function for the RTLE group as it was not expected that there would be enough variability in FA or MD in these participants to determine an association with either type of memory measure.

FRX WMI is hypothesized to be the strongest predictor (above UF and PHC WMI) in a regression model predicting episodic memory performance. In addition, controlling for the semantic factor in this model is hypothesized to improve the association between WMI along all three target tracts for LTLE participants. This result is expected to support previous literature suggesting that episodic memory processes rely upon more focal systems whereas semantic memory function is more distributed (Drane et al., 2013; Heisz, Vakorin, Ross, Levine, & McIntosh, 2014). UF WMI is hypothesized to be the strongest predictor (above FRX and PHI WMI) of semantic memory performance.

2 METHOD

2.1 Participants

Participants in the proposed study were selected from two larger projects investigating psychophysiological correlates to cognitive function in patients with epilepsy (PI: Drane, Grant #'s: K02NS070960-01A1 & K23 NSO49100-01). Clinical participants in these studies were recruited from among patients undergoing presurgical evaluations within the Department of Neurology at the Emory University School of Medicine. Inclusion criteria for epilepsy group participants included having a diagnosis of LTLE or RTLE based on video EEG monitoring and presurgical conference. All patients also underwent photon emission tomography (PET) scans, MRI scans, and a comprehensive neuropsychological evaluation. The majority of participants underwent an intracarotid amobarbital (Wada) procedure and an fMRI study to determine language dominance and risk for memory decline. A few right-handed/right-footed patients with right-sided surgery did not undergo Wada evaluation. Control participants were recruited from the community with flyers. Both parent studies were approved by the Emory University Institutional Review Board. Consent and assent were obtained from all participants and guardians.

2.1.1 *Exclusion Criteria*

All participants with MRI scans distorted by significant artifact due to movement or other imaging artifact (control n=3, TLE n=5 exclusions for artifact) or that did not speak English as their primary language were excluded. No participants in the current sample with DTI data required intracranial monitoring with grids/strip electrodes. Control participants were excluded if they presented with IQ scores determined by the

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008) as below 70, a history of neurological or medical condition that could impact brain functioning, a history of psychiatric illness, scores in the depressed range of the Beck Depression Inventory-Second Edition (BDI-2) or other current emotional symptoms (n=1 exclusion for current symptoms of PTSD) and/or learning disability, or a history of substance abuse.

Controls also were screened for scores in the depressed range of the Beck Depression Inventory-Second Edition (BDI-2) or other current emotional symptoms, and abnormal performance on a symptom validity measure (the oral form of the Word Memory Test) or an abnormal performance on a mental status exam.

2.2 Measures

2.2.1 Verbal Episodic Memory: List Recall

Participants in both TLE groups completed the Rey Auditory Verbal Learning Task (RAVLT). The RAVLT is a measure on which participants are tasked with recalling a verbally-presented 15-item word list that was read aloud by the examiner at a rate of one word per second for five trials (Rey, 1964). After each trial, participants were asked to state all of the words that they could remember from the list while the examiner recorded words recalled after each trial. Following the fifth presentation and recall of the of the word list, an interference list consisting of 15 new words was presented for recall. TLE participants were then asked to recall all of the words that they could remember from the list they heard 5 times. After a 30 minute delay, the participant was asked to state as many words as they could remember from the initial list as a delayed free recall trial. Finally, the participant was tasked with distinguishing

between 15 printed words from the initial list and interference words on a recognition task. Scores on all trials were based on correctly recalled words.

The RAVLT applies to a wide age range (normative data for individuals between 7 and 89 years of age) been used extensively within TLE samples, and has been highlighted as a list learning measure with less demand on semantic processing and organization compared with other list-learning measures (e.g., the California Verbal Learning Test-Second Edition) used with epilepsy samples (Helmstaedter, Wietzke, & Lutz, 2009). Overall test-retest reliability estimates for this measure have ranged from .12-.86 (Schmidt, 1996). The present study was particularly focused on findings from the delayed free recall trial of the RAVLT. This measure has been demonstrated an acceptable test-retest reliability at .67 (Geffen, Butterworth, & Geffen, 1994).

2.2.2 Verbal Episodic Memory: Story Recall

Logical Memory, a subtest from the Wechsler Memory Scale–Fourth Edition (Wechsler, 2009), was used in this study as a measure of episodic recall. The Logical Memory subtest consisted of two narratives that are read aloud to participants. Following each story, the participants were asked to recall as many details about each story as possible. After a 30-minute delay, participants were asked to state as many details as they could remember from each story (LM2). The measure ended with a verbally presented recognition trial consisting of a series of “yes or no” questions about each story.

The Logical Memory subtest references a normative sample spanning from 16-64 years of age. Test-retest reliability for this measure was reported by the authors to range between .73 and .84. The Logical Memory subtest is widely used to assess

verbal memory in patients with epilepsy. An earlier version of the current measure was been reported to be in use in 82% of epilepsy centers (Jones-Gotman, Smith, & Zatorre, 1993). The current project focused on the delayed recall subtest of the logical memory subtest (LM2).

2.2.3 Verbal Semantic Memory: Object Naming

The Boston Naming Test (BNT; Goodglass & Kaplan, 1983) was used in the current TLE sample as a measure of object naming. The BNT is a confrontation naming task on which participants were asked to verbally identify a series of up to 60 line drawings that ranged from very common (e.g., tree) to less common (e.g., abacus). Each item was presented individually and scored as correct when the participant was able to correctly respond within 20 seconds.

The BNT applies to a wide range of ages (normative data available from 18 to 95 years of age) and has been used extensively with patients with epilepsy. This measure has demonstrated strong (e.g., .94) test-retest reliability within samples of participants with epilepsy (Sawrie, Chelune, Naugle, & Lüders, 1996). The BNT has also been found useful in lateralizing LTLE vs. RTLE patients (Raspall et al., 2005; Loring et al., 2008).

2.2.4 Verbal Semantic Memory: Word Definition Recall

The vocabulary subset from the Wechsler Scale of Adult Intelligence – Fourth Edition (WAIS-IV; Wechsler, 2009) or Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was applied to determine word definition recall ability in the proposed sample. On this task, participants were asked to define verbally presented words.

The authors report test-retest reliability ranging from .90 to .98 for the vocabulary subtest within the normative sample. Of note, an earlier form of this subtest has been applied to successfully lateralize between LTLE and RTLE patients (Hermann et al., 1995).

2.3 Imaging Technique: Diffusion Tensor Imaging

Diffusion weighted data was acquired during a 64-direction interleaved dual echo blip-reversed diffusion-weighted DTI sequence with contiguous axial slices with the following specifications: TR/TE=8700/93 ms; b=1000 s/mm²; voxel size: 2.0×2.0×2.0 mm; acquisition matrix 256×256; sequence time: 9 minutes, 52 seconds. T1 weighted images (3D MPRAGE) were acquired for structural registration: TR/TE=2250/3.98 ms, 160 contiguous sagittal slices, 1 mm slice thickness, no gap, voxel size: 0.9×0.9×1.0 mm; sequence time 6 minutes, 44 seconds.

This study applied Diffusion Tension Imaging (DTI) to determine the quality of white matter connections near specific regions of interest (ROIs) in all participants. This method of structural imaging allows visualization of white matter tract structure and coherence in vivo based on a measure of water diffusion through brain tissue (Barnea-Goraly, et al., 2004 and yielded quantitative measures.

If white matter pathways are conceptualized as three dimensional bundles of fibers between areas, DTI data can be reduced to diffusion on three principal eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) along and across axes of the bundles. Two measures are commonly derived from these three principle eigenvalues. Mean Diffusivity (MD) is the average of all three measures of diffusion ($MD = [\lambda_1 + \lambda_2 + \lambda_3]/3$). MD yields an overall measure of diffusion in a brain tissue region. Increases in MD have been related to

neurological insult and brain disease as a gross measure of tissue structure integrity (Wozniak et al., 2006; Thivard et al., 2007; Miles et al., 2008). Fractional Anisotropy (FA) is a proxy measure of the microstructural properties of white matter integrity through analysis of the organization (fiber size, myelination and density) of the tissue (Basser & Pierpaoli, 1996). This measure incorporates additional directional information into the measure of mean diffusivity. A higher FA value (in a range between 0 and 1) is usually considered to denote higher quality white matter integrity in a given direction.

2.3.1 White Matter Tractography Preprocessing

White matter tractography is a method that allows for the application of diffusion imaging measures to the visualization and analysis of selected white matter pathways. All MRI image processing tools mentioned below are components of the FMRIB Software Library (FSL) Diffusion Toolbox (FDT 2.0) to conduct tractography and compute measures of white matter integrity (Smith et al., 2004; Woolrich et al., 2009).

The Brain Extraction Tool (BET) was used to remove non-brain tissue data from structural and diffusion images. Eddy current distortion introduced by standard operation of the scanner and head translation during the scan was corrected using the Eddy Current Correction tool. Diffusion tensor imaging model parameters were adjusted to fit each participant's diffusion data volume with FSL DTIFIT software. The BEDPOSTX tool was used to estimate the diffusion parameters for each voxel in each total diffusion volume.

2.3.2 Probabilistic Tractography Region of Interest Selection

Manually-defined regions of interest (ROIs) along the left uncinate fasciculus (UF), left fornix (FRX), and left parahippocampal cingulum (PHC) were created for each

participant. UF ROI selection was guided per methods described by a previous study that included a TLE group (Voets et al., 2009). Left FRX ROI selection was completed following an approach outlined previously (Concha, Beaulieu, & Gross, 2005) for use within TLE and control samples. Previous recommendations were also followed to delineate the Left PHC (Wakana et al., 2007).

Due to the sensitivity of tractography completed with probtrackX to error contributed by crossing fibers, exclusion masks were applied in an effort to prevent regions of interest in the current study from including these areas (e.g., where the FRX and anterior commissure meet). This function is included the probtrackX tool. ROI selection techniques were based on previous methods that have included the use of exclusion masks (e.g. recommendations suggested by Dineen et al., 2012 for selection of the FRX and the exclusion of the mammillary bodies and anterior commissure, and recommendations provided by Voets et al., 2009 for fiber-tracking of the uncinate fasciculus with exclusion of tracts extending from the fimbria-fornix).

2.3.3 Control Region of Interest Selection

To aid in establishing the specificity of findings along memory-related tracts, a control region was selected along the right CST as suggested by previous studies (McDonald et al., 2008, Zhuang et al., 2012). To anatomically define this control region, recommendations provided by Wakana et al., 2007 for delineation of the corticospinal tract and the exclusion of crossing pontine fibers using exclusion masks was used for all participants.

2.3.4 Probabilistic Tractography and White Matter Integrity Measure

Calculation

Probabilistic tractography was used to determine white matter connections along ROIs. This approach is a measure of structural connectivity which repetitively samples voxel-wise principal diffusion directions to determine the most likely path of a white matter tract. This creates a distribution of the most probable dominant pathway between regions which attempts to account for uncertainty in individual participant data (Behrens, 2007). The PROBTRACKX tool was used to apply a probabilistic tractography algorithm to compute likely white matter connections along each ROI for all participants (Behrens et al., 2003). Of note, it is theoretically possible that significantly damaged white matter could impede tract-tracing. To avoid this probabilistic tractography in FSL was set to not use FA as a decision threshold for fiber tracking. This was accomplished by unticking "Use anisotropy to constrain tracking" in probtrackX. The resulting tracts were thresholded with the FSLMATHS tool. The FSLMEANTS tool allowed for the calculation of average FA and MD values.

2.4 Procedure

TLE patients completed neuropsychological assessment during presurgical work-ups at Emory University Hospital. All neuropsychological assessments were conducted by neuropsychologists, psychometrists, or trained doctoral-level graduate students. All participants were presented with both written and spoken explanations of what neuropsychological assessment would entail. Participants were also informed that their participation in the study was completely voluntary and that they could withdraw at any

time without penalty. Participants were told that all data collected during the study would remain confidential (barring exceptions otherwise required by law).

Participants were tested individually, and were offered opportunity to take breaks from testing as needed. Testing sessions customarily ranged between 4 to 6 hours and were completed within a single session. Structural MRI data was collected during an additional session on a 3-Tesla scanner at Emory University Hospital. Participants were informed that MRI scans do not pose any known risks, and carefully screened for any external or internal ferrous material, preexisting conditions, and any other factors that could endanger them during the scan. Trained MRI technicians operated the scanner during data collection and participants were able to communicate with hospital staff while in the scanner. Structural MRI Data (T1 MPRAGE sequence), myelin mapping (T2 sequence), and DTI data were collected as part of a longer MRI scanning session that also included resting state fMRI active task fMRI with stimuli designed to elicit responses to famous and non-famous faces.

MRI images were stored on a password-protected server at the Coulter BME Biomedical Imaging Technology Center on the Emory University campus. MRI data from participants that satisfied exclusion criteria were copied from this location and analyzed at the Georgia State / Georgia Tech Center for Advanced Brain Imaging on the Georgia Tech University Campus. Cognitive and demographic data were de-identified and stored in a separate password-protected digital database along with data collected as part of the larger Emory IRB-approved studies. The current study was approved via an amendment to the parent study protocol in March of 2014.

2.4.1 Data Entry and Preparation

Data was entered into Apache Open Office and Microsoft Excel. All statistical analyses were conducted with SPSS version 20. Careful attention was applied to descriptive statistics and the distribution of participant scores on each measure in addition to traditional analyses. Scatter plots were reviewed to visualize associations between measures and outliers. Statistical assumptions (e.g., normality and homogeneity of variance) were tested as the initial step of each analysis and transformations were conducted as necessary. Measures of effect size (e.g., Cohen's d , and R-squared) were determined when applicable. Z-scores were computed from normative data from either respective test manuals or Heaton norms (Heaton et al., 2004) for the RAVLT, WMS-4 Logical Memory, BNT, and Wechsler Vocabulary subtests and used for all analyses.

2.5 Aim 1

To address the first aim of the study, determining group differences in limbic system connectivity along the selected tracts, individual univariate analyses of variance (ANOVAs) were conducted with group (i.e., LTLE, RTLE, or control) as the independent variable and WMI for the three memory related tracts and the single control tract as the dependent variable. Assumptions of homogeneity of variance and normally distributed residuals were tested. Two pairwise conditions were tested via contrasts: TLE lower than control, and LTLE lower than RTLE. Gabriel's post hoc test (Gabriel, 1969) was used (in light of the differences in sample size) to reduce the likelihood of type one error due to multiple comparisons.

2.6 Aim 2

To address Aim 2 (determining if verbal memory measures loaded differentially on one semantic and one episodic factor), a Principal Components Analysis (PCA) with an oblique rotation was conducted to verify verbal memory separation into one episodic and one semantic factor. A Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy was used to determine if the current sample was sufficient for PCA analysis. In case the current sample was inadequate for an interpretable PCA, an alternate plan was pre-determined to use word list delayed recall to measure episodic memory and word definition recall to measure semantic memory in subsequent analyses as suggested by previous studies (Giovagnoli, 1999; Smith & Lah, 2011). TLE group differences on semantic and episodic memory were assessed using a 2x2 ANOVA, with Eta squared providing an effect size.

2.7 Aim 3

To address Aim 3, correlations were conducted to determine associations between WMI and both semantic and episodic memory factors within and between TLE groups. To better define relationships between specific memory processes and WMI, additional correlations were also conducted between individual memory measures and WMI. To increase the specificity of correlational findings, an additional correlation was conducted to determine if the control measure (Grooved Pegboard performance) would be related to WMI along any of the target white matter tracts

In the case that associations suggested by previous literature were determined (e.g. positive relationships between WMI along target tracts and episodic and semantic memory function), hierarchical regression analyses were planned to determine the

differential contribution of WMI along each fiber tract to the memory factors. Based on previous findings regarding episodic memory, WMI along the FRX was predicted to explain more variance in episodic recall than either UF or PHC WMI. Secondary analyses were intended to include conducting an additional hierarchical regression to determine if additional variance could be explained by controlling for the semantic memory factor in this model. In an additional planned hierarchical regression predicting semantic memory performance, UF WMI was expected to explain more variance than either FRX or PHC WMI.

3 RESULTS

Descriptive statistics are summarized by Table 3.1. All three groups included a large age range. Participants across groups were predominantly female and generally completed at least 12 years of formal education. No significant differences (explored with ANOVAs for continuous variables and chi-square analyses for categorical variables) were determined for any demographic or treatment-related variables between the groups. TLE groups were also comparable across treatment-related variables and etiology.

In the LTLE group, 73% of participants (n=19) were diagnosed with idiopathic epilepsy. The remaining participants were diagnosed with epilepsy secondary to other causes, including post-traumatic epilepsy (n=1) post encephalitic epilepsy (n=1), epilepsy secondary to a cavernous malformation (n=2), epilepsy following an infectious disease (n=1), and epilepsy following other diagnosis (e.g., liver transplant and cortical dysplasia n=2). In the RTLE group, 55% of participants (n=16) were diagnosed with idiopathic epilepsy. The remaining participants were diagnosed with epilepsy

secondary to other causes, including brain tumor (n=4), post-traumatic epilepsy (n=2) post encephalitic epilepsy (n=1), epilepsy secondary stroke (n=2), epilepsy following an infectious disease (n=3), and epilepsy following other medical diagnosis (e.g., related to an undefined cortical malformation n=1).

In the LTLE group, 89% of participants (n=23) were determined to have left hemisphere dominant language function. Remaining participants presented with right hemisphere lateralization (n=2) and atypical distribution of language function (n=1). In the RTLE group, 72% (n=21) participants were left-lateralized. Additional RTLE participants (n=3) demonstrated right hemisphere language lateralization, atypical language distribution (n=3), and language lateralization for the remainder (n=2) was unknown.

It was important to explore the possibility of potential statistical confounds in the present study. A statistical confound is a threat to internal validity that occurs when an “outside” variable not included in a hypothesis is statistically related to the independent and dependent variables. If demographic or treatment-related variables met these criteria during analysis, they were considered confounds. When a confound is present and not accounted for, a portion (or all) of the variance that the independent variable explains in the dependent variable actually may be due to the confounding factor.

If potential confounds that were significantly different between groups and related to the dependent variable (i.e., presenting a possibility that this difference could contribute to a difference on the dependent variable indistinguishable from the effect of the group difference), they were considered as covariates. When potential confounds met the statistical assumptions for analyses in the current study (i.e., a similar and linear

covariate by dependent variable relationship strength and homogeneous regression slopes between groups) they were included in analyses below as covariates to reduce the error variance.

Potential confounds (Table 3.1) were evaluated to determine if they met criteria to be included as covariates in an ANCOVA to reduce within-group error variance. To be considered as appropriate for inclusion in an ANCOVA, potential confounds were examined to determine independence of the potential covariate and treatment effect (i.e. group membership), and homogeneity of regression slopes. In Aim 1, a potential covariate was age. In the current sample, age did not differ between groups. Although age has previously been demonstrated to have a relationship with WMI (Madden et al., 2004; Voineskos et al., 2012), age was not found to be correlated to WMI in current groups and was not included as a covariate in this analysis.

Age of seizure onset, total number of AEDs prescribed, and dosage of primary AED, did not differ significantly between groups or correlate with WMI. Although number of years treated with AEDs did not differ between groups, it was positively correlated with CST MD, $r=.31$, $p<.05$ (Figure 3.1).

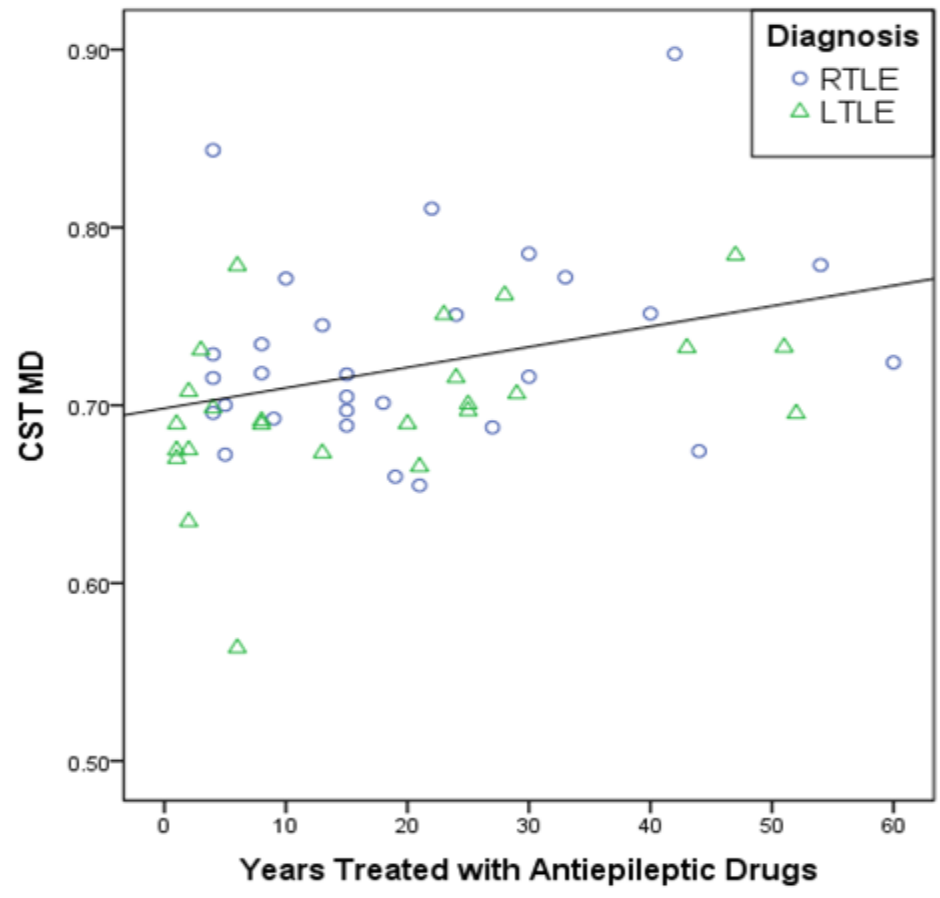


Figure 3.1 Association between years treated with AEDs and CST MD.

In determining relevant relationships between potential covariates and WMI, a “medium” (Cohen, 1998) effect size cut-off of $R^2 > .09$ was applied in place of a p level $< .05$ due to the relatively small sample size. This method did not reveal any additional variables (e.g. sex, education, age, age of seizure onset, AED dosage, or education) as related to WMI.

Table 3.1 Descriptive Statistics Across Samples

	Control Mean(SD)	RTLE Mean(SD)	LTLE Mean(SD)
N	20	29	26
Age Range	19-62	21-64	19-75

Age	37.5(13.88)	40.62(11.64)	39.35(16.92)
Education	14.90(2.20)	14.86(2.82)	13.92(2.42)
% Female	75.0	62.1%	69.2%
% African American	35.0	31.0%	26.9%
% Left-Handed	5 %	10.3%	23.1%
% Idiopathic Epilepsy	NA	55%	73%
% Left Hemisphere Language Dominant	NA	72%	89%
% With MTS	NA	24%	50%
Age of Seizure Onset	NA	17.76(14.84)	21.04(14.91)
Years with Seizures	NA	22.85(15.80)	18.31(15.71)
Years on AEDs	NA	20.62(15.56)	17.92(16.35)
# of AEDs	NA	2.17(1.00)	2.15(8.34)
Dosage Prim AED (mg)	NA	866.67(903.41)	1204.62(1074.75)

Note: All group differences explored. Nominal differences explored with Pearson Chi-Square Tests and independent samples T-tests were used to determine differences in continuous variables. No significant differences were determined. NA = Not Applicable. MTS = mesial temporal sclerosis, AED= anti-epileptic drug.

3.1 Aim 1

Aim 1 was intended to determine whether group differences among neurotypical controls, patients with right temporal lobe epilepsy (RTLE), and patients with left temporal lobe epilepsy (LTLE), could be established based on (WMI) along the left uncinate fasciculus (UF), parahippocampal cingulum (PHC), fornix (FRX), and a control tract (the corticospinal tract; CST). WMI data in the form of average fractional anisotropy (FA) and average mean diffusivity (MD) was successfully extracted from 75 total participants (Table 3.2).

Multiple WMI variables demonstrated significant skewness and kurtosis (e.g., UF FA and MD, PHC MD, FRX MD, and CST FA and MD). Several transformation

strategies were evaluated in an effort to remedy this concern. A log10 transformation was applied to reverse-scored WMI data to reduce negative skew and kurtosis (Field, 2007). Given the nature of reverse-coded data, all subsequent results with WMI data were interpreted appropriately. Table 3.2 presents the exploration of group differences on WMI measurements across groups. One-way univariate analyses of variance (ANOVAs) were conducted with group (i.e., LTLE, RTLE, or control) as the independent variable and WMI for the three target tracts and the single control tract as dependent variables. Aside from PHC FA and UF MD across groups, all variables satisfied assumptions for homogeneity of variance. Results from these ANOVAs revealed a significant effect of group on CST MD, $F(2, 72) = 7.55, p < .01, \omega^2 = .152$. Planned contrasts revealed that controls had significantly higher CST MD compared with the TLE groups $t(72) = 2.63, p < .05$.

Due to violations of the homogeneity of variance assumption, PHC FA and UF MD across groups were analyzed with ANOVAs using Welch's adjusted F ratio. There was a significant effect of group on PHC FA $F(2, 47.94) = 4.71, p < .05, \omega^2 = .040$. Planned contrasts revealed that the LTLE group had significantly lower PHC FA compared to controls, $t(43.02) = 2.95, p < .05$. Of note, FA and MD were negatively correlated in all four white matter tracts in the control and RTLE groups. In the LTLE group, FA and MD were negatively correlated for the PHC and CST, but were not correlated along the FRX or UF.

Exploratory analyses comparing WMI between TLE participants with only left-lateralized language (LTLE $n=23$, RTLE $n= 21$) and controls revealed similar relationships with slightly stronger effect sizes. In these comparisons, controls had

higher CST MD compared to the TLE groups ($\omega^2 = .155$) and left-language lateralized LTLE participants had significantly lower PHC FA compared with controls ($\omega^2 = .045$). Additional exploratory ANOVAs comparing target and control WMI across all tracts between TLE participants with (RTLE $n=7$ and LTLE $n=13$) and without mesial temporal sclerosis (MTS) did not reveal significant group differences in WMI and had generally smaller effect sizes. Similarly, comparing WMI between TLE participants with idiopathic epilepsy vs. other etiologies (across and within the TLE group) did not reveal any additional relationships.

Table 3.2 WMI Variables Across Groups

	Control Group Mean (SD)	RTLE Group Mean (SD)	LTLE Group Mean (SD)
UF FA	.38(.05)	.39(.04)	.37(.04)
PHC FA*	.38(.04) ^A	.35(.08) ^B	.34(.07) ^B
FRX FA	.32(.04)	.32(.07)	.32(.06)
CST FA	.54(.05)	.56(.05)	.56(.04)
UF MD	.08(.01)	.08(.01)	.07(.02)
PHC MD	.09(.08)	.08(.01)	.08(.02)
FRX MD	.09(.02)	.09(.02)	.09(.03)
CST MD*	.08(.05) ^A	.07(.06) ^B	.07(.06) ^B

*Note: UF=uncinate fasciculus; PHC=parahippocampal cingulum; FRX=fornix; CST=corticospinal tract; FA=fractional anisotropy; MD=mean diffusivity (all scores x100); *Values within a row with different superscripts are significantly different.*

3.2 Aim 2

3.2.1 Semantic and Episodic Memory Performance

As control participants did not complete memory measures, only comparisons between TLE groups were possible. Independent samples t-tests did not reveal

significant group differences between the full RTLE or LTLE groups on episodic and semantic memory performance, or on proportion of participants impaired on individual measures (Table 3.3). In addition, no differences on verbal memory measures were determined between TLE participants with or without MTS.

Consistent with findings from previous studies (Kim et al., 2003), LTLE participants with atypically organized language performed qualitatively better on Vocabulary ($g=.48$), BNT ($g=.85$), RAVLT Immediate ($g=.94$), RAVLT Delayed ($g=.96$), and LM Delayed ($g=.23$) compared to their left-lateralized counterparts. However, the limited sample size ($n=3$) for the atypical group limited power to detect significance. Similar differences were not determined in the RTLE group. When both TLE groups only included participants with left-lateralized language (LTLE $n=23$, RTLE $n=21$), LTLE ($M=-1.09$, $SD=.88$) participants demonstrated lower scores than the RTLE group ($M=-.35$, $SD=.93$) on the BNT, $t(42) = 2.57$, $p < .05$. The difference between LTLE participants ($M=-.42$, $SD=1.08$) and RTLE participants ($M=.13$, $SD=.70$) on Vocabulary $t(38.12) = 2.01$, $p = .052$ also approached significance (Table 3.3).

Table 3.3 Semantic and episodic memory performance in left- lateralized language TLE participants

Measures	RTLE Group Mean (SD)	LTLE Group Mean (SD)	Effect Size
Semantic Memory			
Vocabulary [^]	.13(.70)	-.42(1.08)	$d=.57$
Vocabulary Impaired % [*]	0	26	$\Phi=.38$
BNT [*]	-.35(.93)	-1.09(.88)	$d=.82$
BNT Impaired % [*]	0	35	$\Phi=.41$
Episodic Memory			

RAVLT Trial 1	-0.75(.90)	-0.64(1.23)	d=-.10
RAVLT Trial 1 Impaired %	23	24	Φ=.01
RAVLT Trial 5	-0.89(1.40)	-1.17(1.39)	d=.20
RAVLT Trial 5 Impaired %	23	52	Φ=.29
RAVLT Immediate	-1.20(1.28)	-1.61(1.36)	d=.31
RAVLT Immediate Impaired %	42	57	Φ=.14
RAVLT Delay	-1.62(1.43)	-1.91(1.52)	d=.20
RAVLT Delay Impaired %	58	57	Φ=-.02
RAVLT Recognition	-0.22(1.81)	-0.39(1.16)	d=.26
RAVLT Recognition Impaired %	14	24	Φ=.12
LM Immediate	-0.51(.99)	-0.83(1.07)	d=.31
LM Immediate Impaired %	17	35	Φ=.19
LM Delay	-1.12(1.18)	-1.05(.96)	d=-.07
LM Delay Impaired %	25	30	Φ=.06
LM Recognition	-1.28(.43)	-1.22(.37)	d= -.15
LM Recognition Impaired %	27	20	Φ=-.08
Control Task			
GP	-1.17(.83)	-1.17(.60)	d<.00
GP Impaired %	25	26	Φ=.01

*Note: BNT= Boston Naming Test, LM=Logical Memory, RAVLT=Rey Auditory Verbal Learning Test, GP=Dominant Hand Grooved Pegboard Score, Impaired % defined as z-scores of -1.5 or lower. ^=trend at .052, *=significant difference*

To characterize memory performance in the full TLE sample, and because it was necessary to include the largest possible sample size into the factor analysis (section 3.2.2), performance across the full TLE sample are displayed by Table 3.4. Similar to the left-lateralized language sample, a larger proportion of LTLE participants were impaired on semantic measures (Vocabulary and BNT). There were a larger number of

impaired participants in the LTLE group on certain episodic measures (RAVLT trial five recall, RAVLT recognition, and LM immediate recall). The RTLE sample was slightly more impaired on multiple episodic measures (RAVLT delayed recall, LM delayed recall, and LM recognition). Although these differences were not statistically significant, findings suggest that the current sample of RTLE participants had considerable difficulty with verbal memory measures.

Table 3.4 Semantic and Episodic Memory Performance in all TLE Participants

Measures	RTLE Group Mean (SD)	LTLE Group Mean (SD)	Effect Size
Semantic Memory			
Vocabulary	-.10(.90)	-.36(1.06)	d=.26
Vocabulary Impaired %*	7	23	Φ =.22
BNT	-.57(.97)	-1.00(.88)	d=.46
BNT Impaired %	15	31	Φ =.18
Episodic Memory			
RAVLT Trial 1	-.74(.80)	-.39(1.41)	d=-.30
RAVLT Trial 1 Impaired %	19	20	Φ =.02
RAVLT Trial 5	-1.00(1.18)	-.99(1.40)	d=-.01
RAVLT Trial 5 Impaired %	29	46	Φ =.18
RAVLT Immediate	-1.31(1.28)	-1.45(1.39)	d=-.10
RAVLT Immediate Impaired %	55	54	Φ =-.01
RAVLT Delay	-1.89(1.24)	-1.67(1.57)	d=-.16
RAVLT Delay Impaired %	65	50	Φ =.15
RAVLT Recognition	-.17(1.44)	-.20(1.14)	d=.02
RAVLT Recognition Impaired %	9	19	Φ =.29
LM Immediate	-.79(.96)	-.83(1.02)	d=.04
LM Immediate Impaired %	25	31	Φ =.06

LM Delay	-1.37(1.16)	-1.03(.91)	d=-.33
LM Delay Impaired %	40	27	$\Phi=.14$
LM Recognition	-1.38(.47)	-1.26(.41)	d= -.27
LM Recognition Impaired %	35	25	$\Phi=.47$
Control Task			
GP	-1.28(.92)	-1.25(.63)	d=-.04
GP Impaired %	40	31	$\Phi=.10$

Note: BNT= Boston Naming Test, LM=Logical Memory, RAVLT=Rey Auditory Verbal Learning Test, GP=Dominant Hand Grooved Pegboard Score, Impaired % defined as z-scores of -1.5 or lower. No significant differences determined.

3.2.2 Factor Analysis

An initial Principal Components Analysis (PCA) was conducted with the full RTLE and LTLE scores on semantic memory measures and immediate and delayed memory trails for episodic measures (six variables in total) to determine if total verbal memory could be separated into one composite episodic and one composite semantic factor. An oblique rotation (direct oblimin) was selected based on the theoretical assumption that episodic and semantic memory function are unlikely to be independent. The Kaiser-Meyer-Olkin (KMO) measure suggested minimal adequacy for the full sample size, $KMO=0.54$. As such, a decision was made to include both left-lateralized language and right/atypically-lateralized language TLE participants in the PCA. However, KMO values for multiple individual items were below the acceptable limit of .05 (Kaiser, 1974) suggesting that the number of variables in the analysis would need to be reduced.

Immediate delay trails were removed to create an episodic factor more consistent with previous literature (Giovagnoli, 1999; Smith & Lah, 2011) and a second PCA was conducted on all TLE participant scores on the four remaining memory variables: vocabulary, BNT, LM Delayed, and RAVLT Delayed with an oblique rotation (direct

oblimin). The KMO measure verified the sampling adequacy for the total analysis as adequate (Hutcheson & Sofroniou, 1999), KMO=.61, and all KMO values for individual items were >0.50. In addition, Barlett's test of sphericity $\chi^2(6)=36.62$, $p<.001$, indicated that correlations between items were large enough for a PCA.

An initial analysis was run to obtain eigenvalues for each component in the data. Two components had eigenvalues over Kaiser's criterion of 1.0 and in combination explained 76% of the variance. A scree plot displayed subtle inflexions suggesting the first and second components should be retained. The combination of factors indicated by Kaiser's criterion and the scree plot supported retaining two components in the final analysis. Table 3.5 presents the factor loadings after rotation. The three items that clustered on Component 1 were two measures that require a semantic demand (e.g., vocabulary, BNT) and a measure previously found to load on both semantic and episodic memory (LM Delayed Recall). RAVLT Delayed Recall, hypothesized to require more episodic memory had a particularly high load on component 2.

Table 3.5 Semantic and episodic memory performance in all TLE participants

Task	Component 1 (Semantic)	Component 2 (Episodic)
Vocabulary	.925	
BNT	.763	
LM Delay	.748	
RAVLT Delay		.982

*Note: *Factor loadings less than .10 are not included in this table.*

A 2x2 ANOVA was unable to determine a significant effect of group (LTLE and RTLE) on factor (episodic vs. semantic). In addition, no significant correlation was

determined between the episodic and semantic memory factors across the entire TLE sample or within TLE groups.

3.3 Aim 3

3.3.1 Correlations between WMI in Left-Lateralized Language Participants

As Pearson correlations did not reveal significant relationships between WMI variables and semantic memory factors, and the episodic factor was derived from performance on a single measure (RAVLT Delayed Recall), correlations were conducted between WMI and individual memory measures (Figure 3.2). Analyses were restricted to include only left-lateralized language participants (LTLE $n=23$, RTLE $n= 21$) to increase specificity and power.

In the LTLE group, PHC FA was negatively correlated with vocabulary, $r= -.53$, $p<.05$ and BNT, $r=-.51$, $p<.05$. In the RTLE group, PHC FA was positively correlated with RAVLT Immediate Recall, $r=.64$, $p<.05$ and RAVLT Recognition, $r=.58$, $p<.05$. PHC MD in the RTLE group was negatively correlated with both RAVLT Immediate Recall, $r=-.65$, $p<.05$ and RAVLT Recognition, $r=-.80$, $p<.05$. As predicted, No relationships or trends were identified between the control measure (Grooved Pegboard performance) and WMI within either group.

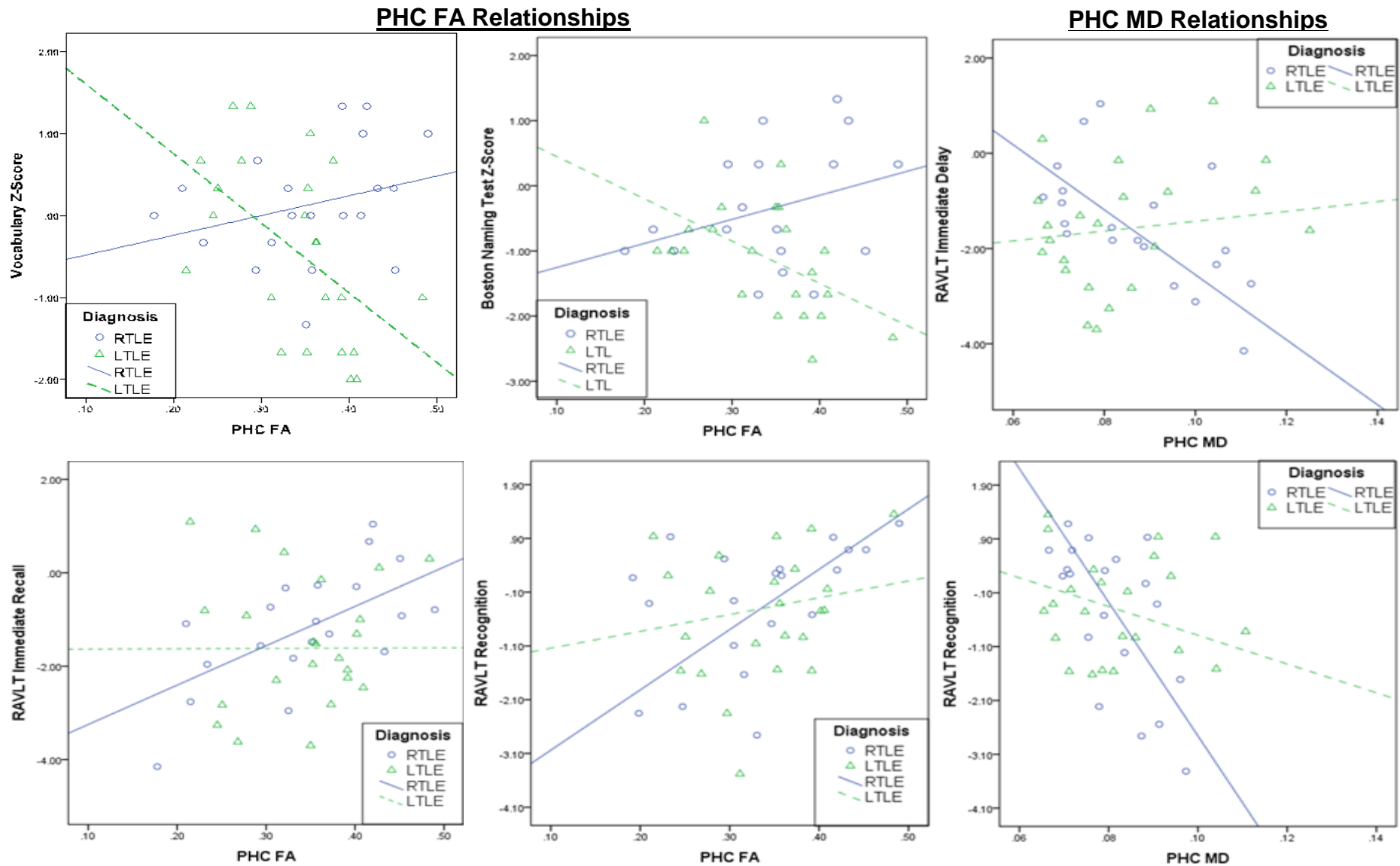


Figure 3.2 Associations between PHC WMI and memory function in left-lateralized sample

Note: RTLE group Demonstrates expected positive relationships with FA and negative relationships with MD. LTLE group demonstrates atypical relationships between PHC and memory measures.

Although variables met statistical assumptions for inclusion in a multiple regression analysis, the lack of findings in correlation analyses supporting previous literature (i.e. relationships between FRX WMI and episodic memory and PHC FA and semantic memory suggesting opposite relationships than hypothesized) suggested against performing hierarchical regression to test specific theory-driven hypothesis for the LTLE group (e.g., determining if WMI along the FRX emerged as a stronger predictor of episodic memory performance when semantic memory was controlled for).

4 DISCUSSION

The purpose of the present study was to examine left temporal lobe WMI along three white matter tracts previously related to verbal memory and seizure propagation in patients with TLE. WMI was explored concurrently with performance on episodic and semantic memory measures in patients with TLE. This study was intended to contribute to the literature by demonstrating underlying semantic and episodic factors that could be applied to the definition of differential relationships between WMI along temporal white matter tracts and memory performance in TLE. Although relationships between underlying semantic and episodic memory factors and WMI were not determined, specific left temporal WMI findings and unique relationships between memory measures and WMI in LTLE and RTLE groups suggest important areas for further study.

4.1 WMI Differences Across Groups

In contrast with much of the previous TLE literature, the current study included a larger and more inclusive sample of TLE participants that were comparable on demographic and treatment factors. Considerable clinical resources and a high volume of presurgical TLE patients allowed for the inclusion of a larger TLE sample compared

with previous studies. The majority of current participants demonstrated well-defined etiologies and few participants with unclear or atypical lateralization (e.g. five patients in the RTLE sample and one in the LTLE sample). This allowed the current study to account for possible group differences related to etiology, and to better isolate variables of interest. Of note, few of the previous studies with similar methods report TLE etiology aside from probable unilateral TLE and MTS (McDonald et al., 2008; Riley et al., 2010; McDonald et al., 2014).

Probabilistic tractography successfully identified the expected white matter tracts within the left temporal lobe in control, LTLE, and RTLE groups. Consistent with previous literature and current hypotheses, participants in the LTLE group demonstrated lower FA along the PHC compared with controls, and a trend toward lower FA compared with the RTLE group. This finding supports previous literature and the hypothesis that LTLE participants would demonstrate the poorest WMI among groups along the PHC secondary to the effect of left-lateralized seizure foci. Lower FA has been hypothesized to be related to multiple neurophysiological processes including reduced density of myelinated axons (Takahashi et al., 2002), possibly secondary to Wallerian degeneration (Pierpaoli et al., 2001), and/or abnormal myelin development/neuroplastic changes in myelin (Song et al., 2002). As such, reduced FA along this inferior section of the cingulum would support previous studies interpreting this finding as poorer connectivity consistent with microstructural alterations. Although the specific mechanism for this damage is unclear, these findings are in line with previous literature identifying the PHC as a path for seizure propagation and secondary neuronal damage in temporal lobe epilepsy (Imamura et al., 2016).

The PHC is a major component of the limbic system that allows for communication between the hippocampus, the ventral aspect of the perirhinal/parahippocampal formation, and joins the superior portion of the cingulum providing connectivity towards the thalamus and posterior cingulate gyrus. Although commonly considered a component of the medial limbic system, the PHC's unique connectivity has also been theorized to be an interface between lateral and medial limbic systems, and by extension, to both semantic and episodic memory function (Levy et al., 2004; Binder et al., 2009).

As such, poor structural connectivity along this tract suggests a possible mechanism for the poorer memory function commonly found in TLE. This finding of lower FA in PHC reinforces previous literature reporting the same finding in LTLE groups with multiple DTI analyses including both manual and automated white matter tractography and TBSS (McDonald et al., 2008; Hagler et al., 2009; An et al., 2014; McDonald et al., 2014; Chiang, Levin, Wilde, & Haneef, 2016). However, (as will be discussed later in this section) these findings are one component of a more complex array of differences in the LTLE group.

Increased MD is commonly considered to be an indication of reduced cellular density and cellular changes consistent with macrostructural changes including edema (Erikson et al., 2001; Gass et al., 2001) and overall reduced WMI. The lack of increased MD findings along the PHC in this sample in the presence of significant FA findings suggests the expression of more subtle microstructural changes in fiber coherence. This pattern of findings is consistent with that described previously in

multiple TLE samples along multiple white matter tracts (Focke et al., 2008; Riley, Moore, Cramer, & Lin, 2011).

Findings that FA and MD along the UF and FRX were relatively comparable across groups did not support our hypothesis of poorer WMI for the LTLE group along the UF. Although previous studies have found decreased FA and increased MD along the UF in LTLE samples (Lin et al., 2008; Hagler et al., 2009; Concha et al., 2012; Imamura et al., 2016), previous studies have also been unable to determine group differences based on UF WMI (Focke et al., 2008; Ahmadi et al., 2009; Voets et al., 2009; An et al., 2014). Similarly, despite previous studies describing decreased FRX WMI in LTLE (Focke et al., 2008; Ahmadi et al., 2009; Hagler et al., 2009), our results are consistent with previous studies that were unable to determine poorer WMI along the FRX for LTLE participants (McDonald et al., 2008; Voets et al., 2009; An et al., 2014; Li et al., 2014; McDonald et al., 2014).

In addition, controls demonstrated higher CST MD compared with both TLE groups. Given the common interpretation of increased MD as reduced macrocellular WMI, this finding was unexpected. However, previous research with neurotypical participants has also revealed increased MD along the CST in subgroups of neurotypical controls. Imfeld, Oechslin, Meyer, Loenneker, and Jancke (2009) reported increased MD along the CST in a group of neurotypical professional musicians versus controls. This increased diffusivity was suggested to result from long-term sensorimotor practice inducing repeated plastic changes and thus increased permeability of the axonal membrane. This finding also suggests that considerable variability in

microstructural white matter integrity exists within neurotypical populations, likely due to factors aside from white matter injury.

There are multiple factors that could contribute to variability across current WMI findings. Previous studies using methods similar to the current analyses and more exploratory approaches have demonstrated variable efficacy in establishing group differences based on WMI along the UF, PHC, and FRX (e.g., Tables 1.1 and 1.1.2). In addition, no single study has been able to demonstrate lower WMI across all three of these tracts in the LTLE group using a single analysis method.

Hagler et. al. (2009) examined the UF, FRX, and PHC (along with additional white matter tracts) concurrently using three separate methods (e.g. manually delineated tracts and atlas-based tract identification both with and without thresholding), and were unable to determine group differences on all three tracts with a single method. Of note, these authors only reported FA differences. Given the level of variability in previous findings and the continually developing nature of DTI analyses, it is also possible that currently published literature does not provide a full account of unexpected or nonsignificant WMI findings. In addition, variability in current results are consistent with findings that limbic structures demonstrate higher variability in WMI measures when compared to other white matter tracts in younger TLE samples (Carlson et al., 2014). Although the reasons for this variability were reportedly unclear, the closer proximity of these tracts to CSF was suggested as a possible factor.

Current results may also reflect a degree of variability in the expression of lower FA in the TLE population. Although previous studies suggest that LTLE groups are more vulnerable to white matter damage in the left temporal lobe given the location and

physiological risks presented by seizure foci (hence current hypotheses), the specific pathophysiological mechanism by which seizures alter WMI remains unclear. For these reasons, specific hypotheses about subsections of lower WMI along the target white matter tracts were not suggested in the current study. However, it is possible that the selection of a mean WMI measure along target tracts was not sensitive enough to capture inconsistent instances of altered WMI along particular tract subsections that could assist in establishing group differences.

FA and MD were negatively associated for the PHC and CST in the LTLE group. This was expected based upon the relationships presented in the current study and across previous DTI literature (Horsfield & Jones, 2002). However, no significant correlations were determined between FA and MD along the FRX or UF in the LTLE group. These findings are unique to some previous work in the TLE population (McDonald et al., 2014), but differences in the strength of the association between FA and MD and findings of a significant group difference on FA found in the absence of a significant group difference on MD has been found previously in samples of participants with atypical white matter and neurodevelopmental disorders including ASD (Catani et al., 2008).

Catani et al. suggest that the degree of uncertainty between measures obtained during tractography and underlying biologic factors makes drawing direct physiological conclusions from FA and MD difficult. The authors also describe studies with neurotypical controls demonstrating uniform MD measures across brain tissues independent of FA differences in specific regions. They suggest that a similar dissociation between FA and MD could be present in clinical populations. When taken

together with results from the present study, dissociation between FA and MD is not an unexpected finding, particularly for the group that was expected to have the most alteration in WMI. In addition, this suggests that FA and MD can be interpreted independently as they each contribute unique information about microstructural organization, especially in clinical populations.

Several demographic and treatment variables were evaluated to determine if additional factors were likely to influence WMI findings and groups were generally comparable. The role of age as a possible influence on WMI was carefully studied in the current sample given previous findings of widespread age-related differences in WMI (Davis et al., 2009) and specifically altered white matter along the UF, PHC, and FRX with age (Michielse et al., 2010), but no significant relationships along currently selected tracts were revealed. This lack of age influence may suggest an alteration in the typical pattern of change in WMI after adulthood expected in neurotypical samples.

Number of years treated AEDs was found to be positively correlated with CST MD, extending findings of reduced WMI in the cerebellum and corpus callosum previously described and attributed to AEDs (Lee et al., 2003; Gunbey et al., 2011) in TLE. Number of years with seizure symptoms and number of years treated with AEDs were not related to WMI along any additional target or control tracts in the current study. A recent study that described multiple TLE vs. control WMI differences (McDonald et al., 2014) included an adult LTLE sample with a younger age of seizure onset, (15.38 vs. 21.04 in the current study) and a longer illness duration (21.23 years vs. 18.31 years in the current study). Similar differences were noted for age of seizure onset (13.00 vs. 17.76 in the current RTLE sample). As such, it is possible that the current sample

represents a group with less exposure to seizure activity related during a period of significant development.

4.2 Episodic and Semantic Memory Performance in TLE

Consistent with previous foundational literature (Wilkins & Moscovitch, 1978), LTLE participants demonstrated more difficulties with semantic tasks than RTLE participants. This difference was best defined after the sample was restricted to include only left-lateralized language participants. Consistent with findings from previous literature (Kim et al., 2003), LTLE participants with atypically organized language performed qualitatively better on both semantic measures and all episodic measures aside from Logical Memory Immediate Delay compared to their left-lateralized language counterparts. Although only three participants in the current LTLE sample fell into this group, this finding is in line with the theory that language lateralization outside of the left hemisphere may sometimes spare verbal memory function in LTLE. Similar differences were not observed between left-lateralized language and atypically lateralized RTLE participants. However, the current RTLE sample did evidence difficulties with episodic measures.

Results demonstrating that LTLE participants had more difficulty with semantic verbal memory when only left-lateralized participants were included are in line with generally accepted findings of a “tighter verbal-left nexus” of memory and language findings in LTLE samples (Saling, 2009). These findings were further defined through examination of the differing impairment profile between TLE groups. Although the impaired RTLE group had similar episodic performance compared to the LTLE group, there were clearly more LTLE participants with semantic difficulties.

Whole-group findings of comparable performance on verbal memory measures between the TLE groups support previous literature suggesting that the relationship between TLE and memory function is more complex than early models suggesting almost complete lateralization of memory function. In addition, a lack of a group differences based on memory measures has been previously described in studies with similar hypotheses (McDonald et al., 2008). It is likely that previous samples may have also been composed of both left and atypically language lateralized participants, but this information is often omitted. The choice to restrict the full sample to TLE groups only including left-lateralized language participants allowed for the detection of a semantic deficit unique to the LTLE sample in the current study.

Although factor analyses were able to define distinct semantic and episodic factors, story memory was found to load more strongly on semantic recall, which was inconsistent with current hypotheses. However, this was not unexpected given previous literature demonstrating story recall loading on both semantic and episodic factors (Smith & Lah, 2011), and other studies reporting story recall as loading entirely on an episodic factor (Giovagnoli, 1999; Giovagnoli et al., 2005), both in TLE samples. This mixture of findings could be attributed to the combined semantic and episodic demand necessary to accurately recall details and semantic structure included in stories (Hermann, Seidenberg, Haltiner, & Wyler, 1992; Saling, 2009). The fact that story memory was the weakest factor among semantic measures in the current study further suggests against it being a purely semantic measure.

The current TLE sample differs from previous larger, Italian-speaking samples that included both temporal and extratemporal epilepsy patients in previous studies by

Giovagnoli et al. describing story memory loading entirely on episodic memory. In addition, the most recent study to apply a similar statistical method to determining semantic and episodic factors included a pediatric sample and applied an orthogonal rotation to a PCA (Smith & Lah, 2011). As orthogonal rotations maximize factor loadings, but are commonly considered more appropriate for factors that are less likely to be related (Tabachnick & Fidell, 2007), an alternate method (oblique rotation) was applied to define factors for the current study as episodic memory and semantic memory are not exclusive processes. Although this method was likely to be more appropriate in defining factors that have previously found to be related, the current sample size was only slightly above a commonly suggested threshold for adequacy (Kaiser, 1974). In addition and possibly due to the semantic factor including a mix of semantic and episodic demands, TLE group differences were not determined based on semantic or episodic factors.

As a result of these memory findings, the RTLE group became less of an “epilepsy control group” as initially hypothesized. Instead, it emerged as an additional sample of TLE participants demonstrating unique verbal memory and WMI relationships.

4.3 Relationships between WMI and Memory Function in TLE

When relationships between memory function and WMI in the TLE sample are analyzed, the PHC emerges as the pathway most consistently related to verbal memory function. Although the PHC plays an important role in verbal recall, the nature of this role differed drastically between participants with LTLE and RTLE. For RTLE participants with seizure foci in the right hemisphere, it is likely that there are fewer

alterations in left temporal white matter. In this group, WMI and memory relationships follow patterns consistent with the majority of previous literature, suggesting that traditional interpretations of increased FA and reduced MD as indicators of better WMI are valid for this group. Greater PHC FA and lower PHC MD were consistently related to higher performance on episodic memory measures. Similar relationships are suggested between PHC FA and MD and semantic performance in the RTLE group, but were less pronounced.

However, in the LTLE group, performance on both semantic measures decreased as PHC FA increased. This was unexpected given previous findings, the commonly held theory that FA indicates greater WMI, and current hypotheses based on this theory suggesting that FA would be positively related to cognitive function. However, this finding becomes less surprising when additional information is considered. The current study is not the first to reveal a mixture of findings both consistent and discordant with previous TLE literature. A recent review article has summarized multiple cases in previous DTI literature where structure-function associations are less coherent, particularly for patients with LTLE (Leyden et al., 2015). The authors suggest that this significant variability in results is due to a combination of partial or atypical reorganization in structure and function in the LTLE population, and both technical and model-based limitations inherent in the many DTI studies (e.g., low spatial resolution relative to actual white matter structure and the difficulty applying the tensor model to areas likely to include crossing fibers). These findings suggest that disrupted PHC white matter in LTLE participants may be atypically organized, and/or less accurately summarized by mean FA.

It is also important to consider that FA is not a direct measure of WMI. As such, increased FA is not exclusively synonymous with increased structural integrity. For example, FA increases along white matter pathways that are more uniform. As such, a neurodegenerative process that damages smaller, more complex white matter pathways with fibers near or crossing the target white matter tract could lead to increased FA as the white matter along that tract would appear more uniform (i.e. have less fibers extending in different directions along a given area).

In this case, an increase in FA would not signify an increase in WMI. In fact, white matter in this area may have less structural connectivity due to the loss of these complex fibers as compared with an area with more intact complex white matter structures. Similar mechanisms have been recently suggested as a likely explanation for increased FA along white matter tracts and related poorer cognitive functioning in multiple clinical samples with and without memory deficits (Hoeft et al., 2007; Douaud et al., 2011; Alba-Ferrara & de Erausquin, 2013).

Although the PHC, FRX, and UF have all been previously theorized to be primary pathways for seizure propagation in TLE, the PHC is theorized to be primary input (PHC through the entorhinal cortex) to the hippocampus (Mayanagi et al., 1996). A recent study (Chiang et al., 2016) that included WMI analyses of the hippocampus and the three target tracts examined in the current study reported significantly increased bilateral MD in the hippocampus, cingulum, and fornix. Current findings of altered FA along the portion of the cingulum most proximal to the hippocampus support and extend Chiang et al.'s findings.

4.4 Limitations

There are limitations to this proposed study that should be considered. As the control group did not complete the same neuropsychological measures as the TLE participants, it was not possible to include the controls in analyses examining group differences on memory performance (Aim 2) or analyses exploring relationships between WMI and memory function (Aim 3). As such, it cannot be determined whether similar associations between WMI and memory performance are present in controls and current findings are only applicable to patients with TLE. In addition, a finding of similar relationships to those found in the current RTLE in a control group would underscore the current LTLE findings are unique to this group and more likely due to side of seizure foci.

Additionally, the scope of the present study did not include consideration of white matter tracts outside of those selected from the limbic system. As noted above (see Table 1.1.2), other white matter tracts, particularly the arcuate fasciculus, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus (Duffau et al., 2009; McDonald et al., 2014) have been found to be related to both semantic and episodic memory performance. This limitation prevents the proposed study from discussing the broader contributions of what is likely a distributed system of interconnected white matter connectivity involved in verbal memory function. In addition, previous studies have also demonstrated the importance of concurrent analysis of the hippocampus to control for the possible influences of variables including hippocampal volume in verbal memory function (McDonald et al., 2014). Accounting for changes in structures previously found

to be altered in patients with epilepsy may also clarify factors underlying current findings.

Although it is clear that additional systems outside the white matter tracts currently examined contribute to verbal memory, the current study was designed to apply a hypothesis-driven approach to focus on structural connections both implicated in verbal memory and hypothesized to be directly impacted by seizure activity. Future studies applying a whole-brain measure of WMI (e.g., TBSS) could test hypotheses about the utility of WMI in particular sections of these tracts (e.g., in proximity to previously identified seizure foci) in the prediction of semantic and episodic verbal memory performance. In addition, an emerging whole-brain approach, Fractional Anisotropy Asymmetry (FAA) was previously able to define whole-brain FA asymmetry (more pronounced for their LTLE group vs. controls) based on disturbances in the left temporal lobe. Combining this approach with the current verbal memory findings may reveal a wider network of white matter differences and verbal memory deficits that would be able to distinguish TLE groups.

A key finding of the current study was a negative association between FA and specific semantic memory measures. It is likely that this unique relationship is secondary to microstructural changes secondary to seizure foci in a hemisphere ipsilateral to where verbal memory function is commonly organized. As the current study did not include WMI analyses in the right temporal lobe or visual memory measures, future studies may choose to test for a similar negative association between FA within the visual memory system and performance on these tasks.

There are also limitations presented by the current use of probabilistic tractography and the tensor model to delineate pathways. This relatively new approach is continually developing and particularly sensitive to noise presented by white matter tracts crossing perpendicular to the target path (Jones, 2008). Crossing fibers are especially common in areas of the brain where several large white matter tracts are in close proximity. As the pathways extending into the temporal lobes are areas where this occurs, the influence of possible error introduced by crossing fibers cannot be ignored. Although steps were taken to limit this type of error with the current method, techniques have been created to allow for better estimation of WMI within regions where several crossing fibers exist (Hirsch, Schwenk, Rossmanith, Hennerici, & Gass, 2003; Tuch, 2004). These approaches require DTI data to be collected during the initial scan with different parameters (e.g., captured from more directions and with longer sequences) and analysis with more complex statistical models than those that were available in the current study.

In addition, the present study did not use anisotropy to constrain probabilistic tracking in either TLE group. This choice was made to reduce difficulties probtrackX has in accurately tracking white matter with lower FA values (Behrens et al., 2003) that were expected to present more commonly in the LTLE sample. Although this allowed for the sample method to be used across samples and reduced the number of participants with failed tractography, it is also possible that this decision allowed for a small inclusion of tissue with lower FA (e.g. grey matter adjacent to white matter tracts).

Finally, current semantic memory measures, though applied in previous literature, also included significant overlap with a wider network of extremely complex

cognitive processes outside of semantic retrieval. For example, good performance on verbal tasks requiring the identification of word require not only an accurate retrieval of a word meaning, but also involve intact working memory and executive function to plan an accurate response, and the engagement of expressive language systems to express the formulated response. Future application of semantic tasks with a reduced language demand (e.g., the Pyramids and Palm Trees Test) could reduce some of this overlap and further focus future research.

4.5 Strengths

No previous study that the authors are aware of has explored differential relationships between WMI along the lateral and medial memory systems measures of episodic and semantic memory. The current study addressed this gap through theorizing specific relationships between WMI along individually delineated white matter tracts along the left lateral and medial temporal lobe circuit and composite episodic and semantic memory factors. Unlike previous studies, a theory-based approach guided hypotheses about specific relationships in an effort to determine if tracts more vulnerable to disruptions in LTLE could differentially predict semantic and episodic memory recall performance.

The current study included a sample of participants that completed a rigorous presurgical workup through a university-based hospital with a dedicated epilepsy center. This allowed for both the inclusion of detailed epilepsy-related data (e.g., age of seizure onset, length of time treated with AEDs) confirmed by medical records and clear differentiation of both epilepsy seizure foci (e.g., LTLE vs. left frontal lobe foci) and language lateralization. The current study was able to explore WMI and memory

relationships within important subgroups (e.g. within a sample with mixed language lateralization and in a left dominant language subgroup) to contrast the strength of WMI and memory relationships revealed. This level of detail and differences in findings based on these variables within the same study are rarely reported. This allowed for the current study to fine-tune comparisons and highlight behavioral mechanisms and important relationships that should be considered in future studies to better understand this complex population.

Special care also was taken during scan acquisition to limit participant movement and DTI data was processed with statistical motion correction software. Likely as a result, few participants were excluded based on motion artifact. Given the sensitivity of DTI data to motion, this is an important strength of the current study. Additionally, data were collected with a higher signal to noise ratio resulting from a scanner with stronger field strength (i.e., 3T compared with equally common 1.5T).

An additional strength of the current study was the use of theory-driven hypotheses. Tract selection was guided by a combination of tracts theorized to be most affected by left TLE seizure foci and by previous theories about the structure and role of specific white matter connections in the limbic system. The majority of previous DTI studies within this sample have been either exploratory, or have focused on describing relationships between single white matter tracts and verbal memory. The current study also featured a control tract and a control task to test the specificity of white matter and verbal memory performance. Theory-based approaches allowed the present study to test and expand upon previously determined theories established through several different models (e.g., animal and lesion studies).

4.6 Conclusions

Results from current study highlight the left PHC as particularly vulnerable in LTLE, related to semantic memory recall in LTLE, and important for episodic memory function in RTLE participants. In addition, the current analyses clearly demonstrate the importance of carefully exploring homogenous subgroups to reveal unique brain-behavior relationships between and within epilepsy diagnoses. Current findings suggest additional verbal memory associations for important limbic tracts in addition to those previously theorized, and further distinguish left-lateralized white matter alternations in TLE.

Distinct between-group differences were noted in the current study and the variability in previous literature aimed at defining relationships between white matter and verbal memory function in TLE is clear. As such, additional work to continue defining these relationships is necessary. The establishment of these relationships would help better inform both TLE patients and physicians about specific white matter tracts and associated risks for verbal memory impairment in TLE.

Specifically, emerging literature has identified developing surgical techniques (e.g., MRI-guided stereotactic laser amygdalohippocampotomy) that are less invasive and comparable to traditional open resections in effectively disrupting epileptogenic foci and reducing seizure symptoms (Gross, Willie, & Drane, 2016). Of particular relevance to the current study, this approach has been demonstrated to have less of a detrimental effect on verbal functioning (e.g. performance on object recognition and naming tasks) than traditional resection in the sample the current study was drawn from. This has been theorized to be related to relative sparing of temporal stem white matter (Drane et

al., 2015). Future studies may explore how presurgical biomarkers suggested by the current study may be informative in future exploration of postsurgical WMI changes and associated performance on verbal tasks.

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APPENDIX: ROI DELINIATION FOR PROBABILISTIC TRACTOGRAPHY

Appendix A: Uncinate Fasciculus

To track the UF, one ROI (Figure 5.1 A) was drawn to include the left temporal lobe at the most posterior coronal slice in which the temporal lobe could be distinguished from the frontal lobe. A second ROI (Figure 5.1 B) was drawn on the same coronal slice around anterior projections of the left UF from the temporal lobe to the frontal cortex (Wakana et al., 2007). Color-coded principal diffusion direction vector maps were overlaid onto FA maps to guide the identification of this fiber bundle (i.e., the ROI was drawn to only include the UF fibers extending in the anterior/posterior direction on the coronal slice). As suggested by a previous study (Metzler-Baddeley et al., 2011), a coronal exclusion slice was placed posterior to the curve of the UF that could be seen on the color-coded sagittal slice.

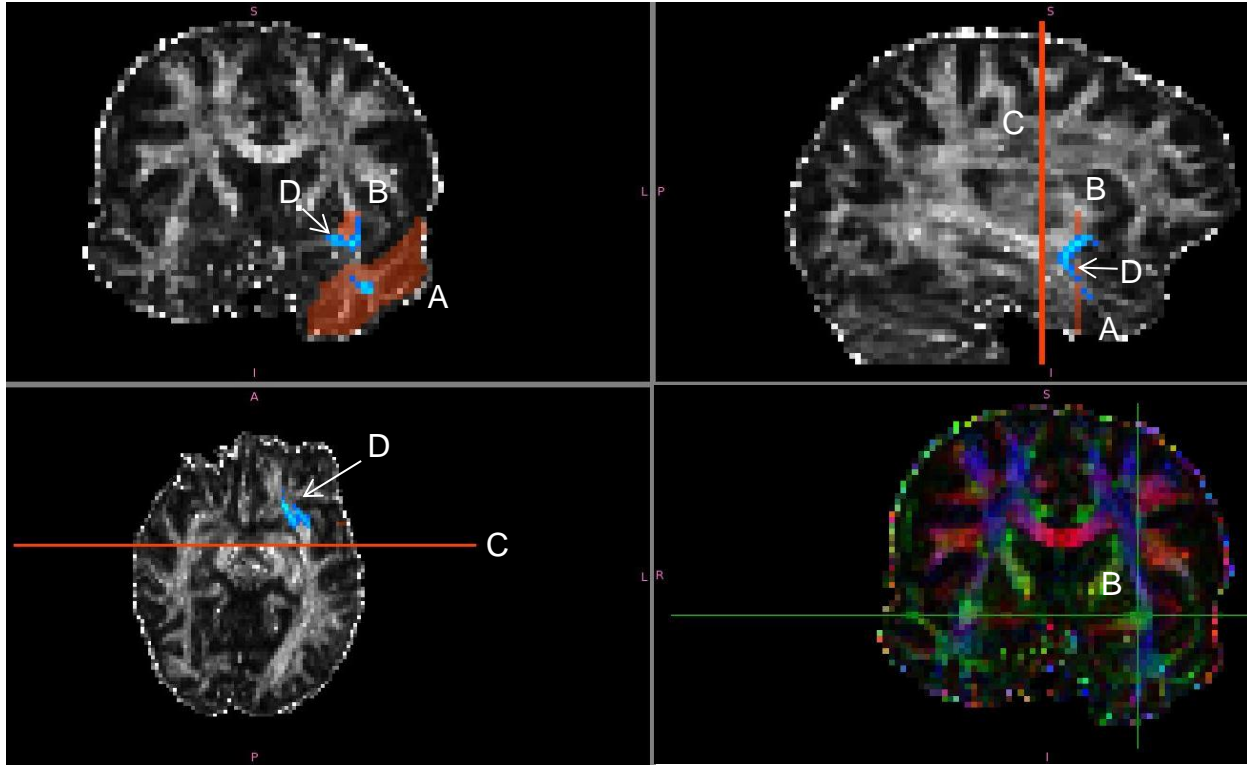


Figure 0.1 UF ROIs and Example Tract

Note: A: Inferior temporal UF ROI; B: Superior UF ROI; C: Posterior exclusion coronal slice mask; D: Resulting UF tract.

Appendix B: Fornix

For tracking of the FRX, one, generally 6x8 rectangular ROI (Figure 5.2 A) was placed on the axial slice in which the inferior portion of the left FRX was last visible before joining with the posterior portion of thalamus (Zhuang et al., 2012). A second, generally 4x7 rectangular ROI (Figure 5.2 B) was drawn on a coronal slice across the body of the fornix immediately before the bifurcation into columns around the anterior commissure (Concha et al., 2005). Color-coded principal diffusion direction vector maps were overlaid onto FA maps to highlight the anterior commissure. To prevent fiber tracking anterior to this point, an exclusion mask was applied on a coronal slice

immediately anterior to the superior fornix ROI. A second exclusion mask was placed on the axial slice perpendicular to the coronal exclusion ROI to prevent fiber-tracking inferior to this point, creating an “L”-shaped exclusion ROI (Figure 5.2 C).

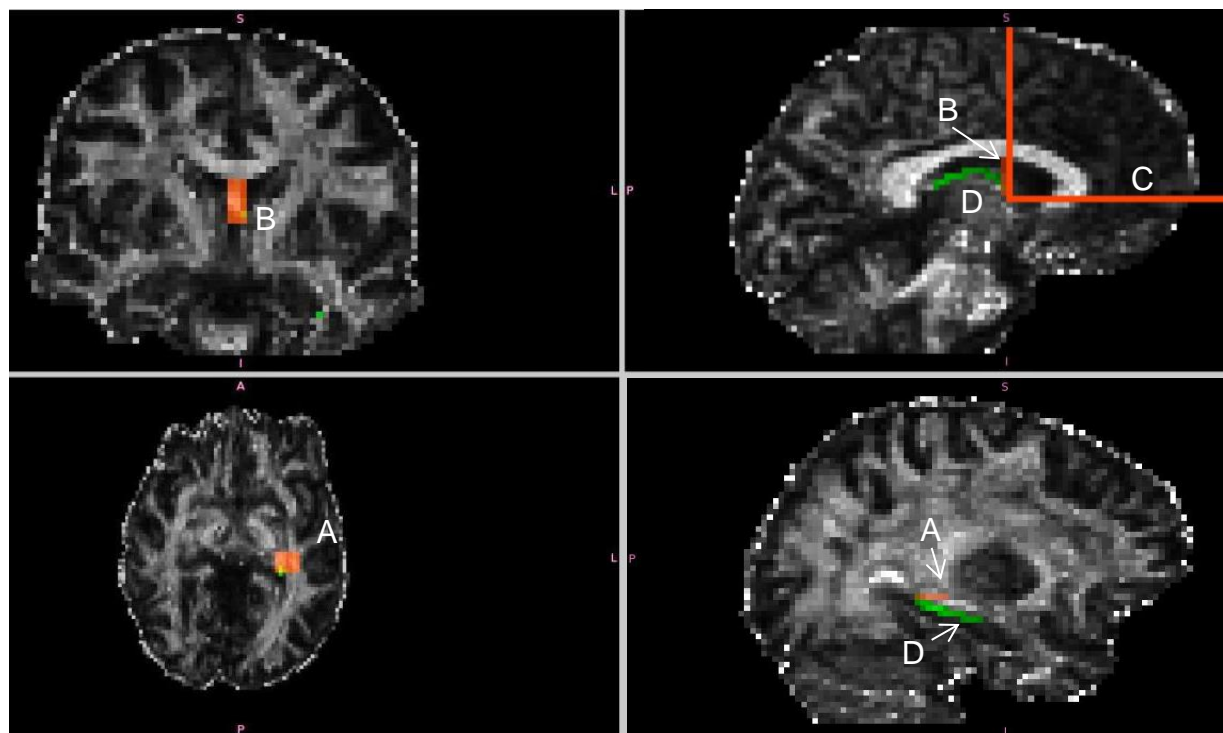


Figure 0.2 FRX ROIs and Example Tract

Note: A: Inferior FRX ROI; B: Superior FRX ROI; C: Anterior exclusion mask; D: Resulting FRX tract.

Appendix C: Parahippocampal Cingulum

To track the left PHC, a sagittal view was used to locate the portion of the PHC immediately below the splenium of the corpus callosum. The superior PHC ROI was then placed on a coronal slice of the left PHC (Figure 5.3 B). To prevent fiber tracking superior and posterior to this point, a coronal exclusion slice (Figure 5.3 C) was included two slices posterior to this ROI (Wakana et al., 2007). An inferior ROI (Figure 5.3 A) was drawn along the PHC on a coronal slice immediately anterior to the pons

(identified on the sagittal plane). Delineation of both ROIs was aided by use of a color-coded FA map.

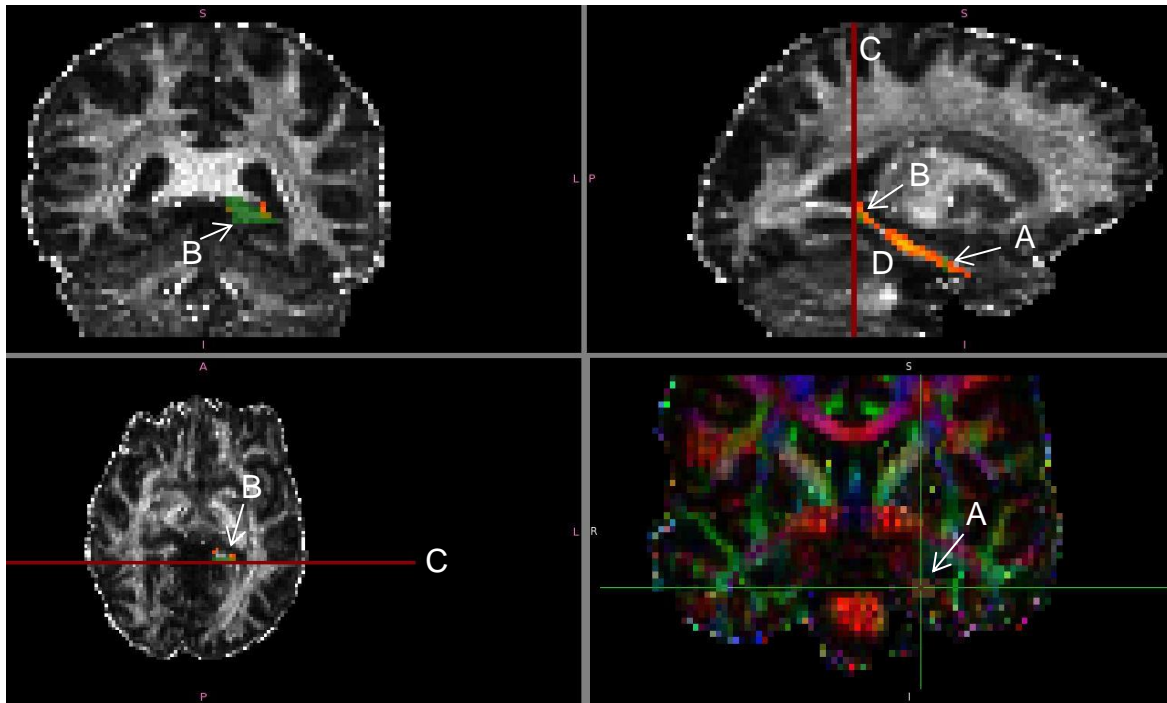


Figure 0.3 PHC ROIs and Example Tract

Note: A: Inferior PHC ROI; B: Superior PHC ROI; C: PHC exclusion mask; D: Resulting PHC tract.

Appendix D: Corticospinal Tract

A section of the left CST between the primary motor cortex and the midbrain was selected. An initial ROI (Figure 5.4 A) was drawn on an axial slice at the level of decussation of the left superior cerebral peduncle (Wakana et al., 2007; Zhuang et al., 2012). A color-coded principal diffusion direction vector map was overlaid onto FA map to highlight superior/inferior fibers. This ROI was then used to plot a single-mask tractography result for the CST. These results were used to confirm projections between the cerebral peduncle and motor cortex. A superior ROI was placed (Figure 5.4 B) to restrict selected fibers to include those extending between the inferior ROI and

the motor cortex (Wakana et al., 2007; Zhuang et al., 2012). To prevent the inclusion of right hemisphere fibers, a sagittal exclusion slice was placed along the longitudinal fissure (Figure 5.4 C).

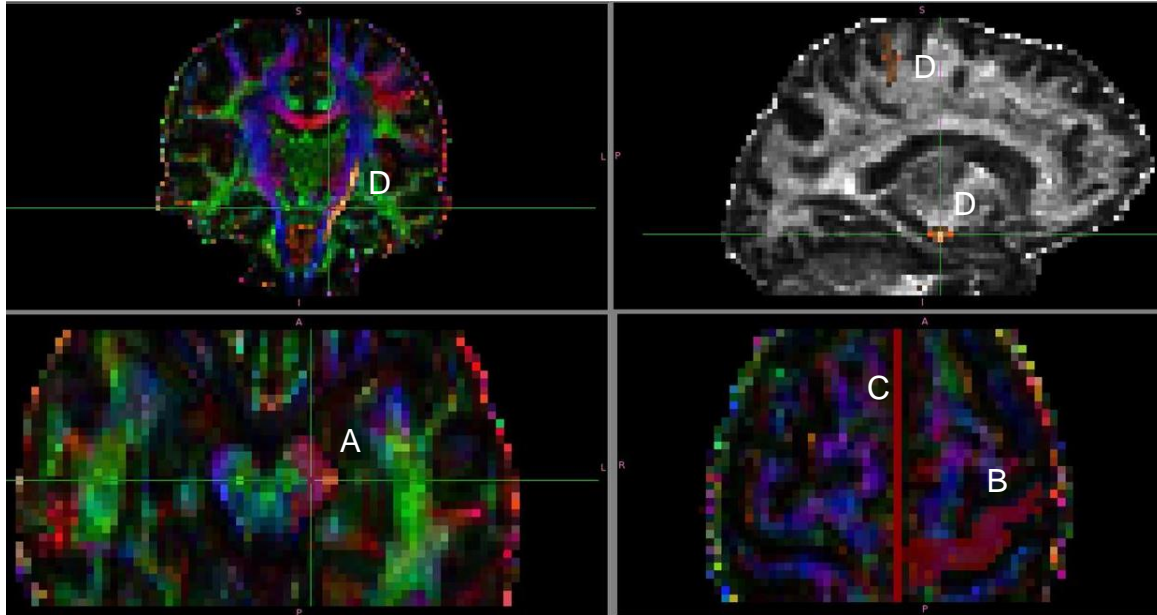


Figure 0.4 CST ROIs and Example Tract

Note: A: Inferior CST ROI; B: Superior CST ROI; C: CST exclusion mask; D: Resulting CST tract.